Review

A transition from the BPharm to the PharmD degree in five selected countries

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Abstract

This review focuses on the studies and opinions around issues of transition from the BPharm to the PharmD degree in the U.S., Japan, South Korea, Pakistan and Thailand.

The transition to the clinically orientated PharmD degree in many countries was seen to be a means of developing the profession. However, some countries have both clinically-oriented and pharmaceutical sciences-oriented PharmD programme that are designed to meet the needs of their countries. Each country created a different process to handle the transition to an all-PharmD programme, but mostly had the process of school accreditation mandated by the regulatory bodies. The main barrier to the transition in most of the countries was the issue of educational quality. A set of indicators is needed to measure and monitor the impact/outcome of the PharmD degree.

Each country has different needs due to the different contexts of health care systems and the scope of pharmacy practice. In order to increase their chances of benefiting from the new programme, academic leaders should critically assess their countries' needs before deciding to adopt a PharmD programme.

Keywords

Education, Pharmacy; Schools, Pharmacy; Students, Pharmacy; Pharmaceutical Services; Clinical Competence; Curriculum; Program Development; United States; Japan; Republic of Korea; Pakistan; Thailand

INTRODUCTION

The Doctor of Pharmacy (PharmD) is a professional doctorate degree, also known as a clinical doctorate - a term only used in the health professions.[1] The professional doctorate degree emphasises practice competencies, which is different from an academic doctorate, such as Doctor of Philosophy (PhD) that focuses on knowledge or original research production.[1] The United States was the first country that has moved to a 6-year PharmD degree as the sole credential for the professional pharmacy programme and focuses mainly on clinical pharmacy.[2] There is an increasing global trend for example in countries towards PharmD degree education.[3-9] The list of countries that transitioned from the BPharm to the PharmD degree, as their entry-level qualification are as follows, U.S., Canada (plan to offer an all-PharmD in 2020), Hungary, Italy, Japan, South Korea, Pakistan, Saudi Arabia, Thailand, Benin, Cameroon, Republic of Congo, Senegal, Tunisia, Nigeria and Gana.[5-9] This paper aims to review the key publications demonstrating the opinions around issues of transition from the BPharm to the PharmD degree in the five selected countries, which are the U.S., Japan, South Korea, Pakistan and Thailand.

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The countries were chosen because there were a number of publications about the transition available. The basic information regarding the pharmacy workforce and education in those selected countries is presented in Table 1. The most popular area of practice in the developed countries is community pharmacy, due to the structure of their health care systems that need a high number of pharmacists in such pharmacies. On the other hand, the popular area of practice in Pakistan is the pharmaceutical industry because of the successful pharmaceutical industry in Pakistan.[10] Thailand has hospital pharmacy as the most popular area of practice, due to the public hospitals being the country's main healthcare facilities.[11]

Educational pathways to become a pharmacist in the five selected countries

The pharmacy educational systems are similar in course length most are approximately 6 years if pre-entry standards and internships are included (Table 2).[3,4,12-16] All countries have a similar education system to cater for those who wish to become a pharmacist: the students enter from secondary school except for the U.S. and South Korea where school leaving qualifications are lower and entry is after a minimum 2 years at the university, followed by a 4-year pharmacy course with one year training experience and then a licensure examination.[13-15] All countries require registration assessment of new pharmacists or their national licensure examination.

Scope of pharmacy practice in the five selected countries

Pharmacists in all countries provide clinical pharmacy services but at different levels of implementation; for example, pharmacists in developed countries have many supporting systems for the implementation of pharmaceutical care practice. On the other hand, in

Table 1. Basic information, education and training in the five selected countries that moved to an all-PharmD degree

Characteristics	U.S.[45,71,72]	Japan[51-53,55,73]	South Korea[20,74]	Pakistan[6,10,75-77]	Thailand[77,78]
General aspects					
Population (millions)	273	128	49.8	176	67
GDP per capita (USD) (2013)	54,353	42,983	18,373	4,700	14,400
Number of licensed pharmacists (per 10,000 of population)	249,642 (9)	276,517 (21)	53,492 (6.5)	12,000 (0.7)	28,272 (4.2)
Pharmacy workforce by practice[79,80]	C[a] 65%, H[b] 25%, O[c] 10%	C 49.6%, H 19.4%, I[d] 11.9%, O 19.1%	C 28.6%, I 21%, H 18.3%, O 32.1%	I 55%, C 10%, H 10%, O 25%	H 40%, C 17%, I 10%, O 33%
Community pharmacies[79]	37,539	71,970	20,633	80,000	11,592
Re-licensure required	Requirements vary by state	No renewal system in pharmacy license	N/A	N/A	Renewed every 5 years
Pharmacy education					
No. of pharmacy institutions[6]	129	74	35	43	19
No. of pharmacy technicians institution[79]	700	0	0	9	17
Pharmacy graduate per year[6]	12,719	9,912	1,372	4,000	1,680
Year that transition to an all-PharmD programme has been started	2000	2006	2009	2004	2010
Academic programme, length (years)	PharmD[e], 6[f], 4[g]	Bachelor, 6	Bachelor, 6	PharmD, 5	PharmD, 6
Practice training[6]	C, H, O (1,000-1,800 practice hours)	C, H (6 months)	N/A	C, H	C, H, I, O (2,000 practice hours)
National licensing exam	Required	Required	Required	Required	Required
The programme that bridge the academic gap between 4-, 5- and 6-year pharmacy programme	Non-traditional PharmD programme	The new curriculum-support training	Master degree programme in clinical pharmacy	N/A	Master degree programme in clinical pharmacy, Residency training programme

[a]C=Community pharmacy; [b]H= Hospital pharmacy; [c]O=Others; [d]I=Industrial pharmacy; [e]nearly half of students hold a bachelor or higher degrees; [f]for PharmD programme with no pre-pharmacy requirements for admission; [g]for PharmD programme that requires at least 2-years of specific pre-professional (undergraduate) coursework prior to 4-academic year of professional study.

developing countries pharmaceutical care implementation still encounters a number of challenges, including the absence of a recognized reimbursement system.[17,18] Pharmacists in the U.S. can be given the authority to be supplementary or independent prescribers via collaborative practice agreements that depend on state regulations; while pharmacists in Japan, South Korea, Pakistan, and Thailand have prescribing authority for 'pharmacist only medicines (POM)' and the over-the counter (OTC) medicines for the symptomatic treatment of minor conditions.

THE TRANSITION FROM THE BPHARM TO THE PHARMD DEGREE

The key publications demonstrating the opinions evolving around the issues of transition from the BPharm to the PharmD degree have been reviewed. There are four main issues that consistently emerged as follows;

1. Needs and context: It seems that the intention of the transition to the PharmD degree in many countries was to use pharmacy education as a way to guide the future of the profession, especially shifting to a more clinically oriented degree.[4,19] On the other hand, Pakistan, South Korea and Thailand needed to expand their pharmacists' roles in clinical pharmacy, as well as meeting the high demand for pharmacists in the pharmaceutical industry.[16,20-24]

It was suggested that the bachelor degree was still needed and should be continued as a basic degree programme, in order to develop pharmacists who have knowledge and skills to work in non-direct patient care areas like the pharmaceutical industry and marketing.[21,22,24]

2. Process: The process of the transition from the BPharm to the PharmD has created similar situations among several countries as follows:

1) Debating about the transition: There were debates about the transition from the BPharm to the PharmD degree for a long period of time in order to establish a consensus at the national level.[19]

2) Mandating by the regulatory bodies: Each country had their regulatory bodies who mandated the PharmD programme as the entry-level pharmacy programme, by moving toward some sort of standardised credentialing methods.[2,19] For example, the curriculum must have been revised to fit the new PharmD programme in order to receive its accreditation or to produce pharmacy graduates who are eligible to sit for the licensure examination.[2,26,27]

3) Supportive regulations concerning the provision of pharmaceutical care in practice settings: In some countries, there are factors that support pharmacists to take up their new roles in direct patient care activities. For example, in the U.S., the pharmaceutical care service called medication therapy management (MTM), has been codified into law, and Medicare Part D providers are required to offered MTM services to a specific subset of patients.[19,25,28-30] This situation differs from many developing countries, which have changed to the PharmD degree, that still have no supporting regulations and often no professional fee framework to reward pharmacists for making high-risk clinical decisions.[4,31,32]

3. Barriers to the transition: The transition from bachelor degree to doctoral level, in most of countries raised concerns about education quality.[32] Most developing

Table 2. Educational pathways to become a pharmacist in the five selected countries that transition from the BPharm to PharmD programme (Adapted with permission from Sripanidkulchai 2012)[13-16]

Approximate age of learner	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
Approximate grade	1	2	3	4	5	6	7	8	9	10	11	12							
US (6-year PharmD)	Primary school						Secondary school						2-year prerequisites or obtaining a transferable bachelors' degree pharmacy		4-year School of Pharmacy, including clerkship 1,000-1,800 practice hours -IPPE[a] 300 hours during first 3 years of course -APPE[b] 36 weeks in the fourth year				State Board exam
Japan (6-year BPharm)	Primary school						Junior High school			High school			6-year BPharm, including 6 months internship (Prior to start outside practice: students have to take common exam at school (CBT[c]+OSCE[d]) in the fourth year)						National Board exam
Korea (2+4 Pharmacy programme)	Primary school						Junior High school			High school			2-year Pre-pharmacy + PEET[e]		4-year School of Pharmacy, including clerkship in the final year; -IPPE[a] 2 credits (70 hours);APPE[b] 1 years (33 weeks/1330 hours for 28 credits)				National Board exam
Pakistan (5-year PharmD)	Primary school					Secondary school (lower level G6-8)			Secondary school (upper level G9-12)				5-year PharmD (There is no clarity regarding pharmacy practice experience)					N/A	
Thailand (6-year PharmD)	Primary school (6-11 years old: Prathom)							High school (12-18 years old: Mattayom)					6-year PharmD, including 2,000 practice hours -IPPE[a] 400 hours during the fourth year -APPE[b] 1,600 hours during the fifth and the sixth year						National Licensure exam

[a]IPPE=Introductory Pharmacy Practice Experience; [b]APPE=Advanced Pharmacy Practice Experience; [c]CBT=Computer based testing-for knowledge; [d]OSCE=(Objective Structured Clinical ability Examination)-for professional skills; [e]PEET=Pharmacy Education Eligibility Test

countries may lack such crucial factors as experienced clinical academic staff, competent preceptors, collaboration with hospitals. Other challenges are likely to include insufficient infrastructure, and economic resources to provide adequate internships, all of which might affect the quality of pharmacists' education.[4,33]

4. Impact/outcome: There is still insufficient information to develop a definite argument to support a relationship between success indicators and the introduction to the PharmD degree.[4,34] Anderson and Futter suggested that there should be a set of indicators to measure and monitor the impact of the PharmD degree.[4] In the following section, the transition from the BPharm to the PharmD programme or similar programme in the U.S., Japan, South Korea, Pakistan and Thailand has been reviewed.

THE UNITED STATES OF AMERICA

Need for the change

The U.S. pharmacy profession decided to move to an all-PharmD programme over 20 years ago, in an effort to enhance pharmacists' competencies and reflect growth in the knowledge base of the profession.[1,35] There was a need to incorporate new competencies into the pharmacy curriculum and a need to provide robust pharmaceutical care, together with the potential for improved economic outcomes.[19]

Process of the transition to the PharmD degree

The origin of the debate over whether to offer the entry level PharmD as the sole professional degree began back in 1948, when the American Council on Education (ACE) recommended that the professional pharmacy curriculum should be a 6-year programme. In 1989, 56% of U.S. pharmacy schools still only offered the bachelor degree, 14% offered the PharmD degree and 30% offered both degrees.

The American Association of Colleges of Pharmacy (AACP) President William Miller appointed a task force, which was termed The AACP Commission of Implement Change in Pharmaceutical Education, to develop recommendations to guide pharmacy education to meet the demands of the profession, the health care system and the society.[25,36,37]

In 1989, the Accreditation Council for Pharmacy Education (ACPE), the body that sets educational standards and accredits colleges of pharmacy, stated that its intent was to accredit only PharmD degree programmes as the entry-level degree into the pharmacy profession; suggesting the year 2000 as a probable target date.[25] This declaration drove much discourse among educators who were doubtful of obtaining adequate resources to add another year into the curricula. Concern was also expressed over the practitioners: in particular fearful that bachelor practitioners would be disenfranchised if pharmacy schools produced only PharmD graduates.[25] Debates about the PharmD as the entry-level degree have continued for approximately 40 years but the issue was finally resolved in July 1992, at the annual meeting of the AACP.[25] The delegates voted overwhelmingly to endorse the PharmD degree as the sole degree leading into the practice of pharmacy.[25] In 1997 with the publication of Standards 2000, the ACPE put in place the requirement that all pharmacy schools develop a plan for transitioning from two degrees to one degree by July 1, 2000.[19] Then, all schools

and colleges of pharmacy revised their curricula in order to receive accreditation.

Enablers

1) Leadership: The close association between the AACP and ACPE played a vital role in the strength of the AACP's suggestions. The AACP influenced the ACPE to revise accreditation standards for all school of pharmacy to include the PharmD degree and the educational elements necessary for providing pharmaceutical care.[38,39]

2) Evidence of support: Between 1986-1991, many articles focused on the important of preparing pharmacists for the changing of the pharmacy profession by shifting towards a more comprehensive patient-focused care and other factors that stimulated a need for change in pharmacy education, particularly the rising cost of health care.[19,35,39-41] There were also a number of studies regarding measuring the effect of the PharmD graduates in practice, compared to the Bachelor of Science in Pharmacy programmes. The conclusions that might be drawn from these studies were as follows: job activities and professional satisfaction of BPharm and the entry-level PharmD graduates were not significantly different.[34,42] However, most of the studies were limited in their methodology due to such issues as low response rates and imbalanced representation by degrees.[7,34]

Barriers

The barriers that have been mentioned are as the follows: 1) lengthening the education programme for a year would cost money. Tuition fees would increase, student debt would rise, and the state would have to contribute more funding to support the programme.[27] 2) there would be a lack of competent preceptors.[43]

The U.S. PharmD curriculum

Compared to the BPharm, the PharmD curriculum was extended by one year that included additional pharmacotherapy and patient care coursework, plus expanded experiential learning with specified activities emphasising clinical skills; for example, counselling patients or advising other health professionals on drug use issues.[44,47-49] Even though the transition from the BPharm to the PharmD programme in the U.S. has been accomplished, the American College of Clinical Pharmacy (ACCP) and the American Society of Health-System Pharmacists (ASHP) think that the pharmacy education should be better. Both organisations share a common vision that all pharmacists who are involved with direct patient care will be required to complete a residency prior to entering practice by 2020.[50]

JAPAN

Need for the change

The curriculum change was made to address the strong demand for highly competent pharmacists to deliver pharmaceutical care for the health care teams.[51]

Process of the transition to the PharmD degree

Changing to a 6-year pharmacy degree programme was proposed by the Japan Pharmaceutical Association (JPA) in 1973. However, the change was not implemented until 2003, when the Council for Pharmaceutical Education approved the transition.[52] In 2006, the pharmacy education system in Japan was in transition from the traditional 4-year programme into two programmes, namely: a traditional 4-year programme and a new 6-year Bachelor of Pharmacy programme, which is similar to the PharmD programme.[51,52] The traditional 4-year programme emphasised pharmaceutical sciences due to the career decisions of graduates; approximately 80% of Japanese pharmacy graduates enter the pharmaceutical industry.[31] The 4-year BPharm graduates are not able to obtain a national pharmacy license.[53] The 6-year programme is mandatory for registration for the licensure examination and is related to the accreditation system.[54] Thus, only the graduates from the new 6-year programme are able to obtain a national pharmacy license.[51]

Enablers

There is a prescription law that separates prescribing and dispensing in Japan (Bungyo).[28,55] This law allows opportunities for pharmacists to provide pharmaceutical care activities within the scope of the prescription law.[31,57]

Barriers

The transition to the 6-year programme in Japan has also had many challenges. Those challenges include insufficient numbers of academic staff in the clinical pharmacy area; lack of experienced preceptors; barriers to providing clinical pharmacy activities due to a high volume of prescriptions; and other health care professionals still having doubts about the role of pharmacists.[30]

The PharmD curriculum

The 6-year programme provides students with more pharmaceutical care, pharmacy practice, and pharmacotherapy courses. It includes 2.5 month rotations in hospital and community pharmacy settings, which are longer than the 4-year programme that included only 2-4 week hospital pharmacy rotation.[30]

SOUTH KOREA

Need for the change

The curriculum changes in the Republic of Korea (South Korea) was made to address the significant change in pharmacy practice, since a new prescription law was enacted in 2000.[15] The new law completely separates the prescribing and dispensing functions between physicians and pharmacists. These conditions were aimed to address certain public health issues; in particular, high rates of drug misuse and overuse.[57] However, pharmacists' compliance with their new roles has been suboptimal. This result is because of the 4-year BPharm programme had mainly focused on the pharmaceutical sciences and most graduates had inadequate preparation to equip them to provide clinical services.[15]

Process of the transition to the PharmD degree

In order to cope with the scope of Korean pharmacy practice and align with the global trend toward 6-year pharmacy programmes, the Ministry of Education and

Human Resources Development of Korea reorganised the pharmacy programme in 2005.[15,20] The transition from the 4-year programme to the 6-year programme was fully implemented in 2009.[20]

Enablers

According to the new situation regarding prescription, Korean pharmacists are required to perform drug use evaluation and medication counselling for a patient prior to dispensing.[15]

Barriers

There is the need to build infrastructure for the pharmacy practice experiences such as networking with training sites and preceptors. There is also a need to develop facilities and resources; in particular funds, manpower and knowledge.[58]

The PharmD curriculum

The new curriculum includes a 2-year pre-pharmacy course and 4 years of pharmacy with practice experience.[15,59]

PAKISTAN

Need for the change

There were two main motivations for the transition to a PharmD programme in Pakistan.[60] The first motivation was to provide a way for future graduates to practice in the U.S.; second was to develop the new curriculum to prepare the future pharmacist to have the capacity to work in various careers in Pakistan, especially in the patient care area.[21,60,61]

Process of the transition to the PharmD degree

In 2004, the Higher Education Commission (HEC) of Pakistan upgraded the 4-year BPharm to the 5-year PharmD programme in order to standardise the Pakistani pharmacy educational system, according to international education and practice needs.[60,62] It had been announced that the 5-year PharmD was the essential condition for a university's PharmD accreditation, and a requirement for a pharmacist to practice in Pakistan.[60]

Enablers

The government hired a broad range of pharmacists in major public hospitals in order to establish and provide pharmaceutical services and to serve as training sites for the PharmD graduates in the future.[21]

Barriers

There were concerns about an inadequate number of experienced and qualified academic staff in the pharmacy practice area, lack of practice based-settings, as well as the insufficient clinical content and practice training in the PharmD programme, all of which may lead to low quality of education and low student satisfaction and performance.[18,24,60,62,63] Secondly, there are many challenges for PharmD graduates in practice; for example, lack of an acceptance by other health professionals, the dispenser in pharmacies and hospitals performing the pharmacists' jobs; lack of the public awareness of the pharmacists' roles, and a severe pharmacy workforce shortage.[4,60,62,64,65]

The 5-year PharmD curriculum

The 5-year PharmD programme had increased content and practice in pharmaceutical care and the clinical pharmacy clerkship. However, there were reports that the clinical and social aspects of pharmacy; in particular patient counselling, research methods and evidence-based medicines, as well as other major areas (e.g., public health pharmacy and drug policy) were not included in the new curriculum.[10,60,66]

THAILAND

Need for the change

Thai policy makers believed that a transition to the 6-year PharmD would meet the needs of the stakeholders by changing pharmacy competencies from generalists to specialists, resolve the issue of curriculum overload for the high-credit 5-year BPharm programme, and produce equal educational standards and outcomes and for the pharmacy profession on a national level.[67]

Process of the transition to the PharmD degree

Enablers

An important influence that has been mentioned on the transition to an all-PharmD programme in Thailand was the cooperation of four faculties of pharmacy and the Bureau of Health Service System Development, Ministry of Public Health (MoPH), in the development and establishment of a master's degree in clinical pharmacy via a modular system programme. This foundation of clinical pharmacy activities in real workplace settings was supported by the U.S.-Thai consortium for the development of pharmacy education in Thailand, which was founded in May 1994 by the Pharmacy Education Consortium of Thailand (PECT). Another big drive for advancement came from the announcement of the Pharmacy Council of Thailand (PCT) in 2008 that, starting in 2014, all new pharmacy graduates who are able to enter national pharmacy license examination would have to graduate from pharmacy faculties accredited by the Council through the 6-year PharmD curriculum only.[67]

Barriers

There were concerns about the higher costs of a longer period of time for study and an insufficient quantity and varying quality of PharmD preceptors and training sites.[67]

The 6-year PharmD curriculum

There are three tracks of PharmD in Thailand which are as follows; the pharmaceutical care PharmD which focused on patient care; the industrial pharmacy PharmD which is pharmaceutical product oriented, and the health consumer protection which focused on consumer protection mechanism regarding pre-marketing control, post-marketing control and consumer empowerment.[68-70]

Table 3. Key points summarising the transition from the BPharm to the PharmD degree or similar programmes in term of need, process and perceived barriers in the five selected countries.

	US[19,38,43,45,52]	**Japan**[30,51,52,54]	**South Korea**[15,20,58,74]	**Pakistan**[21,33,60-62]	**Thailand**[81,82]
Need for the transition	To have a highly skilled clinical pharmacist to provide the pharmaceutical care and work with health care teams	To cope with the regulations that changes in the scope of pharmacy practice in their countries	To cope with the regulations that changes in the scope of pharmacy practice	To standardise the Pakistani pharmacy educational system and enable the graduates to work abroad	The 6-year PharmD will produce pharmacy graduates who had knowledge and skills needed by the job market.
Previous programme	5-year Bachelor	4-year BPharm	4-year BPharm	4-year BPharm	5-year BPharm
New programme	6-year PharmD (PC[a])	6-year BPharm (PC[a])	6-year programme (PC[a], IP[b])	5-year PharmD (PC[a], IP[b])	6-year PharmD (PC[a], IP[b], CP[c])
The difference between the previous and the 6-year curriculum	PharmD curricula were extended by one year that includes additional patient care coursework	The new 6-year BPharm programme focused on patient care.	The new programme increases the number of required courses in clinical pharmacy and training period.	Increase knowledge and practice in pharmaceutical care and the clinical pharmacy clerkship	The 6-year PharmD increased practice hours.
Process of transition	In 1997, the ACPE[c] decreed that they would no longer accredit BPharm programmes in 2000 and all schools of pharmacy had to convert to the PharmD as the sole professional degree.	Proposed by the JPA[e] in 1973 and approved by the Council for Pharmaceutical Education in 2003.	The Ministry of Education and Human Resources Development of Korea reorganised the pharmacy programme in 2005. The new programme was fully implemented in 2009.	In 2004, the HEC[f] of Pakistan upgraded the 4-year BPharm to the 5-year PharmD programme in 2004.	Proposed by the PECT[g] and it was mandated by the PCT[h] for pharmacy licenses in 2008. All schools moved to the 6-year programme in 2010.
Perceived barriers	Difficulties to provide adequate numbers of hospital-based preceptors.	Inadequate number of academic staff in clinical pharmacy and qualified preceptors.	There is need to build infrastructure for pharmacy practice experiences.	Limitations in pharmacy education and limitation of pharmacists' roles in clinical settings	Lack of long-term strategies for reasonable implementation

[a]PC = Pharmaceutical care; [b]IP = Industrial pharmacy; [c]CP = Consumer Protection; [d]ACPE = Accreditation Council on Pharmaceutical Education; [e]JPA = the Japan Pharmaceutical Association; [f]HEC=Higher Education Commission; [g]PECT = Pharmacy Education Consortium of Thailand; [h]PCT = Pharmacy Council of Thailand

CONCLUSIONS

Each country has different needs due to the different contexts of health care systems that are related to the scope of pharmacy practice. The countries should consider their needs critically before they decide to adopt the PharmD programme, in order to increase and ensure the benefits they will get from the new programme. Each country created a different process to handle the transition to an all-PharmD programme, but mostly had the process of school accreditation mandated by the appropriate regulatory bodies (Table 3). The barriers to the transition in most of countries are insufficient numbers of academic staff and preceptors in the clinical pharmacy area; insufficient experienced preceptors and training sites; barriers to providing clinical pharmacy activities in some countries due to a high volume of prescriptions and pharmacy workforce shortage.[18,28,52,54,55,58,60,62,63,67] Finally, there still needs to be a framework or a set of indicators to measure and monitor the impact/outcome of the PharmD degree. This set of indicators should be used as a feedback loop to evaluate whether the transition balances the impacts/outcomes that meet the needs of the adopting country.

CONFLICT OF INTEREST

All authors declared no conflict of interest.

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Original Research

Role of community pharmacists in skin cancer screening: A descriptive study of skin cancer risk factors prevalence and photoprotection habits in Barcelona, Catalonia, Spain

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Abstract

Background: Skin cancer incidence is increasing alarmingly, despite current efforts trying to improve its early detection. Community pharmacists have proven success in implementing screening protocols for a number of diseases because of their skills and easy access.

Objective: To evaluate the prevalence of skin cancer risk factors and the photoprotection habits with a questionnaire in community pharmacy users.

Methods: A research group consisting of pharmacists and dermatologists conducted a descriptive cross-sectional study to assess photoprotection habits and skin cancer risk factors by using a validated questionnaire in 218 community pharmacies in Barcelona from May 23rd to June 13th 2016. All participants received health education on photoprotection and skin cancer prevention. Patients with ≥1 skin cancer risk factor were referred to their physician, as they needed further screening of skin cancer.

Results: A total of 5,530 participants were evaluated. Of those, only 20.2% participants had received a total body skin examination for skin cancer screening in the past by a physician and 57.1% reported using a SPF 50+ sunscreen. 53.9% participants presented ≥1 skin cancer risk factor: 11.8% participants reported having skin cancer familial history and 6.2% reported skin cancer personal history; pharmacists found ≥10 melanocytic nevi in 43.8% participants and chronically sun-damaged skin in 21.4%. Lesions suspicious for melanoma were reported in 10.9% of the participants and urgent dermatological evaluation was recommended.

Conclusions: Pharmacists can detect people with skin cancer risk factors amongst their users. This intervention can be considered in multidisciplinary strategies of skin cancer screening.

Keywords

Sunscreening Agents; Skin Neoplasms; Early Detection of Cancer; Pharmacies; Pharmacists; Cross-Sectional Studies; Spain

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INTRODUCTION

Keratinocyte carcinoma and cutaneous melanoma are the most common forms of skin cancer.[1,2] The former, which comprises basal cell carcinoma and squamous cell carcinoma, accounts for over 90% of all skin cancers, although its mortality is low.[3] In Europe, there is a high estimated incidence of keratinocyte carcinoma although it is greatly under-reported.[2] In the Catalan region of Girona between 2010 and 2012, 21% of all diagnosed cancers were keratinocyte carcinomas.[4] The cumulative lifetime risk of developing non-melanoma skin cancer is 6.16% in women and 7.81% in men.[4] In the United States, keratinocyte carcinoma incidence has doubled since the 1960s up to 8%, and treatment costs are an increasing worldwide economic burden.[5-8] On the contrary, cutaneous melanoma represents only 5% of all skin cancers, but it accounts for 90% of skin cancer deaths. In Catalonia, like all over Europe, cutaneous melanoma incidence is increasing, with 10.2 new cases per year per 100,000 inhabitants in 2016.[9,10]

Different National Health Systems (NHS) have launched skin cancer awareness and early detection campaigns. However, available resources were not enough to reach the necessary uptake to ensure its mainstream success. On the one hand, some initiatives are based on medical evaluation of self-reported suspicious lesions. They show a low detection rate in early stages and miss the diagnosis of occult skin cancer lesions.[11,12] On the other hand, skin cancer population screening initiatives based on total body

skin examination (TBSE) are not cost-effective, despite detecting occult skin cancer lesions in early stages.[13-15] In Servei Català de Salut (NHS in Catalonia), TBSE is not performed systematically due to lack of time in Primary Care settings and referrals to dermatologists are performed by general practitioners (GPs) when they need further evaluation of patient-reported suspicious lesions.[16]

Individual skin cancer risk factors assessment might be a good tool for triaging people with high risk for a more frequent follow-up.[17] However, this information is not compiled systematically in patients' medical records. Skin cancer risk factors are well known and the most important ones may vary in different countries.[18] In southwestern Europe the most important risk factors are a high count of nevi all over the body, having dysplastic nevi, familial history of melanoma, personal history of skin cancer and being of fairer Fitzpatrick phototypes.[18] Some authors propose that arm nevi count could be a proxy assessment of whole body nevi count.[19]

Previous studies suggest that skin self-examination using melanocytic nevi count could be effective to triage skin cancer when combined with medical screening by dermatologists.[11,20-23] However, when skin self-examination is performed by laypeople, nevi count overestimation and missing occult skin cancer lesions may occur.[11] Even healthcare professionals in training overestimate the nevi count, which suggests that proper training is crucial.[24]

We hypothesize that triage of people according to their skin cancer risk factors might be essential to improve screening cost-effectiveness. This triage could be the first step of a skin cancer population screening protocol, which might help to prioritize people needing TBSE. GPs would perform TBSE in higher risk individuals who would be referred to dermatologists in case of skin cancer suspected diagnosis.

The inclusion of pharmacists in collaborative screening programs has successfully broaden the coverage for the detection of colorectal cancer, HIV and bacterial pharyngitis, since many patients more frequently visit pharmacies for health issues rather than their GPs due to the better accessibility and readiness offered by community pharmacists (CPs).[25-30] Specific training on primary prevention has successfully enhanced pharmacists' interventions in skin cancer health education and counselling in the United States of America.[31-33] In Spain, CPs have been promoting photoprotection since late 1990s.[34] In Barcelona, the Col·legi de Farmacèutics de Barcelona (COFB, Barcelona Pharmacists Association) has developed programs sponsored all over Spain and other campaigns of its own.[34,35]

Pharmacists, due to their skin healthcare and disease screening expertise, besides their versatility, proximity and convenience, seem to be part of an optimal strategy for skin cancer risk factor triage. Thus, COFB and the Department of Dermatology of the Barcelona Hospital Clínic have developed a program to evaluate melanoma and skin cancer risk factors and photoprotection use among people attending community pharmacies located in Barcelona, Catalonia, Spain. The programs' slogan was "Abans de deixar-t'hi la pell, consulta" (which means in Catalan Save your own skin, seek advice), and it had two main aims: to evaluate skin cancer risk factors and the photoprotection habits and to assess later on this questionnaire as an initial step for a collaborative triage protocol involving physicians and pharmacists for skin cancer.

The present work has as objective to describe the prevalence of skin cancer risk factors and the fotoprotection habits in community pharmacy users participating in this program. We hypothesize that trained pharmacists could be responsible for triaging people with skin cancer risk factors and for referring them to their GPs in case TBSE is needed. Thus pharmacists' implication might broaden the coverage of skin cancer screening and optimize the use of resources and increase the cost-effectiveness.

METHODS

Study design

We report a descriptive cross-sectional study on photoprotection habits and skin cancer risk factors prevalence conducted by CPs in Barcelona for the future evaluation and development of a professional pharmacy service for skin cancer risk factors triage. The inclusion criteria were: users of community pharmacies, aged over 18 years old and willing to participate in the program during the period between May 23rd (Melanoma World Day) and June 13th (European Skin Cancer Prevention Day), 2016.

Skin cancer risk factor questionnaire

An expert committee, consisting of dermatologists and pharmacists, created and validated by consensus the content of a skin cancer risk factors triage questionnaire (Online appendix 1). The questionnaire collected information on demographic characteristics, photoprotection behaviours and skin cancer risk factors. Data on the five most important skin cancer risk factors in Southern and Central European population were registered: family and personal history of skin cancer, nevi arm count in one arm skin exploration was used as a skin cancer predictor to simplify triage by skin examination and nevi count, presence of sun-damaged skin and self-reported presence of melanoma-like suspicious lesions.[18,19,36] A linguistic copyeditor evaluated the clarity of the questionnaire and its comprehension was validated by 11 laypeople ranging from 18 to 84 years old not related to healthcare professions. The final version of the validated questionnaire can be found on Online appendix 1.

Referral to dermatological follow-up

Those users with at least 1 risk factor were recommended to make an appointment for dermatological check-up with the GP within the next year (group R1). Those users reporting to have similar lesions to those in the skin cancer atlas (Online appendix 2) were advised to, urgently, set up an appointment with a dermatologist (group R2). Remaining participants with no skin cancer risk factors, were advised to report to their GPs any change detected in their skin, even though they do not have any risk factor of

those evaluated for follow-up (group R0). The project was notified to general practitioners from Societat Catalana de Medicina Familiar i Comunitària (CAMFIC, Catalan Society of Community and Family Medicine) who supported the initiative.

Skin cancer health education and perceived satisfaction

The questionnaire also gathered information about: photoprotection habits for skin cancer prevention; dermatological care that patients received from their GPs and dermatologists for skin cancer early detection; and perceived users' satisfaction with the service. Assessment of dermatological self-care was used by pharmacists to provide individualized health education for skin cancer prevention. It was focused on avoiding sunburns, exposure to sun during central hours of the day, to use cloths, hats and sunglasses and finally the use of sunscreen whenever they were exposed to sun, the promotion of higher sun protection factors (SPF), the application of sunscreen before going out at home and debunking myths and detecting barriers to enhance photoprotection habits amongst community pharmacy users. In addition, perceived satisfaction was also inquired using a Linkert-type rating scale.[37]

Community pharmacists' recruitment and training

COFB made an open call to join the project through a communiqué sent on May 2nd 2016 to all registered CPs in the province of Barcelona (5,470 CPs working in 2,300 pharmacies). It introduced epidemiologic aspects of skin cancer, the importance of its early detection and included some information about the protocol, which would be further explained in the master-class to be held on May 12th 2016. This 2-hour cost-free master-class was held by a dermatologist from the Hospital Clínic de Barcelona Department of Dermatology, to train CPs to perform the nevi count technique on the arms; to detect markers of chronically sun-damaged skin; and were also instructed in clinical and epidemiological aspects of skin cancer. CPs were introduced to the use of the questionnaire as a tool for skin cancer risk factor screening, as well as for the evaluation of photoprotection habits to promote individualized health education. Attendees rated their satisfaction with the training session voluntarily. All pharmacies having at least one pharmacist who completed the training were included.

Media impact

A press conference about the project was held to raise awarness about skin cancer early detection and prevention amongst Barcelona population. The project was disclosed by the media with more than 40 pieces of news in television, radio and newspapers, both locally and all over Spain.[38]

Pharmacist intervention

Each participating pharmacy user was first invited personally to take part in the study by a pharmacist, who provided him/her with medicines and healthcare products. CPs' evaluation of skin cancer risk factors and photoprotection habits was performed for free during the campaign. Participants had to grant verbal informed consent to take part in the study, thus complying with the Declaration of Helsinki and Data Protection EU Directives and Spanish Laws. The pharmacist administered the questionnaire to each participant and performed a visible skin exploration to assess chronically sun-damaged skin and arm nevi count. CPs referred those participants who needed it for further dermatological follow-up, according to the results of the questionnaire. Moreover, all participants received personalized skin cancer health education by their CPs. The intervention was designed to take 15 min per participant. The questionnaire data was gathered on carbonless copy paper, so all participants were given the original of their answers to be handed to their physician. The copy was kept by the CP to include anonimized participants' data to a safe COFB-managed web-cloud database for further analysis.

Table 1. Personal phenotypic characteristics.

N = 5530	n	%	95%CI
Age	56 yo	-	55.5:56.4
Gender			
Male	1401	25.3%	24.2%:26.5%
Female	4129	74.7%	73.5%:75.8%
Hair color			
Black	1105	20.0%	18.9%:21.0%
Brown	3576	64.7%	63.4%:65.9%
Red hair	89	1.6%	1.3%:1.9%
Fair	757	13.7%	12.8%:14.6%
Uncertain	3	0.1%	0.0%:0.1%
Eyes color			
Black	164	3.0%	2.5%:3.4%
Hazel	3454	62.5%	61.2%:63.7%
Mixed	316	5.7%	5.1%:6.3%
Grayish	682	12.3%	11.5%:13.2%
Green	910	16.5%	15.5%:17.4%
Uncertain	4	0.1%	0.0%:0.1%
Phototype			
I	151	2.7%	2.3%:3.2%
II	1247	22.5%	21.4%:23.8%
III	2701	48.8%	47.5%:50.2%
IV	1071	19.4%	18.3%:20.4%
V	300	5.4%	4.8%:6.0%
VI	60	1.1%	0.8%:1.4%

Statistical analysis

Statistical analysis was performed using SPSS Statistics software version 22.0 (IBM Corp., Armonk, NY) and RStudio: Integrated Development for R (RStudio, Inc., Boston, MA). Results are expressed as average or its percentage with their corresponding 95% confidence interval.

RESULTS

Two-hundred eighteen (218; 9.5%) community pharmacies from the province of Barcelona were enrolled in the study. A total of 335 (6.1%) CPs received training from a dermatologist. Pharmacists rated the training with 4.42 (SD=0.86) out of 5. Participating pharmacists collected valid registries from 5,530 participants, accounting for about 1% of all the pharmacy users during the campaign. Most participants lived in cities with more than 100.000 inhabitants. The average age was 56.0 (SD=16.9) years old and the women to men ratio was 3 to 1 (Table 1).

Table 2. Photoprotection habits.

N = 5530	n	%	95%CI
Do you use sunscreen when you are exposed to sun?			
Never	763	13.8%	12.9%:14.7%
Sometimes	1154	20.9%	19.8%:22.0%
Usually	1090	19.7%	18.7%:20.8%
Always	2519	45.6%	44.3%:46.9%
If you use sunscreen, which SPF do you use?			
SPF < 15	96	1.7%	1.4%:2.1%
SPF 15	331	6.0%	5.4%:6.7%
SPF 30	1419	25.7%	24.5%:26.8%
SPF 50+	3158	57.1%	56.0%:58.2%
Uncertain	114	2.1%	1.7%:2.4%
You normally apply your sunscreen			
At home. before going out	2727	49.3%	48.0%:50.5%
On the beach or at the pool	2272	41.1%	39.9%:42.3%
Before playing sports	147	2.7%	2.2%:3.1%
Cannot remember when/where	51	0.9%	0.7%:1.2%
If you don't use always sunscreen, state the reason why			
Because it is expensive	92	1.7%	1.3%:2.0%
Because it is uncomfortable to use	303	5.5%	4.9%:6.0%
Because I do not get burnt	243	4.4%	3.9%:4.9%
Because I do not sunbathe	610	11.0%	10.2%:11.8%
Because it irritates the eyes	34	0.6%	0.4%:0.8%
Because I do not remember to use it	765	13.8%	13.0%:14.7%
Other reasons	154	2.8%	2.3%:3.2%

The most common phenotype was brown hair, hazel eyes, and phototype III (Table 1). Regarding photoprotection habits (Table 2), 45.6% referred always using sunscreen, being SPF 50+ the most commonly used. On the contrary, 13.8% reported never using sunscreen. The main reason given not to use sunscreen was forgetfulness and perceived lack of sun exposure (Table 2).

Among all the surveyed users, 42.9% of them had a dermatological consultation in the past (Table 3). In 89.5% the examination had been performed by a dermatologist, but only half of those had a total body skin examination (TBSE) performed. Taking into account all participants, only 19.0% of them received TBSE by a dermatologist in the past and only 1.2% received it from their GP (Table 3).

Skin cancer risk factors prevalence data can be found on Table 3. Group R1 represented 53.9% of the users, and comprised participants who had personal or family skin cancer history, more than 10 melanocytic nevi on an arm and/or chronically sun-damaged skin. They were referred by CP to their GP within the next year. Group R2 represented the 10.9% and reported having similar lesions to those in the atlas, hence, were recommended to urgently see a dermatologist by their CP (Table 3).

Participants older than 70 years old and women were more likely to receive a referral recommendation of any kind (both groups R1 and R2) than younger people (Table 4). Women presented more risk factors (and therefore, R1 referrals) than men, however, men were more likely to self-report suspicious lesions, hence, received an urgent R2 referral (Table 4). More women participated in the study, under the ratio 3 to 1, besides, men´s participation increased with age (Table 4). Participants from rural areas were more likely to self-report suspicious lesions than users living in urban areas (Table 4). Users were asked to rate CPs' role in pathology prevention and they valued it highly positively with 4.9 points (SD=0.4) (in 5-point Likert-type scale).

Table 3. Dermatological control and skin cancer risk factors evaluation.

N = 5530	n	%	CI 95%
Users receiving dermatological assessment	2370	42.9%	41.6%:44.2%
Who were examined by:			
General practitioner	273	4.9%	4.4%:5.5%
with Total Body Skin Exploration	64	1.2%	0.9%:1.4%
Dermatologist	2122	38.4%	37.9%:38.9%
with Total Body Skin Exploration	1049	19.0%	18.7%:19.2%
Others	53	1.0%	0.7%:1.2%
Uncertain	31	0.6%	0.4%:0.8%
Skin cancer risk evaluation			
Users with skin cancer familial history	650	11.8%	10.9%:12.6%
Users with skin cancer personal history	342	6.2%	5.5%:6.8%
Users with skin with > 10 melanocytic nevus on one arm	2423	43.8%	42.5%:45.1%
Users with chronically sun:damaged skin	1184	21.4%	20.3%:22.5%
Users with self:reported skin cancer lesions compared to an atlas	604	10.9%	10.1%:11.7%
Users with pharmaceutical recommendations:			
R1. Risk factor(s) detected: GP referral.	2982	53.9%	53.1%:54.7%
R2. Self:reported suspicious lesions: urgent referral.	604	10.9%	10.1%:11.8%

Table 4. Referral recommendations depending on gender, age groups and municipality.

	R0			R1			R2		
	N	%	95% CI	N	%	95% CI	N	%	95% CI
Gender									
Male (n=141)	530	37.8%	35.3%:40.4%	695	49.6%	47.0%:52.3%	176	12.6%	10.9%:14.4%
Female (n=4129)	1414	34.2%	32.8%:35.7%	2287	55.4%	53.9%:56.9%	428	10.4%	9.5%:11.3%
Age groups									
< 50 yo (n=1913)	783	40.9%	38.7%:43.2%	949	49.6%	47.3%:51.9%	181	9.5%	8.2%:10.9%
50 – 69 yo (n=2278)	807	35.4%	33.5%:37.4%	1252	55.0%	52.9%:57.0%	219	9.6%	8.4%:10.9%
>70 yo (n=1339)	354	26.4%	24.1%:28.9%	781	58.3%	55.6%:61.0%	204	15.2%	13.4%:17.3%
Municipality									
Rural (n=421)	120	28.5%	24.2%:33.1%	270	64.1%	59.3%:68.7%	31	7.4%	5.1%:10.3%
Urban (n=1306)	419	32.1%	29.6%:34.7%	715	54.7%	52.0%:57.5%	172	13.2%	11.4%:15.1%
Big city (n=3803)	1405	36.9%	35.4%:38.5%	1997	52.5%	50.9%:54.1%	401	10.5%	9.6%:9.6%
TOTAL	1944	35.2%	33.9%:36.4%	2982	53.9%	52.6%:55.2%	604	10.9%	10.1%:11.8%

R0: No risk factors. R1: Risk factor(s) detected: referral to general practitioner. R2: Self-reported suspicious lesions: urgent referral to physician.

DISCUSSION

The role of pharmacists in skin cancer has focused mainly on primary prevention in the past.[31-33,39] Today, skin cancer screening experiences have been implemented in community pharmacies across Australia, Norway and UK, based on store-and-forward teledermoscopy imaging.[40-46] Nonetheless, these services raised controversy regarding a possible professional intrusion and the omission of occult skin cancer lesions which could only be detected with total body skin examination (TBSE) by physicians.[13,47-49] Our project has set the basis for an ongoing collaborative practice agreement for skin cancer screening, between pharmacists from Col·legi de Farmacèutics de Barcelona, the only professional registration body for pharmacists in Barcelona, and dermatologists from Hospital Clínic de Barcelona, one of the most important tertiary hospitals in Spain. In our program, diagnostic is exclusively reserved to TBSE by GP or dermatologists, and pharmacists' role is genuinely triaging based in well-described skin cancer risk factors.[18,19,50,51] The prevalence of these skin cancer risk factors in Barcelona community pharmacy users is described here for the very first time.

There are several points to highlight regarding participation: Firstly, we managed to enroll 9.5% of all community pharmacies in the province of Barcelona, making this, the prevention awareness campaign with the highest participation ever. This emphasizes the willingness and motivation of CPs regarding pharmacist expanded role in skin healthcare. Presumably, an incentive to increase participation among pharmacists would be to establish a fee for the screening program, similarly to other screenings found in our NHS service portfolio.[29,52] Secondly, we managed to reach 1% of our target population, a relatively small proportion, but an interesting milestone, since it is the first skin cancer screening strategy developed in our context. Thirdly, the screened population showed a high satisfaction level with an 87.9% of the participants rating the program with the maximum satisfaction score (5 points).

There might has been a potential selection bias, which reveals the gender (mainly women) and age (56 years old average) biases found in our data compared to general population. However, our present data comply the demographic profile found in other studies on disease prevention in community pharmacies.[35,53,54] To avoid this selection bias, invitation letters could be sent to the target population in the future. They should be accompanied with an informative leaflet about the importance of skin cancer early detection and a list of the nearest pharmacies participating in the program. This strategy has been highly effective to ensure the participation in the community pharmacy-based colorectal cancer screening program.[55]

To evaluate individual risk of skin cancer for further medical referral, our triage protocol was based on performing a questionnaire and a simple arm skin examination. There has been a lot of variability amongst the tools to assess skin cancer risk factors in the past.[56-61] Recently, a consensus questionnaire for melanoma risk assessment, has been proposed.[62] Our tool includes a version of it adapted to CPs, which includes most of items included in its section C (clinical examination and personal and familial history).[62]

In 2013, COFB coordinated the Sol i Salut (Catalan for Sun and Health) campaign in which community pharmacies informed about photoprotection habits and spent a web-based survey. From the data obtained, we can detect that there has been an increase in the use of SPF 50+ sunscreen, from a 35% in 2013, to a 57.1% in 2016. Moreover, 23% of the participants reported having had their skin checked by a dermatologist in the past, while it increased to a 38.4%.[35] This increase in check-ups is an important factor for early diagnosis of skin cancer. However, it is worrisome that only 20.2% of all participants had a TBSE, which is essential for a proper screening.[18]

If we compare our current data to studies made in other Spanish settings, we can observe that sunscreen use frequency is lower in our participants.[63] A 2016 study showed that 69.1% of the Spanish people use sunscreen always, while our data revealed that only 45.6% uses it always.[63] SPF 30 is the most used all over Spain (50.1%), while in Barcelona, it is 50+ (57.1%).[63] The two most common Fitzpatrick types are phototype III (35.9%) and IV (36.6%) in a sample gathered in our country, while in Barcelona the two most common skin types are phototypes II (22.5%) and III (48.8%).[63]

Our data has similar values to those observed in other studies performed in Southern Spain, when it comes to skin cancer family and personal history.[64] Furthermore, melanocytic nevi count proportion differs substantially from other studies, with 43.8% of participants with more

than 10 nevi on one arm in our case.[19,20,36,64] This nevi over count could be due to different facts: the average age in our study is 56 years old, and only 31.5% of the participants are younger than 50 years old; while nevi counting of more than 20 nevi in both arms as a skin risk factor tool has only been proved useful in people younger than 50 years old.[19,36] Moreover, the lack of clinical experience of pharmacists in this evaluation may explain the over count, which is similar to the one observed in medical professionals in training.[20] In the following editions, clinical case sessions with dermatologists will be held to improve pharmacists' training. Moreover, the correlation study will be carried out to estimate pharmacists' over count and to apply corrective measures to the protocol.

Participants' awareness of the need to receive periodical dermatological assessment does not cover most of the population, with 38.4% who have been to the dermatologist's and 4.9% who have been dermatologically assessed by their GPs at least once in their lives. Nevertheless, it is worrisome that only 46.9% of those patients receiving assessment by a dermatologist have been through a TBSE. It highlights the need to raise awareness among healthcare authorities to increment the time physicians spend seeing their patients to increase quality and introduce screening protocols.[16] In addition, we propose that pharmacists could help enhance and optimize existing resources by developing collaborative skin cancer screening programs.[27]

The skin cancer risk evaluation found a relatively high percentage of participants with some kind of skin cancer risk factor, with 53.9% people being referred to their doctors for screening and 10.9% reporting self-reported lesions to be evaluated urgently. The association between aging and skin cancer screening referral is concordant with the association between aging and skin cancer diagnosis previously reported, where 80% of the cancers diagnosed, are people older than 55 years.[5,65-67] Moreover, older men living in rural areas are more likely to self-report suspicious lesions, which might be explained by possible occupational skin cancer and less visits to their healthcare professionals, leading to more advanced stages.[68]

Limitations

The main limitation of the current phase of this study is the lack of registration of linkage-to-care and results of the medical evaluation. Even though we reached a considerable population, we could not determine the diagnostic predictive value of our tool, since we did not gather medical diagnostic results. However, it was never included as aim at this point, since we wanted to check the feasibility of CPs involvement in this protocol first. Nonetheless, this will be further evaluated with a comparative correlation study between questionnaire-based evaluation by pharmacists and dermatologists. Furthermore, the selection bias may have caused overestimation of skin cancer risk factors, photoprotection habits, and thus referral rate. However, even if there is a selection bias of patients with higher risk of skin cancer, the value of triaging these patients for further medical evaluation cannot be denied.

CONCLUSIONS

This manuscript reports the initial part of a project, which revealed important data on photoprotection habits and skin cancer risk factors in users at the community pharmacy level in Barcelona. Thus, in the next phase we are planning to compare these risk assessment results with dermatologists' evaluation, therefore making the current results more resilient and contribute to the body of evidence in this topic. Moreover, it is the first step to develop an efficient and cost-effective collaborative screening program for skin cancer to pool physicians' and pharmacists' efforts for skin cancer early detection.

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CONFLICT OF INTEREST

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Biosimilars and implications for pharmacy practice: Ready or not, here they come!

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Keywords
Biosimilar Pharmaceuticals; Biological Therapy; Therapeutic Equivalency; Pharmacists; Pharmacovigilance; Managed Care Programs; United States

INTRODUCTION

Biotechnology, the drug manufacturing strategy that has transformed the healthcare industry over the past 30 years, continues to produce novel, life-saving products. Monoclonal antibodies, biologic response modifiers, and cellular therapies have improved patient outcomes in many debilitating disease-states including hepatitis, cancer, autoimmune and inflammatory diseases. These innovative biologic medications are allowing patients to live longer, healthier lives, and pharmaceutical companies have shifted their focus to the production of these agents to meet the demands of a changing therapeutic landscape.[1]

Biologic medications are unique in that they are derived from living organisms or contain components of living organisms. The creation of proteins within living entities is complicated and leads to the development of structures that are complex, higher in molecular weight, and much less characterized compared to chemical drug products.[2] This makes it virtually impossible to replicate exact structures when manufacturing biologic medications.

Unfortunately, a complicated manufacturing process leads to increased drug development costs.[3] As a result, most biologic agents are expensive, which can create a financial burden for governments, insurers, health systems, and patients. In fact, biologic medications can cost upwards of USD 2.1M per treatment.[4] Even with the availability of insurance coverage and patient assistance programs, the average individual is unable to afford these agents, resulting in reduced patient access to potentially life-saving medications.[5] Considering patients on branded medications are 2-3 times more likely to abandon their treatment than those prescribed generic medications, utilization of a more cost-effective alternative could also lead to better medication adherence.[6]

Generic medications in the United States generated savings as high as USD 265 billion in 2017 and USD 2 trillion from 2009-2018, while accounting for 90% of all prescription dispenses.[6] Biosimilars provide an analogously promising solution to the increased costs associated with biologic agents. They are highly similar versions of reference (or originator) biologics that contain no clinically meaningful differences in terms of safety, purity and potency.[7] If successful, biosimilars would increase patient access to more affordable successors to reference biologic medications, potentially saving 1.2 million USD 54 billion over the next ten years.[8] However, this is no small feat. The differing nature of chemical drug products and biologic therapies creates distinct challenges that complicate regulatory guidance and adoption of biosimilar medications. As medication experts, pharmacists need to be integral educators, advocates and trailblazers of biosimilar integration into clinical practice across all settings. The objective of this commentary is to make pharmacists across healthcare settings aware of the major practice changing effects and opportunities that the widespread introduction of biosimilar medications hold for future clinical practice.

Barriers to the adoption of biosimilars in clinical practice

In the 1980s, the Hatch-Waxman Act created the foundation toward expediting the approval of generic medications in the United States. Following in its footsteps, regulatory bodies around the world have developed abbreviated drug approval pathways for biosimilar medications.[2] However, unlike the generic drug market, manufacturers of biosimilars are tasked with the challenge of developing clinically comparable agents that are similar, but not identical, products. This has resulted in imperfect regulations that govern biosimilar drug approval.

The abbreviated biosimilar application process is slightly different between the European Union and the United States.[2] All biosimilar medications undergo a rigorous evaluation of analytical and nonclinical studies to establish high similarity between the structures of the reference and biosimilar product.[9] However, biosimilars do not require completion of extensive phase III and phase IV clinical studies.[7] This has led regulatory agencies to develop approval pathways that are flexible and subject to individual requirements. While the European Union has opted for a product-specific approval pathway based on biological classification, the United States has adopted a case-by-case approach that takes into account the totality of evidence presented by the manufacturer.[2] Though these

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strategies both address the expected uniqueness of each product, each biosimilar application can likely be different, further confusing defined criteria for approval.

Interchangeability, as it pertains to biologics, is a designation that allows biosimilars to be substituted with reference products without a provider's approval.[7] To date, Europe has not established any regulation on the interchangeability of reference biologic and biosimilar medications.[10] European countries typically employ a single-payer healthcare system, which gives them better control over which biologic agents to offer patients without interchangeability being a large hindrance to biosimilar utilizaton.[11] In contrast, the United States' insurance landscape reflects a multi-payer system which prevents universal standardization of biologic medication utilization. Fortunately, the United States Food and Drug Administration (FDA) has finalized its guidance documents on the interchangeability of biosimilar medications which will eventually allow pharmacists to automatically dispense cheaper, therapeutically equivalent alternatives.[7] Although no products have been deemed interchangeable as of July 2019, the successful completion of interchangeability clinical trial designs will hopefully be the first step in fulfilling the ultimate vision for biosimilar use in clinical practice in the United States.

Pharmacovigilance programs will also be of great importance concerning biosimilar medications. The lack of extensive clinical evaluations during the approval process has created doubt surrounding long-term efficacy, immunogenicity and adverse event data.[2] Though the European Union has established post-marketing monitoring programs for biosimilars, the United States has yet to set defined pharmacovigilance requirements. Without these guidelines, manufacturers do not have the appropriate tools to develop drug monitoring programs. Additionally, limited guidance surrounding post-marketing immunogenicity and adverse event data may hinder the advancement and acceptance of interchangeability designation for biosimilar medications.

Beyond the regulatory barriers facing biosimilar integration into clinical practice, physician knowledge and perception of biosimilar medications has also hindered their uptake in various drug markets. A study conducted by Leonard *et al*. showed that only 22.9% of providers in the United States and the European Union reported having 'good' or 'complete' knowledge of biosimilar medications and their appropriate use.[12] When asked which concepts were most concerning, providers were apprehensive about differences regarding safety, efficacy, interchangeability and the extrapolation of indications between the biosimilar and reference biologic product.[13] This systematic review also showed that, even when providers appeared to be more comfortable with the key concepts of biosimilar medications, they were more likely to prescribe these agents in treatment-naïve patients versus switching patients already on the originator biologic.[12]

Patient perception and acceptance of biosimilar medications should also be taken into account. Ultimately, they will receive this medication and have the ability to accept or deny administration, depending on how comfortable they are with the product. In a web-based study conducted in the European Union, about 80% of patients on biosimilars understood what they were and that they were used to help reduce drug costs.[13] The study further found that patients who were already on biosimilars were confident in their physician's decision to use a biosimilar therapy compared to when the provider recommended switching from original therapy. This further validates that interchangeability remains a concern for patients as well.

Implications of biosimilars for pharmacy practice

There are over 50 approved biosimilars in drug markets around the world.[14] By 2020, nine patents for the top-20 biologic medications are set to expire and pharmaceutical companies have already begun to fill the pipeline with their own biosimilar equivalents. Historically, the United States has lagged behind Europe's expansion of biosimilar drug options and their uptake into clinical practice. For example, an infliximab biosimilar approved in March 2015 has garnered about 80% market share in the European Union.[15] In contrast, Remicade®, the originator infliximab biologic, still holds 96% market share in the United States after the approval of its first biosimilar counterpart in 2016.[16] The European Union has shown that successful biosimilar uptake is possible; however, the key to realization starts with overcoming the aforementioned barriers. Pharmacists are uniquely positioned to take a leading role in this effort.

Though the regulatory challenges facing biosimilar medications will need to be addressed at the federal level, pharmacists working all different practice settings can be integral catalysts for change. The FDA and other regulatory agencies frequently ask for feedback through adverse event reporting databases and other comment forums to collect biosimilar safety data and improve clinical practice. Pharmacists can submit research or case studies involving interchangeability, pharmacovigilance programs or other experiences to provide lawmakers with real-world information to help develop guidance documents. Additionally, industry and regulatory affairs pharmacists can be organizers of improved biosimilar evaluation. Pharmacists working for pharmaceutical companies will need to oversee the development of clinical trials in order to ensure that manufacturers are producing safe and effective agents. Regulatory affairs pharmacists may then be involved in biosimilar application review, which involves clinical judgement when reviewing the totality of evidence presented by the manufacturer. This is an area where pharmacists can take a leadership role as they are trained in biopharmaceutics and literature evaluation.

While the ongoing discussion surrounding interchangeability designation has hindered biosimilar adoption in the United States, managed care pharmacists are preferentially positioned to act as facilitators for the introduction of biosimilars into clinical practice. Companies may determine a biosimilar is preferred over its original biologic counterpart on an institution's formulary and this will require patients to utilize the biosimilar option in order for the therapy to be covered. This is a key strategy to promote the acceptability of biosimilars while regulatory bodies determine the appropriateness of interchangeability between reference biologics and biosimilar medications. Drug manufacturers of biologic agents are working diligently to create financially attractive contracts with managed care companies to designate biosimilars as the

preferred therapeutic option. Pharmacists working in this setting will review safety, efficacy and immunogenicity studies to ensure the proper utilization of biosimilar medications. As key members of pharmacy and therapeutics committees, pharmacists can provide leadership to determine the appropriate restrictions or prior authorizations required for each biosimilar that is considered for addition to their plan's drug formulary. They may also be participating in patient monitoring programs to gather long-term safety data of biosimilar medications.

Once a biosimilar has reached the market, pharmacists working in patient care will need to be aware of the practical, day-to-day handling of biosimilar medications. In the acute care setting, biosimilar utilization will be primarily driven by formulary status. Pharmacists, physicians and other key stakeholders will have the opportunity to decide on a biologic agent of choice to utilize throughout their hospital or health system for each molecule. It will be important to be aware of key biosimilar concepts in order to be a productive member of the team. By developing policies and procedures to prepare for the increasing biosimilar drug market, the integration of biosimilars into the hospital setting can be done in a fairly controlled manner. Nonetheless, hospital pharmacists may encounter biosimilars that will be utilized on a daily basis. Recent reports have stated that the first insulin biosimilar could be available as early as the end of 2019.[17]

Ambulatory pharmacists will likely encounter unique, expensive therapies used to treat Crohn's disease, cancer and other inflammatory or rheumatoid diseases that significantly impact patient morbidity and mortality. As frontline members of the healthcare system, pharmacists will likely be heavily involved in education, benefit verification and medication access. Often, only one biologic agent is covered by an insurance plan and using an alternative agent likely would require a step therapy approach or could result in a claim denial. Ensuring that the patient receives a biosimilar that is appropriate and aligns with their insurance company's formulary will be essential to guaranteeing access and affordability. Furthermore, many insurance companies require extensive paperwork and follow-up to approve a prescribed biologic medication. Pharmacists may need to consistently engage with patients to confirm adherence to treatment regimens so patients may continue to receive benefits or patient assistance. Additionally, some pharmacists may be involved in therapeutic drug monitoring, evaluating patients for efficacy or signs of immunogenicity or drug toxicity.

Interchangeability status will be of great importance in the ambulatory care setting as well. The creation of an interchangeable class of biosimilar medications will allow for the automatic switching of biosimilar products at the pharmacy level, mirroring the generic drug market. Pharmacists will need to become familiar with the Purple Book, which is a list of licensed biological products

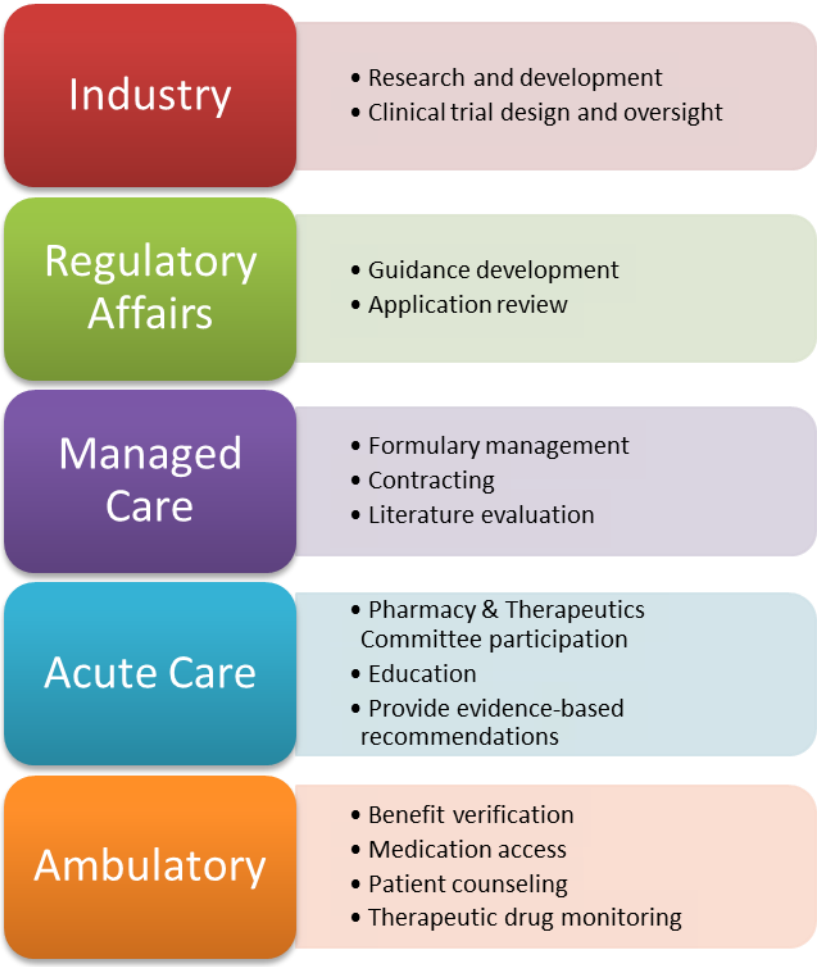

Figure 1. Implications of biosimilars for pharmacy practice.

(including biosimilars and reference biologic agents) approved for interchangeability under the Public Health Service Act.[18] It is important to keep in mind that each state may possess different laws governing the interchangeability of biologic medications.[19] Inappropriately substituting a reference biologic for a non-interchangeable biosimilar without the provider's approval could be prohibited and lead to action taken against a pharmacy's or pharmacist's license. It would behoove pharmacy informatics teams to build logic into electronic health records or retail pharmacy databases that would prevent inappropriate interchanging from happening.

Ultimately, pharmacists working in all settings will need to be educators and advocates for biosimilar introduction into clinical practice (Figure 1). Understanding of the nature of reference biologics and how they relate to their biosimilar counterparts is still challenging for patients, providers and other healthcare practitioners. Therefore, it is important that pharmacists host continuing education programs, in-services or other presentations to explain the basic principles of biosimilar medications and increase confidence in their utility. More than anything, pharmacists will be a resource to answer questions regarding the appropriate use of biosimilars, and it is important that individuals are knowledgeable enough to provide sufficient recommendations.

Future direction

The time is now for pharmacists to get involved with biosimilar introduction into clinical practice. Regulatory and practical barriers have created a slow integration in the United States, and a recent publication posited that the manufacturing of biosimilars could phase out as drug companies become disinterested in the process.[20] The education of pharmacists, physicians, nurses, patients and other key stakeholders will be the most important factor to biosimilar acceptance. Better adoption in clinical practice will occur as clinicians, patients and other stakeholders increase their understanding of the role of biosimilars in patient care. Though the path to biosimilar uptake can be difficult to navigate, pharmacists are positioned to take a lead. If pharmacists fail to prepare and adapt to the changes biosimilars are expected to bring, it may lead to a lost opportunity for the profession to improve patient care.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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Original Research

The Syrian refugee crisis in Jordan: a cross sectional pharmacist-led study assessing post-traumatic stress disorder

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Abstract

Background: The United Nations has declared the Syrian crisis as the worst humanitarian crisis of the twenty-first century. Pharmacists play a vital role in humanitarian aid and in delivering health advices for refugees. Many Syrian refugees are in need of psychosocial assessments.

Objective: Objective of this study was to investigate the prevalence of post-traumatic stress disorder (PTSD), assessed by pharmacists among Syrian civilian refugees residing in Amman, Jordan.

Methods: A cross-sectional study involving Syrian civilian refugees living in Amman, Jordan, was conducted using the published and validated Arabic version of the Harvard Trauma Questionnaire (HTQ). Pharmacists recruited civilian Syrian refugees and completed the HTQ. The questionnaire included 45 questions, with the first 16 questions (HTQ-16) intended to assess the trauma symptoms felt by refugees. Assessments were done by the pharmacists and refugees were categorized to suffer PTSD if their mean item score for the HTQ-16 scale was > 2.5.

Results: Study participants (n=186; mean age 31.5 years; 51.3% males) had a HTQ-16 mean score of 2.35 (SD=0.53), with a range of 1.19 - 3.63. Over a third of participants (38.7%) were categorized as having PTSD. Males reported significantly worse PTSD symptoms (mean=2.42, SD=0.50) compared to females (mean=2.26, SD=0.57). Correlation between the mean item score for the HTQ-16 and characteristics of the study participants showed higher mean item score correlated with being a male, older in age, a smoker, and if trauma was experienced.

Conclusions: Many Syrian civilian refugees living in Jordan suffer from PTSD. Male participants were found to be more affected by the severity of the disorder. Pharmacists are suitably situated to identify civilian Syrian refugees suffering from PTSD in dire need of help, paving the way for much needed healthcare resources to be delivered to this particular group of refugees.

Keywords

Pharmacists; Stress Disorders, Post-Traumatic; Stress, Psychological; Refugees; Altruism; Surveys and Questionnaires; Jordan; Syria

INTRODUCTION

According to the latest UN Refugee Agency's annual Global Trends report, 68.5 million people across the world are forced out of their homeland.[1] Escaping conflict and persecution led 25.4 million refugees to flee their countries, and it is developing countries that are most affected.[1]

The civil war in Syria, which started in March 2011, continues to account for the largest forcibly displaced population globally. As of the end of 2017, there were 12.6 million forcibly displaced Syrians, comprising around 6.3 million refugees, 146,700 asylum-seekers, and 6.2 million internally displaced people.[1] The United Nations declared the Syrian crisis "the worst humanitarian crisis of the twenty-first century"; and as of September 2017, according to the latest statistics of UNHCR, there were 661,859 registered refugees in Jordan, of which 182,011 (27.5%) lived in the capital Amman.[2]

The 1951 Refugee Convention is a key legal document and defines a refugee as "someone who is unable or unwilling to return to their country of origin owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group, or political opinion".[3] Refugees commonly experience physical and emotional traumas that predispose them to psychological disturbances prior to, and following resettlement.[3,4] International studies show that refugees suffer from increased rates of short-term and long-term mental health problems.[5-7] These studies have investigated the general effects of war and living life as a refugee, and shed light on mental health consequences claimed to affect refugees and their descendants for many years. Refugees commonly suffer from severe psychological distress, and many of them suffer from serious psychiatric and trauma-related problems.[8] Post-traumatic stress disorder (PTSD) is the most common consequence of violence or life as a refugee.[9] It has been defined as at least one month of recurrent, painful experiencing of a traumatic event, emotional numbing, or hyper-arousal, and avoidance of trauma-related memories.[9] Approximately one out of three refugees suffers from PTSD or other trauma-related mental disorders.[9-12]

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Services to which refugees have access following resettlement ideally should provide psychological, educational, financial, health, and social support for refugees. Such services need to provide integrated care and flexibility in responding to the diverse needs of heterogeneous refugee groups, in ways that align with their cultural beliefs and norms. In particular, the importance of developing culturally appropriate mental health services delivering psychosocial interventions for such marginalized populations has been highlighted in previous studies.[13-15] Findings stated that working with individuals who are of refugee status presents healthcare professionals with challenges that distinguish refugees' mental health needs from those of other populations. Such mental health services should aim to reduce the symptoms of psychological trauma and enhance the quality of refugees' psychological and social wellbeing.[16,17]

Pharmacists play a vital role in humanitarian aid and in delivering health advice to refugees.[18,19] Pharmacists are readily available and have a firm relationship with people in crises, hence can provide psychological and social needed support.[20] Pharmacists working within a team of healthcare providers can deliver services for refugees with the potential to bridge the gap between differing healthcare professionals' expertise.[21]

Many Syrian refugees were found to be in need of help and psychosocial assessments.[22] However, studies investigating the effect of PTSD on Syrian refugees are scant, and little is known about the prevalence of this problem and its correlates. In light of this unique set of challenges, there is a need for current information on the mental health status of refugees, particularly the displaced Syrian refugees in Jordan.

The aim of this study was to investigate the prevalence, severity and factors associated with PTSD in the Syrian refugee population in Jordan, using a different approach to accessing this community through pharmacists working in Amman, Jordan.

METHODS

Study design and setting

A cross-sectional design was used. A convenience sample of Syrian refugees who reside in Amman, Jordan was approached. Inclusion criteria included: participants over 18 years of age, holding the Syrian nationality, officially of refugee status and willing to provide written informed consent. The exclusion criteria were: participants already diagnosed with a mental illness and/ or major psychiatric illness (such as dementia and depression); those with a history of taking psychotropic agents; and participants having major hearing or visual difficulties). Syrian refugees identified as living in selected areas in Amman (areas high in Syrian residents) were approached. In affluent socioeconomic areas, where refugees resided amongst the Jordanian locals, refugees were approached and recruited through universities (students) and workplaces. And, in lower-socioeconomic areas, Syrian refugees, who resided in designated areas and buildings, were also invited to participate when it was most appropriate for the researcher to approach them.

Ethics approval was obtained from the Faculty of Pharmacy, Applied Science Private University Ethics Committee and from the Jordanian Ministry of Health. Data collection occurred between January and October, 2014.

Those who agreed to participate in the study and provided written informed consent, were informed that the information they provided would help to offer them better care and would not affect their treatment programs, and that they may find some of the questions discomforting or embarrassing, in which case they were free not to answer, and if they did answer; their responses to the questions would be kept confidential if so requested. All transcripts were de-identified by giving each a code to ensure confidentiality.

Face-to-face interviews using a structured questionnaire based on the objectives of the study were utilized to collect the data. These interviews were conducted by three trained pharmacists who attended a 2-day training program concerning the study purpose, questionnaire, protocol, and strategies for conducting interviews.

A pilot study with 15 participants was conducted with the attendance of one of the principal researchers to assure uniformity in interviewing skills among the three pharmacists. No changes to the questionnaires were made after the pilot study. The principal researcher consulted a psychologist about what to do in case serious cases of PTSD were identified.

Instrument

The Arabic version of the Harvard Trauma Questionnaire (HTQ) was used in this study, derived from the Diagnostic and Statistical Manual of Mental Disorder Text Revision (DSM-IV TR) published by the American Psychology Association (APA, 1987, 1994), to assess the trauma symptoms felt by refugees who had experienced painful or horrific events in their lives.[23-25] The HTQ consists of four parts, of which Part 1 (42 questions) explores trauma events and Part IV (45 questions) explores trauma symptoms. This version was validated among Iraqi refugees in the United State by Shoeb, Weinstein, and Mollica in 2007.[26]

To answer the aim of this study, a three-section questionnaire was used to collect data; Section 1 included information related to socio-demographic characteristics (i.e. age, gender, occupation, and educational level), personal characteristics (i.e. residential status (high/ low socioeconomic), smoking, medical history) and trauma-related questions (i.e. experience of trauma, cause of the trauma).

Section 2 included nine closed questions selected from Part 1 of the HTQ.[23] These nine questions were related to the trauma events experienced by the refugees. Participants were instructed to answer them with 'yes' or 'no' with reference to their past suffering and symptoms.

Section 3 included all questions found in the Part IV of the HTQ.[23] The first 16 questions (HTQ-16) of this version assess the trauma symptoms felt by refugees who had experienced painful or horrific events in their lives. The items represent the criteria for the intrusion/ re-experiencing, avoidance/ numbing, and hypervigilance/

arousal symptom clusters (i.e. "Recurrent thoughts/ memories" and "hard to concentrate"). The next set of PTSD symptom items were culture-specific items. Each item was assessed using a level of agreement with four possible categories of responses ranging from: '1' = "Not at all", to '4' = 'extremely'.

The mean item score is obtained by summing the individual item scores and then dividing by the number of items, yielding a mean item score for the scale. The cut-off scores proposed by Mollica and colleagues (2004) was used and the standard cut-off score of 2.5 on the Harvard Trauma indicated probable PTSD.[26]

Scoring the trauma symptoms part of the HTQ Section IV was planned to take between 5 to 10 minutes, which included calculating the mean item score for the first HTQ-16, and the full symptom scale (HTQ-45).

Data analysis

Descriptive statistics were calculated for the demographics of the sample (age, gender, education, marital status, residential status) and for their health characteristics (smoking, trauma experiences and exposure to TV). Categorical variables (such as gender) were presented as percentages and number of cases. The mean and standard deviation (SD) were calculated for quantitative variables. Statistical comparisons between different groups were carried out by using Chi square test and independent t-test; p values ≤0.05 were considered significant. Relationships between the mean item score for the HTQ-16 and the full symptom scale among Syrian refugees and their characteristics were examined using Pearson's correlation coefficient for continuous variables; Epsilon squared, and Glass rank bi-serial for categorical variables. In order to determine associations of PTSD for the refugees, a binary logistic regression analysis was performed. The dependent variable was refugees having been symptomatic of PTSD (having HTQ-16 and the full symptom scale mean score of >2.5 or not). Variables included in the model were: age, gender, educational level, marital status, residential status, smoking, watching TV, experienced a trauma and the kind of trauma.

RESULTS

A total sample of 186 participants completed the questionnaire. The mean age of participants was 32.65 years (SD=13.90), and 53.2% of study participants were

Table 1. Socio-demographic and clinical characteristics of the study participants according to the scores on HTQ-16 and the full symptom scale* (n= 186)

Characteristics n (%)	Asymptomatic PTSD	Symptomatic PTSD	Total	Test statistics
Age (Years)				chi-square=8.96
Youth (18-24)	55 (21.0)	21 (79.0)	76 (41.0)	***p* < 0.01**
Adult (25- 64)	60 (56.6)	46 (43.4)	106 (57.0)	
Senior (≥ 65)	3 (75.0)	1 (25.0)	4 (2.00)	
Gender				chi-square=0.304
Females	57 (65.5)	30 (34.5)	87 (46.8)	*p*= 0.58
Males	61 (61.6)	38 (38.4)	99 (53.2)	
Education				chi-square=12.92
Not educated	17(85.0)	3(15.0)	20 (10.8)	***p* = 0.012**
Elementary or less	14 (43.7)	18 (56.3)	32 (17.2)	
Secondary	21 (55.3)	17 (44.7)	38 (20.0)	
Bachelor's degree	63 (76.8)	30 (32.2)	93 (50.0)	
Postgraduate degree	0 (0.00)	3 (100.0)	3 (1.0)	
Marital status				chi-square=7.57
Single	28 (34.1)	54 (65.9)	82 (44.0)	*p* = 0.56
Married	31 (76.8)	51 (76.8)	82 (44.0)	
Divorced/ Widowed	15 (0.00)	8 (0.00)	23 (12.0)	
Residential status				chi-square=0.051
Urban	45 (36.0)	80 (64.0)	125 (67.2)	*p* = 0.82
Rural	23 (37.7)	38 (62.3)	61 (32.8)	
Smoking status				chi-square=12.0
Yes	28 (58.3)	20 (41.7)	48 (25.8)	***p* = 0.002**
Ex-smoker	2 (18.2)	9 (81.8)	11 (5.9)	
Never	38 (30.0)	89 (70.0)	127 (68.3)	
Medical history				chi-square=3.57
No	68 (37.8)	112 (62.2)	180 (96.7)	*p* = 0.059
Yes	0 (00.0)	6 (100.0)	6 (03.0)	
Experiencing trauma				chi-square=11.03
No	1 (4.54)	21 (95.45)	22 (11.8)	***p* = 0.001**
Yes	67 (40.9)	97 (59.1)	164 (88.2)	
Kind of trauma				chi-square=0.180
Social	2 (28.6)	5 (71.4)	7 (4.30)	*p* = 0.671
War	95 (60.5)	62 (39.5)	157 (95.7)	
Watching TV				chi-square=0.420
No	4 (16.0)	21 (84.0)	25 (13.4)	*p* = 0.517
Yes	60 (37.3)	101 (62.7)	161 (86.5)	

*Total scores >2.5 in HTQ-16 and the full symptom scale were considered symptomatic of PTSD

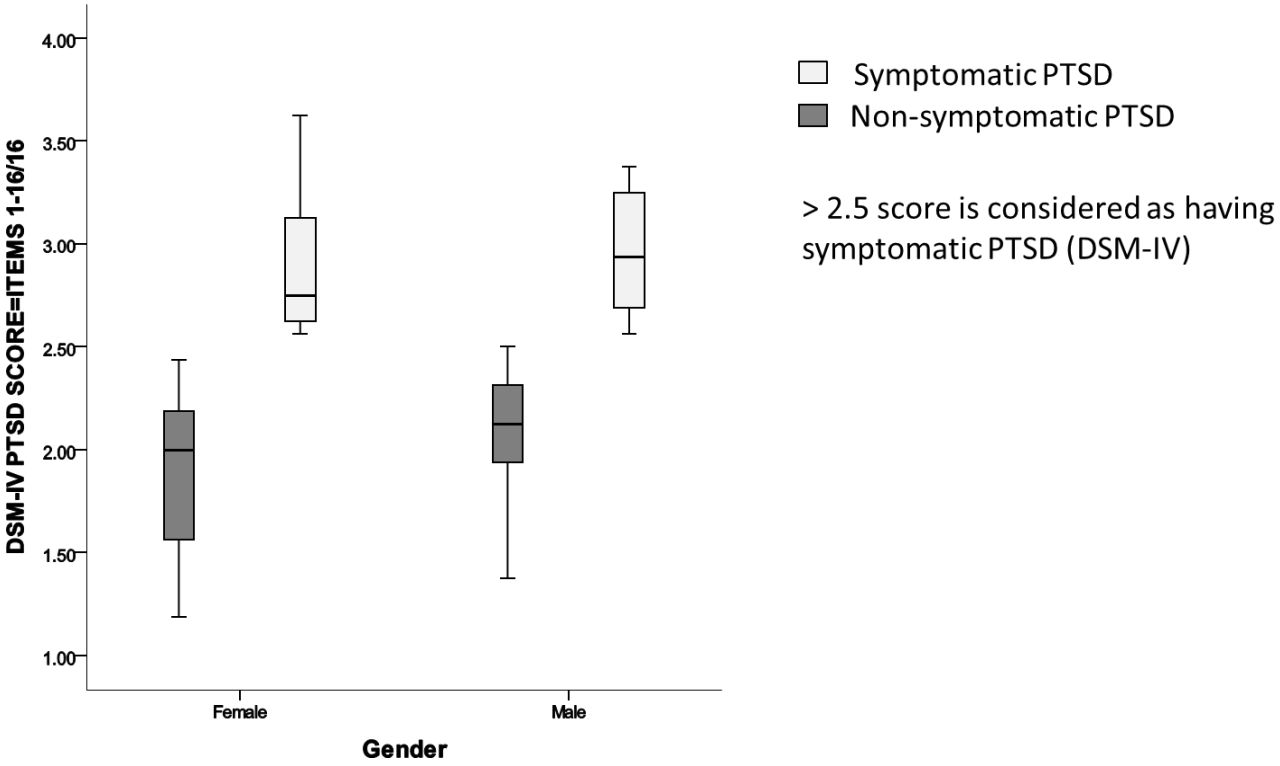

Figure 1. Proportion of respondents (n= 186) with symptomatic versus non-symptomatic post traumatic stress disorder (the mean item score for the HTQ-16) showing gender differences.

males. Half the participants (50.0%) reported having a bachelor's degree level of education and 44.0% of them were married. Regardless of the type of trauma, 88.2% of the participants reported having suffered trauma. Most patients (86.5%) reported TV watching. Table 1 presents information on these characteristics.

Completing the trauma symptoms part of the HTQ (HTQ-45) with the refugees took from 3.45 to 7.0 minutes. The mean item score for the HTQ-16 was 2.35 (SD=0.53) with a range of 1.19 - 3.63, and 38.7% categorized to have PTSD (mean item score for the HTQ-16 and the full symptom scale >2.5). Independent t-tests were performed to assess if the mean item score for the HTQ-16 and the full

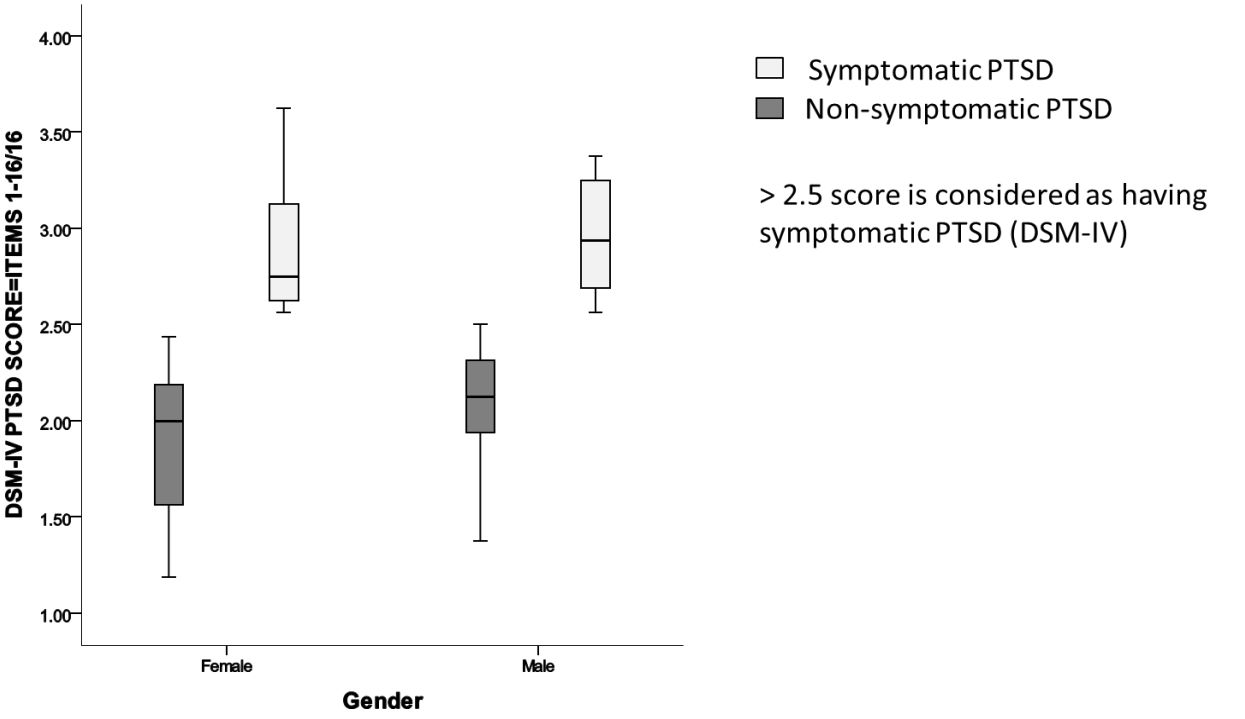

Figure 1. Proportion of respondents (n= 186) with symptomatic versus non-symptomatic post traumatic stress disorder (the mean item score for the HTQ-16) showing gender differences.

Table 2. Proportion of participants answering 'yes' to each of the 9-trauma assessment questions in Part 2 of the Questionnaire (n = 186).

Proportion of patients who answered with 'yes'	Female n= 87	Male n= 99	chi-square	p-value
1. Have you suffered from ill health without access to medical care or medicine during your stay in your country?**	43 (49.4)	60 (60.8)	2.34	0.126
2. Have you suffered ill health without access to medical care or medicine during your stay in Jordan?	21 (24.1)	24 (24.2)	0.00	0.987
3. Have you seen massive execution of civilians?*	21 (24.1)	37 (37.3)	3.78	0.052
4. Have you been exposed to combat situation (explosions, artillery fire, shelling) or landmine?**	50 (57.5)	61 (61.6)	0.33	0.565
5. Have you got serious physical injury from combat situation or landmine?**	32 (36.8)	44 (44.4)	1.23	0.289
6. Have you been\ witnessed someone being physically harmed (beating, knifing, etc.)?	49 (56.6)	58 (58.6)	0.10	0.565
7. Have you witnessed sexual abuse or rape?**	16 (18.3)	25 (25.2)	1.27	0.260
8. Have you been kidnapped/ taken as a hostage?**	12 (13.8)	19 (19.1)	1.10	0.294
9. Have you been tortured (while in captivity have you received deliberate and systematic infliction of physical and/ or mental suffering)?**	4 (4.5)	36 (36.4)	27.7	**<0.001**

*Significantly correlated with the scores on HTQ-16 and the full symptom scale (p< 0.05).
** Significantly correlated with the scores on HTQ-16 and the full symptom scale (p< 0.001).

symptom scale differed significantly for female compared with male participants. The analysis revealed that the mean item score for the HTQ-16 differed significantly, t (184) = -2.161, p=0.032. Overall, females were found to experience less PTSD than males (HTQ-16 mean item score for females= 2.26, SD=0.57 and males=2.42, SD=0.50).

Regarding the full symptom scale, the mean item score for the HTQ-45 was 2.33 (SD=0.47; range 1.1 - 3.24), and 31.2 % were categorized to have PTSD (mean item score for the full symptom scale >2.5). Median scores and IQR for the mean item score for the HTQ-16 and full symptom scale based on gender are presented in Figure 1 and Figure 2, respectively.

Trauma assessment involving the nine trauma assessment questions (Section 2) was performed based on gender-specific differences (Table 2). The analysis showed more than 50% of participants suffered ill-health without access to medical assistance whilst in Syria. However, compared to their residence in Jordan, only 24.0% of both genders reported to have had no access to medical assistance. Many participants reported having witnessed someone being physically harmed (e.g. beating and knifing), however significantly more males (36.4%) experienced torture. Comparisons based on gender for the rest of the questions are presented in Table 2.

Table 3 presents the correlation between the mean item score for the HTQ-16, the full symptom scale and characteristics of the study participants. Participants were more likely to have higher mean item score if they were males, older, smokers, and experienced trauma. However, no significant correlations were found between depression categories and the remainder of patients' characteristics, including watching TV.

The model resulting from the binary logistic regression analysis explained between 12.3% (Cox and Snell R-square) and 18.6% (Nagelkerke R-square) of variance in whether participants had mean scores on HTQ-16 and the full symptom scale > 2.5, therefore classified to have PTSD. The variables 'smoker', and 'experienced trauma' made a unique statistically significant contribution to the model (chi-square (df 4)=25.05, p<0.001). Online appendix summarizes the raw score logistic regression coefficient, Wald statistics and the estimated odds ratio for symptomatic PTSD compared with asymptomatic along with 95%CI.

DISCUSSION

Refugees are vulnerable and share similar experiences regardless of the country they come from, or the culture they belong to.[27,28] Several reports have mentioned that mental and social health problems (e.g. the inability to adapt comfortably to different social situations or to form satisfying interpersonal relationships with others) were the most common problems experienced amongst refugees.[11,12] With the Syrian refugees currently constituting 20.0% of Jordan's population, studies investigating their current state, needs and safe settlement in the country are urgently needed.[29] Previous literature investigating the effect of trauma and the factors that contribute to PTSD were more focused on military personnel, despite the fact that larger numbers of refugees suffered from the problem.[30] This current study sheds light

Table 3. Correlations between mean item score for the HTQ-16, the full symptom scale and patients' characteristics (n = 186)

	mean item score for the full symptom scale		mean item score for the HTQ-16	
	r	p-value	r	p-value
Age (years)	0.349	<0.001	0.273	<0.001
Gender (F=0, M=1)	0.145	0.049	0.145	0 .049
Educational level	-0.137	0.063	-0.166	0.150
Marital status (single= 1, married=2, widowed or divorced=3)	-0.107	0.155	-0.115	0.124
Residential status (rural=1, urban=2)	-0.037	0.616	-0.036	0.612
Smoker (0=smoker, 1=ex-smoker, 2=never)	0.330	<0.001	0.257	<0.001
Experienced a trauma (0= no, 1= yes)	0.298	<0.001	0.402	<0.001
Kind of trauma (0= war, 1=social, 3= economical, 4= others, 5= none)	-0.035	0.488	-0.075	0.342
Watching TV (no=1, yes=2)	0.060	0.429	0.104	0.171

on the prevalence and severity of PTSD in Syrian refugees in Jordan. Understanding the gender difference helps pave the way towards allocating appropriate services/resources for the management of the refugees' health.

PTSD is a common psychiatric condition in primary care patients. In the general population, a national sample of 5877 people in the USA, aged 15 to 54 years, showed a 7.8% estimated lifetime prevalence of PTSD.[31] However, among special populations, such as veterans of Iraq and Afghanistan wars, 58.2% of 238,098 veterans who received a health care service in the USA were diagnosed with PTSD.[32] As for PTSD diagnosis among refugees, a report by the US Committee for Refugees demonstrated a wide variation in the prevalence of the symptoms of PTSD (4-86%).[33] This study revealed the prevalence of PTSD amongst adult refugees in Jordan to be 35.0%. The identified proportion falls within the wide range of prevalence identified earlier, but is well below the upper ranges (86.0%).[33] Immigration-related stressors such as language difficulties and cultural differences are not found in the Middle East region, which could have played a role in keeping that proportion at the lower rate. Moreover, religious beliefs and family ties in the Arabic region provide a network of healing, again, neutralizing some war effects and keeping PTSD proportion at the lower rate.[33]

Although exposure to war-related violence does not necessarily lead to PTSD, the incidence of PTSD has been known to increase in populations exposed to war.[31] A study conducted in Canada in the year 2011 emphasized that the prevalence of common mental health problems increased for refugees who had severe exposure to previous violence, as they have higher rates of trauma-related disorders, including PTSD.[34] Also, time does not seem to resolve the problem; individuals who have experienced great levels of trauma have a greater risk of developing psychological disorders long after resettlement.[35] A study conducted in Netherlands showed an unchanged high prevalence of PTSD (16.3% in 2003 and 15.2% in 2010) amongst refugees, attributable in part to the late onset of PTSD symptoms and the low use of mental healthcare services.[36]

The World Health Organization (WHO) defined health in its broader sense in the 1948 constitution as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity".[37] Fear of stigma, unawareness of mental illness, lack of appropriate services that suit people's needs all form barriers to accessing mental healthcare, contributing to people not seeking treatment in time.[38] It is important to note that people with PTSD are more than twice as likely to experience non-psychiatric medical conditions as those without PTSD, even when adjusting for other factors such as age, socioeconomic status, and major depression.[39] In addition, mental health assessment is not easy, with certain factors preventing accurate assessment, including high patient volume, the presence of multiple family members within the room, and natural hesitancy to discuss extremely sensitive matters.[40] Findings indicate that refugees would stand to benefit from long-term contact with mental health and social work teams, thus further interventional research in this area is called for.[40]

Many factors affect PTSD development and severity amongst refugees. It has been reported that psychological distress is exacerbated by both environmental conditions (financial stress, poor housing, lack of employment) and psychosocial outcomes (loss of role, poor social support and reduced activity), which are themselves stressors.[41] Length of time following exposure to war and trauma could also play a role. A study in Jordan conducted in six different areas in the country, indicated that there are significant effects of gender, marital status and educational level on PTSD symptoms of Syrian refugees.[27] Another study conducted in the northern part of Jordan showed that there are differences among the Syrian refugees in the extent and degree of PTSD; revealing that females, higher educated or married participants showed more symptoms of PTSD than males and females who were less educated or single.[28]

The significant association identified in this study between trauma and PTSD in symptomatic refugees is consistent with previous findings, where individuals with higher rates of trauma were shown to have correspondingly more severe mental health symptoms, including PTSD.[42] Another factor associated with more severe PTSD symptoms was smoking. A study conducted in the USA in 2012 suggested that certain PTSD symptoms may uniquely be associated with particular indicators of smoking behavior.[43,44]

Longer hours of watching TV showed no association with PTSD, unlike many previous findings.[45,46] A study conducted in Pakistan in 2009 showed high rate of PTSD symptoms by TV viewers, confirming the association between watching TV and PTSD.[45] PTSD symptoms have also been related to the type of TV show watched by affected people. A study conducted in the USA revealed that three to five days following the 2001 September 11 attacks, people reported watching an average of eight hours of television a day related to the attacks. Those who watched the most coverage, and for 12 or more hours, had more substantial stress reactions and 3.4-fold increased risk of new-onset PTSD.[46] On the other hand, it is likely that having access to a TV could be associated with being more settled and having a better income as a refugee, so watching TV for long hours may not really be a concern for Syrian refugees.

Results of this study showed a relatively high proportion of participants (60.8% males; 49.4% females) reporting having ill health without access to medical aid or medicines after the war during their stay in Syria, with the proportion decreasing significantly after their settlement in Jordan (24.2% males; 24.1% females). It is important to note here that refugee's ill health usually differ from the host countries' population health pattern, hence, healthcare professionals are advised to collaborate in investigating and improving healthcare among refugees.[47] A study conducted on 756 Syrian refugees from six different cities in Jordan in 2016 examining the impact of chronic diseases and availability of medications for PTSD, showed that PTSD was comorbid with chronic diseases in more than half of the participants.[48]

Gender differences also play a role in manifestation of mental illnesses.[39] This study pointed to gender as a contributing factor to the experience of PTSD; results appear to suggest that there is a variation in the prevalence

rate of PTSD, with males having significantly worse PTSD symptoms than females. Males reporting greater trauma experiences in the Syrian conflict, such as seeing mass execution of civilians and being tortured whilst in captivity, could be linked to the higher reported PTSD levels. Exposure to torture has been shown to account for higher rates of reported prevalence of PTSD and depression.[35] Interestingly our results differ from previous studies conducted in this area, where female Syrian refugees were found to suffer more PTSD symptoms than males.[49] Another study reported that both genders involved in the Syrian conflict were equally affected by the war, as the rates of depression did not differ between both genders.[50]

Many studies have been conducted in the geographical area surrounding Syria, shedding light on the psychological impact of war on the Syrian refugees for adults, women and children.[13,40,51] The need for psychological and mental health services was emphasized in all studies.

In addition, since many refugees have PTSD which often goes under-diagnosed because of the many competing priorities experienced by refugee communities, it would be valuable if refugees with PTSD could be identified more readily. Pharmacists can be engaged in this field, forming a link between refugees and mental health specialists. Pharmacists are accessible primary care providers for refugees in Jordan, ideally positioned to screen for refugees with PTSD, referring those in need of care to healthcare specialists. Pharmacists can perform this role through their presence in the community pharmacy, an accessible health care facility to the public, where pharmacists are available to provide personalized advice about health and medicine on a walk-in basis, without the need for a costly appointment.[52] Pharmacists can also be engaged in new services targeting refugees, such as the successful, previously trialled, specialized medication management review service delivered to Syrian refugees in Jordan'.[53] Most importantly, pharmacists need to be resourced to provide helpful information about services they could access and brief information about PTSD, clarifying how much their engagement is helpful. It took the pharmacists an average of 5 minutes to complete the survey with each refugee, indicating the feasibility of this assessment. Engaging pharmacists with refugees can create new and needed services that can be delivered by pharmacists not only in the Middle East, but wherever refugees reside. This is in line with the WHO recommendations supporting the implementation of the recently published report by the High-Level Commission on Health Employment and Economic Growth established by United Nations Secretary in March 2016 calling for "ambitious solutions to ensure that the world has the right number of jobs for health workers with the right skills and in the right places to deliver universal health coverage".[54,55]

Limitations

Limitations of this study involved the sampling strategy, which was minimized as much as possible by having a clear stringent protocol followed by the investigators when interviewing the refugees. Although the study presents a unique approach to research in the Middle East, it is challenging to draw conclusive deductions for the recruited study sample, and generalization of the results are restricted to the refugees residing in Amman, Jordan. The in-person interview aspect of this study could have made some participants uncomfortable sharing their personal mental health. The pharmacists conducting the interviews in this study were of both genders. Female refugees could have been more open when a female pharmacist interviewed them versus a male pharmacist. Such gender differences of the pharmacist may have influenced the females comfort level when speaking about their mental health, which could have affected the results.

Although it would have been useful to extrapolate socioeconomic factors in the analysis by questioning the participants about their income, this question was left optional due to the refusal of many participants to respond to such questioning. The questionnaire (HTQ) used for the Syrian refugees (non-Western population) in this study to assess their mental health problems is an internationally validated questionnaire.[24] The questionnaire was translated and validated in the Arabic language and was found useful when used across different cultures and populations.[23,25,33] Yet, to adapt the HTQ to the Syrian refugee context for a better understanding of the situation, researchers can benefit from investigating the effects of trauma on the Middle Eastern populations in general, and on Syrians in particular.

CONCLUSIONS

Civilian Syrian refugees interviewed by pharmacists in Jordan showed a high incidence of PTSD. The prevalence rate of Syrian refugees in Jordan who report symptoms of PTSD on DSM-IV score was 35%. More males than females were found to be affected by the disorder. Many refugees have suffered different types of traumas, mainly exposure to combat situation and being or witnessing someone physically harmed. More males were tortured and witnessed massive execution of civilians than females. Having experienced previous trauma, being older in age, a smoker or a male showed significant association with PTSD severity. Results of this study highlight the ability of pharmacists to identify refugees with PTSD in need of dire help, directing needed resources to treat civilian refugees affected by PTSD. Further research exploring PTSD for refugee children residing in the countries surrounding Syria is needed. Longitudinal studies are called for, considering that individuals who have experienced great levels of trauma have a greater risk of developing psychological disorders years after resettlement.[35] Future studies could also investigate if less intensive training with a shorter questionnaire could be enough for pharmacists to take on this role.

Data availability

The datasets generated during or analyzed during the current study are available from the corresponding author on reasonable request.

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CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

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Pharmacists and Medicare's Annual Wellness Visit: implications for pharmacy education and interprofessional primary care

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Introduction

Older adults largely receive medical services in ambulatory primary care venues. Unfortunately, there is often a mismatch between the structure of primary care and senior patients' needs, including multimorbidity, frailty, cognitive impairment, and polypharmacy. These attributes do not lend themselves to the typical, short primary care visit wherein multiple concerns are addressed in a "tyranny of the urgent".[1] Instead, interventions emphasizing patient-centered care, wellness, prevention, and care coordination are necessary. Medicare's Annual Wellness Visit (AWV) provides a means to deliver such care.[2]

The AWV, an hour-long encounter, addresses multiple concerns in a coordinated fashion, including preventative care for beneficiaries over age 65. In a national sample of Medicare recipients, AWV completers were more likely to receive subsequent preventative services versus non-completers.[2] Odds were uniformly increased for mammography, bone density, depression and colon cancer screening, and alcohol misuse. Increased screening for sexually transmitted illnesses and cognitive impairment were also associated with completion.[3,4] Additionally, completers were over twice as likely to receive a PCV-13 vaccination and 20% more likely to receive an influenza immunization.[5]

The AWV allows for an interprofessional approach wherein varied clinicians, including pharmacists, can lend their expertise by conducting the AWV under direct supervision from a physician. This "incident-to" billing model allows non-physician providers to bill for services as if they were conducted by the physician.

The AWV remains vastly underutilized, especially among high risk groups.[6] Physician advocacy for its completion may be limited by complexity and competing agendas. With their training and scope of practice, pharmacists may serve as care extenders and enhance completion rates. It is incumbent that pharmacists have good understanding of the AWV. Accordingly, this commentary aims to:

1. Illustrate a pharmacist-led AWV service;
2. Review the impact of pharmacist-led AWVs;
3. Characterize pharmacist workforce preparedness to conduct AWVs.

Pharmacist-led AWV Model

The required elements of AWV are publicly available, well described, and outlined in Table 1.[7] Required AWV components include an updated history, coordination of care, medication reconciliation, identification of preventative service needs, optional advance care planning, as well as functional assessment and screening for geriatric syndromes, including falls, depression, cognitive impairment, vision and hearing.[8] Physical assessment is limited to weight and vital signs. Patients also complete a health risk appraisal which further delineates behavioral and psychosocial risks (Table 2). The end product is a personalized, written plan of care summarizing preventative interventions, follow-up visits, and referrals for education, counselling, or specialty consultation. The case study in Table 3 illustrates the integration of these elements into a pharmacist-led AWV.

Pharmacist impact of conducting AWVs

It is widely recognized that pharmacists have the skills and experience to conduct and manage the medication-centric components of an AWV, including medication reconciliation, review for appropriateness, adherence, and alignment with patient goals. Studies show that medication histories conducted by pharmacists are more robust and accurate versus those conducted by other professionals.[9,10] Indeed, pharmacists conducting AWVs are more likely to identify and intervene on medication-related concerns.[11,12] Moreover, pharmacists are also highly trained in the conduct of patient evaluation, communication, and health promotion.[13]

Several studies illustrate the benefits of AWV completion by pharmacists. With an average of 3.5 to 5.4 interventions per patient, pharmacists have effectively facilitated completion of preventative services, including

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Table 1. Pharmacist-Led Annual Wellness Visit case vignette

Jane Doe, a 72- year old woman, is eligible for an initial AWV and scheduled to see her primary care physician for a standard office visit next week. The clinic pharmacist calls JD to schedule the AWV to coincide. The pharmacist reviews her record to develop a pre-visit plan.

*JD completes a **health risk assessment (HRA)** before being seen to summarize health and functional status, behavioral, and psychosocial risks. After clinic staff obtains vital signs, the pharmacist explains the purpose of the visit, reviews JD's **care providers** and **updates medical, social family, surgical and immunization history.** Of note, JD is a person with diabetes being treated with insulin with a recent emergency department visit for hypoglycemia.*

*The pharmacist then conducts a **medication reconciliation** and finds several discrepancies, including errors in insulin administration and a new prescription for an over-the-counter sleep aid.*

JD's HRA is reviewed and is notable for low intake of healthy food and unsteady balance. A review of preventative needs indicates need for pneumonia and influenza vaccines as well as bone density screening. Cancer screening is up to date.

*Geriatric screening includes a two-question **depression screen** which is negative. JD appears well-groomed, answers questions appropriately, and has no evidence of **functional impairment**; as a result, the pharmacist does not conduct further **cognitive screening**. As JD reported trouble with balance, the pharmacist conducted a timed up & go test, which indicates a risk for falling.*

*The pharmacist provides a **written screening schedule** and a summary of JD's **health risks, current interventions and recommendations** specifically addressing adherence, risk of falls and hypoglycemia, immunization history, and need for bone density testing. These are ordered, immunizations administered, and a **referral** for physical therapy placed. JD agrees to stop her over-the-counter sleep aid to reduce fall risk. **Health education materials** for sleep hygiene and healthy eating are provided. The pharmacist clarifies the proper use of JD's mealtime insulin and recommends follow-up with the pharmacy clinic. JD is provided information and resources around advance care planning.*

The pharmacist documents the components of the AWV within the electronic health record and discusses findings with the primary care physician who reinforces the wellness plan and factors the findings into her management of other chronic conditions.

At 3-month follow up, JD brings in an advance directive. Her bone density revealed osteoporosis and she is started on weekly alendronate. She has had no further falls or hypoglycemic episodes.

immunizations, mammography, diabetes, and lipid screening.[14-16] Not surprisingly, pharmacists are more likely to identify and implement medication management interventions versus other clinicians conducting AWVs.[11,12,14] In an evaluation of pharmacist-led AWVs followed by comprehensive medication management, 278 medication-related problems were identified in 48 of 53 participants.[17] Of these, 247 (88.8%) were rectified during the AWV or subsequent follow-up. Neither hospitalization nor emergency room usage changed following the intervention. However, this study used a pre-post comparison design and thus could not account for effects of disease progression on usage rates.[17] In addition to medication-related interventions, pharmacists delivering AWVs has resulted in a comparable rate of interventions compared to physicians, including provision of health advice, immunization recommendations, and screenings.[11,18]

There are opportunities for pharmacists to enhance AWV outcomes research. Despite the aforementioned observations, evidence that AWVs improve clinical and economic outcomes remains elusive.[14,19] There are several potential explanations inherent to practice-based research, including lack of randomization and control groups. Unique to the AWV, differences in health, access to care, and valuation of care of completers versus non-completers, and failure to link the AWV to follow-up management that might reduce care disparities and utilization, are limitations.[15,20] Given the salience of medication use to these outcomes, further studies of pharmacist-led AWV on these outcomes are warranted.[21]

Pharmacist-led AWVs are well-received by other providers. Physicians in a family medicine practice strongly agreed that their patients benefited from a pharmacist-led AWV and strongly disagreed that they would prefer conducting the visit themselves.[22] Patients who received pharmacist-

Table 2. Requirements of initial and subsequent Annual Wellness Visits

Component	Initial visit	Subsequent visits
Conduct a health risk appraisal (see Table 2) including demographics, self-assessment, psychosocial and behavioral risks, and function	X	X
Establish medical and family history	X	X
Establish current providers and suppliers	X	X
Assess height, weight, BMI, heart rate, blood pressure and other measures as appropriate (physical exam not necessary)	X	X
Cognitive assessment	X	X
Review depression risk	X	
Review functional ability and safety, including hearing, falls and home safety	X	
Establish a written screening schedule for following 5-10 years	X	X (update)
Establish list of risk factors and conditions and interventions recommended or underway	X	X
Provide health advice or referrals related to health education or preventative counseling or programs	X	X
Provide advanced care planning services if requested	X	X

Table 3. Health Risk Appraisal requirements[1]

Category	Specific Elements
Demographic Data	Age, gender, race, ethnicity
Self-Assessment	Health Status, frailty, physical function, pain, fatigue
Psychosocial Risks	Depression, stress, anger, loneliness, lack of social support, safety/concern for abuse-exploitation
Behavioral Risks	Smoking, physical activity, nutritional/oral health, alcohol and illicit usage, sexual behavior, seat belt use, firearms, home safety
Basic Activities of Daily Living (ADLs)	Bathing, toileting, ambulating, transfers, eating, dressing
Instrumental Activities of Daily Living (IADLs	Shopping, meal preparation, telephone use, housekeeping, laundry, medication management, transportation, finances
Advanced Activities of Daily Living	Driving, computer literacy, health literacy

[1]Examples available at:
American Academy of Family Physicians. Accessed August 1, 2019 at:
https://www.aafp.org/journalpdfrestricted/fpm/2012/0300/fpm20120300p11-rt1.pdf
HealthConfidence.org. "Medicare, Medicaid and Other Short Forms" Accessed August 1, 2019 at: http://www.healthconfidence.org/static/HYHModifications.pdf

led AWV have reported high rates of satisfaction, noting that they were just as comfortable with that visit as they would have been with their physician, and strongly agreed that they would like to see the same pharmacist provider next year.[19,23] For practices struggling to recruit patients for AWV completion, pharmacist-led visits can be a recruiting strategy, particularly if patients express questions and concerns about their medications.

At a reimbursement rate of USD 175 (initial visit) and USD 118 (subsequent visits), conduct of the AWV also represents a source of revenue for practices that can underwrite the pharmacist salary. For example, AWV net revenues exceeded USD 50,000 even after accounting for overhead and not accounting for secondary revenue from immunizations, laboratory draws, and other related, billable services to the AWV.[25] Additionally, the AWV allows other opportunities for remuneration, including depression screening, alcohol misuse screening, and advance care planning.[26] Completion of 1,070 visits annually would offset the salary for a full-time pharmacist. Assuming 2,632 available visits per year, this income may facilitate pharmacist-led, non-reimbursable activities in the remaining 60% of visits.[27] The AWV can deliver further return on investment by offering a structure for completing and documenting quality measures that enhance performance under value-based reimbursement programs. When used by Accountable Care Organizations, AWV completion is associated with a 5.7% reduction in costs.[23]

Pharmacist Workforce Preparedness to Conduct AWVs

As opportunities for pharmacists to participate in health promotion initiatives such as the AWV expand, the profession should work to ensure preparedness. Current accreditation standards for schools of pharmacy require programs to provide learners with skills well aligned to those necessary to conduct AWVs. The standards require programs to focus on health promotion activities to manage chronic disease and promote wellness, to work in interprofessional teams, advocate for patient interests and provide patient-focused care.[13] Required curricular elements to meet these standards, such as patient evaluation via objective and subjective means and exploration and implementation of activities that advance public health, ensure that graduates are able to conduct the key elements required of an AWV. Pharmacy accreditation standards have increasingly focused on public health and chronic conditions, as evidenced by the emphasis on immunization delivery and certification with the Standards 2016.[13] Geriatric screening and assessment for falls reduction, home safety, advanced care planning, depression, sensory impairment, and cognition are less appreciated in many curricula.[28,29] Schools aiming to meet accreditation-required elements for patient assessment should look to explicitly address these issues to enhance AWV preparedness. Such efforts should include opportunity to practice these elements in a coordinated fashion that accurately simulates pharmacist-led conduct of the AWV.

Concurrently, practice management, innovation and entrepreneurship content should provide learners with the knowledge and skills to systematically advocate for participation and demonstrate success, when implementing a service such as the AWV. This includes ensuring that pharmacists can facilitate collaborative practice relationships with physicians. With the need to demonstrate and share both clinical and economic outcomes related to the AWV, academic institutions, training programs, and continuing professional development providers should supply opportunities for learners to develop practice management, evaluation, and quality improvement skills. The development of further resources, such as the National Alliance of State Pharmacy Association's "Pharmacist's Guide to Medicare Annual Wellness Visits" and the American Society of Health Systems Pharmacists "FAQ: Medicare Annual Wellness Visits" are also critical.[30,31]

Conclusion

It is clear that adding pharmacists to the team to conduct AWVs can favorably impact patients' health by identifying medication-related problems, ensuring appropriate preventative screening, and promoting wellness. Fully realizing this value will require continued emphasis on interprofessional training for all disciplines. There is a need to ensure that pharmacist education embraces principles of geriatric assessment, clinical prevention, and advance care planning in order to fully prepare pharmacists to complete all AWV elements. Additionally, educators should ensure that pharmacists obtain the practice management skills necessary to develop models that support the AWV. Finally, there is both the challenge and opportunity for pharmacists to engage in outcomes research that demonstrates that the conduct of AWVs translates into improved quality, reduced costs, and enhanced patient-centered outcomes through systematic evaluation and dissemination.

CONFLICT OF INTEREST

None to declare.

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Original Research

Agreement between units of measure for paediatric antibiotic utilisation surveillance using hospital pharmacy supply data

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Abstract

Background: Drug utilisation studies from paediatric hospitals that do not have access to patient level data on medication use are limited by a lack of standardised units of measures that reflect the varying daily dosage requirements among patients. The World Health Organization's defined daily dose is frequently used in adult hospitals for benchmarking and longitudinal analysis but is not endorsed for use in paediatric populations.

Objective: Explore agreement between standard adult-based defined daily doses (DDD) and paediatric estimates of daily injectable antibiotic use in a Paediatric Intensive Care Unit that does not have access to individual patient-level data.

Methods: Hospital pharmacy antibiotic use reports and age-specific occupied bed-day data from 1 January 2010 to 31 May 2016 were extracted. Paediatric reference dosages and frequencies for antibiotics were defined and applied to three paediatric units of measure. Measures were applied to extracted data, agreement between antibiotic use measured in the adult DDD and each of the paediatric measures was assessed visually via Bland-Altman plots and linear regression for each antibiotic.

Results: Thirty one different antibiotics were used throughout the study period. Despite varying daily dosages in grams, the daily use of vials was unchanged from birth to 18 years for thirteen antibiotics. Agreement between DDD and vial-based measures was closer than the total recommended daily dose that did not account for wastage during preparation and administration. Vial-based measures were unaffected by vial size changes due to drug shortage.

Conclusions: Agreement between the DDD and vial-based measures of use supports the use of DDD for select antibiotics that may be targeted by antimicrobial stewardship programs. Vial based measures should be further explored in hospitals with single vial policies; detailed understanding of hospital practice is needed before inter-hospital comparisons are made.

Keywords

Drug Utilization; Reference Standards; Anti-Bacterial Agents; Hospitals, Pediatric; Pharmacy Service, Hospital; Antimicrobial Stewardship; Quality of Health Care; Retrospective Studies; Australia

INTRODUCTION

Monitoring hospital antimicrobial use and resistance is key to antimicrobial stewardship (AMS) efforts to curtail the rise of antimicrobial resistance. AMS programs monitor compliance with interventions that aim to optimise therapy and identify utilisation patterns that warrant further investigation. In many countries hospital-level data also contribute to large-scale surveillance programs that enable benchmarking and epidemiological research.[1]

In the absence of patient-level data (typically from electronic prescribing or medication administration systems) to capture actual days of therapy (DOT) and prescribed daily doses, antimicrobial use in adult hospitals is frequently sourced from pharmacy information systems and reported using the defined daily dose (DDD). These numerators are standardised by a measure of activity (denominator) such as patient days or admissions. The World Health Organization's DDD is considered a technical unit of measure based on the average daily dose of each agent for its most common indication in an adult. As the DDD is a fixed value, it cannot account for variations attributed to individual patient requirements such as indication, age or weight-based dosing or dose adjustment for comorbidities such as renal impairment.[2] For this reason, DDD is not validated or endorsed for use in paediatric populations where individualised prescribing is commonplace.[3] As a consequence, hospital utilisation data for paediatric patients may be excluded from larger antimicrobial surveillance programs that rely on DDD to monitor use in hospitals and the community.[1,4]

Despite these limitations, AMS programs in children's hospitals without access to patient level records are expected to monitor antimicrobial usage patterns, and demonstrate cost-effective antimicrobial therapy.[5,6] Surveys of actual prescribing, though ideal, are resource intensive in the absence of electronic systems and may not be feasible for routine surveillance. Therefore, pharmacy information systems continue to be used for antimicrobial utilisation using measures such as drug costs, DDD and paediatric defined daily doses.[7]

In the absence of any endorsed paediatric measure for hospitals without access to patient level data, The WHO recommend prescribed doses and indications are

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compared to DDD values.[2] However, the relationship between prescribing and reported use from pharmacy information systems is further complicated by the amount of drug discarded in the process of preparing individualised doses from standard sized vials.[3,8]

This study explored the levels of agreement between adult DDD and feasible paediatric estimates of daily antibiotic use (numerators) in the context of a paediatric hospital that does not have access to individual patient-level data.

METHODS

Setting

This retrospective study was conducted in a 170-bed university affiliated tertiary paediatric hospital in New South Wales, Australia. The hospital is adjoined by two public hospitals for general adult and specialist women's and newborn care. A range of services are shared across the campus including operating theatres, radiology and pharmacy. The hospital's level six paediatric intensive care unit (PICU) accepts complex surgical and oncology patients from birth to 18 years, including preterm neonates transferred from the neonatal intensive care unit (NICU) at the adjoining hospital.

Nursing staff order routinely prescribed antimicrobials that have been approved as "imprest" items from a pharmacy warehouse shared between the adult and paediatric hospitals. Pharmacy warehouse staff distribute imprest items to individual wards with limited or no direct contact with pharmacists; non-imprest antimicrobials are dispensed as whole vials to individual patients by pharmacists in the hospital dispensary. Pharmacists review and endorse both imprest and non-imprest medications prescribed by doctors on paper-based medication charts but do not collect data on the patients or medications reviewed.

Due to these ordering methods antimicrobial use is not consistently linked to individual patients. All injectable medications, other than those associated with high cost or special handling requirements, are prepared by nurses on the ward from whole vials. State-wide infection control and medication handling policies mandate the use of single dose vials over multi-dose products and require nurses to discard any unused portions of injectable medicine.[9]

Data collection and analysis

Antimicrobial and patient demographic data

Records of antimicrobial supply to PICU inpatients from 1 January 2010 to 31 May 2016 were extracted from the hospital pharmacy information system (iPharmacy, CSC, Sydney Australia). In keeping with the National Antimicrobial Utilisation and Surveillance Program methods used for adult hospitals in Australia, the data combined records of imprest distribution from the pharmacy warehouse and individual inpatient dispensing by pharmacists.[4] Discharge and outpatient dispensing associated with the PICU cost centre code were excluded. WHO Collaboration Centre for Drug Statistics Methodology Anatomical Therapeutic Chemical (ATC) classification system for antimicrobials category J01, and J04 injectables were extracted.[10]

Tobramycin and colistin for injection and inhalation could not be differentiated consistently throughout the study period and were excluded from further analysis. Injectable erythromycin was also excluded because it is more commonly prescribed for gastric motility in our institution. Gentamicin was excluded due to a transition from 8 hourly to once daily gentamicin for neonates and oncology patients during the study period, sporadic supply of two vial sizes to the PICU via imprest.

Data entry errors were corrected after confirmation from pharmacy and warehouse managers; records of unused items returned to stock after initial supply were subtracted from the original month of supply. Antibiotic use for each agent was reported as monthly vial counts according to vial size in grams. Date of birth and occupied bed-day (OBD) data were obtained from the hospital performance unit. Patient age (in months) was calculated for each patient at each day of their PICU admission and used to create a database of monthly age-specific PICU occupied bed-days.

Measures of antibiotic use

Three paediatric measures of daily antibiotic consumption were derived from the dosage and frequency recommendations published in the national paediatric medication reference text and the New South Wales Neonatal Medicines Formulary.[11,12] Where there were no local or national recommendations these were obtained from Lexi-Comp® via UpToDate and the British National Formulary for Children.[13,14] For consistency across measures reference dosages and frequencies were defined. Where possible, the reference dosage in milligram per kilogram and reference frequency were roughly equivalent to the adult values assigned by WHO. For example, DDD assignments for J01CR beta-lactams with beta-lactamase inhibitors (piperacillin-tazobactam and ticarcillin-clavulanate) were an average of two commonly prescribed dosage schedules, therefore, the same approach was taken. Where the DDD assignment reflected maintenance or severe infection, the same principle was applied to the reference dosage and frequency. Patient gender and actual weight was not available, therefore, the median weight for age (in months) was obtained from the United States Centers for Disease Control and Prevention weight-for-age percentile reference ranges for girls.[15]

Paediatric measure 1: Estimated daily use of vials

The estimated daily use of vials was a fixed value equal to the reference frequency children. A single vial was assigned to each dosage administration within 24-hours without modification for patient weight, age, dosage delivered, or vial size supplied. For example, the estimated use of vials for vancomycin was fixed at four vials per day despite the fact that some patients would require more than a single vial for each dosage administration due to age, weight or the prescribed dose.

Paediatric measure 2: Age-adjusted daily use of vials

Age-specific dosage and frequency, potential residual antibiotic and age-specific occupancy in PICU (age-specific occupied bed days) were incorporated into the age-adjusted daily use of vials. First, individual dosages were calculated for each antibiotic for ages 3 months to 18 years

(reference dosage in mg/kg x 50th percentile weight-for-age, up to the maximum reference dosage). The number of whole vials required to administer the calculated dosage was assigned according to the vial sizes supplied to PICU; dosages were allowed to be rounded down to the nearest whole number of vials where the dosage delivered would remain within 5% of the calculated dosage. Average daily vial requirements were obtained by multiplying the number of whole vials required per dosage administration by the reference frequency. Average daily vial requirements for neonates broadly accounted for gestational age by taking the lowest or most commonly used frequency in neonates. Unless otherwise stated, gestational and postnatal age-adjustment was applied uniformly to all patients under 3 months old to account for possible preterm birth.

The age-adjusted daily use of vials was calculated for each month of the study period, by applying the proportion of age-specific PICU occupied bed days to the corresponding average daily vial requirements for each age. i.e., Age-adjusted daily use of vials= ∑ (Average daily vial requirement for age × Proportion of occupied bed-days for age).

Neonatal dosage adjustments were not performed for antibiotics that were deemed rare or unsuitable for neonatal use. The proportion of age-specific occupied bed-days was recalculated accordingly.

Paediatric measure 3: Recommended daily dose (RDD)

The median PICU admission age each month was used to select the age-specific reference dosage (mg/kg), reference frequency and 50th percentile weight used to calculate the monthly RDD unit of measure i.e., RDD = (Reference dosage in milligram per kilogram × reference frequency) × 50th percentile weight for age.

PICU antibiotic use

Monthly use of each agent in PICU was reported as the number of WHO ATC DDDs ([vial count × vial size]/ ATC DDD 2016); the number of estimated daily use of vials (vial count/Estimated daily use of vials); the number of age-adjusted daily vials (vial count /Age-adjusted daily use of vials and the number of RDDs ([vial count × vial size]/ RDD). Notably, PICU antibiotic use in measured in RDDs and age-adjusted daily use of vials were obtained by dividing monthly use by the age-adjusted daily use of vials or RDD unit of measure for the month in question.

Ethics

Ethics approval was granted by the hospital Human Research Ethics Committee (LNR/16/SCHN/445) and ratified by the University of Technology Sydney.

Statistical analysis

Data was extracted to a Microsoft Excel 2016 database (Microsoft Corporation, Redmond, WA, USA) for initial calculations. Statistical analysis was performed in R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics were used to report the monthly age-adjusted estimated daily use of vials measure that resulted from the PICU patient population throughout the study period. Agreement between the DDD and the estimated daily use of vials, the DDD and the age-adjusted daily use of vials, and the DDD and the RDD was assessed visually via Bland-Altman plots for each antibiotic with at least 10 months of use in the PICU (10 observations).

Differences in estimated monthly use between DDD and each of the paediatric use measures were plotted against the Averages of the two measures, i.e. y = Differences = use in DDD – use in paediatric measure, x=Averages = (use in DDD + use in paediatric measure)/2. Shapiro-Wilk tests and visual inspection of Bland-Altman and quantile-quantile plots confirmed whether the calculated differences were normally distributed. Where the assumption of normality was not met linear regression was used to describe the mean difference as a function of Averages. As described by Bland and Altman, the mean differences are obtained from a fitted regression model (model 1), B0 + B1Averages = Differences. The limits of agreement are then derived from a second linear regression model, C0 + C1Averages = Residuals, where the residuals are the absolute residuals from model 1. Statistical significance was determined by the p-value of the coefficients of the Averages, B1 and C1. The limits of agreement were calculated as ± 2.46 (C0 + C1Averages) of the mean difference (B0 + B1Averages).[16] Where distributions varied between antibiotics the most common distribution determined the method of analysis, and a single approach was applied to antibiotics. All tests were two-tailed, and p-values <0.05 were considered statistically significant.

RESULTS

Monthly OBD in the PICU ranged from 228 in January 2010 to 510 in July 2013 (mean=388, SD=64). Median PICU admission age was 16 months (IQR 3 months – 6 years 6 months). Of the 30 different injectable antibiotics supplied to the PICU throughout the study period, 60% (18/30) were supplied in one vial size. Cefotaxime was the only antibiotic supplied in more than two sizes. A reference dosage and frequency was assigned for all the included antibiotics.

For 12 antibiotics that were limited to a single vial size, the estimated daily use of vials was equal to adult DDD in terms of the reported grams of use, and the number of vials required (Online appendix: Table 1). These were; azithromycin, cefalotin, cefazolin, imipenem, lincomycin, metronidazole, moxifloxacin, piperacillin-tazobactam, rifampicin, teicoplanin, ticarcillin-clavulanate and tigecycline. Whilst amikacin, aztreonam, cefoxitin, linezolid, daptomycin, trimethoprim-sulfamethoxazole were also supplied in a single size the estimated daily use of vials was not equal to DDD (Online appendix: Table 1). For eight antibiotics the measure accounted for the average daily vial requirements in all patients after the neonatal period, despite 2-fold or greater variation if reported as DDD (ampicillin, cefepime or flucloxacillin = 1.0–2.0 DDD, meropenem and ceftazidime = 0.75–1.5 DDD, clindamycin = 0.5–1.0 DDD, benzylpenicillin ~0.67–1.33 DDD, cefotaxime = 0.5–2.0 DDD).

Almost half of the included agents (14/30) had an estimated daily use in vials that accounted for average daily vial requirements for all patients, regardless of age-

occupied bed days assigned to neonatal and older children (Online appendix: Table 1). Neonatal daily vial requirements varied from the reference frequency for children (i.e., estimated daily use of vials) for nine agents, (ampicillin, benzylpenicillin, cefazolin, cefotaxime, ceftazidime, flucloxacillin, metronidazole, ticarcillin-clavulanic acid and vancomycin). Calculated average daily vial requirements for age identified antibiotics that required changes to the estimated daily use of vials to account for weight or age in children (cefoxitin, ceftriaxone, aztreonam, trimethoprim-sulfamethoxazole, amikacin, ciprofloxacin, vancomycin, linezolid).

The age-adjusted daily use of vials for vancomycin (Figure 1) varied more than any other agent due to differing average daily vial requirements in both neonates and children (range 3.3–5.0 vials), followed by cefoxitin (range 3.3–4.6 vials) and trimethoprim/sulfamethoxazole (range 2.3–3.2 vials).

Agreement between reported use in DDD and the paediatric units of measure was completed for the 20 antibiotics that were supplied to the PICU during 10 or more months of the 77 month study period. Shapiro-Wilk tests of the differences confirmed normal distributions for only two antibiotics and thus regression methods were used to determine the mean difference and limits of agreement. Bland-Altman plots of PICU use in DDD and estimated daily use of vials showed perfect agreement for azithromycin, cefalotin, cefazolin, lincomycin, metronidazole, piperacillin-tazobactam and ticarcillin-clavulanic acid (7/20).

The relationship between the differences between DDDs and estimated daily use of vials used in PICU versus their averages was perfectly linear for amikacin, trimethoprim–sulfamethoxazole and linezolid, as these were all limited to a single vial size there was no deviation from the regression lines (Figure 2). The mean difference for vancomycin in DDD and estimated daily use of vials was not statistically significant (p=0.059), with only three deviations attributed to months during which a small number of larger sized vancomycin vials were supplied.

As expected, agreement varied for antibiotics that were supplied in multiple vial sizes. Flucloxacillin plots exhibited the narrowest limits of agreement, and the most prominent slope (Figure 2). The steep incline suggested

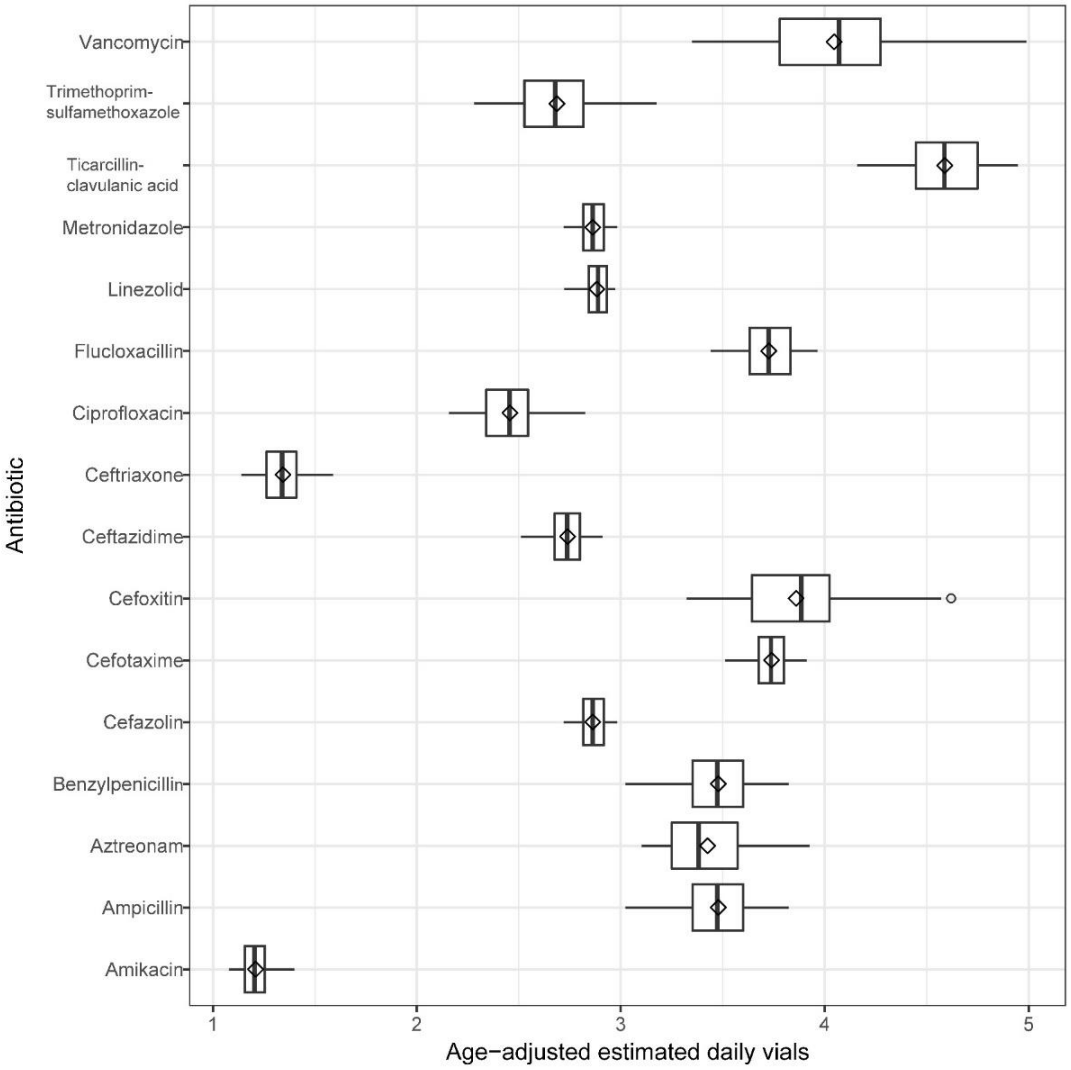

Figure 1. Age-adjusted estimated daily vials unit of measure generated from age-specific occupied bed-days in the Paediatric Intensive Care Unit. (values reported in Online appendix: Table 1).

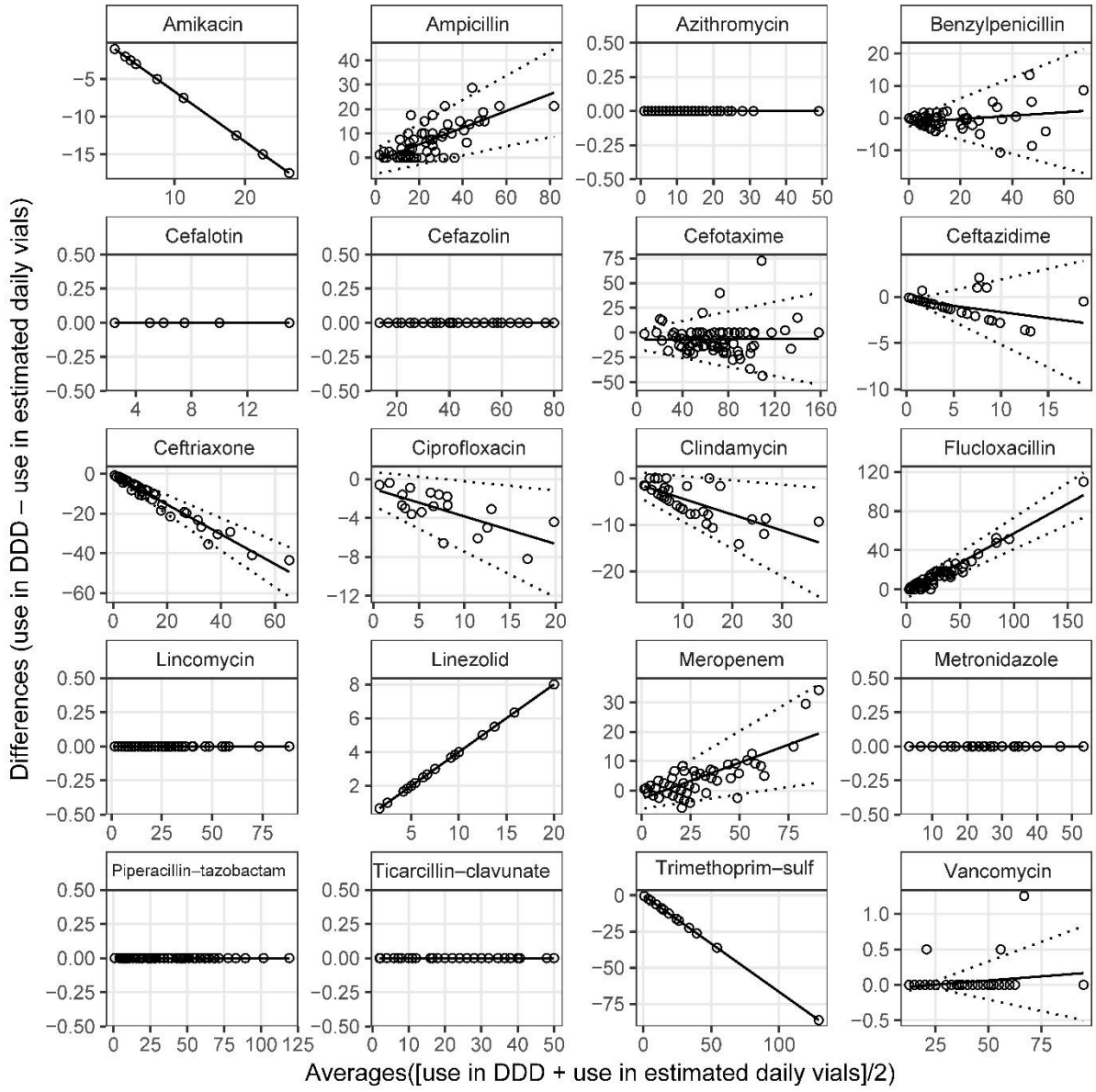

Figure 2. Bland-Altman plots of World Health Organization defined daily doses and Estimated daily use of vials.
Mean difference (solid line) and limits of agreement (broken lines) obtained from linear regression (Online appendix Table 2, DDD vs Estimated daily use of vials).

that higher usage months measured in DDD may vastly overestimate days of use compared to estimated daily use of vials. Bland-Altman plots for ampicillin produced wider limits of agreement as various vial sizes were more consistently used, including lower usage months. One in every four months of cefotaxime use were in perfect agreement (19/76, difference=0) without a statistically significant change in the mean difference in relation to the averages (p=0.922). Differences between cefotaxime use in DDD and estimated daily use of vials were both negative and positive, suggesting DDD measures could potentially under- and over-report use. The largest negative difference and most extreme positive outlier occurred during periods of high cefotaxime use, the former when large quantities of predominantly small vials were supplied (difference= -43.73, 67% vials 0.5g), the latter when larger vial sizes were supplied difference = +72.5, 100% of vials 2g) (Figure 2).

After adjustment for daily vial requirements and age-specific OBD, metronidazole, cefazolin and ticarcillin–clavulanate were no longer in perfect agreement (Figure 3). However, the impact on the differences remained small (Online appendix: Table 2). Differences between use in DDD and age-adjusted daily use of vials for ampicillin and flucloxacillin remained statistically significant, and positive in relation to the averages. Despite changes in the appearance of the cefotaxime and vancomycin plots, the mean differences were not statistically significant (Online appendix: Table 2); the limits of agreement were, however, narrower and wider respectively as expected. The magnitude of the mean difference in relation to the averages changed significantly after age adjustment to benzylpenicillin and ciprofloxacin as demonstrated by the changes to the slopes (Figure 2 and Figure 3).

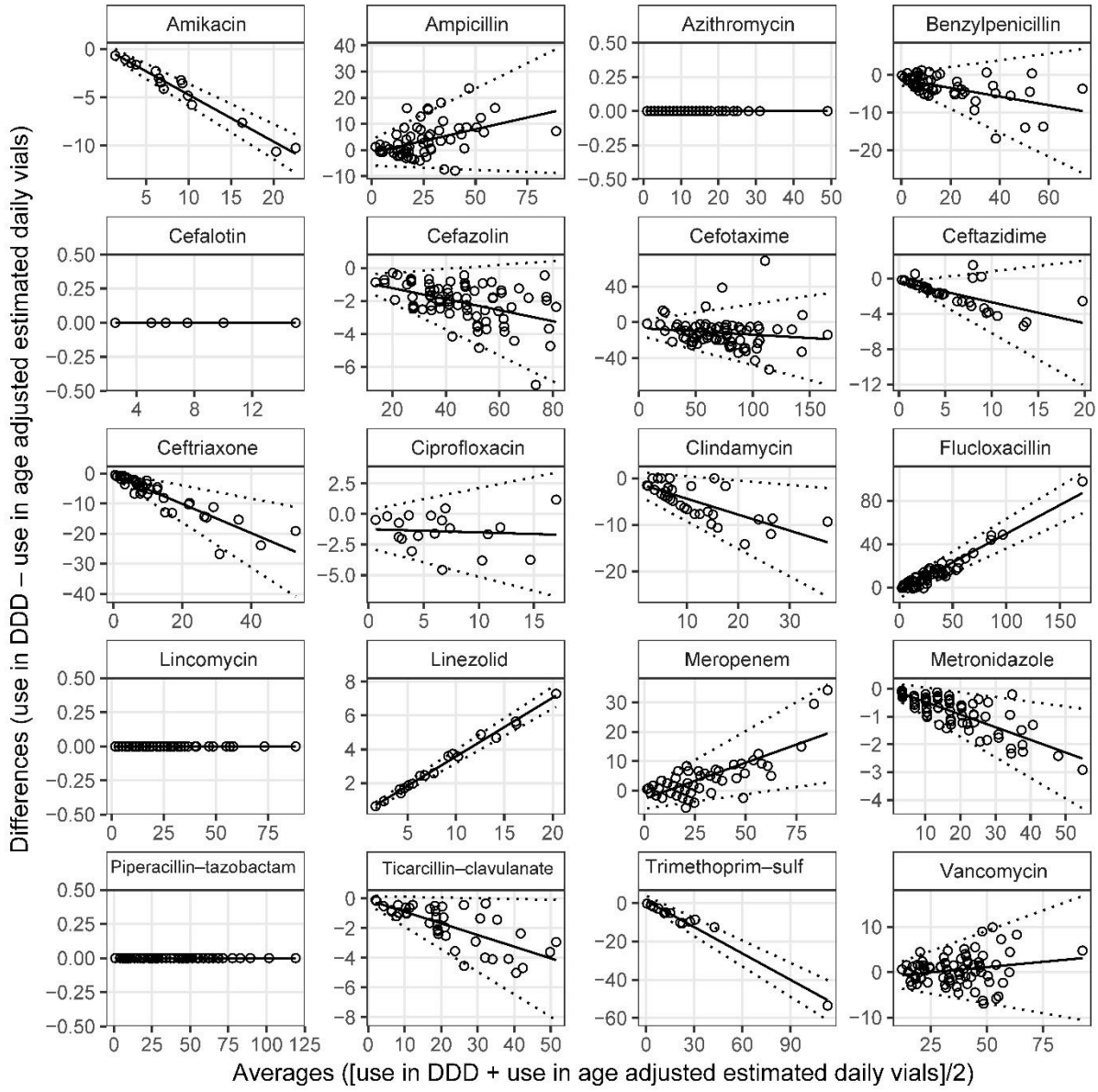

Figure 3. Bland-Altman plots of World Health Organization defined daily doses and Age-adjusted estimated daily use of vials. Mean difference (solid line) and limits of agreement (broken lines) obtained from linear regression (Online appendix Table 2, DDD vs Age-adjusted estimated daily vials).

Agreement between DDD and total recommended daily doses was poor. Visual inspection of Bland-Altman plots and linear regression showed obvious discrepancy between use in DDD and RDD, the relationship between the differences and the averages of the two measures was statistically significant and inversely proportional (Figure 4). Differences between DDD and RDD increased dramatically with higher average use; negative differences indicated that the estimated days of antibiotic use measured in RDD far exceeded that which was reported in DDD.

DISCUSSION

Despite its exploratory nature, this study offers some insight into a range of patient and organisational factors such as pharmacy distribution systems, single-vial policies and external factors such as drug shortages that influence the approach to antimicrobial surveillance in children's hospitals. Extracted records of use together with medication reference texts identified a range of antibiotics that are likely to be reliably reported in children and teenagers in DDD without any adjustment, and with only minor adjustment in neonates. This list of agents includes 10 that are restricted or highly restricted agents in our hospital. Also included is injectable metronidazole, which, while unrestricted, is a potential target for antimicrobial stewardship activities that promote IV to oral switch or reduce therapeutic duplication. Approximately half of the antibiotics used in PICU required estimated daily use of vials measure to be adjusted for age and weight and only one antibiotic, vancomycin, required adjustment for both neonates and children.

Bland-Altman plots of antibiotic use measured agreement between each of the paediatric antibiotic use measures and DDD, illustrating how vial size, age and waste may impact drug usage reports from pharmacy supply records.

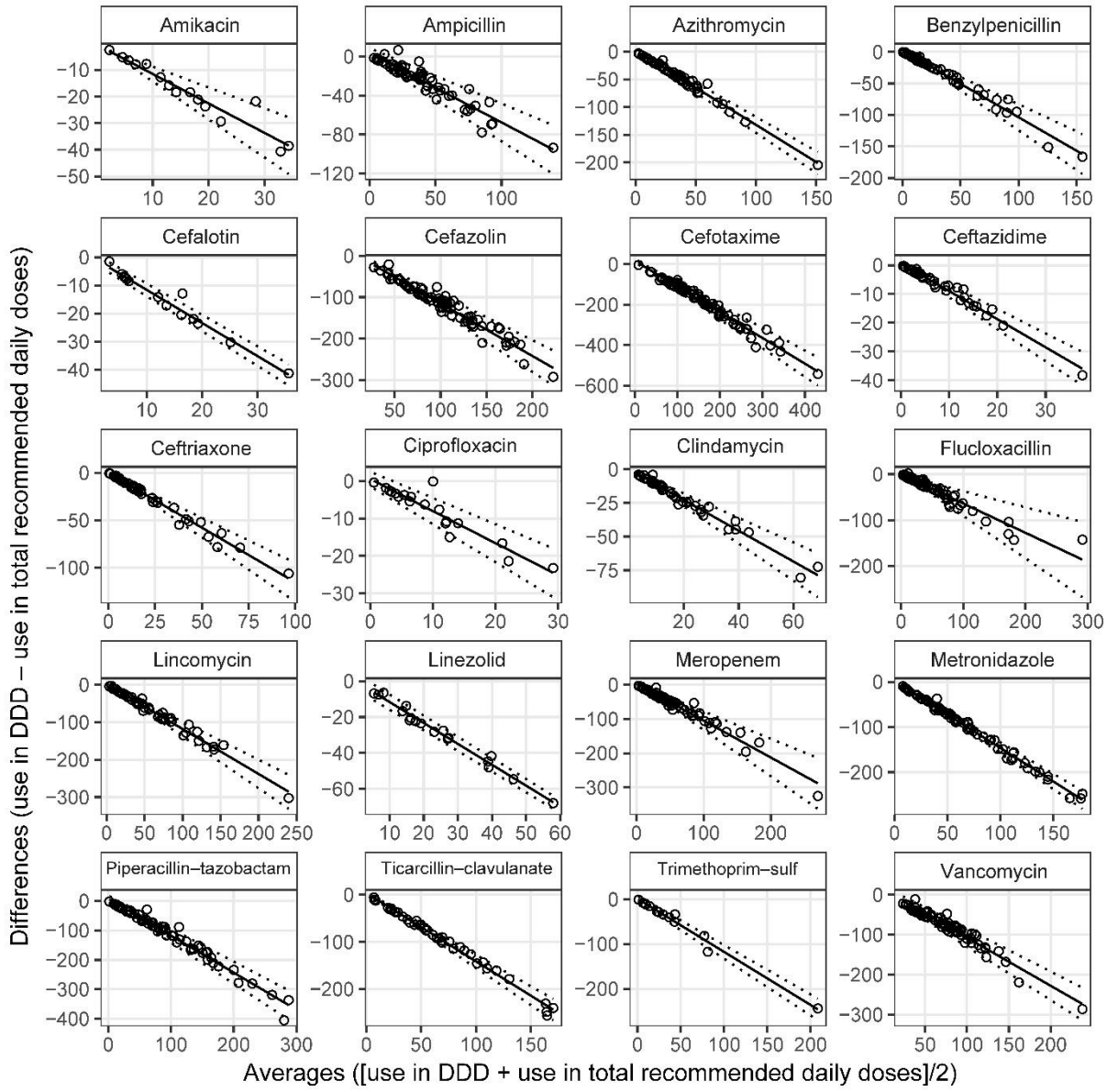

Figure 4. Bland-Altman plots of World Health Organization defined daily doses and Recommended daily doses. Mean difference (solid line) and limits of agreement (broken lines) obtained from linear regression (Online appendix Table 2, DDD vs Recommended daily doses).

Compared to DDD, the vial-based units of measure appeared more robust against cefotaxime formulary change and drug shortage by focusing on the dosage frequency, rather than the actual dose. In contrast, agreement between PICU use measured in DDD and RDD suggested RDD would report considerably higher estimates of monthly use, even where all other measures were equal or similar.

To the best of the author's knowledge, previous weight-adjusted methods using pharmacy data have largely focused on the dosage prescribed reporting use in RDD or proportions of DDD rather than vial requirements.[3,8,17,18] For example, Liem *et al*. suggest that "neonatal DDD" for ampicillin could be one tenth of the adult DDD values.3 Applying the single vial policies in the study hospital would result in a reported daily use of 1g (2 vials) to 4 g (4 vials) of ampicillin depending on gestational and postnatal age. Others have argued against weight-based adjustments due to the broad range of paediatric doses and the wide range of indications, choosing to use DDD for benchmarking and trend analysis.[19] Whilst DDD generally appeared to be closer to the minimum quantity reported for a single day of use in this setting, these conclusions may not be generalisable to hospitals without single vial policies, and different vial sizes in use. These variations are likely to limit the capacity for benchmarking between hospitals and comparisons with published surveillance reports internationally.

This study has a number of other limitations. The measures developed in this study were modelled similar to DDD and share some of the same limitations, including that they might be based on recommended dosages that do not accurately reflect the most common dosage regimens actually used in hospitals. Prescribers may choose alternate regimens within the medication reference range for convenience (i.e., to limit the number of daily dosages),

severity of infection or presence of comorbidities (e.g., renal impairment). However, these concerns are not limited to vial-based measures or children and are likely to be present in adult hospitals that use DDD. Vial-based measures may not identify a shift to higher dosages in milligram per kilogram that do not change the daily vial requirements and may overestimate use when multiple smaller vials are used to deliver a dose that could have been administered with a single vial. Furthermore, the age adjustments applied in our study are estimates. Complete records of gestational age were not available and patients under 3 months old were assumed to be neonates. In addition to possibly over-estimating the adjustments required for neonates, this also meant detailed adjustments could not be made for postnatal vial requirements. For children and teenagers, average daily vial requirements were extrapolated from standard paediatric weight-for-age reference ranges and not actual patient weight. Due to the preliminary nature of this work we did not perform any a priori sample size calculations, nor did we assess agreement as a function of time. While these are limitations of this study, they may be overcome in future studies; gestational and postnatal age are collected by Australian PICU's and measured weights are now available for electronic extraction in the study hospital. Age adjustments may also be influenced by the ordering process if antibiotics were supplied and administered in separate months. Finally, the measures were not compared to actual days of use. Such validation would require a prospective observational study or access to electronic medication administration or prescribing data, which were neither feasible nor available. However, this work is an important initial exploration in an area in which there remains an unmet need and highlights the need to include detailed information on the local setting when reporting on antimicrobial use. Namely, pharmacy drug distribution systems and relevant infection control or medication handling policies. In addition, the principles applied in this study may be utilised for other injectable medications in hospitals with similarly limited pharmacy services, particularly those with a narrow dosage range.

Further research is needed to assess whether agreement between estimated vial-based measures or selected antibiotic DDD and actual use are acceptable for local surveillance, national benchmarking programs and/or epidemiological studies. Initial studies should investigate drug distribution systems, presence of single vial policies, hospital formularies and medication dosage guidelines for similarities. Broad-spectrum agents associated with hospital acquired and resistant infections including, but not limited to carbapenems, vancomycin, linezolid and daptomycin should be prioritised. Consensus based methods may be required to reconcile discrepancies between prescribed doses and reference ranges used to define paediatric measures.

CONCLUSIONS

Paediatric antibiotic use reports generated from pharmacy information systems may not reflect actual administration because of the influence of variable vial size, patient age, pharmacy drug distribution systems and local medication handling and infection control policies. These factors should be assessed before inter-hospital comparisons are made. Agreement between the DDD and estimated daily vials and age-adjusted daily vials were superior to total recommended daily doses and unchanged by drug shortages in a PICU with a single vial policy. In this setting, a considerable number of antibiotics targeted by AMS programs may be reported in DDD when used for children and teenagers.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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Original Research

Potentially inappropriate medications among the elderly in primary care in Thailand from three different sets of criteria

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Abstract

Objective: The primary objective was to examine potentially inappropriate medications (or PIMs) in the elderly using three different criteria: Beers 2015, STOPP version 2, and Winit-Watjana (for Thai elderly patients). The secondary objective was to examine PIM-related factors.

Methods: This is a retrospective cross-sectional study. Eligible patients were aged ≥65 years in a primary care unit. Demographic data, medical prescriptions in the past year, clinical data and diagnoses were collected from electronic medical records. PIMs, including the use of ≥2 medications, were identified using the three criteria. Descriptive and analytical statistics were conducted. The type I error was 0.05. Multiple logistic regression analysis was used to examine associations between PIMs and other factors.

Results: A total of 400 patients were recruited, and 1,640 prescriptions were reviewed. The median age was 70.5 years, and the median numbers of diseases, medications, and prescriptions were 3 (interquartile range or IQR=2), 11 (IQR=20), and 3 (IQR=4), respectively. Of all the patients, 213 (53.3%) showed a use of ≥5 medications, and 301 (75.3%) were prescribed PIMs. Of the 1,640 prescriptions, 60% had at least one PIM. The Winit-Watjana criteria, Beers 2015 criteria and STOPP version 2 identified 66.8%, 59.0% and 40.3% of the patients receiving PIMs, respectively. Approximately 16% of the patients showed at least one potential drug-drug interaction. The use of duplicate drug classes accounted for the highest proportion of potential drug-drug interactions (41.3%). Polypharmacy (odds ratio or OR 3.93, 95% confidence interval or 95%CI 2.17-71.2) and the presence of ≥4 diseases (OR 2.78, 95%CI 1.39-5.56) were associated with PIMs.

Conclusions: PIMs are common among the elderly patients in primary care in Thailand. Prescriptions of the elderly with polypharmacy or multiple concurrent diagnoses should be reviewed for PIMs because they have a high chance of receiving PIMs.

Keywords

Inappropriate Prescribing; Potentially Inappropriate Medication List; Outpatients; Primary Health Care; Polypharmacy; Electronic Health Records: Cross-Sectional Studies; Multivariate Analysis; Thailand

INTRODUCTION

Polypharmacy, the concurrent use of multiple medications in elderly patients is common worldwide.[1] Polypharmacy increases the risk of negative health outcomes, including adverse drug events (ADEs), drug-disease or drug-syndrome interactions, and potentially inappropriate medications (PIMs).[2,3] PIMs are medications that can potentially harm patients and are associated with a 44% increase in mortality compared to no PIM usage.[4-6]

A systematic review reported there were up to 46 assessment tools for identifying PIMs: 28 criteria-based or explicit tools, eight judgment-based or implicit tools, and 10 assessment tools using both approaches.[7] Of those reported in the review, only 19 tools applied consensus methods. Two explicit tools with the most citations are the Beers criteria, developed in America, and the Screening Tool of Older People's Prescriptions (STOPP) criteria, developed in Europe. The latest versions of the Beers criteria and the STOPP were published in 2019 and 2015, respectively.[5,8]

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High proportions of PIMs are reported in various settings, such as 30-50% in primary care and 43% in nursing homes.[9-11] Differences in the prevalence rates of PIMs in different settings and countries may be a result of different assessment tools used to identify PIMs. Many studies have found that the prevalence rates of PIMs identified by the Beers criteria were higher than those identified by the STOPP criteria. Using the STOPP version 1 in primary care, the prevalence of PIMs was 37.3% and 33.8% in Ireland and Brazil, respectively.[9,12] However, the prevalence of PIMs in Brazil was higher using the Beers criteria than using the STOPP criteria: 51.8% vs. 33.8%, respectively.[9] Another study found that 50% of community-dwelling older adults reported the use of at least one PIM based on the Beers criteria compared to 46% based on the STOPP criteria.[10]

In Thailand, an assessment tool for PIMs was published in 2008 based on a literature review of high-risk medications and the Delphi method with 17 geriatricians.[13] This assessment tool, though based on theoretically sound methods, is not widely used. PIMs in the Thai elderly were reported in secondary and tertiary hospitals with different prevalence rates, partly because of different criteria used in each study. Of 430 outpatients in a district tertiary hospital in southern Thailand, 28.1% received at least one PIM, as identified by the 2012 Beers criteria.[14] In contrast, based on lists of risk drugs for Thai elderly adults, 79% of Thai elderly

adults in a community secondary hospital received at least one PIM.[15]

There are no data in Thailand regarding PIMs in primary care. Therefore, we conducted the study reported herein to close this knowledge gap. The primary objective of the study was to examine and compare the prevalence of PIMs in primary care using three different criteria for PIMs. The secondary objective was to examine associations between PIM and other independent factors, such as age and gender.

METHODS

This study was approved by the Human Research Ethics Committee of Thammasat University No.1, Faculty of Medicine (MTU-EC-CF-1-230/59). The permission to review and collect data from medical electronic records was approved by the director of the primary care unit (PCU). To protect patients' confidentiality, PCU staff removed all personal identifications, including national identification numbers, names, and addresses, before sending the data to the authors.

Study design and setting

This was a retrospective cross-sectional study exploring PIMs among elderly patients in a semiurban PCU in Pathum Thani, Thailand, which is overseen by the Faculty of Medicine of Thammasat University. Doctors in the PCU were family physicians, general practitioners (doctors without specialty training), residents in family medicine, and internists.

Participants

Patients aged >65 years were eligible for this study. Those without a prescription in the past year were excluded. The sample size was calculated to be 369 patients, with an estimated PIM prevalence of 40%, a 95% confidence interval, and a 5% margin of error.[11] We rounded this number up to recruit 400 patients to increase estimation accuracy.

Eligible patients were selected using systematic random sampling. The patient identification numbers of all patients were listed in order and the first patient was selected randomly. Every sixth patient was then selected until the sample size reached 400 patients.

Data collection

The electronic medical records of the patients were reviewed. The following data from the previous year (2016-2017) were collected: demographic data, including age and gender; diagnoses according to the 10th Revision of International Classification of Diseases and Health-Related Problems (ICD-10), medical prescriptions, and creatinine levels. Other laboratory findings were not collected because ICD-10 codes for abnormal findings, such as hypokalemia, were used to identify conditions that meet PIM criteria. ICD-10 codes starting with V to Z (V to Y for external causes of morbidity and mortality and Z for factors influencing health status and contact with health services) were not collected for data analysis. Quality control for data entry was performed. If input errors were found, the first author rechecked the errors with a data source and correct every mistake.

PIMs

Three sets of criteria were used to identify PIMs: the 2015 Beers, the STOPP version 2 (v2), and the Winit-Watjana.[4,5,13] The 2015 Beers criteria comprise of 5 groups of PIMs, including 1) medications for many or most older adults to avoid, 2) medications for older adults with specific diseases or syndromes to avoid, 3) medications to be used with caution, 4) potentially clinically important non-anti-infective drug-drug interactions, and 5) non-anti-infective medications to avoid or the dosage of which should be adjusted based on the individual's kidney function.

In contrast to the Beers criteria, the STOPP v2 does not divide PIMs into five groups. All criteria are divided according to organ systems or medication classes. For the Winit-Watjana criteria, PIMs were divided into two groups: high-risk medications with potential adverse reactions and high-risk medications with drug interactions (drug-drug and drug-disease). Each Winit-Watjana criterion comprises one of four recommendations: 1) should be avoided, 2) rarely appropriate, 3) with some indications for older patients, and 4) unclassified. Inhaled and topical medications were not collected for data analysis because they were not in the criteria (except estrogen patch and vaginal cream) and may lead to misinterpretation of results.

All authors manually identified PIMs in each prescription using both clinical (ICD-10 codes and laboratory findings) and prescription (dosages and numbers of medications) data. The first author (VP) verified all prescriptions to detect discrepancies in PIM identification. The authors discussed resolving all discrepancies and, if needed, verified PIM identification with prescriptions and patients' medical records.

Analysis

Both descriptive and analytical analyses were conducted. For descriptive analyses, medians and interquartile ranges (IQRs) were used to describe the following variables: age, number of diseases, medications, and prescriptions. Proportions were used for gender and PIMs. Persons and prescriptions were used as units of analysis for the prevalence of PIMs. The prevalence of prescriptions with PIM was calculated to answer how often doctors prescribed PIMs. A person was coded as 1 if the person received at least one PIM according to at least one of the three criteria in the past year, and a prescription was coded as 1 if the prescription contained at least one PIM according to at least one of the three tools. The use of ≥2 medications that were identified as PIMs according to these three criteria were subsequently analyzed. Comparisons for PIMs prevalence from each criterion were done using Chi-square tests.

For bivariate analyses, Student's t-test and chi-square or Fisher's exact test were used to compare the means and proportions of independent variables between individuals with PIMs and those without PIMs. A p-value of 0.05 was used to indicate statistical significance in this study. Variables with $p<0.05$ were included in multiple logistic regression analysis to explore associations between

Table 1. Characteristics of 400 elderly patients		
Variables	**Median**	(**P25, P75, IQR**)
Age	70.5	(67, 75, 8)
Female – *n* (%)	264	(66)
Number of diseases	3	(2, 4, 2)
Number of medications	11	(5, 25, 20)
Number of prescriptions	3	(2, 6, 4)
IQR: interquartile range; P25: percentile 25%; P75: percentile 75%		

independent variables and PIMs. Adjusted odds ratio with 95% confidence interval was calculated. All analyses were conducted using STATA software version 13 (Stata, College Station, TX, USA).

RESULTS

The records of 400 elderly patients were retrieved with the median age of 70.5 years (Table 1). A total of 1,640 prescriptions, comprising 6,852 medications, were reviewed. Of all the prescriptions, almost 40% had polypharmacy or a concurrent use of ≥5 medications.

Of 400 patients, 301 (75.3%) received PIMs in either criterion at least once in the past year (Figure 1). The Winit-Watjana criteria identified the highest proportion of patients with PIMs in the samples (66.8%), which was 7.8% and 25% higher than those identified by the 2015 Beers criteria and the STOPP v2, respectively (p <0.001).

When considering the proportions of PIMs per prescription, 56.5% of the 1,640 prescriptions included at least one PIM based on any of the three criteria (Figure 1). Of these criteria, Winit-Watjana identified the highest proportion of PIMs (46.5%), followed by the 2015 Beers and the STOPP v2.

The most common PIMs identified by any criteria were orphenadrine, nonsteroidal anti-inflammatory drugs (NSAIDs), and angiotensin-converting enzyme inhibitors (ACEIs). Table 2 shows the top five PIMs in each criterion. Overall, orphenadrine, a first-generation antihistamine, was the most common PIM identified by all three criteria. ACEIs and flunarizine were identified only by the Winit-Watjana criteria, while dimenhydrinate and tramadol were identified only by the 2015 Beers criteria and the STOPP v2, respectively.

The use of ≥2 medications that were identified as PIMs were identified against each criterion. Of all the patients, 15.5% received these PIMs at least once in the past year (Figure 2). The STOPP v2 identified the highest proportion of the use of ≥2 medications in the samples (14%), which were 7.2% and 11.2% higher than those identified by the 2015 Beers and Winit-Watjana criteria, respectively.

Of the 1,640 prescriptions, 6.4% had the use of ≥2 medications that were identified as PIMs. The STOPP v2 identified 88 prescriptions with these PIMs (5.4%), which were 43 and 61 more prescriptions with these PIMs than those identified by the 2015 Beers and Winit-Watjana criteria, respectively (Figure 2). The most common uses of ≥2 medications that were identified as PIMs by any of the three criteria were duplicate drug classes (41.3%), two medications with anticholinergic activity (33.9%), aspirin and NSAIDs (12.8%), warfarin and NSAIDs (8.3%), and warfarin and aspirin (3.7%). An example of duplicate drug classes was chlorpheniramine and hydroxyzine. An example of two medications with anticholinergic activity was dimenhydrinate and amitriptyline.

Bivariate analysis showed that all variables, except gender and age, were associated with PIM prescriptions for any criteria. The associations were similar in each criterion. However, age was associated with PIM prescriptions using the STOPP v2, and gender was associated with PIM prescriptions using the 2015 Beers and Winit-Watjana criteria.

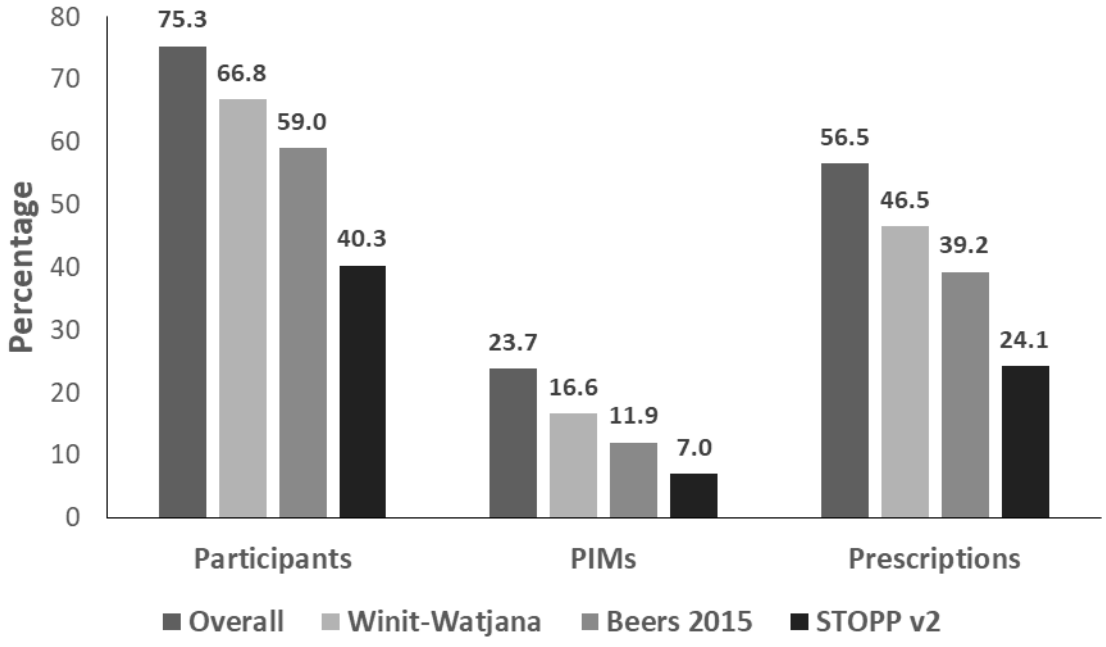

Figure 1. Proportions of PIMs by criteria.
Chi-square tests shows statistically significant differences in the PIMs proportion from each criterion with p<0.001.

Table 2. Top five PIMs by criteria (2016-2017)

Rank	Overall			Rank	Winit-Watjana		
	PIMs	N	(%)		PIMs	n	(%)
1	Orphenadrine	255	(15.9)	1	Orphenadrine	255	(22.7)
2	NSAIDs [a]	231	(14.4)	2	NSAIDs [a, e]	231	(20.5)
3	ACEI [b]	208	(13.0)	3	ACEI [b]	208	(18.5)
4	Dimenhydrinate	155	(9.7)	4	Benzodiazepine [c]	112	(10.0)
5	Benzodiazepine	112	(7.0)	5	Flunarizine	101	(9.0)
6	Others	642	(40.0)	6	Others	218	(19.4)
	Total	1603	(100.0)		Total	1125	(100.0)

Rank	2015 Beers			Rank	STOPP version 2		
	PIMs	n	(%)		PIMs	n	(%)
1	Orphenadrine	255	(32.7)	1	Benzodiazepine	112	(22.2)
2	Dimenhydrinate	155	(19.8)	2	1st-generation antihistamine	108	(21.4)
3	Benzodiazepine	112	(14.3)	3	Opioid	96	(19.0)
4	1st-generation antihistamine [d]	108	(13.8)	4	NSAIDs [e]	79	(15.6)
5	Omeprazole	78	(10.0)	5	Omeprazole	78	(15.4)
6	Others	73	(9.3)	6	Others	32	(6.3)
	Total	781	(100.0)		Total	496	(100.0)

[a] nonsteroidal anti-inflammatory drugs
[b] angiotensin-converting enzyme inhibitors
[c] examples of benzodiazepine: lorazepam and alprazolam
[d] examples of 1st-generation antihistamine: brompheniramine, chlorpheniramine and hydroxyzine
[e] Numbers of NSAIDS differed depending on criteria

With adjusted analyses, ORs were 3.93 (95%CI 2.17-7.12), 2.78 (1.39-5.56), and 0.97 (0.50-1.87) for polypharmacy, four or more diagnoses, and four or more prescriptions in the past year, respectively. In a multivariate analysis, polypharmacy and ≥ 4 diagnoses were associated with PIM prescriptions in any criteria (Table 3). The findings were similar for PIMs that were identified by each category. Female gender was associated with PIM prescriptions when PIMs were identified by the 2015 Beers [adjusted OR = 1.72 (1.10-2.70)] and Winit-Watjana [adjusted OR = 1.78 (1.12-2.84)] criteria.

DISCUSSION

This study examined the prevalence of PIMs in a PCU in Thailand using three criteria: the 2015 Beers, the STOPP v2, and Winit-Watjana. In general, three out of four patients

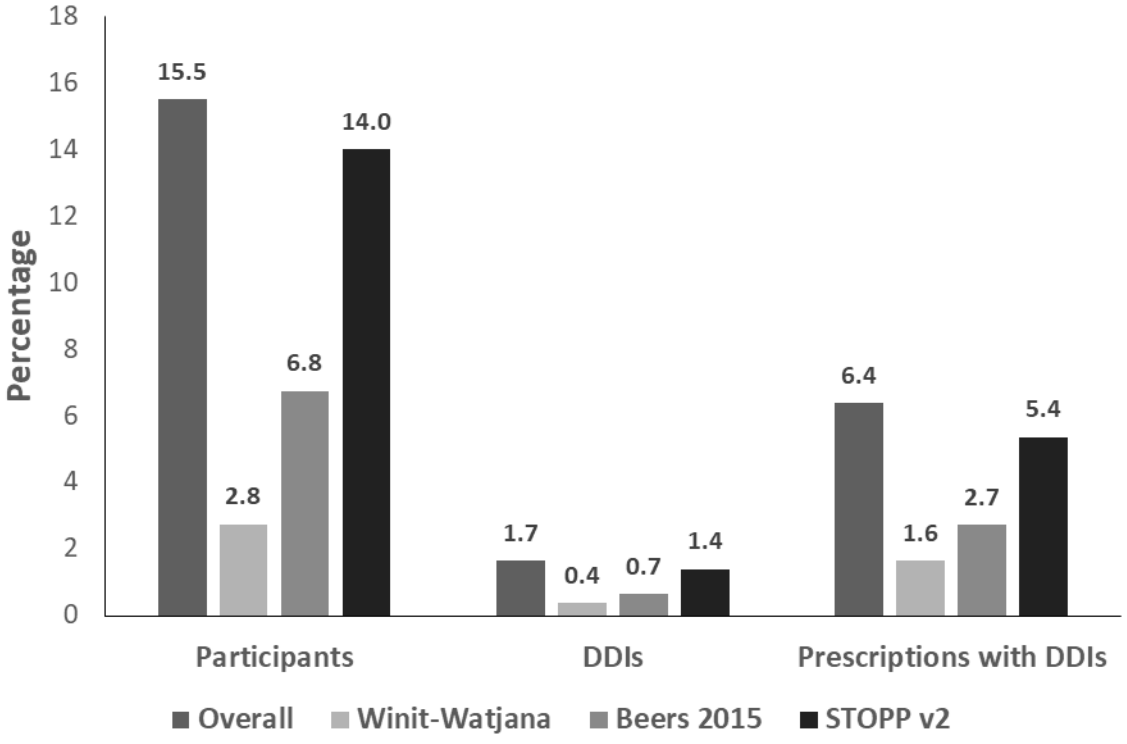

Figure 2. Proportions of the use of ≥2 medications that were identified as PIMs according to these three criteria were subsequently analyzed by criteria.
Chi-square tests shows statistically significant differences in the proportions from each criterion with p<0.001.

Table 3. Multiple regression analysis by criteria (2016-2017)

Variables	Adjusted OR	95%CI	p-values
Age			
Overall	1.01	0.96 - 1.05	0.708
Winit-Watjana	1.01	0.97 - 1.05	0.622
2015 Beers	1.00	0.96 - 1.04	0.957
STOPP version 2	1.03	0.99 - 1.06	0.165
Female			
Overall	1.40	0.84 - 2.32	0.197
Winit-Watjana	1.01	0.97 - 1.05	0.622
2015 Beers	1.00	0.96 - 1.04	0.957
STOPP version 2	1.03	0.99 - 1.06	0.165
Polypharmacy			
Overall	3.93	2.17 - 7.12	**<0.001**
Winit-Watjana	2.78	1.66 - 4.65	**<0.001**
2015 Beers	2.19	1.34 - 3.58	**0.002**
STOPP version 2	1.87	1.14 - 3.05	**0.013**
≥4 diseases			
Overall	2.78	1.39 - 5.56	**0.004**
Winit-Watjana	2.43	1.35 - 4.37	**0.003**
2015 Beers	3.04	1.76 - 5.26	**<0.001**
STOPP version 2	1.01	0.58 - 1.75	0.980
≥4 prescriptions			
Overall	0.97	0.50 - 1.87	0.927
Winit-Watjana	1.10	0.61 - 1.98	0.743
2015 Beers	2.79	1.67 - 4.67	**<0.001**
STOPP version 2	1.20	0.70 - 2.04	0.507

aged >65 years were prescribed PIMs at least once, and more than half of all prescriptions included at least one PIM.

Using 2015 Beers, the prevalence of PIMs per person was high (59%) compared to other studies, such as 22.6% in Europe, 38.5% in Ireland and 51.8% in Brazil.[9,12,16] However, all of these studies used previous versions of Beers criteria that comprised less criteria for PIMs than the 2015 versions. The prevalence of PIMs in our study may have been similar to these studies if the same criterion was applied. The most common PIMs identified by the 2015 Beers criteria in our study included orphenadrine, dimenhydrinate, and benzodiazepine, which, in the majority of cases, were prescribed for acute symptoms.

Using the STOPP v2, the prevalence of PIMs per person was similar or lower (40.3%) when compared to other studies, such as 40.4% in Spain and 51.0% in Ireland.[17,18] The most common PIMs identified by STOPP v 2 in our study were similar to those by the study in Ireland including Benzodiazepine, PPIs and the first-generation antihistamine.[18] When compared to the 2015 Beers criteria, the STOPP v2 was better in identifying the use of strong opioids and NSAIDs but not in identifying the use of medications with anticholinergic effect.

To the best of our knowledge, no prior studies have used Winit-Watjana's criteria, so our findings cannot be compared. Similar to the 2015 Beers criteria, orphenadrine and benzodiazepines were common PIMs. Of the five most common PIMs, three were medications for acute conditions, such as muscle strain and vertigo.

In comparing the findings from the three criteria, Winit-Watjana identified the highest prevalence of PIMs, followed by the 2015 Beers and the STOPP v2. Flunarizine and ACEIs, which were not PIMs according to the 2015 Beers and the STOPP v2 criteria, accounted for 27.5% of PIMs according to the Winit-Watjana criteria. The three criteria used in our study identified the following different PIMs: NSAIDs were best detected by the Winit-Watjana criteria; orphenadrine by the Winit-Watjana and the 2015 Beers criteria; and 1st generation antihistamine and PPIs by the 2015 Beers and the STOPP v2 criteria. All three sets of criteria identified benzodiazepines as PIMs, while only the STOPP v2 detected opioid use as PIMs. A difference in the PIMs prevalence among these three criteria does not reflect which criteria are better than the others. Instead, the findings show differences in the usefulness and limitations of these criteria. For example, the Beers and STOPP v2 criteria include medications that are unavailable in our country, while the Winit-Watjana criteria are out-of-date and need a revision.

For all the criteria, the most common PIMs were for acute conditions, such as muscle strain and dizziness, and for chronic conditions that required an intermittent use of medications such as insomnia and low back pain. In contrast, PIMs for chronic diseases that required continuous use of medications, such as cardiovascular disease and diabetes, were less common than PIMs for acute conditions. Thus, compared to medications for chronic conditions, elderly patients with acute conditions have a greater risk of receiving PIMs.

There are two possible reasons for the high prevalence of PIMs in our study. First, the PCU did not have alternative medications, such as diazepam, so doctors had no choice but to prescribe PIMs. Limited knowledge about PIMs among physicians, especially residents in family medicine and internists, might be another reason contributing to the prescription of PIMs. A previous study documented a higher prescribing error rate in younger than in older physicians.[19] Young physicians in the PCU in our study, specifically internists, rotated monthly with other specialties, such as surgery and pediatrics. Therefore, the limited time spent in the PCU may compromise their learning.

For some common PIMs in our study, such as PPI, ACEIs, and orphenadrine, there is evidence supporting the use of these PIMs with indications. Avoidance of these medications, therefore, may be inevitable. For example, the long-term use of PPIs (≥8 weeks) is indicated in patients with chronic relapsing GERD and NERD and those that require PPIs for gastroprotection.[20,21] Similarly, ACEIs are recommended medications listed in standard guidelines for hypertension.[22] Unlike PPI and ACEIs, skeletal muscle relaxants, such as orphenadrine, in combination with NSAIDs are indicated for the short-term use in acute musculoskeletal pain when pain relief is not achieved with NSAIDs alone and patients tolerate adverse drug reactions.[23] The intermittent use of orphenadrine in Thai primary care is also preferable for patients with chronic musculoskeletal pain despite a lack of evidence.[23] The use and avoidance of PIMs, therefore, do not depend only on these criteria but also other evidence and physicians' clinical knowledge and experiences. For those, who prefer a patient-centered approach, may continue prescribing PIMs until a patient feels confidence to stop taking the PIMs.[24]

The prevalence of the use of 2 or more medications that were identified as PIMs was low compared to that of other studies.[25] All three criteria include a list of concurrent use of 2 or more medications, but the criteria are not comprehensive.[4,5,13] Doctors should be aware of this limitation. However, the use of 2 or more medications included in these criteria are common in the elderly, potentially resulting in negative health outcomes, and increased awareness among doctors is necessary for them to avoid the use of 2 or more medications that were identified as PIMs.

The most common use of 2 or more medications in our study were duplicate drug classes and two medications with anticholinergic effects, which may lead to unpleasant symptoms, such as dry mouth and acute urinary retention. Both were identified by the STOPP v2, while the 2015 Beers criteria included only the latter. The STOPP v2, therefore, is better than the 2015 Beers and Winit-Watjana criteria for detecting drug class duplications. Our study also identified the use of NSAIDs with other medications, including aspirin and warfarin, which leads to a higher bleeding risk if combined.

Our findings support those of other studies showing that polypharmacy is associated with PIMs.[3.26] In comparing the three criteria, the association between polypharmacy and PIMs was highest according to Winit-Watjana, followed by the 2015 Beers and the STOPP v2, which can be explained by a difference in PIM proportions in each criterion. Thus, reducing unnecessary medications may prevent doctors from prescribing PIMs. Nevertheless, findings from a recent review of the effectiveness of interventions to reduce PIMs are inconclusive.[27] In addition, the lack of alternative medications to PIMs may leave doctors no choice but to prescribe PIMs. Hence, offering alternative medications in PCUs will provide an opportunity for doctors to prescribe safer medications for the elderly.[28]

While an increased number of comorbidities is associated with polypharmacy, its association with PIMs is unclear.[11,29] Our study found a positive association, consistent with the findings of Prasert *et al*.[15] The small difference between our study and that of Prasert *et al*. was the number of diagnoses: ≥4 vs. ≥5, respectively.[15] Hence, doctors need to be aware of and assess PIMs in patients with multiple comorbidities. This notion is especially relevant in Thailand, where patients have the freedom to visit multiple doctors for each health condition. The number of prescriptions as a risk factor for PIMs has not been well examined in other studies.[3,11,15] Our study found that the number of prescriptions was not associated with PIMs.

In our study, age and gender were not associated with PIMs across all criteria. Previous studies have reported mixed results.[3,11,15] However, the findings in our study indicate that gender is associated with the PIMs identified by the Winit-Watjana and 2015 Beers criteria, in which female patients had a slightly higher likelihood of using PIMs than did male patients.

The strengths of our study include that prescriptions from the past 12 months were collected to decrease the effects of seasonal influence and that clinical reviews were conducted with two doctors and one pharmacist to ensure the accuracy of PIM identification. Our data were collected from a PCU where doctors work full-time. This situation is different from that of some PCUs in Thailand, where doctors generally visit at least twice a month. In addition, available medications in the Kukot PCU may differ from those in other PCUs without full-time doctors. Hence, the findings from our study may not be generalized to other PCUs with different contexts. However, the findings indicate a need to explore PIMs in general PCUs and implement evidence-based interventions to reduce PIMs in the elderly.

CONCLUSIONS

The prevalence of PIMs in PCUs in Thailand was high. PIMs were associated with polypharmacy and increased comorbidity. Most PIMs were prescribed for acute conditions, such as muscle strain and dizziness.

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CONFLICT OF INTEREST

None.

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Original Research

Evaluation of vitamin B12 monitoring in patients on metformin in urban ambulatory care settings

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Abstract

Background: Previous studies linked metformin use to vitamin B12 deficiency and demonstrated that the prevalence of vitamin B12 monitoring remains low.

Objective: This study aimed to assess the occurrence of monitoring vitamin B12 levels in a diverse population.

Methods: This was a retrospective chart review of adult patients with type 2 diabetes on metformin doses ≥ 1000 mg for ≥ 6 months at five Federally Qualified Health Centers (FQHC) and one Program of All-Inclusive Care for the Elderly (PACE). Charts were reviewed for occurrence of monitoring vitamin B12 levels in the past 5 years. Data collected included patient demographics, laboratory data, other potential vitamin B12 level lowering agents, active prescription for vitamin B12 supplementation, concomitant diabetes medications and metformin total daily dose.

Results: Of the 322 patients included, 25% had a vitamin B12 level measured in the previous five years. Among the patients with a vitamin B12 level, 87.7% were within the normal range (>350 pg/mL), 11.1% were low (200-300 pg/mL), and only one patient (1.2%) was deficient (<200 pg/mL). These patients were older (69.2 vs. 56.4, p<0.001); more likely to be white (56.8% vs. 37.8%, p=0.04); and more likely to use proton pump inhibitors (34.6% vs. 20.7%, p=0.02) and vitamin B12 supplementation (27.2% vs. 4.6%, p<0.001). Vitamin B12 monitoring differed between the FQHC (15.2%) and PACE (97.4%) sites (p<0.001). Each greater year of age was associated with a 5% increased odds of vitamin B12 monitoring (aOR: 1.05; 95%CI: 1.02-1.08).

Conclusions: The majority of patients seen at the FQHC sites did not have vitamin B12 levels monitored, however, most of the patients who were monitored had normal vitamin B12 levels, which may warrant extending the monitoring time. This finding may also support monitoring patients who have additional risk factors for vitamin B12 deficiency such as concurrent medication use with other vitamin B12 lowering agents or clinical symptoms of deficiency such as peripheral neuropathy. Future studies are needed to determine appropriate frequency of monitoring.

Keywords

Vitamin B 12; Vitamin B 12 Deficiency; Metformin; Diabetes Mellitus, Type 2; Quality of Health Care; Health Knowledge, Attitudes, Practice; Prevalence; Retrospective Studies; United States

INTRODUCTION

Metformin is the first-line agent for the treatment of type 2 diabetes if no contraindications exist.[1] In response to the 2016 Diabetes Prevention Program Outcomes Study (DPPOS), the 2017 American Diabetes Association (ADA) Standards of Medical Care in Diabetes introduced a new recommendation for periodic monitoring of vitamin B12 levels in patients with type 2 diabetes on metformin, particularly in those with an additional diagnosis of peripheral neuropathy and/or anemia.[2] The most recent version of the ADA guideline continues to include this recommendation and sites evidence from the DPPOS study and a post-hoc analysis of a recent randomized control trial.[1-3] The American Association of Clinical Endocrinology (AACE) and American College of Endocrinology (ACE) consensus statement for the management of type 2 diabetes recommends monitoring vitamin B12 levels in patients taking metformin who develop neuropathy and supplementing with B12 as needed, citing a single study by Sing *et al*. which showed a causal relationship between metformin use and peripheral neuropathy.[4,5] Prescribing information for metformin in the United States includes annual monitoring of hematologic parameters for anemia secondary to a potential for decreased vitamin B12 absorption. In addition, monitoring of vitamin B12 every two to three years in patients with inadequate vitamin B12 and calcium intake or absorption is recommended.[6]

Previous studies examined vitamin B12 deficiency in patients with type 2 diabetes on metformin doses of 500 mg to 2700 mg daily for durations ranging from 6 months to greater than 10 years.[7-11] A 2006 investigational study on risk factors for vitamin B12 deficiency in patients on metformin therapy found that each one gram-per-day dose increase resulted in a greater than two-fold increased risk of vitamin B12 deficiency.[9] Despite evidence confirming metformin-induced vitamin B12 deficiency and its

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associated complications, the frequency of monitoring vitamin B12 levels remains low in clinical practice.[1,2,8,11] There is limited research outside of the Veterans Health Administration on the practice of vitamin B12 monitoring in the ambulatory care setting for patients on metformin.

The aim of this study was to examine the frequency of vitamin B12 monitoring in a diverse patient population within ambulatory care settings, including Federally Qualified Health Centers (FQHC) and a Program of All-Inclusive Care for the Elderly (PACE). The primary objective was to assess the occurrence of vitamin B12 level monitoring within the past 5 years in patients with type 2 diabetes treated with metformin, and to determine if these levels were normal, low, or deficient.

METHODS

A retrospective chart review was performed at six ambulatory care sites (five FQHCs and one PACE) for patients seen by a provider between January 1, 2017 and December 31, 2017. The FQHC sites are community health centers that provide affordable primary and preventative care services to patient populations in medically underserved areas. Patients served represent a wide range of ethnic and socioeconomic backgrounds. Four of the FQHCs are affiliated with one organization and provide services for >30,000 patients located in Boston, MA and the southeastern part of the state, of which 40% report an income 100% below the poverty guideline. The fifth FQHC, also located in Boston, MA, serves a predominantly low-income population of over 14,000 patients that is 42% Hispanic/Latino and 32% black/African American. The PACE program serves high-risk, frail patients 55 years and older who are nursing home eligible in an attempt to keep them community dwelling. Patient care in the PACE program utilizes interdisciplinary care teams trained in geriatrics and mandatory medical assessments at least every 6 months. Institutional review board (IRB) approval was granted by Northeastern University and supported by individual IRB committees at each clinic site.

Patients aged 18 years and older with a diagnosis of type 2 diabetes and an active prescription for metformin were identified through search queries of each site's electronic medical records (EMR) system. Inclusion criteria included a total daily metformin dose of ≥ 1000 mg for ≥ 6 months and a documented primary care provider visit during the year-long study period. Duration of metformin use was selected based on previous studies that have reported vitamin B12 serum concentrations may decrease after 6 months of metformin therapy. These studies also noted that patients may not present with clinical symptoms of vitamin B12 deficiency for an additional two to five years which provided rationale for looking back five years.[7,12] Patients were excluded if they had a diagnosis of type 1 diabetes, drug-induced diabetes, abnormal glucose elevations, prediabetes, polycystic ovarian syndrome, celiac disease, Crohn's disease, Graves' disease, chronic pancreatitis, alcoholism, human immunodeficiency virus (HIV), H.pylori infection, or pernicious anemia. The tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes were used for identifying diagnoses.

Data collected included patient demographic information (age, race, and gender), laboratory data (glycosylated hemoglobin A1C, estimated glomerular filtration rate, and the most recent vitamin B12 level obtained within the previous five years), current vitamin B12 supplementation, concomitant diabetes medications and metformin total daily dose. Researchers ensured that patients had an active prescription for metformin at the time a vitamin B12 level was drawn. Use of the following medications was also collected to account for other possible sources of vitamin B12 deficiency: proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), colchicine, and oral contraceptives.

The primary outcome was occurrence of vitamin B12 monitoring within the past five years, and the prevalence of normal (>350 pg/mL), low (200-350 pg/mL), and deficient (<200 pg/mL) vitamin B12 levels. Due to small proportions of our sample with low and deficient vitamin B12 levels, these two categories were combined for analysis. Demographic and clinical data were compared by vitamin B12 monitoring (yes vs. no) using chi-squared tests for categorical variables (with Fisher's exact test used when cell sizes were <5) and Student's t-test for continuous variables.

Logistic regression models were used to compare variables significant at a $p<0.05$ level in the bivariate comparison of vitamin B12 monitoring (yes vs. no). The initial model included site, age, race, eGFR, proton pump inhibitor use, vitamin B12 supplementation, sulfonylurea use, and DPP-4 inhibitor use as predictors of vitamin B12 monitoring. A backward stepwise selection method was used to retain variables significant at the $p<0.05$ level. To check for collinearity between age and site, two additional multivariable models were run, including all significant bivariate factors with the exception of site in the first model and age in the second model. Final results were similar when including site and age in the model, therefore both were included in the final model. Adjusted odds ratios (aOR) and 95% confidence intervals (CIs) were calculated for the final model.

A sensitivity analysis was conducted to compare low/deficient versus normal categories of B12 levels in the subgroup of patients for whom data was available (n=81, 25%). Using chi-squared and Fisher's exact tests and Student's t-test, demographic and clinical characteristics were examined between these two groups. Analyses were conducted using SPSS statistics software (version 24) and R (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

RESULTS

Three hundred twenty-two patients met inclusion criteria and were included in the study: 283 from the five FQHC sites and 39 from the PACE program. Table 1 shows patient demographic and clinical information by vitamin B12 monitoring in the last five years (yes vs. no) (Figure 1). Among the patients with a vitamin B12 level (n=81, 25%), 87.7% were within the normal range (>350 pg/mL), 11.1% were low (200-300 pg/mL), and only one patient (1.2%) was

Table 1. Baseline characteristics by vitamin B12 monitoring

Patient Characteristic	Vitamin B12 Monitoring		p-value
	Yes (n=81)	No (n=241)	
Site, n (%)			<0.001
FQHC	43 (53.1)	240 (99.6)	
PACE	38 (46.9)	1 (0.4)	
Age (years), mean (SD)	69.23 (12.89)	56.42 (12.15)	<0.001
Gender, n (%)			0.34
Female	50 (61.7)	132 (54.8)	
Male	31 (38.3)	109 (45.2)	
Race, n (%)			0.04
White	46 (56.8)	91 (37.8)	
African American	21 (25.9)	66 (27.4)	
Hispanic	8 (9.9)	47 (19.5)	
Asian/Pacific Islander	2 (2.5)	18 (7.5)	
Other	1 (1.2)	7 (2.9)	
Declined	3 (3.7)	12 (5.0)	
eGFR, n (%)			<0.001
< 30 ml/min/1.73m2	1 (1.2)	0 (0.0)	
30-44 ml/min/1.73m2	4 (4.9)	1 (0.4)	
45-60 ml/min/1.73m2	19 (23.5)	12 (5.0)	
> 60 ml/min/1.73m2	42 (51.9)	117 (48.5)	
NA	15 (18.5)	111 (46.1)	
Metformin daily dose, n (%)			0.89
1000 mg to < 2000 mg	36 (44.4)	103 (42.7)	
≥ 2000 mg	45 (55.6)	138 (57.3)	
Other antidiabetic agents, n (%)			
Insulin	21 (25.9)	55 (22.8)	0.68
Sulfonylurea	35 (43.2)	73 (30.3)	0.05
Thiazolidinedione	2 (2.5)	10 (4.1)	0.73
DPP-4 inhibitor	20 (24.7)	20 (8.3)	<0.001
GLP-1 receptor agonist	15 (18.5)	34 (14.1)	0.44
SGLT-2 inhibitor	0 (0.0)	7 (2.9)	0.27
Other B12 lowering agent(s) use, n (%)			
Proton pump inhibitor	28 (34.6)	50 (20.7)	0.02
Histamine-2 receptor antagonist	5 (6.2)	14 (5.8)	0.99
Colchicine	1 (1.2)	4 (1.7)	0.99
Oral contraceptive	0 (0.0)	5 (2.1)	0.43
B12 supplementation, n (%)	22 (27.2)	11 (4.6)	<0.001
Peripheral neuropathy diagnosis, n (%)	4 (4.9)	3 (1.2)	0.13

eGFR: estimated glomerular filtration rate; FQHC: Federally Qualified Health Center; PACE: Program of All Inclusive Care for the Elderly

deficient (<200 pg/mL) (Figure 2). Those with vitamin B12 monitoring were older (69.2 vs. 56.4, p<0.001); more likely to be white (56.8% vs. 37.8%, p=0.04); and more likely to use proton pump inhibitors (34.6% vs. 20.7%, p=0.02), vitamin B12 supplementation (27.2% vs. 4.6%, p<0.001), sulfonylurea (43.2% vs. 30.3%, p=0.05), and DPP-4 inhibitors (24.7% vs. 8.3%, p<0.001). Additionally, eGFR differed between groups, with more patients with a record of vitamin B12 monitoring having an eGFR of 45-60 ml/min compared to those without monitoring (p<0.001) (Table 1). Vitamin B12 monitoring differed between the FQHC (15.2%) and PACE (97.4%) sites (p<0.001; Figure 1).

The final multivariable model included site, age, sulfonylurea use, and DPP-4 inhibitor use. Each greater year of age was associated with a 5% increased odds of B12 monitoring (aOR: 1.05; 95%CI: 1.02-1.08). Both sulfonylurea (aOR: 2.30; 95%CI: 1.16-4.55) and DPP-4 inhibitor use (aOR: 2.50; 95%CI 0.99-5.98) were associated with just over twice the odds of vitamin B12 monitoring. PACE patients were over 100 times more likely to receive vitamin B12 monitoring; however, these results are likely inflated due to the small sample size of PACE patients (n=39) compared to FQHC patients (n=283). The results from the final multivariable model with backward selection were comparable to the initial model including all significant factors from bivariate comparisons (data not shown).

Sensitivity analyses examining differences in patients with a record of vitamin B12 monitoring (n=81, 25%) with low/deficient vs. normal B12 levels, revealed no significant differences between groups with the exception of site, where a greater proportion of the deficient/low group were from a FQHC site. However, these results should be interpreted with caution given the small sample size included in this analysis (data not shown).

DISCUSSION

The results of this study expand our understanding of current vitamin B12 monitoring practices in a diverse, urban setting and identify potential interventions to increase adherence to recommended monitoring guidelines. We found that the majority of patients in ambulatory care settings are not being monitored for vitamin B12 deficiency as recommended by national diabetes guidelines and the metformin prescribing information for patients with type 2 diabetes on metformin therapy. Overall, only 25% of patients prescribed metformin for a diagnosis of type 2 diabetes were

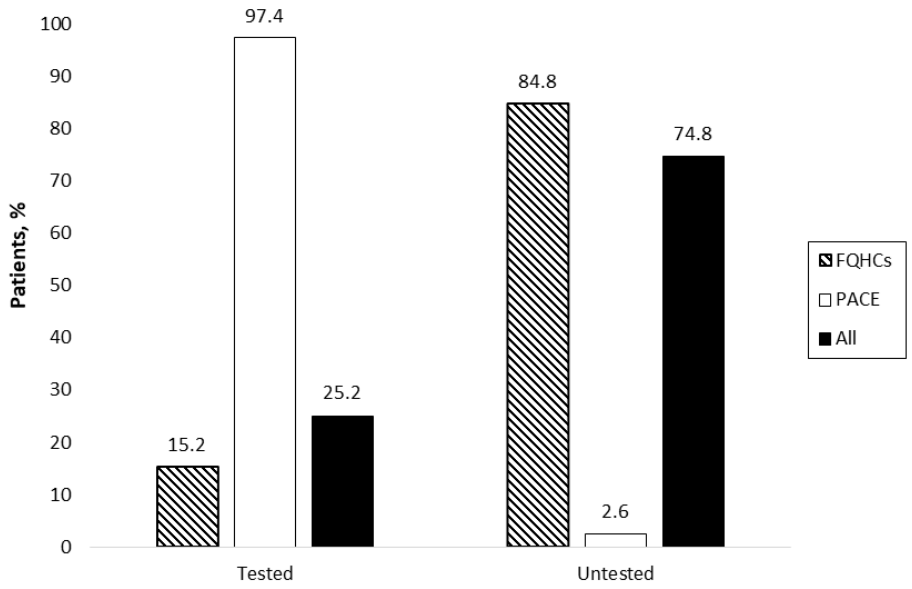

Figure 1. Occurrence of B12 Monitoring

monitored for vitamin B12 within a 5-year look back period. Although guidelines differ on the timeframe for monitoring, the ADA recommends periodic monitoring and the package insert for metformin states hematologic parameters should be obtained annually and vitamin B12 monitoring every 2-3 years.[1,6] Two previous studies were conducted in the United States veteran population of predominantly Caucasian males. Kancherla *et al*. found that a high percentage of patients (63%) with type 2 diabetes on metformin were not being periodically monitored for vitamin B12 levels.[9] Pierce et al. excluded patients on <2000mg of metformin daily and also found that 47% of patients were not monitored for vitamin B12 levels.[10] We found higher rates of discordance with monitoring recommendations (74.8%) in a more diverse population, both in race and gender, compared to the veteran population.

We found difference in monitoring between FQHCs and the PACE program, where the predominant medical specialties are internal and family medicine versus geriatrics, respectively. Older patients often have multiple risk factors for vitamin B12 deficiency such as decreased absorption due to vitamin B12/intrinsic factor complex and the additive effects of drug-induced vitamin B12 deficiency due to polypharmacy. Vitamin B12 levels are obtained in this particular PACE program upon enrollment for all patients and then annually based on risk factors. Compared to the FQHCs, patients at the PACE program were more likely to be on vitamin B12 supplementation (41%), have a diagnosis of peripheral neuropathy (28%), and prescriptions for proton pump inhibitors (41%). Although 97% of PACE patients in this study received vitamin B12 monitoring, we are unable to determine if this was due to metformin use or other indications for monitoring.

The prevalence of normal (87.7%), low (11.1%) and deficient (1.2%) vitamin B12 levels was examined to gain an

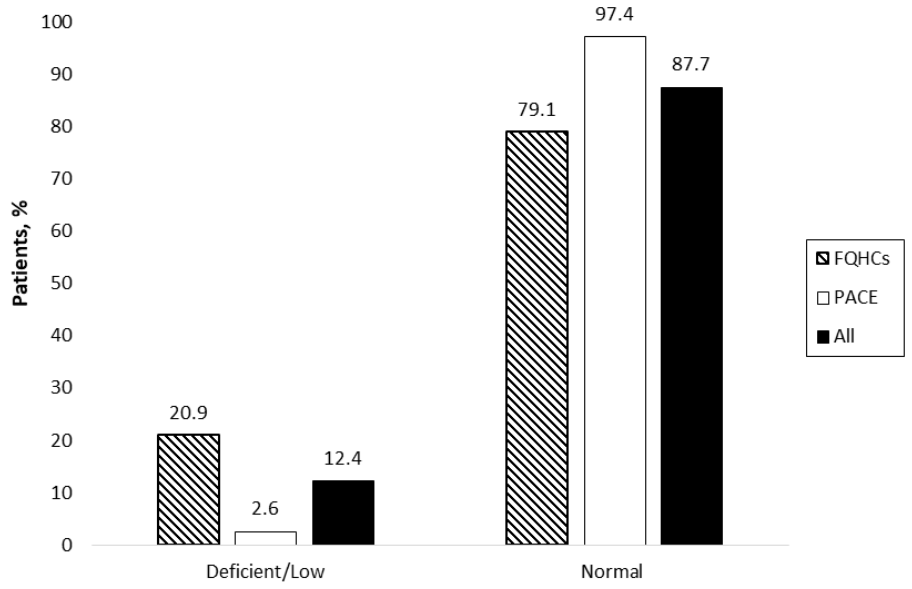

Figure 2. Distribution of Vitamin B12 Levels

understanding of the potential impact and utility of vitamin B12 monitoring. Premarketing trials of metformin found decreased vitamin B12 levels in up to 7% of patients over a 29-week study.[6] This can be compared to our study where 88% of vitamin B12 levels were within the normal range for patients on metformin for more than one year. In our sample, we found that one third of the patients in the normal range of B12 (28%) were currently prescribed vitamin B12 supplements. Of the ten patients with low or deficient vitamin B12 levels, 80% did not have an active prescription for vitamin B12 supplementation and 20% were on an additional agent that may potentially lower the vitamin B12 level. Nearly 10% of our sample without a vitamin B12 level had a diagnosis of peripheral neuropathy, and 5% had an active prescription for vitamin B12 supplementation but no vitamin B12 level checked. This highlights the need for provider education and improvements in current patient care processes to ensure that vitamin B12 levels are being monitored periodically in patients on metformin or receiving supplementation. Optimal monitoring of vitamin B12 would allow for early intervention in patients with low or deficient levels in order to provide appropriate vitamin B12 supplementation and prevent complications or further comorbidity.

The available data regarding peripheral neuropathy linked to metformin-induced vitamin B12 deficiency is conflicting and limited. Ahmed *et al*. did not find a correlation between metformin-induced vitamin B12 deficiency and peripheral neuropathy.[8] Aroda *et al*. found that patients on metformin with low vitamin B12 levels had higher prevalence of peripheral neuropathy.[2] In our study, 7.1% of patients diagnosed with peripheral neuropathy did not have a vitamin B12 level measured in the last five years. However, all 15 patients with a vitamin B12 level and peripheral neuropathy had a level within the normal range and 53.3% had an active prescription for vitamin B12 supplementation. Although all patients with a vitamin B12 level and peripheral neuropathy diagnosis had normal levels, it is still important to rule out vitamin B12 deficiency as a potential cause or contributing factor of peripheral neuropathy. Additionally, for patients who have a low or deficient level and a diagnosis of peripheral neuropathy, vitamin B12 supplementation could reduce the need for prescription medications for treatment of peripheral neuropathy.

Results of this study can be used to support quality improvement initiatives to increase the frequency of vitamin B12 monitoring in ambulatory care settings. Although our study was not designed to explore causes of lack of monitoring, we hypothesized several reasons for the low percentage of patients with vitamin B12 levels including lack of knowledge regarding monitoring recommendations; low prioritization of vitamin B12 monitoring compared to other diabetes recommendations; and the likelihood that vitamin B12 levels would be within the normal range. Interventions to increase vitamin B12 monitoring may include: EMR optimization by adding vitamin B12 levels to a standardized lab order set for patients with type 2 diabetes, automatic data reporting of patients that may need a vitamin B12 level, or a lab monitoring policy for patients on metformin. Clinical pharmacists, as part of the interprofessional patient care team, could be utilized to help educate providers on the value of vitamin B12 monitoring, current recommendations for patients on metformin and to identify patients at high-risk of vitamin B12 deficiency. In addition, it is important to continue monitoring patients with vitamin B12 deficiency and those receiving vitamin B12 to prevent unnecessary supplementation. Although unnecessary vitamin B12 supplementation may not be harmful, it increases pill burden or intramuscular injections and adds unnecessary healthcare costs.

Based on our study design and data extraction methods, a few limitations were present. We were unable to determine the total duration of metformin treatment for multiple reasons. Information prior to the conversion from paper to electronic medical records was not available. Additionally, metformin prescription initiation dates prior to care at the study sites were unknown. Since duration of use was not collected, a correlation could not be made between duration of metformin therapy and vitamin B12 levels. Additionally, the metformin dose was determined based on the active prescription included in the EMR, which does not account for patient adherence. Although vitamin B12 supplementation was prescribed for some patients, the indication for its use was often undocumented and over-the-counter supplementation was not accounted for in this study. Lastly, it is unknown if patients receiving vitamin B12 supplementation had previously low or deficient levels due to metformin use.

CONCLUSIONS

In conclusion, the majority of patients at the FQHCs were not being monitored in accordance with the ADA guidelines. This revealed the need to educate providers and implement quality improvement projects to improve vitamin B12 monitoring in patients on chronic metformin therapy in ambulatory care settings. Providers should also consider obtaining vitamin B12 levels in patients with a current diagnosis and/or treatment for peripheral neuropathy and prior to initiating treatment in patients with a new diagnosis of peripheral neuropathy to rule out deficiency. However, most of the patients in our study who were monitored had normal vitamin B12 levels, which may warrant extending the monitoring time. It would be beneficial for future studies to assess longitudinal vitamin B12 monitoring in order to better define the ideal frequency of vitamin B12 monitoring in patients with type 2 diabetes treated with metformin.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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Original Research

Evaluation of vitamin B12 monitoring in patients on metformin in urban ambulatory care settings

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Abstract

Background: Previous studies linked metformin use to vitamin B12 deficiency and demonstrated that the prevalence of vitamin B12 monitoring remains low.

Objective: This study aimed to assess the occurrence of monitoring vitamin B12 levels in a diverse population.

Methods: This was a retrospective chart review of adult patients with type 2 diabetes on metformin doses ≥ 1000 mg for ≥ 6 months at five Federally Qualified Health Centers (FQHC) and one Program of All-Inclusive Care for the Elderly (PACE). Charts were reviewed for occurrence of monitoring vitamin B12 levels in the past 5 years. Data collected included patient demographics, laboratory data, other potential vitamin B12 level lowering agents, active prescription for vitamin B12 supplementation, concomitant diabetes medications and metformin total daily dose.

Results: Of the 322 patients included, 25% had a vitamin B12 level measured in the previous five years. Among the patients with a vitamin B12 level, 87.7% were within the normal range (>350 pg/mL), 11.1% were low (200-300 pg/mL), and only one patient (1.2%) was deficient (<200 pg/mL). These patients were older (69.2 vs. 56.4, p<0.001); more likely to be white (56.8% vs. 37.8%, p=0.04); and more likely to use proton pump inhibitors (34.6% vs. 20.7%, p=0.02) and vitamin B12 supplementation (27.2% vs. 4.6%, p<0.001). Vitamin B12 monitoring differed between the FQHC (15.2%) and PACE (97.4%) sites (p<0.001). Each greater year of age was associated with a 5% increased odds of vitamin B12 monitoring (aOR: 1.05; 95%CI: 1.02-1.08).

Conclusions: The majority of patients seen at the FQHC sites did not have vitamin B12 levels monitored, however, most of the patients who were monitored had normal vitamin B12 levels, which may warrant extending the monitoring time. This finding may also support monitoring patients who have additional risk factors for vitamin B12 deficiency such as concurrent medication use with other vitamin B12 lowering agents or clinical symptoms of deficiency such as peripheral neuropathy. Future studies are needed to determine appropriate frequency of monitoring.

Keywords

Vitamin B 12; Vitamin B 12 Deficiency; Metformin; Diabetes Mellitus, Type 2; Quality of Health Care; Health Knowledge, Attitudes, Practice; Prevalence; Retrospective Studies; United States

INTRODUCTION

Metformin is the first-line agent for the treatment of type 2 diabetes if no contraindications exist.[1] In response to the 2016 Diabetes Prevention Program Outcomes Study (DPPOS), the 2017 American Diabetes Association (ADA) Standards of Medical Care in Diabetes introduced a new recommendation for periodic monitoring of vitamin B12 levels in patients with type 2 diabetes on metformin, particularly in those with an additional diagnosis of peripheral neuropathy and/or anemia.[2] The most recent version of the ADA guideline continues to include this recommendation and sites evidence from the DPPOS study and a post-hoc analysis of a recent randomized control trial.[1-3] The American Association of Clinical Endocrinology (AACE) and American College of Endocrinology (ACE) consensus statement for the management of type 2 diabetes recommends monitoring vitamin B12 levels in patients taking metformin who develop neuropathy and supplementing with B12 as needed, citing a single study by Sing *et al*. which showed a causal relationship between metformin use and peripheral neuropathy.[4,5] Prescribing information for metformin in the United States includes annual monitoring of hematologic parameters for anemia secondary to a potential for decreased vitamin B12 absorption. In addition, monitoring of vitamin B12 every two to three years in patients with inadequate vitamin B12 and calcium intake or absorption is recommended.[6]

Previous studies examined vitamin B12 deficiency in patients with type 2 diabetes on metformin doses of 500 mg to 2700 mg daily for durations ranging from 6 months to greater than 10 years.[7-11] A 2006 investigational study on risk factors for vitamin B12 deficiency in patients on metformin therapy found that each one gram-per-day dose increase resulted in a greater than two-fold increased risk of vitamin B12 deficiency.[9] Despite evidence confirming metformin-induced vitamin B12 deficiency and its

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associated complications, the frequency of monitoring vitamin B12 levels remains low in clinical practice.[1,2,8,11] There is limited research outside of the Veterans Health Administration on the practice of vitamin B12 monitoring in the ambulatory care setting for patients on metformin.

The aim of this study was to examine the frequency of vitamin B12 monitoring in a diverse patient population within ambulatory care settings, including Federally Qualified Health Centers (FQHC) and a Program of All-Inclusive Care for the Elderly (PACE). The primary objective was to assess the occurrence of vitamin B12 level monitoring within the past 5 years in patients with type 2 diabetes treated with metformin, and to determine if these levels were normal, low, or deficient.

METHODS

A retrospective chart review was performed at six ambulatory care sites (five FQHCs and one PACE) for patients seen by a provider between January 1, 2017 and December 31, 2017. The FQHC sites are community health centers that provide affordable primary and preventative care services to patient populations in medically underserved areas. Patients served represent a wide range of ethnic and socioeconomic backgrounds. Four of the FQHCs are affiliated with one organization and provide services for >30,000 patients located in Boston, MA and the southeastern part of the state, of which 40% report an income 100% below the poverty guideline. The fifth FQHC, also located in Boston, MA, serves a predominantly low-income population of over 14,000 patients that is 42% Hispanic/Latino and 32% black/African American. The PACE program serves high-risk, frail patients 55 years and older who are nursing home eligible in an attempt to keep them community dwelling. Patient care in the PACE program utilizes interdisciplinary care teams trained in geriatrics and mandatory medical assessments at least every 6 months. Institutional review board (IRB) approval was granted by Northeastern University and supported by individual IRB committees at each clinic site.

Patients aged 18 years and older with a diagnosis of type 2 diabetes and an active prescription for metformin were identified through search queries of each site's electronic medical records (EMR) system. Inclusion criteria included a total daily metformin dose of ≥ 1000 mg for ≥ 6 months and a documented primary care provider visit during the year-long study period. Duration of metformin use was selected based on previous studies that have reported vitamin B12 serum concentrations may decrease after 6 months of metformin therapy. These studies also noted that patients may not present with clinical symptoms of vitamin B12 deficiency for an additional two to five years which provided rationale for looking back five years.[7,12] Patients were excluded if they had a diagnosis of type 1 diabetes, drug-induced diabetes, abnormal glucose elevations, prediabetes, polycystic ovarian syndrome, celiac disease, Crohn's disease, Graves' disease, chronic pancreatitis, alcoholism, human immunodeficiency virus (HIV), H.pylori infection, or pernicious anemia. The tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes were used for identifying diagnoses.

Data collected included patient demographic information (age, race, and gender), laboratory data (glycosylated hemoglobin A1C, estimated glomerular filtration rate, and the most recent vitamin B12 level obtained within the previous five years), current vitamin B12 supplementation, concomitant diabetes medications and metformin total daily dose. Researchers ensured that patients had an active prescription for metformin at the time a vitamin B12 level was drawn. Use of the following medications was also collected to account for other possible sources of vitamin B12 deficiency: proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), colchicine, and oral contraceptives.

The primary outcome was occurrence of vitamin B12 monitoring within the past five years, and the prevalence of normal (>350 pg/mL), low (200-350 pg/mL), and deficient (<200 pg/mL) vitamin B12 levels. Due to small proportions of our sample with low and deficient vitamin B12 levels, these two categories were combined for analysis. Demographic and clinical data were compared by vitamin B12 monitoring (yes vs. no) using chi-squared tests for categorical variables (with Fisher's exact test used when cell sizes were <5) and Student's t-test for continuous variables.

Logistic regression models were used to compare variables significant at a $p<0.05$ level in the bivariate comparison of vitamin B12 monitoring (yes vs. no). The initial model included site, age, race, eGFR, proton pump inhibitor use, vitamin B12 supplementation, sulfonylurea use, and DPP-4 inhibitor use as predictors of vitamin B12 monitoring. A backward stepwise selection method was used to retain variables significant at the $p<0.05$ level. To check for collinearity between age and site, two additional multivariable models were run, including all significant bivariate factors with the exception of site in the first model and age in the second model. Final results were similar when including site and age in the model, therefore both were included in the final model. Adjusted odds ratios (aOR) and 95% confidence intervals (CIs) were calculated for the final model.

A sensitivity analysis was conducted to compare low/deficient versus normal categories of B12 levels in the subgroup of patients for whom data was available (n=81, 25%). Using chi-squared and Fisher's exact tests and Student's t-test, demographic and clinical characteristics were examined between these two groups. Analyses were conducted using SPSS statistics software (version 24) and R (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

RESULTS

Three hundred twenty-two patients met inclusion criteria and were included in the study: 283 from the five FQHC sites and 39 from the PACE program. Table 1 shows patient demographic and clinical information by vitamin B12 monitoring in the last five years (yes vs. no) (Figure 1). Among the patients with a vitamin B12 level (n=81, 25%), 87.7% were within the normal range (>350 pg/mL), 11.1% were low (200-300 pg/mL), and only one patient (1.2%) was

Table 1. Baseline characteristics by vitamin B12 monitoring

Patient Characteristic	Vitamin B12 Monitoring		p-value
	Yes (n=81)	No (n=241)	
Site, n (%)			<0.001
FQHC	43 (53.1)	240 (99.6)	
PACE	38 (46.9)	1 (0.4)	
Age (years), mean (SD)	69.23 (12.89)	56.42 (12.15)	<0.001
Gender, n (%)			0.34
Female	50 (61.7)	132 (54.8)	
Male	31 (38.3)	109 (45.2)	
Race, n (%)			0.04
White	46 (56.8)	91 (37.8)	
African American	21 (25.9)	66 (27.4)	
Hispanic	8 (9.9)	47 (19.5)	
Asian/Pacific Islander	2 (2.5)	18 (7.5)	
Other	1 (1.2)	7 (2.9)	
Declined	3 (3.7)	12 (5.0)	
eGFR, n (%)			<0.001
< 30 ml/min/1.73m2	1 (1.2)	0 (0.0)	
30-44 ml/min/1.73m2	4 (4.9)	1 (0.4)	
45-60 ml/min/1.73m2	19 (23.5)	12 (5.0)	
> 60 ml/min/1.73m2	42 (51.9)	117 (48.5)	
NA	15 (18.5)	111 (46.1)	
Metformin daily dose, n (%)			0.89
1000 mg to < 2000 mg	36 (44.4)	103 (42.7)	
≥ 2000 mg	45 (55.6)	138 (57.3)	
Other antidiabetic agents, n (%)			
Insulin	21 (25.9)	55 (22.8)	0.68
Sulfonylurea	35 (43.2)	73 (30.3)	0.05
Thiazolidinedione	2 (2.5)	10 (4.1)	0.73
DPP-4 inhibitor	20 (24.7)	20 (8.3)	<0.001
GLP-1 receptor agonist	15 (18.5)	34 (14.1)	0.44
SGLT-2 inhibitor	0 (0.0)	7 (2.9)	0.27
Other B12 lowering agent(s) use, n (%)			
Proton pump inhibitor	28 (34.6)	50 (20.7)	0.02
Histamine-2 receptor antagonist	5 (6.2)	14 (5.8)	0.99
Colchicine	1 (1.2)	4 (1.7)	0.99
Oral contraceptive	0 (0.0)	5 (2.1)	0.43
B12 supplementation, n (%)	22 (27.2)	11 (4.6)	<0.001
Peripheral neuropathy diagnosis, n (%)	4 (4.9)	3 (1.2)	0.13

eGFR: estimated glomerular filtration rate; FQHC: Federally Qualified Health Center; PACE: Program of All Inclusive Care for the Elderly

deficient (<200 pg/mL) (Figure 2). Those with vitamin B12 monitoring were older (69.2 vs. 56.4, p<0.001); more likely to be white (56.8% vs. 37.8%, p=0.04); and more likely to use proton pump inhibitors (34.6% vs. 20.7%, p=0.02), vitamin B12 supplementation (27.2% vs. 4.6%, p<0.001), sulfonylurea (43.2% vs. 30.3%, p=0.05), and DPP-4 inhibitors (24.7% vs. 8.3%, p<0.001). Additionally, eGFR differed between groups, with more patients with a record of vitamin B12 monitoring having an eGFR of 45-60 ml/min compared to those without monitoring (p<0.001) (Table 1). Vitamin B12 monitoring differed between the FQHC (15.2%) and PACE (97.4%) sites (p<0.001; Figure 1).

The final multivariable model included site, age, sulfonylurea use, and DPP-4 inhibitor use. Each greater year of age was associated with a 5% increased odds of B12 monitoring (aOR: 1.05; 95%CI: 1.02-1.08). Both sulfonylurea (aOR: 2.30; 95%CI: 1.16-4.55) and DPP-4 inhibitor use (aOR: 2.50; 95%CI 0.99-5.98) were associated with just over twice the odds of vitamin B12 monitoring. PACE patients were over 100 times more likely to receive vitamin B12 monitoring; however, these results are likely inflated due to the small sample size of PACE patients (n=39) compared to FQHC patients (n=283). The results from the final multivariable model with backward selection were comparable to the initial model including all significant factors from bivariate comparisons (data not shown).

Sensitivity analyses examining differences in patients with a record of vitamin B12 monitoring (n=81, 25%) with low/deficient vs. normal B12 levels, revealed no significant differences between groups with the exception of site, where a greater proportion of the deficient/low group were from a FQHC site. However, these results should be interpreted with caution given the small sample size included in this analysis (data not shown).

DISCUSSION

The results of this study expand our understanding of current vitamin B12 monitoring practices in a diverse, urban setting and identify potential interventions to increase adherence to recommended monitoring guidelines. We found that the majority of patients in ambulatory care settings are not being monitored for vitamin B12 deficiency as recommended by national diabetes guidelines and the metformin prescribing information for patients with type 2 diabetes on metformin therapy. Overall, only 25% of patients prescribed metformin for a diagnosis of type 2 diabetes were

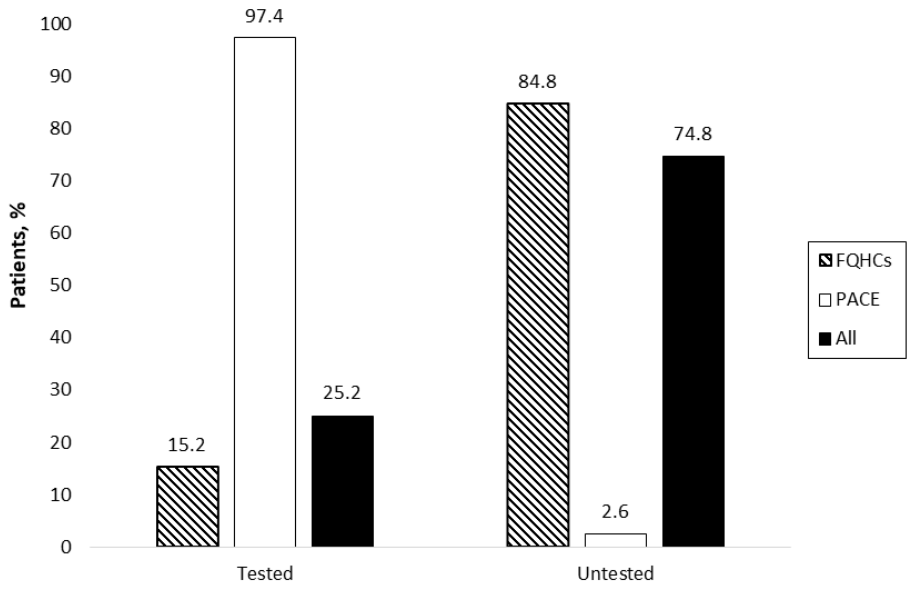

Figure 1. Occurrence of B12 Monitoring

monitored for vitamin B12 within a 5-year look back period. Although guidelines differ on the timeframe for monitoring, the ADA recommends periodic monitoring and the package insert for metformin states hematologic parameters should be obtained annually and vitamin B12 monitoring every 2-3 years.[1,6] Two previous studies were conducted in the United States veteran population of predominantly Caucasian males. Kancherla *et al*. found that a high percentage of patients (63%) with type 2 diabetes on metformin were not being periodically monitored for vitamin B12 levels.[9] Pierce et al. excluded patients on <2000mg of metformin daily and also found that 47% of patients were not monitored for vitamin B12 levels.[10] We found higher rates of discordance with monitoring recommendations (74.8%) in a more diverse population, both in race and gender, compared to the veteran population.

We found difference in monitoring between FQHCs and the PACE program, where the predominant medical specialties are internal and family medicine versus geriatrics, respectively. Older patients often have multiple risk factors for vitamin B12 deficiency such as decreased absorption due to vitamin B12/intrinsic factor complex and the additive effects of drug-induced vitamin B12 deficiency due to polypharmacy. Vitamin B12 levels are obtained in this particular PACE program upon enrollment for all patients and then annually based on risk factors. Compared to the FQHCs, patients at the PACE program were more likely to be on vitamin B12 supplementation (41%), have a diagnosis of peripheral neuropathy (28%), and prescriptions for proton pump inhibitors (41%). Although 97% of PACE patients in this study received vitamin B12 monitoring, we are unable to determine if this was due to metformin use or other indications for monitoring.

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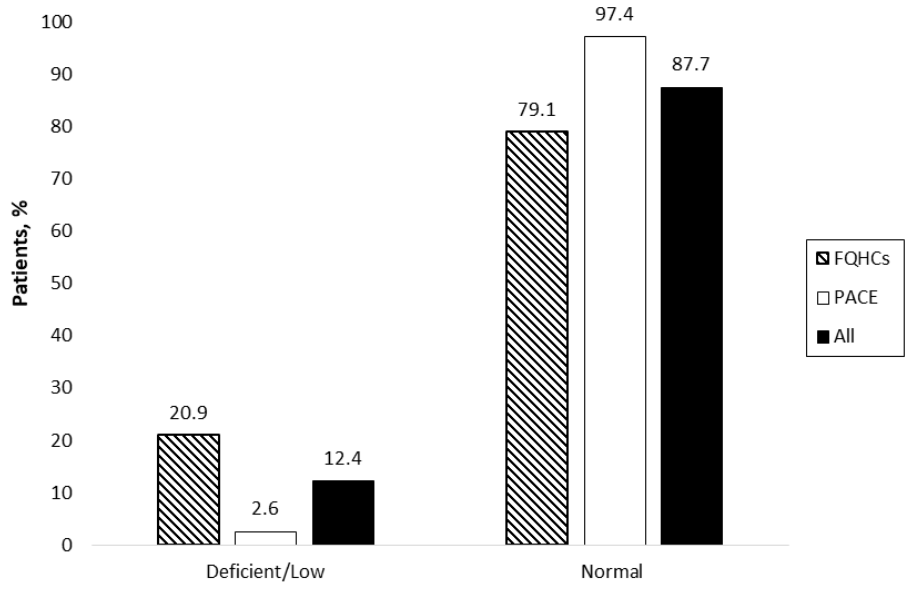

Figure 2. Distribution of Vitamin B12 Levels

understanding of the potential impact and utility of vitamin B12 monitoring. Premarketing trials of metformin found decreased vitamin B12 levels in up to 7% of patients over a 29-week study.[6] This can be compared to our study where 88% of vitamin B12 levels were within the normal range for patients on metformin for more than one year. In our sample, we found that one third of the patients in the normal range of B12 (28%) were currently prescribed vitamin B12 supplements. Of the ten patients with low or deficient vitamin B12 levels, 80% did not have an active prescription for vitamin B12 supplementation and 20% were on an additional agent that may potentially lower the vitamin B12 level. Nearly 10% of our sample without a vitamin B12 level had a diagnosis of peripheral neuropathy, and 5% had an active prescription for vitamin B12 supplementation but no vitamin B12 level checked. This highlights the need for provider education and improvements in current patient care processes to ensure that vitamin B12 levels are being monitored periodically in patients on metformin or receiving supplementation. Optimal monitoring of vitamin B12 would allow for early intervention in patients with low or deficient levels in order to provide appropriate vitamin B12 supplementation and prevent complications or further comorbidity.

The available data regarding peripheral neuropathy linked to metformin-induced vitamin B12 deficiency is conflicting and limited. Ahmed *et al*. did not find a correlation between metformin-induced vitamin B12 deficiency and peripheral neuropathy.[8] Aroda *et al*. found that patients on metformin with low vitamin B12 levels had higher prevalence of peripheral neuropathy.[2] In our study, 7.1% of patients diagnosed with peripheral neuropathy did not have a vitamin B12 level measured in the last five years. However, all 15 patients with a vitamin B12 level and peripheral neuropathy had a level within the normal range and 53.3% had an active prescription for vitamin B12 supplementation. Although all patients with a vitamin B12 level and peripheral neuropathy diagnosis had normal levels, it is still important to rule out vitamin B12 deficiency as a potential cause or contributing factor of peripheral neuropathy. Additionally, for patients who have a low or deficient level and a diagnosis of peripheral neuropathy, vitamin B12 supplementation could reduce the need for prescription medications for treatment of peripheral neuropathy.

Results of this study can be used to support quality improvement initiatives to increase the frequency of vitamin B12 monitoring in ambulatory care settings. Although our study was not designed to explore causes of lack of monitoring, we hypothesized several reasons for the low percentage of patients with vitamin B12 levels including lack of knowledge regarding monitoring recommendations; low prioritization of vitamin B12 monitoring compared to other diabetes recommendations; and the likelihood that vitamin B12 levels would be within the normal range. Interventions to increase vitamin B12 monitoring may include: EMR optimization by adding vitamin B12 levels to a standardized lab order set for patients with type 2 diabetes, automatic data reporting of patients that may need a vitamin B12 level, or a lab monitoring policy for patients on metformin. Clinical pharmacists, as part of the interprofessional patient care team, could be utilized to help educate providers on the value of vitamin B12 monitoring, current recommendations for patients on metformin and to identify patients at high-risk of vitamin B12 deficiency. In addition, it is important to continue monitoring patients with vitamin B12 deficiency and those receiving vitamin B12 to prevent unnecessary supplementation. Although unnecessary vitamin B12 supplementation may not be harmful, it increases pill burden or intramuscular injections and adds unnecessary healthcare costs.

Based on our study design and data extraction methods, a few limitations were present. We were unable to determine the total duration of metformin treatment for multiple reasons. Information prior to the conversion from paper to electronic medical records was not available. Additionally, metformin prescription initiation dates prior to care at the study sites were unknown. Since duration of use was not collected, a correlation could not be made between duration of metformin therapy and vitamin B12 levels. Additionally, the metformin dose was determined based on the active prescription included in the EMR, which does not account for patient adherence. Although vitamin B12 supplementation was prescribed for some patients, the indication for its use was often undocumented and over-the-counter supplementation was not accounted for in this study. Lastly, it is unknown if patients receiving vitamin B12 supplementation had previously low or deficient levels due to metformin use.

CONCLUSIONS

In conclusion, the majority of patients at the FQHCs were not being monitored in accordance with the ADA guidelines. This revealed the need to educate providers and implement quality improvement projects to improve vitamin B12 monitoring in patients on chronic metformin therapy in ambulatory care settings. Providers should also consider obtaining vitamin B12 levels in patients with a current diagnosis and/or treatment for peripheral neuropathy and prior to initiating treatment in patients with a new diagnosis of peripheral neuropathy to rule out deficiency. However, most of the patients in our study who were monitored had normal vitamin B12 levels, which may warrant extending the monitoring time. It would be beneficial for future studies to assess longitudinal vitamin B12 monitoring in order to better define the ideal frequency of vitamin B12 monitoring in patients with type 2 diabetes treated with metformin.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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Original Research

Effectiveness of a pharmacist-led quality improvement program to reduce medication errors during hospital discharge

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Abstract

Background: Patients requiring medications during discharge are at risk of discharge medication errors that potentially cause readmission due to medication-related events.

Objective: The objective of this study was to develop interventions to reduce percentage of patients with one or more medication errors during discharge.

Methods: A pharmacist-led quality improvement (QI) program over 6 months was conducted in medical wards at a tertiary public hospital. Percentage of patients discharge with one or more medication errors was reviewed in the pre-intervention and four main improvements were developed: increase the ratio of pharmacist to patient, prioritize discharge prescription order within office hours, complete discharge medication reconciliation by ward pharmacist, set up a Centralized Discharge Medication Pre-packing Unit. Percentage of patients with one or more medication errors in both pre- and post-intervention phase were monitored using process control chart.

Results: With the implementation of the QI program, the percentage of patients with one or more medication errors during discharge that were corrected by pharmacists significantly increased from 77.6% to 95.9% ($p<0.001$). Percentage of patients with one or more clinically significant error was similar in both pre and post-QI with an average of 24.8%.

Conclusions: Increasing ratio of pharmacist to patient to complete discharge medication reconciliation during discharge significantly recorded a reduction in the percentage of patients with one or more medication errors.

Keywords

Patient Discharge; Medication Reconciliation; Medication Errors; Prescriptions; Pharmacy Service, Hospital; Pharmacists; Quality Assurance, Health Care; Malaysia

INTRODUCTION

Patients admitted to hospital undergo various investigations, procedures and prescribed medications to manage their medical conditions. Prescribing medications during admission require initiating medication(s) for the current medical condition(s) as well as continuing patients' pre-existing medications for any underlying medical conditions. In some cases, the patients' pre-existing medications, could be the reason for admission and discontinuation or dosing adjustment of the offending medications may be required. A formal process to obtain an accurate and complete list of medications that patient was previously taking (including prescription medications, over-the-counter, supplements and herbal preparations) is defined as admission medication reconciliation.[1] Information is obtained through various sources: patient, caregiver, hospital records, health-care providers and community pharmacists.

During discharge, an accurate patients' discharge medication list is prepared based on comparison of admission medication reconciliation list, medications prescribed in the ward, and medications planned at discharge with the agreement of physicians, patients and caregivers. These changes have to be documented and communicated to patients or caregivers. These processes are collectively defined as discharge medication reconciliation.[1]

Medication reconciliation is a highly complex and time-consuming process, demanding significant skills. The American Society of Health-System Pharmacists (ASHP) recommends pharmacists who are uniquely qualified, to lead, establish and maintain effective medication reconciliation processes in hospitals.[2] In additional, pharmacists are able to communicate with community pharmacist counterparts to obtain and relay relevant medication details.[3]

Medication reconciliation lists are used to compare with discharge prescription orders either in same health-care facilities, primary care physicians or community pharmacies; and any inconsistencies between both lists are identified as medication discrepancies. Discrepancies that are without any clinical rationale or without the attending

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physicians consciously altering the therapy are defined as unintentional discrepancies; which are categorized as medication errors.[4,5] Such medication errors among adult patients discharged from the general medical wards ranged from 23% to 70%.[6-14] The most common medication error at discharge was found to be unintentional omission of medications.[10,11,13] Medication review during patient's home visit by pharmacists within 2 week of hospital discharge revealed variety of medication issues such as untreated indication, improper doses and medications with no indication.[15] It has been reported that unintentional medication changes or unintentional medication omission that are not correct during discharge contributed readmission in adult patients.[16,17]. Unintentional omission of insulin human isophane during discharge caused patient's blood sugar rise to 517 mg/dL and vomiting at nursing home which resolved after restarting insulin therapy.[13] Unintentional increase of clonazepam dose; caused lethargy in patient and subsequently fall at nursing home.[13]

Hence, the aim of this study was to modulate interventions to reduce percentage of patients with one or more medication errors during discharge.

METHODS

Study design and setting

We conducted a prospective, quasi-experimental, pre-post intervention study to evaluate the effectiveness of a pharmacist-led quality improvement (QI) program for reducing medication errors during hospital discharge.

This study was conducted in nine adult general medical wards at a 990-bedded tertiary care public hospital in Ipoh, Malaysia. These wards have a total of 276 beds with multiple medical specialities such as cardiology, nephrology, neurology, haematology, endocrinology and pulmonology.

Prior to the study, each medical ward has one ward pharmacist assigned to work during office hours (8.00 am to 5.00 pm) on weekdays. The ward pharmacists' core responsibilities are to perform medication reconciliation at admission, review medication therapy, prevent medication errors and participate in clinical ward rounds. During daily medication review, all medications prescribed in ward are reviewed for correct doses, formulations, route of administrations, indications, contraindications, compatibilities, side-effects, interactions, efficacy, monitoring, adherence issues and evidence-based treatment. Medication-related issues identified as mentioned above are discussed with attending physicians during ward rounds to optimize medication therapy based on an individual patient's condition. Ward pharmacists perform discharge medication reconciliation during discharge; comparing admission medication reconciliation lists, ward medications are compared and discharge plans. Patient-related issues (adherence, social support, preferences etc.) are identified. Attending physicians are consulted and the discharge medication reconciliation list is obtained. Bedside discharge medication counselling is done to communicate medication changes and other medication-related information.

Discharge prescription are ordered by house officers (qualified doctor practising under supervision after first year of graduation) through electronic ordering system. If discharge prescriptions are ordered after officer hours, patients collected their medications from the hospital outpatient pharmacy.

Medication error detection

Discharge medication reconciliation list is compared with prescription order by ward pharmacist either on the same day of patient discharge (prescription ordered within office hours) or the following morning (prescription ordered after office hours). Any discrepancies detected by ward pharmacist are discussed with the attending physician in the ward and decided if the discrepancies are intended or unintended.[5] Unintended discrepancies are recorded by ward pharmacist as medication error in the data collection sheet provided. Medication errors that are detected the following morning by ward pharmacist are non-intercepted medication. Non-intercepted errors are errors that reached patient.[18] Type of medication errors (wrong dosing, wrong drug, unintentional omission or addition of medication) for this study are adapted based on work by Pippins *et al*. (2008) and classified as shown in Online appendix 1. Although the research pharmacist retrieved information on the prescription medications, over-the-counter medications as well as supplements and herbal preparations, this study only focused on prescription medicines only for the purpose of medication error identification.

All prescribing errors detected were reviewed for clinical significance by two senior pharmacists and a medical specialist independently. Errors were categorized into two categories: clinically significant or non-clinically significant. Clinically significant errors are errors that would cause detrimental effect to patients' health, treatment delay and ineffective treatment if not detected and corrected before reaching patients (Code E – I). The coding are based on National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP).[19] Any differences in coding were discussed and a consensus agreement was reached among the three reviewers.

Improvement team

The pharmacy department initiated this QI program. The improvement team consisted of the manager of medical department, manager of the pharmacy department, physicians and pharmacists. A key driver diagram was developed as depicted in Figure 1.

Phase 1: Pre-Intervention

This study was conducted over a period of 9 months in three phases. In the first phase, pre-intervention data on prescribing errors during hospital discharge were collected on 4 consecutive weekdays (Mondays to Thursdays) on selected weeks in each month over a 3-months period (July, August and September 2017) as decided by the researchers. We selected the study points of 4 consecutive weekdays for data collection based on availability of all nine-ward pharmacists and no presence of public holidays in the selected week.

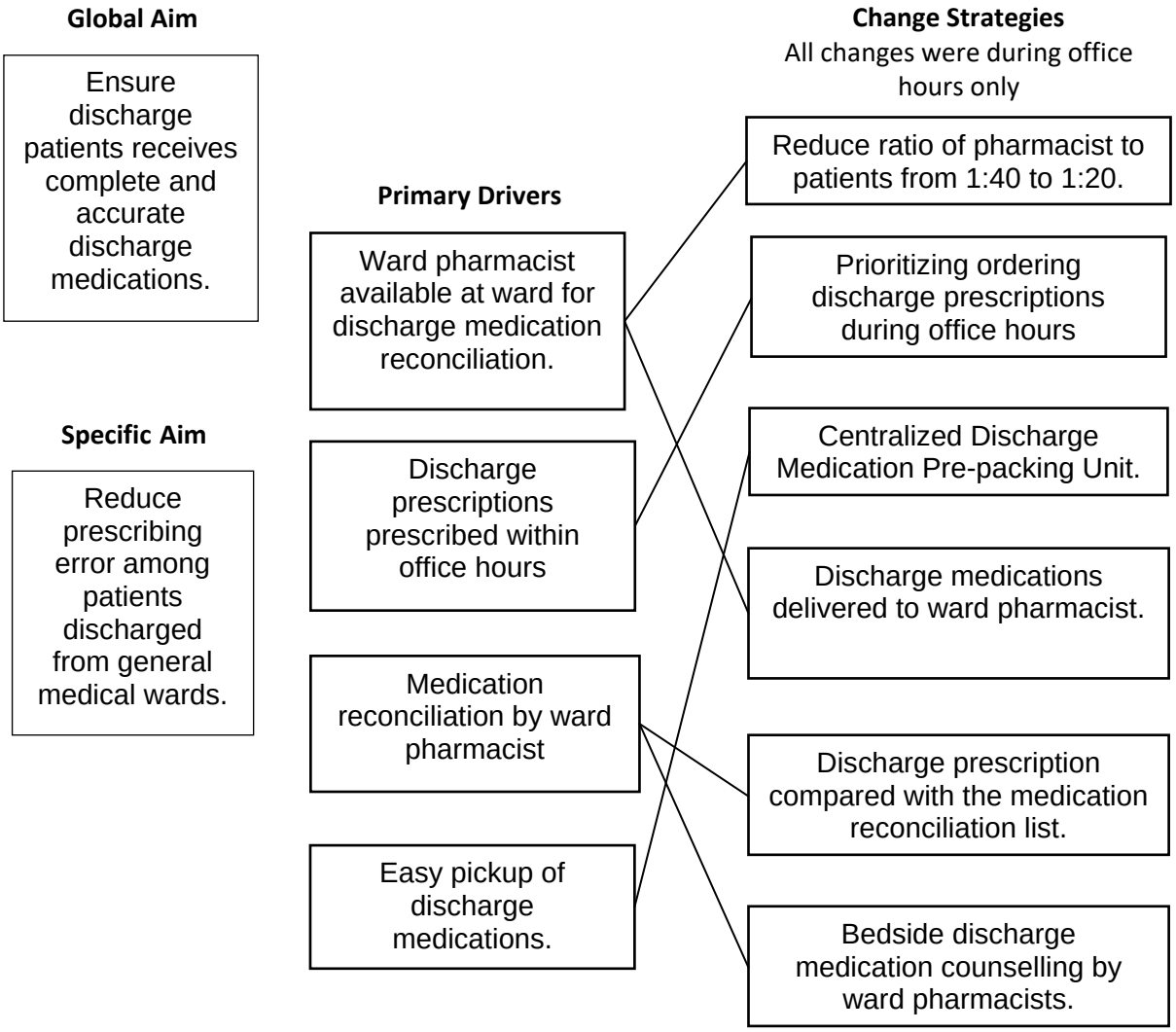

Figure 1. Key driver diagram

Discharge prescriptions from medical wards that are received by ward pharmacists or outpatient pharmacists by 10 pm weekdays were printed and collected for the purpose of this study. Discharge prescriptions which were not collected on the same date of prescriptions order date were excluded.

Discharge prescriptions after office hours are screened by outpatient pharmacists in the routine manner for correct dosing regime based on standard dosing references. Errors detected are corrected subsequently either by the prescribers, or by the pharmacists, who would have contacted the prescribers (adhering to standard protocol), in the electronic ordering system. Errors detected were highlighted using red ink ball pen on printed prescriptions.

Discharge prescriptions during office hours and after hours are compared with the discharge reconciliation medication list by ward pharmacists. If the ward pharmacists detected any unintentional discrepancies, it was discussed with the attending physician in the ward. Unintentional discrepancies are recorded as medication errors. Unintentional discrepancies in discharge prescription after office hours are recorded as non-intercepted errors; hence patients are contacted to provide correct medications and prescriptions. All medication errors detected are corrected in the electronic ordering system by ward pharmacists.

All nine ward pharmacists that are involved in data collection had at least a minimum of 3 years of working experience in the medical wards.

An instructive letter from the Chief Pharmacist was issued to the ward pharmacists and outpatient pharmacists during each point of study as a reminder to collect discharge prescriptions as proposed above. All pharmacists involved in the data collection were briefed for a maximum of 30 minutes per session before each point of data collection.

Phase 2: Quality Improvement

Phase 2, the intervention phase was conducted over three-months (October to December 2017) and no data was collected during this phase. Pre-intervention data of medication errors at discharge were presented to managers of both the pharmacy and medical department. Subsequently, the following improvement measures were implemented:

1. The number of ward pharmacists was increased in all medical wards from one to two to accommodate a ratio of pharmacist to patients of 1 to 15-20.
2. House officers were instructed to prioritize ordering discharge prescriptions within office hours in order for the ward pharmacists to complete discharge medication reconciliation process.
3. Ward pharmacists performed discharge medication reconciliation (compared all prescriptions ordered by house officers against the discharge medication reconciliation list) and provide bedside discharge medication counselling. In the past, this was an ad hoc activity where only about 5-10% of the ward pharmacists' total working time per day was allocated for this activity. As a quality improvement strategy, this was emphasized as part of the ward pharmacists' routine responsibilities.
4. A Centralized Discharge Medication Pre-packing Unit was set up to facilitate packing of discharge medication to enable ward pharmacists to provide bedside dispensing and medication counselling. In the past, respective ward pharmacists had to leave the ward to return to the pharmacy to pack discharge medications. In this study, staffs at the Centralized Discharge Medication Pre-packing Unit packed the discharge medication based on discharge prescriptions ordered in the system and delivered to the wards where the QI program was implemented.

Phase 3: Post-Intervention

In phase 3, similar to the pre-intervention data collection, post-intervention data collection was done for another 3 months (January to March 2018). Outpatient pharmacists on duty were briefed before each point of data collection. The same nine designated ward pharmacists in the pre-intervention data collection were involved in the data collection process in the wards.

Study outcomes

The primary outcomes of the study were the percentage of discharged patients with: 1) medication error, 2) clinically significant medication error, and 3) non-intercepted medication error. The denominator for the primary outcomes was the total number of patients that were discharged from the nine medical wards as shown in the Equation 1-3.

Equation 1: Percentage of patients discharged with medication errors

$$patients\ with\ one\ or\ more\ prescribing\ error / total\ patients\ discharged$$

Equation 2: Percentage of patients discharged with clinically significant medication errors

$$patients\ with\ one\ or\ more\ clinically\ significant\ prescribing\ error / total\ patients\ discharged$$

Equation 3: Percentage of patients discharged with non-intercepted medication errors

$$patients\ with\ one\ ore\ more\ non-intercepted\ prescribing\ error / total\ patients\ discharged$$

The sampling size was calculated by setting a power of 90% and significance level of 5% for independent cases using PS Power and Sample Size Calculation Version 3.0. Baseline error was assumed at a rate of 40% based on a pilot study conducted in this hospital for a month prior this study. Assuming that with a 15% decrease in discharge prescription error post-intervention, given various interventions in literature resulted in 20 – 40% of absolute reduction in rates of error in discharge prescriptions, a total of 203 prescriptions were required in each pre and post-intervention phase.[20-22]

Statistical analysis

The data collected at the end of each week was entered into Stata V.13 Statistical Software for analysis. Categorical data were presented as frequency with percentages, while continuous data were summarized as means with standard deviations (SD) if approximately normally distributed, or median and interquartile ranges (IQR) otherwise.

The statistical process control (SPC) chart was employed to illustrate the impact of the QI program on the primary outcomes.[23-26] This method of evaluating the effectiveness of interventions to reduce prescribing errors in the primary care settings provided valuable information to managers for decision-making.[27] The p-chart (p stands for percentage) was chosen to chart the percentage of patients with prescribing error as the outcome measures were binary (error versus no error) and the number of discharged patients (sample size) at each point was not constant. To enable the comparison of primary outcome measures between pre- and post-intervention phases, we calculated the mean percentage error for each phase using the total number of patients with error prescriptions and as the nominators and total discharge patients as the denominators. The upper control limit (UCL) and lower control limit (LCL) denoted the boundaries within which 99% of the data points will be found when the limits are set at a distance of 3 sigma [3 SDs] from the mean. Changes in the mean process error between phases were evaluated using the Chi-square test. Data with two-sided p-value of less than 0.05 ($p<0.05$) was considered statistically significant.

Ethical considerations

The study was registered with the National Medical Research Registry (NMRR) [NMRR-17-1628-36539] and code of ethics approval was obtained from Medical Research and Ethic Committee (MREC).

Attending physicians were notified of non-intercepted prescribing errors. The ward pharmacist and attending physician discuss each of these prescribing errors. Patients are contacted to provide correct medications and prescriptions. Decision was made not to contact patient by attending physician when error did not pose any harm to patient. Examples of such errors was oral prednisolone was prescribed 4 days instead of 3 days for a patient with acute exacerbation of asthma. In another error, inhaler beclomethasone was omitted from prescription order but the device was already supplied to patients during device counselling in hospital and furthermore patient has a doctor's follow-up appointment in two weeks. All non-intercepted errors were corrected in the electronic system.

Table 1. Characteristics of patients, prescribers, and prescriptions during the study

Characteristics	Pre-Intervention Phase	Post-Intervention Phase	p-value
Total patients, n	505	482	
Gender of patients, n (%)			0.3
Male	294 (58.2)	264 (54.8)	
Female	211 (41.8)	218 (45.2)	
Age of patients (in years), mean (SD)	59.9 (16.2)	58.9 (17.6)	0.4
Diagnosis on Prescription, n (%)			
Cardiovascular Diseases	176 (34.9)	146 (30.2)	
Infection	44 (8.7)	41 (8.5)	
Renal Diseases	41 (8.1)	39 (8.1)	
Lung Infections	37 (7.3)	44 (9.1)	
Stroke	30 (5.9)	25 (5.2)	
Acute Exacerbations of BA or COPD	23 (4.6)	17 (3.5)	
Diabetes Related Admissions	22 (4.4)	30 (6.2)	
Blood Disorders	22 (4.4)	19 (3.9)	
Seizures	17 (3.4)	23 (4.8)	
Cancers	10 (2.0)	11 (2.3)	
Liver Diseases	10 (2.0)	9 (1.9)	
Electrolyte Imbalances	9 (1.8)	13 (2.7)	
Adverse Drug Events	7 (1.4)	5 (1.0)	
Others	5 (1.0)	8 (1.7)	
Unclear	46 (9.1)	24 (5.0)	
Missing	6 (1.2)	28 (5.8)	
Prescriber category, n (%)			
House Officer	465 (92.1%)	440 (91.3%)	0.6
Medical Officer	40 (7.9%)	42 (8.7%)	
No. of medications, mean (SD)	6.5 (3.2)	6.6 (3.5)	0.5
Duration of prescription, n (%)			0.8
One month or more	423 (83.8)	406 (84.2)	
Less than a month	82 (16.2)	76 (15.8)	
Time of prescription order (%)			< 0.001
Office hours	214 (42.4)	382 (79.3)	
After officer hours	291 (57.6)	100 (20.7)	

SD - standard deviation, BA – bronchial asthma, COPD – chronic obstructive pulmonary disease

One researcher followed-up with ward pharmacists regarding decision made regarding all non-intercepted errors. The prescriptions collected were labelled according to their prescription dates and stored with rest of the prescriptions received by the pharmacy for 2 years, based on instructions from the Ministry of Health Malaysia (Ref: ANM.600- 1/24/4/8 dated 3rd October 2012). Stata database and excel spreadsheets did not include any unique identifiable details for the involved patients or prescribers.

RESULTS

During the study period, 1014 patients were discharged from nine general medical wards. Of these, 27 patients were excluded as their discharge medications were not collected on the day of discharge. Therefore, 987 patients were included in the final analysis with 505 patients in the pre-intervention phase and 482 patients in the post-intervention phase. The characteristics of patients, prescribers, and prescriptions during the study period are summarised in Table 1. All characteristics were similar in both phases, except for the percentage of discharge prescriptions that were ordered during office hours, which increased as a result of implementing the second component of the QI program.

Figure 2 illustrates the impact of the QI program on percentage of patients with medication errors during hospital discharge. Study phases were directly annotated onto charts. On average, the percentage of patients with one or more errors was 32.2%, but could be as high as 42.7% or as low as 20.0%, which represented the variation found in errors from discharge prescriptions (Figure 3A). During the entire six months study period, only common variations were observed and therefore, the process was considered stable and predictable. The process remained under similar conditions after the implementation of the QI program for a period of three months. The mean percentage of error during the pre-intervention and post-intervention phases were not dissimilar (29.7% vs. 34.9%, p=0.08). Same patterns were observed in the percentage of patients with one or more clinically significant errors (Figure 3B). The process was stable and predictable, exhibiting only common cause variation, where an average 24.8% of patients experienced clinically significant errors (ranged between 15.2% and 34.4%). The mean percentage of patients with clinically significant errors during the pre-intervention and post-intervention phases were similar (23.8% vs. 25.9%, p=0.40). Figure 2C illustrates the percentage of patients with one or more non-intercepted errors. The baseline reflects common cause variation with a process mean of 22.4%. The team began implementing the QI program at the end of the pre-intervention phase of three months; during which no data were collected Subsequently, the plotted data for the post-intervention phase after implementation of the QI program strongly suggested that the percentage of patients with one or more non-intercepted errors progressed in a positive downward manner, culminating in a special cause (8 consecutive points below the baseline process mean). This special cause reflected the introduction of the QI program into a process

in transition, resulting in a reduction in the mean percentage of non-intercepted errors from 22.4% to 4.1% (p<0.001), and tighter control limits (indicating less variation in the process).

Patients had a median of 7 (interquartile range, IQR 4, 9) medications in their discharge prescriptions. Total medications prescribed in the pre-intervention was 3264 and in post-intervention was 3192. Extend of error per patient ranged from 1 to 6. With the implementation of QI program, total non-intercepted errors reduced significantly from 176 (5.4%) to 28 (0.9%) (p<0.001). Most of discrepancies detected, 99.6% (512/514), by ward pharmacists was accepted by the attending physicians as unintentional discrepancies and as medication errors. Eight of the errors were not corrected in the electronic ordering system as errors was considered not clinically significant by attending physicians and all of it involved wrong duration of medications. Some examples of clinically significant medication errors were summarized in Online appendix 2.

Types of errors are summarized in Table 2. In both pre-intervention and post-intervention phase, the most common type of errors was omission of medication, wrong dose and wrong frequencies. All types of errors were similar in both phases but wrong duration significantly increased after the introduction of the QI program.

The common medication classes that were omitted were medications classified under the cardiovascular system, 57 errors (36%) followed by the alimentary tract and metabolism, 42 errors (27%) and blood and blood forming organ, 20 errors (13%). Medications that was most often omitted were sublingual glycerine trinitrate (in 15 prescriptions), atorvastatin (in 11 prescriptions), and clopidogrel (in 8 prescriptions) while various types of insulins, calcium carbonate and pantoprazole were omitted each in 7 prescriptions. Medication classes that were most often involved in other than omission of medications were alimentary tract and metabolism, and cardiovascular systems, involving 104 errors (29%), and 86 errors (24%) respectively. Various types of insulins 23 errors (6%), frusemide 21 errors (6%), acetylsalicylic acid 19 errors (5%), metformin errors (5%) and calcium carbonate 12 errors (3%) topped the list of medications of other than omission errors. A complete list of medications according to class and medications involved in the discharge prescribing errors, were sub-categorised as shown in Online appendix 3 and Online appendix 4 respectively.

DISCUSSION

The intervention program successfully attained high percentage of patients with medication errors that was

Table 2. Discharge Prescribing Errors by Sub–category Pre and Post-Quality Improvement Program. Total medication prescribed: Pre, N=3264 and Post, N=3192

Type of Errors errors (%)	Pre	Post	p-value
Total Error	231 (7.1)	281 (8.8)	0.03
Total Error Per Patient			
None	355 (70.3)	314 (65.2)	
1	103 (20.4)	88 (18.2)	
2	29 (5.7)	57 (11.8)	
3	11 (2.2)	13 (2.7)	
4	2 (0.4)	10 (2.1)	
5	1 (0.2)	0	
6	4 (0.8)	0	
Total Clinically Significant Errors	172 (5.3)	182 (5.7)	0.1
Clinically Significant Errors Per Patient			0.4
None	385 (76.2)	357 (74.1)	
1	89 (17.6)	88 (31.3)	
2	19 (3.8)	34 (7.05)	
3	7 (1.4)	7 (1.5)	
4	2 (0.4)	3 (0.6)	
5	2 (0.4)	0	
6	1 (0.2)	0	
Non-Intercepted Errors	176 (5.4)	28 (0.9)	< 0.001
None	392 (77.6)	465 (95.9)	
1	79 (15.6)	15 (3.1)	
2	19 (3.8)	3 (0.6)	
3	9 (1.8)	1 (0.2)	
4	2 (0.4)	1 (0.2)	
6	4 (0.8)	0	
Types of Errors			
Omission of Medication	91 (39.4)	69 (24.6)	0.2
Wrong Dose	64 (27.7)	84 (29.9)	0.07
Wrong Frequency	28 (12.1)	44 (15.7)	0.05
Wrong Duration	10 (4.3)	48 (17.1)	<0.001
Medication Not Indicated	20 (8.7)	6 (2.1)	0.1
Wrong Formulation	9 (3.9)	13 (4.6)	0.3
Wrong Drug	6 (2.6)	9 (3.2)	0.4
Polypharmacy	1 (0.4)	3 (1.1)	0.3
Wrong Instruction	0	3 (1.1)	0.1
Wrong Route	1 (0.4)	2 (0.7)	0.5
Omission of Instruction	1 (0.4)	0	0.9

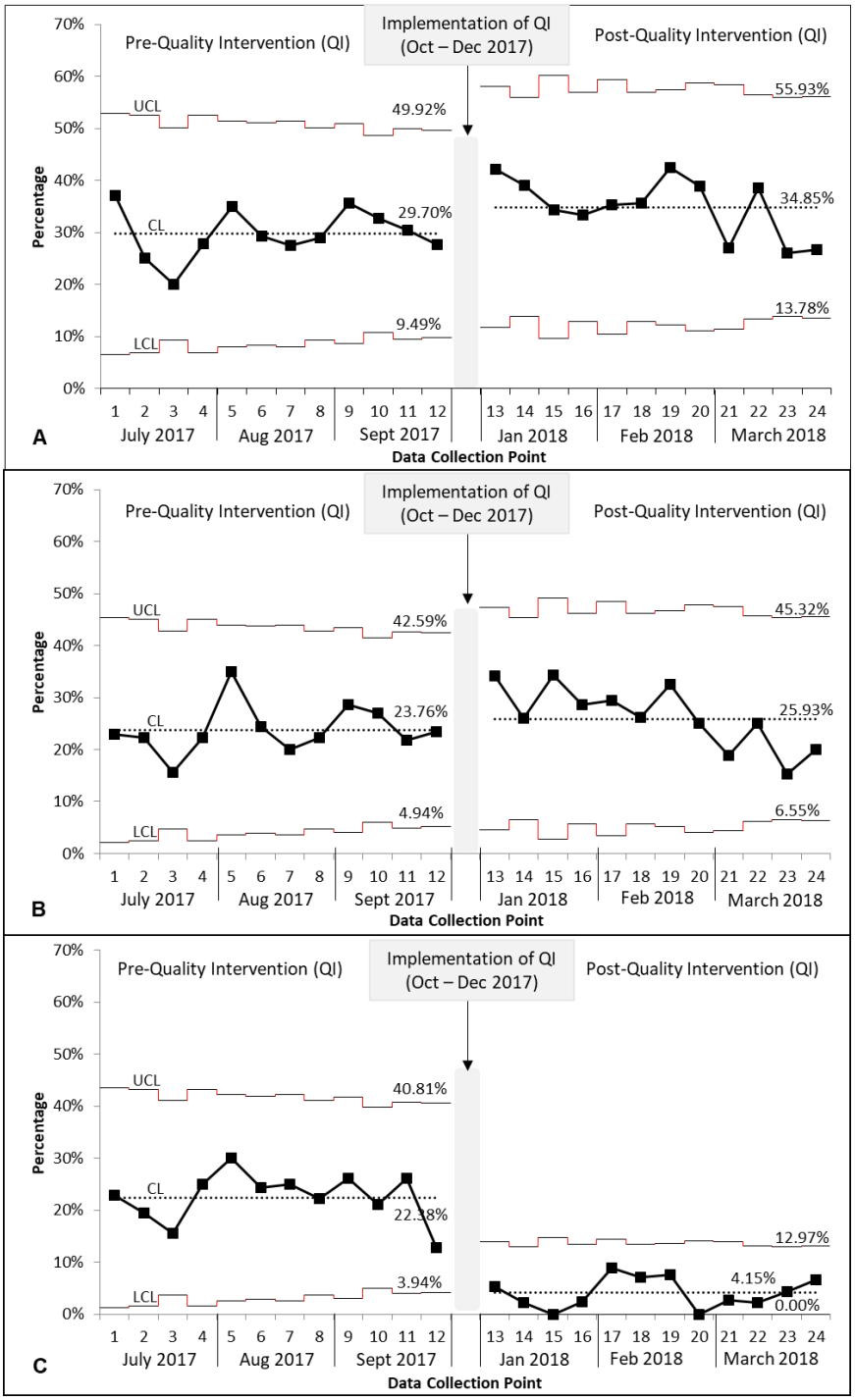

Figure 2. p-chart illustrating serial percentages in pre-intervention phase (July to September 2017) and post-intervention phase (January to March 2018) of patients discharged with one or more medication errors (A), clinically significant medication errors (B) and non-intercepted medication errors (C).

intercepted and corrected at discharge. The major component of this QI program was the complete reconciliation of medications at admission to discharge including bedside discharge medication counseling by ward pharmacists. In various studies; pharmacists play an important role in medication error reduction through discharge medication reconciliation.[28-35] A recent randomized control trial which included pharmacists to completed the medication management plan in the medical discharge summaries, reduced at least one medication error by an absolute risk reduction of 47%.[20]

In a recent systematic review, during discharge medication reconciliation; median clinical significant error (discrepancies) identified was 34% (IQR 28% - 49%).[36] The median percentage of patients with one or more clinically significant errors was 45% (IQR 31% - 56%).[36] Average percentage of patients in this study with one or more clinically significant errors was 24.8% and accounted to 5.5% of the total medication errors identified during

discharge. The low percentages could have been contributed to medications in wards were reviewed by pharmacist daily in this setting and errors such as dosing adjustments, contraindications and polypharmacy were already intervened much earlier before discharge. Pharmacists detected significantly higher errors involving incorrect duration in the pre-QI phase, we hypothesized that the attentiveness of ward pharmacist increased with the implementation of the QI program.

The most common error, identified during discharge medication reconciliation in this study was omission of medications, 160 (31.2%). This result is in line with other studies, that reported, omission of medications as the most common type of medication errors during discharge which ranged from 85% to 23%.[7,10,12]

Limitations

The results of this study should be viewed in the light of some limitations. The study was conducted only on weekdays, therefore excluding the percentage of medication errors on weekends, whereby, staffing of physicians and medical officers are lower.

Percentage of discharge patients prescribed with at least one or more errors remained similar and consistent as other components that affect prescribing of discharge medications were not addressed in this QI program. House officers who are responsible for ordering discharge medications are scheduled on a 4-weekly rotation to each medical ward. House officers only require to prioritize ordering discharge and not involved in any other component of the QI program. In order to improve overall medication error, house officers should also be an important part of the QI component.

Interventions that have not been implemented in our setting but have been implemented elsewhere proven to have reduced prescribing error at discharge, such as planning the discharge medications during ward rounds and computerized discharge assistance to ease prescribing discharge medications.[21,22,37,38] Giving constructive feedback and training on a regular basis for house officers, who are involved in prescribing discharge medication but rarely discuss these plans with their specialists or medical officers, has also shown a reduction overall errors in discharge prescription order.[39,40]

Implications and future research

The discharge medication reconciliation service by ward pharmacists continues at the medical wards in this hospital. Discharge medication reconciliation service by ward pharmacists have been expanded to two pediatric wards and two surgical wards.

Sustainability of this service can be tested using similar method use in the study in the future. Future study can also include other components such as training, feedback, allowing other than house officer to order discharge medication can be used to explore overall reduction in discharge medication errors. Other areas of research are to explore (i) implication of medication error in discharge medication on patients' outcome and (ii) cost implication of pharmacist to prevent clinically significant medication errors at discharge.

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CONFLICT OF INTEREST

None declared.

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Original Research

Resident physicians' perceptions of ambulatory care pharmacy

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Abstract

Background: Physicians' acceptance of clinical pharmacy services is dependent on exposure to those services, with use increasing as resident physicians progress through their training. Resident physicians train within environments that have a multidisciplinary teaching and clinical care approach, working closely with other healthcare professionals. Ambulatory care pharmacists are increasingly working with resident physicians in clinic settings as part of the multidisciplinary team, and identification of resident physicians' perceptions may influence future collaboration.

Objective: The objective of this research is to evaluate the perception of ambulatory care clinical pharmacy services from the perspective of resident physicians.

Methods: A statewide network of ambulatory care pharmacists was identified and received an electronic questionnaire. Pharmacists working within clinics that serve as training sites for resident physicians then completed and distributed questionnaires to the resident physicians within their clinical site. Items related to demographics and perception of involvement and interactions with clinical pharmacists.

Results: Forty-five resident physicians responded from four unique clinical sites (response rate = 42%). They agreed or strongly agreed that pharmacists help patients obtain their therapeutic goals (97.8%), are able to educate patients effectively (95.6%), provide high quality care (97.8%), and do a good job helping co-manage patients (91.1%). Previous exposure to pharmacists was limited primarily to the drugstore (48.9%) and hospital (51.1%) settings. Resident physicians in the third year of training and those reporting a friend was a pharmacist, were more likely to have a positive perception of the pharmacist's role as a resident educator (p=0.048 and p=0.044, respectively).

Conclusions: Resident physicians with a longer duration of exposure and personal friendship with a pharmacist are more likely to express positive perceptions. Areas for further enhancements in this interprofessional relationship related to perceptions about pharmacist autonomy and patient relationships were identified.

Keywords

Pharmacists; Physicians; Interprofessional Relations; Attitude of Health Personnel; Patient Care Team; Professional Role; Ambulatory Care; Surveys and Questionnaires; Indiana

INTRODUCTION

Ambulatory care clinical pharmacy practice has shown significant recent growth with increased numbers of pharmacists managing multiple disease states under collaborative drug therapy management protocols.[1] In addition to preventative care, pharmacists may provide chronic disease management for a variety of conditions including the management of diabetes, hypertension, and dyslipidemia. Under Collaborative Practice Agreements (CPA) or Collaborative Drug Therapy Management (CDTM) protocols, prescribers can delegate aspects of patient care such as initiating, modifying, and discontinuing drug therapy.[2,3] Pharmacists may also order and interpret any necessary laboratory tests as it pertains to the disease state(s) being monitored. Physicians' acceptance of clinical pharmacy services is highly dependent on the level of exposure to those services and expectations of pharmacists are associated with the number of years post-graduation from medical school, with those physicians who graduated within the past ten years having higher expectations of pharmacists.[4-6] Expectations include assisting in the design of drug therapy treatment plans, monitoring response to drug therapy, and patient education regarding safe and appropriate use of medications. Additionally, physicians that are young, group practice-oriented, and write higher numbers of prescriptions are more likely to utilize, and have a positive view toward, clinical pharmacy services.[6]

A collaborative working relationship (CWR) is built in stages. In order for pharmacists to establish CPAs or CDTM protocols, the first step is to build strong working relationships with physicians. The Physician-Pharmacist Collaborative Instrument (PPCI) measures provider exchange characteristics through a framework consisting of five stages: Stage 0 - Professional Awareness, Stage 1 - Professional Recognition, Stage 2 - Exploration and Trial, Stage 3 - Professional Relationship Expansion, Stage 4 - Commitment to the Collaborative Working Relationship.[7] As the relationship progresses through the various stages, the establishment of mutual trust and respect is established, ultimately strengthening the professional relationship to improve patient outcomes.[7] While progressing to Stage 4 may take time to achieve, pharmacy residents may be more receptive to this collaboration as they become familiar with the pharmacist's professional

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abilities and have confidence in the benefits of the collaboration.

The Collaboration Among Pharmacists and Physicians To Improve Outcomes Now (CAPTION) trial evaluated a physician-pharmacist collaborative model for blood pressure management and found that pharmacists with direct patient care improve control of chronic conditions and should be members of the care team for patients with hypertension.[8] The inclusion of pharmacists on the care team likely translates to the management of other chronic conditions, especially those related to cardiovascular disease.[8]

Throughout clinical training, resident physicians are placed within environments that have a multidisciplinary teaching component requiring working closely with other healthcare professionals. As part of this multidisciplinary teaching approach, ambulatory care pharmacists often work with resident physicians in clinic settings. Approximately 25-50% of family practice residency programs report the presence of clinical pharmacists within their program, although limited data is available describing details of this practice setting.[9,10] First-year resident physicians in family medicine programs that offer clinical pharmacy services have a more favorable attitude towards clinical pharmacist's participation on the health care team compared to those residency programs that lack these services. In addition, these residents prefer to practice as part of a multidisciplinary team that includes a pharmacist and see the value in hiring a clinical pharmacist within a private practice setting.[5] Resident physicians value the clinical pharmacist educator and thought their experiences with the pharmacist improved their quality of patient care, drug knowledge, and confidence.[11,12] Lastly, the clinical pharmacist educator was found to positively impact resident physicians' abilities to work as part of an interdisciplinary team.[12,13]

Additional data show that use of clinical pharmacy services increases as resident physicians progress through their training programs. This is consistent with the CWR framework and existing literature on pharmacist-physician collaboration: development of mutual trust, sustaining the relationship, and understanding of one another's role.[8,14] Based on reporting of pharmacist-physician encounters, first- and second-year resident physicians do not fully utilize clinical pharmacy services, perhaps due to the lack of education and communication regarding the available services offered.[11,15] Third-year resident physicians may utilize clinical pharmacy services more frequently due to increased patient contact, development of a professional relationship with the clinical pharmacist, and/or a better understanding of the importance for therapeutic information.[11]

Currently, there has not been any literature identified that has assessed the role of ambulatory care pharmacists from the viewpoint of resident physicians. Due to the increasing presence of ambulatory care pharmacists as part of resident physician clinical training programs and sites, it is necessary to understand resident physicians' awareness and perceptions of the capabilities of ambulatory care pharmacists.[9,10] These physicians-in-training can impact future collaboration, patient care, and expansion of ambulatory care pharmacy. The purpose of this study is to evaluate the perception of ambulatory care clinical pharmacy services from the perspective of resident physicians in Indiana.

METHODS

In order to identify appropriate participants for this observational cohort study, a two-step recruitment strategy was utilized. The first step involved identifying pharmacists within clinics that serve as a training site for resident physicians throughout Indiana. The second step involved seeking pharmacist volunteers to distribute questionnaires to the resident physicians within their clinical site. Pharmacists were identified through convenience sampling based on a comprehensive list provided by the office of experiential education from colleges of pharmacy in Indiana, namely Purdue and Butler Universities. Though there is now a third pharmacy program within Indiana, at the time this research was conducted this program had not yet established their experiential training sites. Inclusion criteria for pharmacist participation required self-identification as a clinical practice site that provides longitudinal training for resident physicians, clinical site located within Indiana, and willingness to participate. Inclusion criteria for the resident physicians included currently participating in longitudinal ambulatory care clinical training at a site that includes an ambulatory care pharmacist as part of the healthcare team, clinical practice site located within Indiana, and completing an Internal Medicine, Family Medicine or Transitional Year medical residency. All participants were required to be greater than 18 years old and able to read English. Pharmacists and resident physicians not meeting the inclusion criteria were excluded from participation. This research was deemed exempt by the Indiana University Institutional Review Board (IRB).

Two unique questionnaires were developed, one to be completed by ambulatory care clinical pharmacists and one to be completed by resident physicians. The pharmacist questionnaire sought to describe the characteristics of their clinic settings and other aspects of their job. The resident physician questionnaire sought to assess perceptions and attitudes regarding working with ambulatory care pharmacists within clinics. Prior to item creation, researchers developed five main themes for which to assess resident physician perceptions and attitudes: quality of patient care provided by the pharmacist, level of autonomy provided by the pharmacist, role of the pharmacist as patient educator, role of the pharmacist as resident educator, and the pharmacists' integration within the clinical care team. These themes were identified based on researchers' past experiences with resident physicians and felt to encompass the unique roles an ambulatory care clinical pharmacist may be asked to undertake. Five point Likert scale items ranging from strongly agree to strongly disagree were developed by researchers for inclusion in the questionnaires, and had not been previously validated.

Pharmacist Survey

A statewide web-based questionnaire was developed for ambulatory care clinical pharmacists. An email was sent to

Table 1. Pharmacist Questionnaire Items and Responses (n=15)

Item	Response n(%)
How many pharmacists provide ambulatory care clinical pharmacy services on a regular basis at your individual clinic site? (mean SD)	2.93; SD 1.91
What services do you personally provide in your ambulatory care clinic? Please select all that apply.	
Disease state education	14 (93.3)
Drug therapy management	14 (93.3)
Medication therapy management services	9 (60)
Transitions of care	6 (40)
Wellness visits/disease screening	4 (26.7)
Formulary approval	4 (26.7)
Immunizations	1 (6.7)
Other	2 (13.3)
What disease states do you provide drug therapy management for based on approved protocol or collaborative practice agreement? Please select all that apply.	
Smoking cessation	10 (66.7)
Anticoagulation	8 (53.3)
Hypertension	8 (53.3)
Diabetes	7 (46.7)
Hyperlipidemia	7 (46.7)
Weight loss	4 (26.7)
COPD	3 (20)
Asthma	2 (13.3)
Heart failure	2 (13.3)
Metabolic syndrome	2 (13.3)
Osteoporosis	2 (13.3)
Hypothyroidism	1 (6.7)
GERD	1 (6.7)
Other(s)	1 (6.7)
GI (nausea/vomiting/constipation/diarrhea)	--
HIV	--
Mental health disorders	--
Migraine	--
Pain	--
Renal impairment/chronic kidney disease	--
Seizure	--
What best describes the location of the clinic in which you work with resident physicians?*	
Urban	11 (78.6)
Suburban	3 (21.4)
Rural	--
How many half-days per week do you personally provide the clinical pharmacy services identified in question 1, at your practice site? (mean SD)	5.07; SD 2.58
How many FTE (full-time equivalent) hours do you personally provide clinical pharmacy services at your clinic site?*	
0.1-0.25	1 (7.1)
0.26-0.50	7 (50)
0.51-0.75	3 (21.4)
0.76-1	2 (14.3)
1.1-2	1 (7.1)
How long have you been providing clinical pharmacy services at your practice site with resident physicians?	
< 6 months	3 (20)
6-12 months	2 (13.3)
1-2 years	2 (13.3)
2-3 years	2 (13.3)
3-4 years	3 (20)
4-5 years	1 (6.7)
5-6 years	1 (6.7)
> 6 years	1 (6.7)

*n=14; **n=7

the identified pharmacists asking if their clinic served as a training site for resident physicians and included a link to an electronic questionnaire soliciting additional clinical practice information if they responded affirmatively. Only data indicating that they were part of an ambulatory care clinic that served as a training site for resident physicians were analyzed for the purposes of this study. Descriptive demographic information focused on the number of clinical pharmacists within the clinic who worked directly with resident physicians in a longitudinal manner, the number of full-time equivalent hours (FTE) the pharmacist(s) worked in the clinic, the number of half-days per week dedicated to providing clinical services, the types of services and activities that were offered within the longitudinal resident physician-training clinic and how long they had specifically provided services in their clinic. Finally, questions were asked about the types of involvement that the resident physicians had directly and indirectly with the clinical pharmacist and how often that interaction occurred.

Table 1 (cont.). Pharmacist Questionnaire Items and Responses (n =15)

Item	Response n(%)
How long have clinical pharmacy services been provided by any pharmacist at your clinic site with resident physicians?*	
< 6 months	1 (7.1)
6-12 months	--
1-2 years	1 (7.1)
3-4 years	2 (14.3)
4-5 years	2 (14.3)
5-6 years	1 (7.1)
> 6 years	7 (50)
How many resident physicians work at your practice site?	
0-5	2 (13.3)
6-10	3 (20)
11-15	1 (6.7)
16-20	2 (13.3)
21-25	--
26-30	3 (20)
31-35	1 (6.7)
36-40	--
> 40	3 (20)
What specialty are the resident physicians at your practice site? (Select all that apply)	
Family practice	9 (60)
Internal medicine	5 (33.3)
Transitional	2 (13.3)
Other	3 (20)
What is your primary method of communication with the resident physicians at your practice site?*	
Face-to-face	8 (57.1)
Patient chart (paper or electronic)	3 (21.4)
Electronic communication via EMR	2 (14.3)
Other	1 (7.1)
E-mail	--
Do you provide formal resident physician education at your site?	
Yes	7 (46.7)
No	8 (53.3)
How often do you provide formal resident physician education at your practice site?**	
Quarterly	3 (42.9)
Monthly	2 (28.6)
Weekly	1 (14.3)
More than once per week	1 (14.3)
2-3 times per month	--
Annually	--
In what form do you provide formal resident physician education at your practice site?**	
Structured clinical rotation	2 (28.6)
Formal presentation	2 (28.6)
Clinical shadowing experience	1 (14.3)
Preparation of written materials for distribution	--
Other	2 (28.6)
How often do resident physicians shadow your clinical encounters?	
Never	6 (40)
Weekly	3 (20)
Quarterly	2 (13.3%)
Annually	2 (13.3%)
Monthly	1 (6.7)
Once throughout residency	1 (6.7)

*n=14; **n=7

Resident Physician Survey

Pharmacists identified as practicing in a longitudinal resident physician clinic were asked to forward an electronic questionnaire link to each resident physician within their clinic. Due to a low initial resident physician response rate, this data was discarded and a hard copy questionnaire was mailed to each participating pharmacist for the resident physicians within their clinics. All questionnaires were anonymous and, once complete, were placed in an envelope that was not located within the pharmacist's office or direct workspace to maintain confidentiality and anonymity. The questionnaire focused on the perceptions of the resident physician and inquired about the types of services the ambulatory care pharmacist provided within their longitudinal clinic. Additional demographic information included the type of residency they were completing, current year of residency, and prior exposure to pharmacists and/or pharmacy students. Questionnaires were distributed April 1, 2015 through April 30, 2015. A reminder was electronically sent to participating pharmacists to encourage the resident physicians at their clinic to complete the questionnaire.

Data Analysis

Data were analyzed using SPSS 22 (IBM) software. A range of statistical tests were completed including basic

Table 2. Resident Physician Demographics

Resident Physician Characteristic	Response n (%)
Clinic Location	
Urban	36 (80)
Suburban	8 (17.8)
Response omitted	1 (2.2)
Type of Medical Residency	
Internal Medicine	32 (71.1)
Family Practice	12 (26.7)
Response Omitted	1 (2.2)
Year of Residency	
First	17 (37.8)
Second	15 (33.3)
Third	12 (26.7)
Response omitted	1 (2.2)
Primary Method of Communication with Pharmacist	
Face-to-Face	32 (71.1)
Electronic via EMR	10 (22.2)
E-mail	1 (2.2)
Patient Chart	1 (2.2)
Response omitted	1 (2.2)
Frequency of Patient Referral to Pharmacist Service(s)	
Less than once per clinic session, at least once per month	22 (48.9)
Less than once per month	18 (40)
Never	4 (8.9)
Response omitted	1 (2.2)
At least once per clinic session	--
Frequency of Medication-Related Discussion with Pharmacist	
Less than one time each clinic session, at least once per month	22 (48.9)
Less than once per month	12 (26.7)
One time each clinic session	5 (11.1)
Several times each clinic session	2 (4.4)
Never	2 (4.4)
Response omitted	2 (4.4)
Participated in Discussion(s) of the PharmD Curriculum and/or Various Career Options for Pharmacists	
No	34 (75.6)
Yes	11 (24.4)
Number of Lectures Taught by a Pharmacist During Medical School Education	
An entire course	13 (28.9)
A few lectures	11 (24.4)
Several lectures	10 (22.2)
I did not have a pharmacist teach me in medical school	7 (15.6)
I do not remember, but a pharmacist did teach me	4 (8.9)
One lecture	--
Frequency of Collaboration with Pharmacy Students on Projects During Medical School	
Not at all	37 (82.2)
Once during medical school	8 (17.8)
Each semester	--
Once per year	--
Exposure to Pharmacists Before Longitudinal Clinic*	
Hospital pharmacy	23 (51.1)
Team member on inpatient ward as student/intern	23 (51.1)
Drugstore pharmacy	22 (48.9)
Ambulatory clinic as student/intern	6 (13.3)
No prior exposure	6 (13.3)
Faculty member during medical school was a pharmacist	1 (2.2)

*Total n=44; resident physicians able to select all applicable responses

descriptive statistics for summarizing demographic information and frequencies, one-way ANOVA for analyzing the summed category responses and independent samples t-test to assess specific demographic items, such as year of residency and summed category responses, such as role as resident educator. Prior to project initiation, researchers determined that means of Likert scale responses would be reported.[16] The significance level (alpha) was pre-determined to be 0.05.

RESULTS

A total of 72 pharmacists received an invitation to participate. These pharmacists represented 51 unique clinical sites, although it is unknown how many serve as resident physician longitudinal training sites. Fifteen clinical pharmacists responded to the questionnaire (response rate=20.8%). As the clinic location was not a required response in order to maintain anonymity, it is unclear how many unique clinic sites these responses represented. Of the 15 pharmacists that completed the questionnaire, four agreed to facilitate distribution of the resident physician

questionnaire. Responding clinical pharmacists within these medical residency program sites provided a wide range of services with more than 90% reporting involvement in disease state education and collaborative drug therapy management via approved protocol or scope of practice (Table 1). There was a mean (SD) of approximately three clinical pharmacists providing services within each site (2.93; SD 1.91), with each individual pharmacist providing services over a mean of 5 half-days each week (5.07; SD 2.58). The majority of pharmacists within resident physician training clinics had been providing services for fewer than four years. Less than half reported being formally involved in resident physician education (n=7; 46.7%), with this education taking the form of shadowing experiences, structured clinical rotations, and presentations.

It is unknown how many resident physicians received the initial electronic questionnaire. A total of 107 resident physicians from four unique clinical sites received printed questionnaires. Forty-five resident physicians responded (response rate =42%). Most resident physicians were from Internal Medicine programs (71%) in urban areas (80%) with similar representation from all 3 years of their programs (1^{st}: 38%; 2^{nd}: 33%; 3^{rd}: 27%). Almost half of the resident physicians referred patients for clinical pharmacy appointments at least once per month, and the primary method of communication with the pharmacist was face-to-face (71.1%) rather than through less direct methods such as email (2.2%) or via the EMR (22.2%) (Table 2).

Resident physicians reported that prior to working with a pharmacist in their clinical practice sites, most had been exposed to pharmacists in the drugstore (48.9%) and hospital (51.1%) settings, with only 13.3% indicating they had worked with a pharmacist practicing in an ambulatory clinic as a student or intern. There was a wide spectrum of exposure to pharmacists in the resident physician medical school curriculum, with pharmacists' responsibilities ranging from no didactic teaching (15.6%) to teaching an entire course (28.9%). Few resident physicians (24.4%) had ever discussed the PharmD curriculum and/or various career field options for pharmacists.

Most resident physicians agreed or strongly agreed that pharmacists help patients obtain their therapeutic goals (97.8%), are able to educate patients effectively (95.6%), provide high quality care (97.8%), and do a good job helping co-manage patients (91.1%). Despite this, they reported that clinical pharmacists are given too much independence in clinical encounters (28.9%) and some worry that referring patients to a clinical pharmacist hurts their relationship with their patients (8.8%). Most resident physicians reported working collaboratively with the clinical pharmacist at their longitudinal clinic site (82.2%); however many (26.6%) reported not spending enough time with the clinical pharmacist to gain an understanding of their capabilities. Most are confident in the clinical pharmacist's abilities to manage patients (97.8%), and more than half (53.3%) think the pharmacist is qualified to provide additional services than those currently being offered at their clinic sites such as management of chronic pain, heart failure, and weight loss (Table 3).

Resident physicians felt that the clinical pharmacist is a strong resident educator (73.3%) and most agreed that they would like the clinical pharmacist to be more formally involved in their clinical education (84.4%). They believed pharmacists provide education in a way that is different from physicians (86.7%) and that they use specific educational techniques to improve resident physician understanding of pharmacotherapy (84.4%).

Only four of the demographic items evaluated were associated with significant differences in responses. Resident physicians in the third year of their training and those that reported having a friend that was a pharmacist, were more likely to have a positive perception of the pharmacist's role as a resident educator (p=0.048 and p=0.044, respectively). Those resident physicians who referred patients more frequently for clinical pharmacy appointments or reported prior exposure to pharmacists practicing in inpatient settings were more likely to respond favorably to the clinical pharmacist having autonomy with patient care (p=0.016 and p=0.033, respectively). Also, resident physicians responding with high levels of agreement to statements about the integration of pharmacists within the clinic team were more likely to report that one of their friends was a pharmacist (p=0.038).

Both pharmacists and resident physicians were asked the same questions to describe the types of pharmacy services offered and disease states managed within the clinics (Table 4). There were differences in pharmacist identified activities and resident physician identified pharmacist activities, with resident physicians over-identifying the types of services the clinical pharmacist provides, as compared to the pharmacist self-report.

DISCUSSION

Medical resident perceptions of pharmacists have not been well established in scientific literature. Based on the findings from this study, resident physicians perceive pharmacists that work within their longitudinal ambulatory clinic as providing effective patient education and a high quality of care to the patients that are referred for clinical pharmacy services. The majority of respondents indicated that they strongly agreed or agreed that the pharmacists in their clinics had the appropriate clinical training to provide the level of care for the services offered and were confident in the abilities of the pharmacist with whom they have a relationship, similar to reports of non-resident physicians.[14,17] Additionally, the majority of resident physicians in this study either strongly agreed or agreed that care provided by the pharmacist is different than the services offered by the physicians. Pharmacists are able to conduct focused visits for one or two disease states that incorporate not only pharmacotherapy, but also non-pharmacological elements pertaining to the patient's lifestyle such as dietary and physical activity. This varies from an appointment conducted by a physician that may need to focus on a wide array of disease states not allowing for adequate time to fully incorporate pharmacologic and non-pharmacologic treatment options.

Table 3. Resident physician questionnaire perception items and responses. n (%)

Item (*Category*) **The clinical pharmacist at my longitudinal, continuity clinic…**	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
… provides a high quality of care to my patients. (*Quality of care*)	31 (68.9)	13 (28.9)	0 (0)	0 (0)	1 (2.2)
… helps my patients achieve their goals more quickly than if I managed them alone. (*Quality of care*)	30 (66.7)	12 (26.7)	3 (6.7)	0 (0)	0 (0)
… helps patients obtain their therapeutic goals. (*Quality of care*)	28 (62.2)	16 (35.6)	1 (2.2)	0 (0)	0 (0)
… does a good job helping to co-manage my patients. (*Quality of care*)	26 (57.8)	15 (33.3)	3 (6.7)	1 (2.2)	0 (0)
… effectively provides patient education. (*Patient educator*)	29 (64.4)	14 (31.1)	2 (4.4)	0 (0)	0 (0)
… serves as a reliable source for patient education material. (*Patient educator*)	34 (75.6)	11 (24.4)	0 (0)	0 (0)	0 (0)
… takes into account the individual needs of my patients when providing patient education. (*Patient educator*)	22 (48.9)	21 (46.7)	2 (4.4)	0 (0)	0 (0)
… provides education to patients in a way that is different from what a physician provides. (*Patient educator*)	21 (46.7)	18 (40)	6 (13.3)	0 (0)	0 (0)
… provides care to my patients that is different than the care I provide or the care a staff physician provides. (*Patient educator*)	20 (44.4)	22 (48.9)	2 (4.4)	1 (2.2)	0 (0)
… has the education and training to perform the type of services that they provide. (*Autonomy*)	32 (71.1)	13 (28.9)	0 (0)	0 (0)	0 (0)
… is qualified to provide additional services that are not currently being offered at my clinic site. (*Autonomy*)	13 (28.9)	11 (24.4)	17 (37.8)	3 (6.7)	0 (0)
… is given too much independence in clinical encounters. (*Autonomy*)	2 (4.4)	3 (6.7)	8 (17.8)	23 (51.1)	9 (20)
… is an expert in the therapeutic areas in which he/she provides care. (*Autonomy*)	27 (60)	16 (35.6)	2 (4.4)	0 (0)	0 (0)
… should be given more independence in clinical encounters. (*Autonomy*)	12 (26.7)	12 (26.7)	16 (35.6)	4 (8.9)	1 (2.2)
… is actively involved in my clinical education. *(Resident educator*)	17 (37.8)	18 (42.2)	3 (6.7)	5 (11.1)	0 (0)
… is a strong resident educator. (*Resident educator*)	20 (44.4)	13 (28.9)	8 (17.8)	3 (6.7)	0 (0)
… uses educational techniques that improve resident understanding of pharmacotherapy. (*Resident educator*)	18 (40)	20 (44.4)	6 (13.3)	1 (2.2)	0 (0)
… provides education to residents in a way that is different from what a physician provides. (*Resident educator*)	21 (46.7)	18 (40)	4 (8.9)	2 (4.4)	0 (0)
… provides value that is uniquely different from other providers (i.e., physicians, nurses, dieticians, etc.). (*Integration*)	25 (55.6)	17 (37.8)	2 (4.4)	1 (2.2)	0 (0)
… should be involved with making medication-related decisions for patients with complex medication regimens. (*Integration*)	21 (46.7)	21 (46.7)	2 (4.4)	1 (2.2)	0 (0)
… functions as an integrated member of the clinic healthcare team. (*Integration*)	24 (53.3)	17 (37.8)	4 (8.9)	0 (0)	0 (0)
Ambulatory care clinical pharmacists are able to educate patients effectively to achieve desired outcomes. (*Patient educator*)	19 (42.2)	26 (57.8)	0 (0)	0 (0)	0 (0)
I spend enough time with the clinical pharmacist to gain an understanding of the capabilities of ambulatory care pharmacists. (*Resident educator*)	6 (13.3)	14 (31.1)	13 (28.9)	11 (24.4)	1 (2.2)
I would like the clinical pharmacist at my longitudinal clinic to be more formally involved in my clinical education. (*Resident educator*)	14 (31.1)	24 (53.3)	7 (15.6)	0 (0)	0 (0)
I work collaboratively with the clinical pharmacist at my longitudinal clinic. (*Integration*)	18 (40)	19 (42.2)	7 (15.6)	1 (2.2)	0 (0)
I feel comfortable asking the clinical pharmacist at my longitudinal clinic questions about medication therapy, even if outside of the areas for which he/she currently provides service. (*Integration*)	32 (71.1)	13 (28.9)	0 (0)	0 (0)	0 (0)
The level of care provided to patients would suffer if there was not a clinical pharmacist as part of the clinic team. (*Integration*)	16 (35.6)	24 (53.3)	2 (4.4)	2 (4.4)	1 (2.2)
I value the opinion of the clinical pharmacist at my longitudinal clinic on decisions regarding medication therapy. (*Integration*)	26 (57.8)	18 (40)	1 (2.2)	0 (0)	0 (0)
Ambulatory care pharmacists are able to motivate patients to achieve improved quality of care. (*Quality of care*)	20 (44.4)	20 (44.4)	5 (11.1)	0 (0)	0 (0)
Referring patients to a clinical pharmacist for medication management hurts my relationship with the patient. (*Quality of care*)	0 (0)	2 (4.4)	2 (4.4)	27 (60)	14 (13.1)
I am confident in the clinical pharmacist's ability to manage, monitor, and counsel patients on their medications and disease state(s) based on current guidelines. (*Quality of care*)	26 (57.8)	18 (40)	1 (2.2)	0 (0)	0 (0)
I am comfortable with the care my patients will receive when referred to the clinical pharmacist at my longitudinal clinic. (*Quality of care*)	24 (53.3)	20 (44.4)	1 (2.2)	0 (0)	0 (0)

Perhaps the most surprising finding from this survey is that despite the resident physicians viewing the pharmacist as being qualified to provide education and clinical services, while also being confident in the clinical pharmacists' ability to manage, monitor, and counsel patients on their medications, a small subset of resident physicians felt that referring patients to the clinical pharmacist for medication management could hurt their relationships with patients. While this research was not designed to discover reasons for these perceptions, a number of possibilities may exist. These perceptions could be a direct reflection of resident physicians indicating that they did not get to spend enough time with the clinical pharmacist to become completely comfortable with the concept of patient referral and independent pharmacist management, while also lacking a full awareness of the disease states managed and broad scope of services provided by the pharmacist. This could be remedied through formal shadowing or joint appointments between the resident physician and clinical pharmacist at the start of, and periodically throughout, the longitudinal clinic experience, or simple distribution of a handout during the resident physician's first year in clinic that clearly explains and identifies the various roles of the clinical pharmacist.

There is a need for increased awareness of the role of the clinical pharmacist as shown by the discrepancy seen

Table 4. Comparison of Pharmacist Services. n (%)		
Activity/Service	**Resident Response**	**Pharmacist Response**
Disease state education	26 (57.8)	14 (93.3)
Drug therapy management per protocol or collaborative practice agreement	45 (100)	14 (93.3)
Formulary approval	22 (48.9)	4 (26.7)
Immunizations	5 (11.1)	1 (6.7)
Medication Therapy Management Services	37 (82.2)	9 (60)
Transitions of Care	24 (53.3)	6 (40)
Wellness visits/Disease screening	19 (42.2)	4 (26.7)
Other	1 (2.2)	2 (13.3)
Disease States Managed	**Resident Response**	**Pharmacist Response**
Anticoagulation	35 (77.8)	8 (53.3)
Asthma	23 (51.1)	2 (13.3)
COPD	17 (37.8)	3 (20)
Diabetes	39 (86.7)	7 (46.7)
GERD	5 (11.1)	1 (6.7)
GI (nausea/vomiting/ constipation/diarrhea)	5 (11.1)	0 (0)
Heart failure	11 (24.4)	2 (13.3)
HIV	7 (15.6)	0 (0)
Hyperlipidemia	13 (28.9)	7 (46.7)
Hypertension	19 (42.2)	8 (53.3)
Hypothyroidism	10 (22.2)	1 (6.7)
Mental health disorders	6 (13.3)	0 (0)
Metabolic syndrome	6 (13.3)	2 (13.3)
Migraine	6 (13.3)	0 (0)
Osteoporosis	6 (13.3)	2 (13.3)
Pain	7 (15.6)	0 (0)
Renal impairment/ CKD	8 (17.8)	0 (0)
Seizure	4 (8.9)	0 (0)
Smoking cessation	28 (62.2)	10 (66.7)
Weight loss	13 (28.9)	4 (26.7)
Other(s)	1 (2.2)	1 (6.7)

among the responses from pharmacists regarding their clinical activities compared with the responses from the resident physicians (Table 4). Of note, only 57.8% of resident physicians responded that the pharmacist provides disease state education versus 93.3% of the pharmacists. A lack of awareness of the pharmacists' services by resident physicians may reduce referrals and limit the pharmacist from being fully utilized in providing patient care at the practice site. It should be noted that the 15 pharmacists who responded may practice at up to 15 different sites, whereas the resident physicians came from only 4 different practice sites, possibly contributing to the discrepancy noted between the pharmacists and resident physicians for services provided. Future research should continue to explore these hypotheses.

One of the largest benefits to utilizing ambulatory care pharmacists for patient management is that by allowing the pharmacist to focus on the management of specific disease states through frequent follow-up visits, resident physicians may have more room in their schedules to see medically complex patients or address additional concerns of patients for whom chronic disease management would otherwise dominate their visits. The frequency of patient follow-up with the pharmacist perhaps plays a part in the perception that patient referral to the pharmacist hurts the resident physician's relationship with the patient, particularly if the patient is relatively new to the resident physician. Due to patient panel size, pharmacists are often able to see patients back every few weeks whereas the first available resident physician appointment may not be for a few months.

Additionally, the concern regarding impact on patient relationship may support the idea that the resident physicians would like the pharmacist to be more directly involved in their clinical education during their ambulatory care learning experience by leading topic discussions or providing relevant presentations. In certain settings, such as what is seen within the Veteran's Affairs (VA) environment, the view of the clinical pharmacist's role in the approval or denial of non-formulary medication requests may contribute to this view of "harm" to the patient relationship. Almost half (48.9%) of the resident physicians identified non-formulary medication requests as a service in which their pharmacist was involved. When a non-formulary medication is denied or an alternate medication is suggested in place of the non-formulary medication being requested, this could be viewed by the resident physician as hindering the relationship the physician has with the patient.

Slightly more than half of the resident physicians in this study strongly agreed or agreed that the pharmacist is qualified to provide additional services than those currently being offered at their clinics. Resident physicians' limited knowledge of the PharmD curriculum and limited collaboration with pharmacy students on projects during medical school may be contributing factors as to why a notable number of resident physicians were neutral and a few disagreed with pharmacists being able to provide additional services. Medical and pharmacy schools throughout the United States are focusing on incorporating interprofessional education (IPE) into the curriculum. It is worth noting that residency training, whether pharmacy or medical, is a perfect venue to implement IPE. While this

study did not specifically focus on IPE, it is worthwhile to note that 82.2% of resident physicians had not collaborated with pharmacy students on any projects during their medical school training and 13.3% had no prior exposure to pharmacists prior to starting their longitudinal clinic experience. While this does not represent all medical schools, it showcases the struggle that some medical programs may have with incorporating IPE into professional school training, and how a lack of IPE early in training can influence perceptions of working with varied healthcare disciplines. Additionally, the responses which differed based on demographic factors all follow what is known about establishing effective pharmacist-physician collaboration; colocation, past experiences, and ability to communicate effectively are important factors in establishing collaboration.[14,18] The responses of resident physicians that have a friend that is a pharmacist support these concepts as a deeper relationship has been formed. Concerted efforts should be made to provide all health care professionals in training with opportunities to work closely with trainees from other disciplines, whether through the completion of multidisciplinary group projects while in school or some other manner while receiving clinical training.

One limitation that should be noted is that of survey bias. While all efforts were made to minimize any bias from the survey instrument, the use of a hard copy survey instrument may have impacted resident physicians' responses if there was concern that responses would be viewed by the clinical pharmacist with whom they directly work. Selection bias may also have occurred. Pharmacists were identified based on established preceptor relationships with pharmacy programs, which would exclude any non-preceptor pharmacists from participating. Additionally, pharmacists were asked to distribute the questionnaires to all resident physicians at their practice site, but may have only distributed questionnaires to the resident physicians at their site with whom they had good relationships or expected positive feedback from. An additional limitation is the small sample size and moderate response rate, however physician response rates to surveys are typically low and some studies have shown that response rates in this population are declining over time.[19-23] Our resident physician response rate of 42% is similar to other studies.[19-22]

This research highlights the perceptions of resident physicians within Indiana and may not be representative of views throughout the country. Investigators successfully attempted to increase the response rate following the initial study pilot period by changing the questionnaire administration method. However, based on the research methods it is uncertain how many medical residency programs include clinical pharmacists as part of the ambulatory care healthcare team or how many unique training sites were represented among the 15 pharmacist responses. Given the small number of distributing pharmacists, the results may be more of a reflection of these specific pharmacists rather than overall perceptions of ambulatory care pharmacy services throughout Indiana, although aligned with the perceptions of non-resident physicians.[14,17] Researchers attempted to be as comprehensive as possible in identifying potential sites for participation, however there is not a master list of pharmacists practicing in the ambulatory care setting, nor is there a comprehensive list of longitudinal ambulatory care training sites for resident physicians in Indiana.

CONCLUSIONS

This novel research highlights the perceptions of ambulatory care clinical pharmacists within resident physician longitudinal ambulatory care clinics. Resident physicians with a longer duration of exposure and personal friendship with a pharmacist are more likely to express positive perceptions. Areas for further enhancements in this interprofessional relationship have been identified related to perceptions about pharmacist autonomy and patient relationships.

PRESENTATIONS

A poster presentation about this project was presented in December 2014 at the American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting in Anaheim, CA; a lecture presentation about this project was delivered at the Family Medicine Midwest Conference on October 8, 2016 in Indianapolis, IN.

CONFLICT OF INTEREST

No authors report any conflicts of interest.

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Original Research

Assessment of pharmacists' knowledge, attitude and practice in chain community pharmacies towards their current function and performance in Indonesia

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Abstract

Background: The introduction of universal healthcare coverage in 2014 has affected the practice of community pharmacies in Indonesia. Studies regarding the practice of pharmacist in the chain community pharmacy setting in Indonesia are very limited. The chain community pharmacies in Indonesia are operated and controlled by the same management. The chain community pharmacies usually show better services compared to independent community pharmacies in Indonesia.

Objective: The study aimed to assess the knowledge, attitude and practice (KAP) of pharmacist working in chain community pharmacy towards their current function and performance in delivering pharmacy services

Methods: A cross-sectional study using questionnaires was conducted between January and March 2017 in KF, one of the largest chain community pharmacies in Indonesia. The total sampling method was used in the recruitment process. The data were analyzed using descriptive statistics, independent t-Test and one-way ANOVA. The KAP scores were assessed and categorized as "poor", "moderate" and "good" based on the standardized scoring system.

Results: A total of 949 KF's pharmacists (100% response rate) were participated in the study. The majority of pharmacists showed a good score in terms of knowledge and attitude, which is in contrast to practice as majority only obtained a moderate score. Working experience, age and the availability of standard operating procedures (SOP) for both dispensing and self-medication services were found to be statistically significant ($p<0.005$) aspects to KAP of pharmacists in delivering pharmacy services.

Conclusions: This study identified several important aspects that could affect the KAP of pharmacists working in chain community pharmacies in Indonesia. Specific policies should be conceived to improve the competencies of pharmacist and to ensure the compliance with the SOP and standardization system within pharmacy sector.

Keywords

Professional Practice; Pharmacies; Pharmaceutical Services; Pharmacists; Self Medication; Surveys and Questionnaires; Indonesia

INTRODUCTION

Community pharmacy is currently undergoing a transformation from its traditional function as a supplier of medicines towards a health hub destination.[1] Internationally, the development of policy has changed the practice of community pharmacy significantly. The increasing pressure to provide effective, efficient and affordable care under constrained healthcare budget has encouraged policymakers and professional bodies to expand pharmacist's contribution within the healthcare system.[2] For example, a number of cognitive services such as medicine use reviews (MURs), medication therapy management for chronic illness and home medication reviews (HMRs) are now widely available in pharmacies in UK, USA, New Zealand, Australia and Canada.[3,4] Moreover, community pharmacists in some of these countries have also been involved in providing services beyond their conventional scope of practice e.g. health screening, vaccination and prescribing for minor ailments.[5,6]

The need for pharmacists to change the current practice is crucial in Indonesia. The recent health care system changes marked by the introduction of universal health care coverage (Jaminan Kesehatan Nasional – JKN) in 2014 has created an opportunity for community pharmacist to be more involved in the primary care services.[7] This could provide opportunity for pharmacist to expand their roles in community care. However, on the other hand, the preparedness of pharmacist to provide such roles has become a major concern. For example, whilst Indonesia has legislation that a community pharmacy can only be operated under pharmacist's responsibility and supervision, low pharmacist presence has been evident in the large proportion of pharmacies.[8,9] The similar trend is noticeable in other low and middle-income countries (LMICs) reflecting an intractable problem towards pharmacist role expansion.[10]

Since 2018, there were 26,658 community pharmacies in Indonesia with the large proportion (>90%) are independent pharmacies.[11] The Indonesian government give no restriction in the ownership structure of pharmacy and allow corporations and non-pharmacists to own more than one pharmacy.[8] As a result, community pharmacy in

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Indonesia ranges from small independent community pharmacies to a large network of chain community pharmacies, most of which are operated in private sectors. Whilst independent pharmacy is generally owned by individual or group of individuals, the chain community pharmacy model can be classified into three main categories. The first category is chain pharmacy operated under centralized management structures. This means the local pharmacy branches must firmly follow the policy and management system as regulated by the main company for running the business including in logistic and staffing. KF, Century and Guardian are some examples of chain pharmacies operated under this model.[12] The second category is chain pharmacy operated under franchise system. This type of pharmacy allows local branches to self-regulated and use brand identity for the pharmacy operation (e.g. K-24 pharmacy).[12] The last category is buying groups pharmacy. While the first two pharmacy models are operated under organized chain system and use a unified business name, the buying groups are formed by a number of individual pharmacies to collectively increase their purchasing power, thus obtaining cheaper prices than they would possibly do individually. Apart from purchasing purposes, this type of pharmacy is independently operated by the owner.[12]

Community pharmacy in Indonesia has been known as the primary source for public to obtain medicines and pharmacy services.[13] While the majority of pharmacies focused on the supply function of medicines and retail services, there is a small proportion provided extended services such as early detection and health management services as an adjunct to dispensing model.[14] Typically, pharmacies providing such services are operating under chain model pharmacy. This is not surprising as these pharmacies generally have at least one pharmacist in duty to organize and supervise pharmacy operation.[15] Arguably, this has made such pharmacies are in greater position to maximize opportunity within the universal health care era.[7]

The evidence in other LMICs demonstrated that pharmacist working in chain pharmacies had a better understanding and attitude towards pharmaceutical care and provided more advanced services as compared to their colleagues working in individual pharmacies.[16] Nevertheless, there is a paucity of research investigating the performance of pharmacists working in chain community pharmacies in Indonesia. The corporatization of pharmacy in Indonesia on one hand has become a consolidated effort to provide better access and larger economics scale in the increased of competition and dynamic changes within pharmacy and healthcare sectors.[17] However, on the other hand, the forces of corporatization have been found to challenge the autonomy and professional rigor of pharmacists leading to moral dilemmas experienced by pharmacist regarding their professional roles.[18,19] Evidence has shown that the performances of independent pharmacies in Indonesia were below the minimum standards, however there were no evidence that the chain community or franchise model pharmacies gave the same results.[20] Therefore, this study aimed to assess the knowledge, attitude and practice of pharmacist working in chain community pharmacy towards their current function and performance in delivering pharmacy services.

METHODS

Study design and setting

A cross-sectional study was conducted between January and March 2017 using a self-developed and pre-validated questionnaire to assess the knowledge, attitude and practice (KAP) of chain community pharmacist working in KF, one of the largest chain pharmacy networks in Indonesia. All pharmacists signed the consent form and willing to participate were included in this study. The exclusion criteria included pharmacists who did not complete the survey responses.

Study instrument

The questionnaire was developed from the literatures regarding the pharmacists' work experiences and attitude towards pharmaceutical care services in Indonesia, also based on the discussion among research team and feedback from KF managerial members.[21,22] The questionnaire was developed in Indonesian language and it was consisted of five sections. Section one comprised four questions about the demographic profile including gender, age, educational level and years of working in KF. Section two (11 questions) inquiring about the pharmacy characteristics including the average number of patients, the availability of Standard Operating Procedure (SOP) and the number of workforces in pharmacy (pharmacists and non-pharmacists). Section 3, 4 and 5 focusing on Knowledge (24 questions), Attitude (34 questions) and Practice (26 questions), respectively.

Questions pertaining to KAP included concept of pharmaceutical care, services evaluation, patient expectation, understanding and compliance regarding drug therapy. A correct answer for each item of knowledge was given a score of 1, while wrong and unsure answer were marked as 0 (zero). The Likert scales were adopted in the section of attitude (four scales ranging from strongly agree to strongly disagree) and practice (four scales ranging from always to never), respectively. Highest score (4 points) reflected the most positive option and the lowest score (1 point) reflected the most negative option. The maximum score from each KAP aspect was used to rank the level of knowledge, attitude and practice, respectively. Subsequent analysis was conducted to classify the score as "poor" (low score), "moderate" (medium score) and "good" (high score). For example, if the respondent answered all questions correctly in Knowledge aspect, 24 scoring points were given. The total of 24 points were divided into three categories in which 0-8 points attributed to poor, 9-16 points attributed to moderate and 17-24 points attributed to good knowledge.

The representatives of the Faculty and KF examined and approved the face and content validity of the questionnaire. The questionnaire was then piloted to ten KF's pharmacists resulted in minor changes on the wording and questionnaire lay-out. The Internal consistency of the modified questionnaire was measured using Cronbach

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Table 1. Characteristics of participants (N=949)

Characteristics	n (%)
Gender	
Male	390 (41.1)
Female	559 (58.9)
Age group (years)	
≤ 30	694 (73.2)
31-40	172 (18.1)
41-50	58 (6.1)
> 50	25 (2.6)
Educational level	
Undergraduate + Pharmacist	915 (96.4)
Master + Pharmacist	33 (3.5)
Doctor + Pharmacist	1 (0.1)
Working experience in KF (years)	
< 5	728 (76.7)
5-10	111 (11.7)
11-15	49 (5.2)
> 15	61 (6.4)

Alpha resulting coefficient 0.724 reflecting good internal consistency of the questionnaire (>0.70). Ethics approval was not deemed necessary as the study was part of internal audit to observe performance of pharmacists and pharmacy.[23] However, each participant was required to provide signed consent prior to fill the questionnaire. In addition, participants received information about the nature of the study and procedure for completing the questionnaire.

Participants and data analysis

The study used a total sampling method to recruit all community pharmacists (n=949) working in 825 KF pharmacy outlets throughout the country (34 provinces). The questionnaire was distributed to each pharmacist through KF system in which the research team was provided access to collect the results. The data were analyzed using SPSS v22. The categorical variables were presented as frequencies and percentages while the continuous variables were reported as mean and standard deviation (SD). Independent t-Test and one-way ANOVA were used to compare means between KAP groups with p-value <0.05 was considered to be statistically significant. To address the objective of this study, five variables were analyzed as indicator for pharmacists' performance in delivering services with respect to their KAP, namely working experience, age, educational level and the availability of SOP for both dispensing and self-medication services. These variables were selected as they were intrinsic factors that contribute to the performance of individual pharmacist in delivering the service.[24]

RESULTS

A total of 949 pharmacists returned the questionnaire resulting in 100% response rate. The majority of participants are female. Most of the participants are novice pharmacists with aged less than 30 years old with working experience in KF less than 5 years. Characteristics of the respondent are provided in Table 1.

The majority of pharmacies served less than 20 patients with prescriptions each day (Table 2). In contrast, the provision of self-medication was relatively high with 20-100 patients were treated as self-medication per day. As a corporate chain pharmacy network, the availability of SOP for services is highly important. Although all pharmacies were expected to have SOP for delivering their services as required by the legislation, there was small yet significant proportion which deviated from such policy, both SOP for dispensing services (9%) and SOP for self-medication services (15%), respectively.[25]

Table 2. Characteristics of KF pharmacies (N=949)

Characteristics	n (%)
The average number of patients with prescriptions per day	
< 20	462 (48.7)
20-50	278 (29.3)
51-100	140 (14.8)
> 100	69 (7.2)
The availability of SOP for dispensing prescribed medicines	
Available	855 (91)
Not available	94 (9)
The average number of patients for self-medication per day	
< 20	80 (8.4)
20-50	348 (36.7)
51-100	339 (35.7)
> 100	182 (19.2)
The availability of SOP for self-medication services	
Available	811 (85)
Not available	138 (15)
The average number of patients purchasing medical devices with prescriptions per day	
< 20	867 (91.4)
20-50	63 (6.6)
51-100	11 (1.2)
> 100	8 (0.8)
The number of pharmacists in each pharmacy	
1	813 (85.6)
2	113 (11.9)
3	12 (1.3)
4	6 (0.6)
5	3 (0.3)
> 5	2 (0.2)
The number of pharmacy assistants in each pharmacy	
1	247 (26)
2	406 (42.8)
3	118 (12.4)
4	97 (10.2)
5	38 (4)
> 5	43 (4.5)
The number of other pharmacy staffs (non-pharmacists and non-pharmacy assistants)	
1	819 (86.3)
2	87 (9.2)
3	23 (2.4)
4	8 (0.8)
5	3 (0.3)
> 5	9 (0.9)

SOP = Standard operating procedure

It was not surprising that majority of participants had good knowledge and attitude about their function and services they provided in pharmacy. However, the overall score for practice reflected a contradiction to this notion. The majority of participants only had moderate practice with relatively high proportion scored poor practice (15%). Table 3 shows the distribution of score for KAP and frequency of participant with particular level of KAP.

Table 4 displays the comparison between KAP and selected variables. Three statistically significant differences (p<0.05) were found namely (1) between attitude-practice and working experience, (2) between attitude-practice and age,

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Table 3. Distribution of KAP score and frequency of participant with particular level of knowledge, attitudes and practice.			
	Mean (SD)	**Minimum**	**Maximum**
Total knowledge score	22.73 (1.77)	14	24
Total attitude score	119.99 (11.98)	89	136
Total practice score	85.75 (12.29)	47	104
	Poor	**Moderate**	**Good**
Number of participants with particular level of knowledge. n(%)	-	7 (0.7)	942 (99.3)
Number of participants with particular level of attitude. n(%)	-	92 (9.7)	857 (90.3)
Number of participants with particular level of practice. n(%)	146 (15.4)	803 (84.6)	-

and (3) between knowledge-attitude-practice and availability of SOP both for dispensing and self-medication services. There was no significant difference in terms of educational level with the KAP score.

With respect to working experience, it was found that pharmacists who worked for 5-10 years in KF had the lowest score for attitude and practice. Pharmacist aged of 31-40 had the lowest level of attitude, while the age above 50 years had the lowest score of practice. Moreover, pharmacies which did not have SOP resulted in the lowest score in three elements of KAP.

DISCUSSION

This study aimed to assess KAP of pharmacists working in Indonesian chain community pharmacy towards their function and performance in delivering pharmacy services. There were three main findings which should be part of concerns both for pharmacists as a profession and pharmacy stakeholders particularly the owners/managers of pharmacies in Indonesia. Firstly, it was observed that pharmacists who already worked for 5 to 10 years showed the lowest score in terms of attitude and practice. While this study was unable to explore the factors behind such result, pharmacists' burnout, job stress and dissatisfaction to work were reported to moderately increase in the later stage of work.[26] The escalating pharmaceutical demand and dynamic changes in pharmacy practice have contributed to the increase of pharmacists' workload and requirement for more interpersonal interaction with the patients.[27] A number of literatures mentioned that individuals who already worked for 10 years in particular setting tend to experience exhaustion and burnout feeling from their works.[28-30] Specific to KF, the low volumes of prescription in contrast to high volumes of self-medication consultations to some extent may have put pharmacist under constant pressure of conflict of interest affecting their professionalism. It is true that pharmacist can play unique role in self-medication for instance by facilitating individuals for appropriate self-care or medication.[31] However, in environment where commercial-consumerism influences inflict with personal-professional decision like in pharmacy, such practice can be problematic. Several studies highlighted the lack of pharmacist ability to consistently and appropriately facilitate self-medication which may lead to adverse reaction and public risk e.g. drug resistance.[32,33] Such situation is without a doubt affecting pharmacists' behavior in delivering services which may become greater concern in the future if it goes unrecognized and untreated. This study implied that pharmacists are in a need of professional practice development to update, refresh and maintain their professional roles and competence. Such attempt may take in a number of forms ranging from an individual training and continuing education to a collective practice building such as teamwork exercise.

Table 4. The comparisons between KAP and selected variables

Variable	N	Knowledge			Attitude			Practice		
		Mean	Std. Error	Sig.	Mean	Std. Error	Sig.	Mean	Std. Error	Sig.
Working experience in KF (years)*										
< 5	728	22.780	0.063	0.336	120.0618	0.438	**0.005**$^{+}$	86.520	0.441	**0.015**$^{+}$
5-10	111	22.522	0.192		116.3604	1.229		81.657	1.227	
11-15	49	22.551	0.331		121.7551	1.666		83.612	1.829	
> 15	61	22.721	0.195		124.4262	1.343		85.852	1.760	
Age (years)*										
≤ 30	694	22.796	0.063	0.336	119.956	0.450	**0.005**$^{+}$	86.448	0.455	**0.015**$^{+}$
31-40	172	22.564	0.154		118.546	0. 973		83.337	0.959	
41-50	58	22.620	0.240		125.034	1.262		85.982	1.671	
> 50	25	22.440	0.416		119.400	2.509		82.760	2.990	
Educational level*										
Undergraduate + pharmacist	915	22.732	0.058	0.772	119.875	0.396	0.229	85.617	0.403	0.119
Master + pharmacist	33	22.757	0.261		123.060	2.077		89.212	2.492	
Doctor + pharmacist**	1	24.000	-		130.000	-		101.000	-	
The availability of SOP for dispensing prescribed medicines**										
Available	855	22,773	0. 060	**0.043**$^{+}$	120.366	0. 406	**0.004**$^{+}$	86.349	0.414	**<0.001**$^{+}$
Not Available	94	22,383	0.190		116.638	1.286		80.383	1.312	
The availability of SOP for self-medication services**										
Available	811	22,812	0.061	**0.001**$^{+}$	120.607	0.416	**<0.001**$^{+}$	86.612	0.422	**<0.001**$^{+}$
Not Available	138	22,275	0.159		116.4058	1.029		80.739	1.070	

*Using one-way ANOVA to compare means between three or more groups
**Using Independent *t* Test to compare means between two independent groups
$^{+}$Statistically significant (p<0.05)

Secondly, age of pharmacists influences the attitude and practice in delivering care regardless their knowledge and educational level. Pharmacists in KF were found to have overall good knowledge and understanding about their function and performance in services. This is perhaps due to the fact that they have pursued adequate educational program and acquired basic and essential knowledge to become a pharmacist. Additionally, the corporate system in KF may have forged this knowledge through capacity building program.[34] However, pharmacists who fall into particular group of age had the lowest score for attitude (31-40 years old) and practice (>50 years old) which becomes a fact that should not be ignored by KF. It is not surprising that pharmacists in the late career or pension age may experience a diminished performance and function. Several studies have indicated that pharmacists who have been in the profession for 30 years may intend to leave the profession.[35,36] What might be greater concern is that early career person, 31-40 years as reflected in this study, also experienced a decreasing attitude towards their practice. This may a warranty to examine developmental process between career and life stage especially in KF. A study by Magola *et al*. indicated that early-career pharmacist was challenged with the same routine and responsibilities in the pharmacy as late-career pharmacist.[37] This may influence the transition of novice practitioners into practice and having negative implications for patient care. Pharmacists in this group of age are likely to find certain things – desire, expectation and motivation to deserve more – in work which are translated in their attitudes and intentions.[38] The ability to identify and response to such condition can be a winning program for a pharmacy particularly KF. What is perhaps interesting is the finding that pharmacist aged 41-50 years showed better overall KAP results as compared to the early and late career pharmacist. In terms of career management, this study argued that mid-career professionals may have developed resilience and adaptability, both intellectually and personally in viewing their career.[39] A number of studies underlined that mid-career level professionals have strong commitment and endorsement for learning, increasing autonomy and supporting others.[40-42] The key challenge, however, is to maximize such adaptive behavior to help pharmacists realize their career aspirations and hone their full potential constructively.

Thirdly, the availability of SOP significantly influenced the KAP of pharmacists. This study revealed that pharmacies that were not equipped with SOP for services proved to have the lowest level of three element of pharmacists' KAP. WHO and FIP have underlined the importance of having SOP as step-by-step guidance for good pharmacy practice.[43] The findings in England and Wales showed that the availability of SOP has helped pharmacist in applying procedures to their everyday work. This is particularly the case for novice pharmacists which were relied on SOP as a guide to practice.[44] In Indonesia, pharmacies are required to have a number of SOP from the procurement, storage of medicines, dispensing and services to elimination of expired medicines.[25] This study adds to this notion that the availability of SOP can be an indicator for good pharmacy practice and therefore it is essential for the government and pharmacy stakeholders to ensure that SOP for service is available in every pharmacy. Learning from KF, a top down approach can be one way to encourage the availability of SOP. The fact that pharmacies involved in this study were operated under centralized management might explain why there was only small proportion of pharmacies without SOP in KF. It is important to note that centralized management system as developed by KF is likely to reduce variation and gap of performance between pharmacies which is common in pharmacies operating in LMICs.[45] Alternatively, the government in LMICs can endorse the availability of SOP for example by including requirement to have SOP prior seeking approval and renewal of pharmacy permits which is currently the norm in Indonesia.

To the best of our knowledge, this is the first study examining KAP of pharmacists towards their function and performance in delivering pharmacy services in the setting of chain pharmacy in Indonesia. The findings of this study provoke deeper understanding about pharmacists' role and behavior and provide insight to the influence of a number of important aspects such as age, working experience and availability of SOP for services. This is similar to the findings of a study by Schafheutle *et al*. concluding that age and factors associated with workplace affected pharmacists' performance.[24] In addition, this study also highlights three main tasks for policymakers and pharmacy stakeholders in Indonesia. First, as a pharmacist continues to age and he/she constantly experiences pressure for change, there is significant need for training and competency development program to improve pharmacist's professional practice. Such training may comprise any unique approach to boost the cognitive, moral, emotional and social side of the pharmacist. Second, despite there are policies in place that requires pharmacy to have SOP, the evaluation for compliance to the SOP is unnoticed. This reflects more specific efforts should be made to ensure pharmacy compliance with the regulation and relevant documentation system. Third, this study demonstrates that practice of pharmacist in chain community pharmacies is overrated despite the good level of knowledge and attitude as shown by the pharmacists. As the co-existence of chain and independent pharmacies is crucial to Indonesian healthcare system, it is imperative that there is a standardization system e.g. accreditation program to ensure that community pharmacy meets the minimum standard for practice. Such program is literally not available in Indonesian pharmacy legislation.

This study, however, is not without limitations. The administration of the questionnaire which is part of internal audit process may affect the integrity and honesty of the response. While the research team strived to ensure that participation in this study did not affect individual pharmacist *per se*, there is no guarantee that such method was effective to overcome bias in participants' response. Subsequently, despite the effort to measure pharmacist KAP based on five selected variables, this study did not analyze other variables such as the number of patients, number of pharmacists and other pharmacy characteristics which may or may not influence the KAP results. This is a call for further research to observe other variables using KAP approach.

CONCLUSIONS

This study examines pharmacist's function and performance working in chain pharmacy in Indonesia which can be an insight for policymakers and managers/owners in the context of LMICs. Using KAP approach, this study highlights that working experience, age and availability of SOP for services are significant aspects affecting pharmacists' function and performance. Evidence of poor practice were apparent indicating an imperative for improving pharmacist competence, ensuring compliance to SOP and standardization system in pharmacy.

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CONFLICT OF INTEREST

None Declared.

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Original Research

Evaluation of aminoglycosides utilization in intensive care units of a teaching hospital in southern Iran

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Abstract

Background: Inappropriate use of antimicrobial agents is one of the most important factors in inducing resistance and prolonged hospitalization as well as increase in patient mortality rate.

Objective: The aim of this study was to evaluate aminoglycosides (AGs) usage pattern at intensive care units (ICUs) of Nemazee hospital Shiraz, Iran.

Methods: In this cross-sectional study, the usage pattern of AGs was evaluated during 32 months. Guidelines for AGs usage were approved by the drug and therapeutic committee of the hospital, and criteria were developed to assess 11 parameters involving AGs therapy, such as proper indication for the use of the drug, dosage and duration of therapy. Clinical parameters, such as microbial culture and sensitivity, serum creatinine (SCr) and creatinine clearance, and white blood cell count were evaluated.

Results: Ninety-five patients were recruited, 50 male and 45 females. In most patients (64%) the origin of infection was hospital and only in 36% of them, community was the source. Ventilator associated pneumonia (27%), central nervous system (25%) and urinary tract infection (10%) were the most important indications for AGs prescription. Scores of AGs usage at Nemazee hospital was calculated as 5.9 out of 11, which meant that in only 54% of cases AGs prescription was based on guideline proposed by the Department of Clinical Pharmacy of Nemazee Hospital.

Conclusions: Non-adherence to the guidelines occurred frequently in the ICUs of Nemazee hospital. Prescription of loading dose, and AGs level measurement were not done and evaluating microbiological data was often neglected. Incorporating pharmacists in the health care team and holding training programs for physicians and nurses with the goal of raising awareness about the proposed guideline.

Keywords

Aminoglycosides; Inappropriate Prescribing; Drug Utilization; Professional Practice; Guideline Adherence; Creatinine; Pharmacy Service, Hospital; Intensive Care Units; Pharmacists; Cross-Sectional Studies; Iran

INTRODUCTION

Inappropriate antibiotic prescription can increase the duration of hospitalization and mortality.[1-4] Inappropriate use and dosing of antibiotics can lead to antimicrobial resistance. Increasing antimicrobial resistance by itself is a reason for increased usage of AGs. On the other hand, improper dosing of AGs can lead to resistance, adverse drug reactions, such as nephrotoxicity and ultimately treatment failure.[5] Hospital-acquired infection (HAI) is defined as infections that develop after 48 hours of hospitalization, which did not exist at the time of admission. HAI is associated with increasing medical costs, duration of hospitalization, complications, and increasing morbidity and mortality.[6]

Antibiotic misuse has led to increased adverse effects, drug resistance and the outburst of multidrug resistant (MDR) organisms.[7,8] To reduce medication cost and to control the prevalence of antibiotic-resistant bacteria in the community, there is no doubt that physicians must optimize the use of antibiotics. Pharmacists can play a pivotal role in order to reach this objective.[11] Drug Utilization Evaluation (DUE) is a method to understand the drug administration problems and to see if drugs are administrated appropriately.[12] It is also a tool to optimize the use of antibiotics.[13] Several studies were conducted in this regard.[11,14,15]

Early and appropriate treatment of patients in intensive care unit (ICU) is critical when managing infections, which could help to reduce mortality rates in patients with severe sepsis or septic shock.[16,17] Aminoglycosides (AGs) are one of the most essential antibiotics used in ICUs.[18] AGs are suggested as an adjunct to extended spectrum beta-lactams by surviving sepsis campaign (SCC) international guidelines to manage sepsis and septic shock.[19] Therefore, AGs are often given as part of empirical therapy for severe sepsis and septic shock, especially when Gram-negative bacteria are suspected.[20]

Several studies showed suboptimal AG in the early phase of therapy in critically ill patients.[21-23] In Iran, it has become a routine practice to prescribe AG in combination with beta-lactam antibiotics in severe gram-negative infections.

As improper usage and dosage of antibiotics can lead to antimicrobial resistance, DUE as a tool to detect the antibiotics utilization flaws can lead to optimization of the antibiotic administration by reducing resistance. As far as we know, no study was conducted on aminoglycoside utilization in Iran; hence, the present study focused on AGs usage pattern based on global standard drug consumption in ICUs to optimize its administration and to reduce drug resistance to this antibiotic in a referral hospital in southern Iran.

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METHODS

The usage pattern of AGs (Amikacin, Gentamicin) was evaluated in a prospective study during 32 months from January 2015 to August 2017 on patients admitted to 4 (internal, general, central, and surgical) ICUs at Nemazee hospital, a general multispecialty, referral, tertiary healthcare setting affiliated with Shiraz University of Medical Sciences, Iran. The Institutional Review Board and the Medical Ethics Committee of the hospital approved the study protocols. Written informed consent was obtained from all participating patients or their guardians.

All hospitalized patients in ICUs who had received at least three consecutive fixed-dose of AGs (to reach to the steady state concentration) were included in this study without considering age and gender. Those who had received less than three consecutive fixed-dose of AG due to ward transfer, hospital discharge, or death were excluded. Data gathering was done by a general pharmacist under the supervision of a senior clinical pharmacy attending.

General demographic information, such as age, gender, height, total body weight, body mass index, date of admission and discharge were filled in the case report format. The patient's medical history, diagnosis, reason for patient's referral to the ward, final diagnosis, pre-existing medical conditions, and whether the patient's infection was acquired from the community or hospital, were recorded. Laboratory data consisting of microbiological culture, hematologic parameters, including white blood cell (WBC), biochemical data, including blood urea nitrogen, serum creatinine, and immunologic factors (procalcitonin, c-reactive protein) were also recorded before and during the course of AG treatment.

To evaluate AG usage, a local guideline proposed by the Department of Clinical Pharmacy of Nemazee Hospital based on European guideline was used.[24] The guidelines were intended for use after adaptation to local resistance data by local therapeutic and drug committee. As an objective, eleven indexes were taken into account. Each index was scored as either 0 or 1 based on whether the index was evaluated as inappropriate or appropriate, respectively. A sheet, which consisted of eleven indexes, was completed for each patient. By adding up the scores for each index, the total score was determined for each patient, and at the end the mean was calculated.

These items are as follows: 1) Administration of loading dose, 2) Route of administration, 3) Dosing method, 4) Appropriate dose, 5) Indication, 6) Dose readjustment if necessary (including reduction of renal function), 6) Evaluation of patient's serum creatinine and blood urea nitrogen levels before prescription, 7) Assessment of patients' serum creatinine levels periodically, 8) Evaluation of microbial culture from the suspicious site of infection before prescription dosing method, 9) Evaluation of microbial cultures 48–72 hours after prescription, 10) Discontinuation or reduction in dose of AG in patients with AG nephrotoxicity (a rise in serum creatinine by more than 0.3 mg/dL within 48 hours, a rise in serum creatinine increased to more than 1.5 times baseline within the last 7 days or urine output less than 0.5 mL/kg/hr for more than 6 hours), 11) An increase in dose or a change in the type of antibiotics in the case of inappropriate responses to treatment.[25] Appropriate dosing method was considered as mg/kg dosing of the AG based on calculated CrCl. It is also worth mentioning that the patients' response to treatment was assessed based on fever, white blood cells count, microbial cultures, level of consciousness, radiological images, and clinical features. Computerized physician order entry (CPOE) was used in the ICUs as an electronic prescribing system.

Statistical analysis was performed by SPSS) version 20. Continuous and discrete variables were reported as mean, standard deviation and percentage, respectively. Comparison between numerical variables between two groups was performed, using independent t-test.

RESULTS

In this study 95 patients with the mean age of 40±18.2 were screened for 963 days. Forty-seven percent of the study population were women. Patients' demographic data are shown in Table 1.

Table 1. Demographic and clinical characteristics of the study population (n = 95)

Age (years)	
Mean (SD)	56.7 (18.2)
Range	2-92
Gender, n (%)	
Male	45 (47%)
Female	50 (53%)
Weight (Kg)	
Mean (SD)	62.0 (16.9)
Range	9-88
Height (Cm)	
Mean (SD)	162.0 (8.3)
Range	96-185
Ideal body weight (Kg)	
Mean (SD)	47.1 (3.4)
Range	40-51.8
Creatinine clearance using MDRD equation (mL/min/1,73)	
>50 mL/min/1.73	74 (78%)
10-50 mL/min/1.73	17 (18%)
<10 mL/min/1.73	4 (4%)
Creatinine clearance using MDRD equation (mL/min/1.73)	
>50 mL/min/1.73	65 (68%)
10-50 mL/min/1.73	28 (30%)
<10 mL/min/1.73	2 (2%)
Type of Aminoglycosides	
Gentamicin	60 (63%)
Amikacin	35 (37%)
Type of Infection, n (%)	
Ventilator associated pneumonia	26 (27%)
Central nervous system	23 (25%)
Urinary tract infection	9 (10%)
Abdominal infection	7 (8%)
Other sources (Sepsis)	6 (6%)
Abscess	4 (4%)
Pyelonephritis	4 (4%)
Endocarditis	4 (4%)
Cystitis	4 (4%)
Catheter associated infection	3 (3%)
Peritonitis	3 (3%)
Skin infection	2 (2%)
Source of infection, n (%)	
Community acquired	34 (36%)
Hospital acquired	61 (64%)

In 69% of the patients, AG was initiated empirically and 31% of the prescriptions were based on microbiological culture data. Among empirical treatment, 17% of the prescriptions were non-indicated.

Scores of AGs usage at Nemazee hospital was calculated as 5.9 out of 11, which meant that in only 54% of the cases AGs prescription was based on the aforementioned guideline.

Only for 31% of the patients, microbial culture was collected before treatment, and microbial culture was collected 48-72 hours after initiating therapy with AG for 47% of them.

In 83% of the cases AGs indication was correct. In 86% of patients, the first dose of AG was adjusted according to the patient's SCr.

The route of AG administration was appropriate for all patients, but loading doses were not administered for any of the patients. Also, therapeutic drug monitoring was not performed on any of the patients and dosage adjustments were determined as mg/kg dosing of the AG. Despite the differences between calculated creatinine clearance in the two formulas (MDRD and Cockcroft and Gault) in the studied population, there was no significant difference in dosage (p=0.12).

The response to treatment was assessed by clearance of cultures. In 19% of patients, response to treatment was not observed, and only for half of them appropriate action was taken; for 22%, AG dose was increased and for 78% of them the antibiotic was changed. Fifty-eight percent of the administered doses were appropriate.

In 21% of patients, nephrotoxicity was developed. In 60% of the patients who developed nephrotoxicity, no action was taken and in the remaining, the AG administration was discontinued. In 96% of patients, SCr was evaluated every day.

On the first day of AG administration, white blood cells count of 48% of the studied population was more than 10,000/ml. In contrast, only 28% of the study population had white blood cells counts above 10,000/ml at the end of treatment.

The treatment period in this study was 6.6 (SD 4) days, ranging between 2 and 18 days. Table 2 has shown the 11 studied indexes of AGs usage in this study.

DISCUSSION

Present study was conducted to evaluate the pattern of AGs prescription in 4 ICUs of a referral hospital in Shiraz, Iran. The results showed that the overall adherence of AGs usage to guideline is relatively inappropriate in the ICUs of Nemazee hospital. It seems that absence of pharmacists in the health team, lack of physicians' information about the pharmacokinetic of AGs, and inappropriate training and educational programs for physicians and nurses regarding the correct guideline implementation were the main reasons for non-adherence to AG treatment guidelines. In our study, in only 54% of cases AGs prescription was based on the guideline proposed by the Department of Clinical Pharmacy of Nemazee Hospital. The main errors in the prescription of AGs were lack of administration of loading dose, inappropriate dosing method, lack of re-evaluation in the case of required dose adjustments, and ignorance of the microbiological data.

In a similar study by Namazi *et al.*, conducted in the internal medicine ward of the same hospital, the usage pattern of amikacin, one of the most widely used AGs, was evaluated. Their results showed that the overall adherence of this drug's usage to the guideline was 48% and inappropriate dosing method, poor patient monitoring, and ignorance of microbiological data were the most common reasons for the none-adherence to standard guidelines.[26] In this study, serum concentration of Amikacin was assayed using a Cobas Mira AutoAnalyzer, but in our study the serum concentration of AGs was not assessed. In their study, they concluded that the desired peak and trough concentrations were obtained in 38% and 45% of the patients. Therapeutic drug monitoring (TDM) of AGs has become a standard practice in many clinical settings, but no serum level was measured for the patients in our hospital and the AGs dose was determined merely according to the patients' clinical status and some other data, such as the patient's GFR calculated by MDRD or G-C formula, as well as his weight. It was shown that AGs TDM can minimize toxicities, maximize efficacy, and improve health outcomes.[27]

In our study, AGs dosage was calculated according to the conventional method for all patients, and the prescribed dose was correct in 58% of the patients. Also, conventional method was used to calculate amikacin dosage in Namazi *et al*. study, but the prescribed dose was correct only in 25% of the patients. Using pharmacokinetic dosing can reduce the risk of adverse effects, such as nephrotoxicity and also allows administration of a significantly greater cumulative dose.[28]

Table 2. Eleven indexes of aminoglycosides use in the study population (n=95)

Index	Appropriately Performed
Loading dose	0%
Route of administration	100%
Dosing method	0%
Dose	58%
Indication	83%
Considering the patient's renal function before prescribing	86%
Monitoring serum creatinine level periodically during the treatment	96%
Evaluation of the microbiological culture before prescription	31%
Evaluation of microbiological culture 48-72 hours after administration	47%
Reducing the dose or discontinuation in patients who developed AGs nephrotoxicity	40%
Increase the dose or change the type of antibiotic if there is no appropriate response	47%

Also, in two other studies conducted in ICUs of Nemazee hospital, it was reported that the rate of Vancomycin and Colistin use, as two commonly used antibiotics in critically ill patients, were in accordance with standard guidelines in 47.3% and 67.3% of the cases, respectively.[11,29]

Adherence to AG guideline was also evaluated in a survey conducted in French healthcare facilities. They observed that in more than one third of patients, AG indications were inappropriate and the primary indication use was concordant with the guidelines in 65.2% of the cases. Unlike our study, AG serum concentration was measured in this survey and the results showed that only, in 62.9% of the cases, the AG dose was based on the recommended range.[30] In another Australian study, appropriateness of the initial dose of gentamicin dose was evaluated based on the local guidelines. Based on the existing hospital guidelines, their study result showed that 66% of the patients did not receive appropriate gentamicin initial dosage.[31] An adequate loading dose of AGs is critical to achieve rapid therapeutic drug levels. It was suggested that critically ill patients require larger doses of AGs loading dose due to considerable variation in their pharmacokinetic parameters and also the higher resistance of microorganisms in comparison with none-complicated infections.[32] Pleural effusion, ascites, mediastinitis and hypoalbuminaemia are associated with the expansion of extracellular space, which result in a lower than desirable Cmax with the usual loading dose. Thus, it is suggested to increase the loading dose in this specific population in order to improve the probability of attaining the target Cmax.[33] However, administration of the AGs loading dose was one of the issues that was apparently ignored by the clinicians in our hospital. One possible reason for this issue was lack of physicians' information regarding the pharmacokinetic of AGs. It seems that the clinicians were not aware of the necessity of administering loading doses to attain adequate drug concentrations immediately after the antibiotic administration.

In our study only in 31% of patients, AG administration was based on microbiological laboratory evidence while 69% of the cases received AGs empirically. It is worth mentioning that short term adjunctive treatment of sepsis with AGs in critically ill patients is suggested in some guidelines. The reasons for this suggestion are the ability of AGs to reduce the risk of inappropriate empirical therapy, sterilize the bloodstream faster and act synergistically with b-lactam antibiotics.[19,34] However, this approach has never been evaluated in randomized studies.[35]

Currently, many hospitals have developed and implemented local guidelines for the use of antimicrobial agents in the empirical treatment of infections.[36] A study conducted in the United States showed that limiting the use of antibiotics was considered in 56% of the newly published guidelines, and also in 81% of medical teaching centers.[37] Marquet *et al*. evaluated the inappropriateness of antibiotic therapy in critically ill patients with bloodstream infections in a systematic review and meta-analysis of 37 articles . The rate of inappropriate empiric antibiotic prescription varied between 14% and 79%. Approximately half of the studies reported the incidence of 50% or more. The mortality rates were significantly higher in patients receiving inappropriate antibiotics in studies with outcome parameter 28-day and 60-day mortality. Also, inappropriate antibiotic prescription increased the 30-day and in-hospital mortality rates.[38]

In our study, the results showed that 17% of AG prescriptions were inappropriate. To some extent, it is similar to the Thuong *et al*. study stating that the selection of primary antibiotics was appropriate for only 73% of patients.[36] Unspecified diagnosis, lack of documentation as to why antibiotics were prescribed for patient, inappropriate microbiological sample collection before prescribing and lack of reviewing the available results, might be the reasons of inappropriate prescription or its continuation.

In this study source of infection in 64% of the cases was reported to be hospital acquired. In another study on patients who were admitted to the ICU after surgery in France, the origin of infection in 55% of the cases was community and in 45% of the cases was hospital.[39]

Obtaining a second microbiological culture 48 to 72 hours after the starting AGs is recommended in order to evaluate patient response to treatment. In our study, only 47% of patients' cultures were collected from the site of infection at 48-72 hours after AG administration and the decisions for drug prescription were made based on that. One of the reasons for this issue is that the physicians in our center did not believe in the accuracy and precision of microbiological tests and they preferred to prescribe antibiotics according to their own experience and clinical judgement. During the study, nephrotoxicity was developed in 21% of the patients. The reported incidence of nephrotoxicity varies widely due to variations in study design, toxicity definitions, study population, and concomitant risk factors. A reasonable estimate (depending on definition) might be 10 to 20 percent, even when careful patient selection and close monitoring is performed.[40]

It is recommended that SCr should be evaluated regularly during AGs treatment. This study was conducted in the ICU and in the ICUs of our hospital the SCr is measured on a daily basis. Hence, in 96% of patients, SCr was measured every day. It seems that daily measurement of SCr level in hospitalized patients was considered as a routine practice for all patients without considering its changing trend.

In this study, creatinine clearance was calculated with both Cockcroft and Gault (C-G) and MDRD methods. Correct administration of the AGs dosage regimen according to correct dosing method using the two Cockcroft and Gault and MDRD equations was 58% and 57%, respectively. In one study conducted amongst Iranian adults, the authors concluded that MDRD and C-G formulas are accurate in Iranian adults, but it needs a correction factor.[41]

According to protocols, treatment of AGs-induced nephrotoxicity is basically supportive, including discontinuation of AGs (if possible) and substituting it with another non-nephrotoxic antibiotic. If this is not possible, the dose of AG should be adjusted and the interval between doses should be increased. Use of other nephrotoxic drugs should be avoided.[42] However, only in 40% of the cases with nephrotoxicity, administration of AGs was discontinued and no action was taken in the case of

the remaining patients. In Namazi *et al*. study, 19% of the patients developed nephrotoxicity due to amikacin, but only in 50% of the cases it was discontinued.[26] Several approaches including prescribing less nephrotoxic AGs when possible, extended interval dosing, therapeutic drug monitoring, using nebulized AGs, morning administration of AGs, daily monitoring of serum creatinine and using novel renal biomarkers such as kidney injury molecule-1 (KIM-1) which identifies AG-induced proximal tubular injury earlier than traditional markers have been suggested to prevent AG-induced nephrotoxicity.[43]

Considering the results of this study, developing a detailed plan is an essential step to improve the AGs usage pattern in the ICUs of our hospital. Clinical pharmacists should be incorporated in this setting to have an active role in prescribing AGs as well as pharmacokinetic consultation in the case of drug prescription for critically ill patients. Also, they can participate in arrangements held periodically for monitoring the utilization of drugs by stating their suggestions. They should be involved in training of medical and other healthcare personnel including physicians and nurses with respect to prescription, usage and administration of AGs. An evidence-based, peer reviewed local guideline should be developed in our ICUs based on the latest guidelines on the use of AGs in treating infections and regularly updated whenever new information becomes available. All the barriers to guideline implementation should be identified, using suitable strategies to overcome these barriers.

Limitations

Our study was a single center study and the sample size was relatively small. Hence, the results cannot be generalized. The incidence of adverse effects was not studied, since measuring some AGs side effects, such as hearing loss, required special instruments (audiometer) which were not available in these ICUs. Also, the studies that were performed to determine the incidence of adverse drug effects require very large sample sizes. Only the increase in SCr was evaluated as an indicator of renal toxicity as part of treatment assessment for AGs. On the other hand, the group with nephrotoxicity was at increased risk for toxicity due to other factors and not solely AG exposure.

CONCLUSIONS

In summary, the results of this study indicated that the overall adherence of AGs usage to guideline is relatively inappropriate in the ICUs of Nemazee hospital. Administration of the AGs loading dose is an issue that has not been taken into account in this center. Additionally, measurement of serum AG concentration was not performed in this hospital. It seems that consumption control and training programs are required to improve the pattern of AG usage in the ICUs of this hospital. Also, the presence of pharmacists in the ICUs of this center and providing pharmacokinetic consultation service can greatly help to increase the adherence of AGs usage to the guidelines.

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CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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Original Research

A descriptive study of antithrombotic medication patterns in adult patients with recent venous thromboembolism

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Abstract

Objectives: The objective of this study is to describe the most common self-reported antithrombotic therapy utilization patterns in a national cohort of patients with recent venous thromboembolism (VTE).

Methods: Extant data from a national online survey administered to 907 patients 18 years of age or older with VTE in the last two years were analyzed. Patients' self-reported antithrombotic usage patterns used during three phases of treatment for the most recent VTE episode were summarized using descriptive statistics.

Results: The following overall antithrombotic usage patterns were identified: warfarin (38.7%), direct oral anticoagulants (DOACs) (26.1%), switching between warfarin and DOACs (13.3%), aspirin only (8.7%), switching between different DOACs (4.5%), injectable anticoagulants only (3.9%), and no treatment (4.7%). Extended antithrombotic therapy beyond 90 days was reported by 65.7% of patients. Aspirin coadministration with anticoagulant therapy occurred for 33.7%.

Conclusions: In this national sample of recent VTE sufferers warfarin therapy remains the most used anticoagulant followed closely by DOAC therapy. Switching between warfarin and DOACs and between different DOACs was common which could indicate adverse events or affordability issues. Aspirin coadministration with anticoagulant therapy was present in 1 of 3 patients and is a potential medication safety intervention for anticoagulation providers.

Keywords

Anticoagulants; Thrombolytic Therapy; Venous Thromboembolism; Drug Utilization; Practice Patterns, Physicians'; Cohort Studies; Utah

INTRODUCTION

Venous thromboembolism (VTE) is a medical condition where a blood clot originates in the veins and is potentially life threating when clots embolize to the lungs.[1] The estimated average annual incidence rate of overall VTE ranges from 104 to 183 per 100,000 person-years.[2] These statistics and the relatively high cost of treating VTE underscore the importance of understanding VTE treatment strategies and their impact on the care of patients with VTE.[3]

VTE treatment generally consists of using anticoagulants.[4] Since its introduction in 1954, warfarin has been the mainstay of VTE treatment but is prone to drug and diet interactions and requires frequent dosing titration using the international normalized ratio (INR).[5] Due to recognized difficulties with warfarin, the direct oral anticoagulants (DOACs) are becoming increasing prescribed for VTE management. Recent randomized clinical trials show that DOACs are safer and either more effective or non-inferior to warfarin in the treatment of VTE.[4] Additionally, evidence-based guidelines now recommend DOACs as the drugs of first choice for VTE treatment over warfarin.[4]

Studies have analyzed prescribing trends of warfarin and DOACs for stroke prevention in atrial fibrillation and show an increasing utilization of DOACs.[6] General prescribing trends for oral anticoagulants in the treatment of VTE have recently been published, but anticoagulant utilization data for VTE treatment during different stages of therapy (initial, long-term and extended) are not available.[7] Furthermore, most data regarding prescribing trends is derived from electronic pharmacy claims data which have known limitations, including discrepancies between drug prescribing and actual drug taking behavior, and missing data.[8] Further, electronic pharmacy claims data is often limited to a particular healthcare system or insurance type (e.g., Medicare, Medicaid). Information on injectable anticoagulants such as heparin, low-molecular-weight heparin and fondaparinux, and concomitant aspirin use as well as information regarding patients who switch between anticoagulant types during VTE treatment is also needed to better characterize the realities of anticoagulant utilization during various phases of VTE therapy. Previous studies have provided evidence that self-reported medication use

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reports may provide a more complete picture of individuals' current medication profiles than do electronic pharmacy claims data.[9,10] Thus, for the purpose of collecting medication information to ascertain what medications individuals are actually taking at a particular time self-reported data may be better than electronic claims data. Therefore, the purpose of this study was to describe the most common self-reported anticoagulant therapy utilization patterns during three phases of VTE treatment including injectable anticoagulants, concomitant aspirin use, and switching between anticoagulants in a large, national cohort of patients with recent VTE who completed a comprehensive online survey regarding their VTE experiences.

METHODS

Sample and procedure

The study was approved by the University of Utah's Institutional Review Board (IRB) before initiating data collection. All participants provided informed consent prior to commencing the survey. The survey sample was comprised of participants recruited by an independent contract research agency (Hall & Partners, New York, NY) from a nationally representative panel of consumers who pre-enrolled to participate in research studies (Research Now®, Research Now Group, Inc., New York, NY). Between May and July 2016 eligible patients accessed and completed an online survey, through a link in an invitation e-mail. Patients eligible to complete the survey were those aged 18 years or older who experienced at least one VTE event in the past 2 years. Patients diagnosed with cancer within the past 2 years were excluded. A sample size of approximately 1,000 patients was targeted to provide sufficiently accurate estimates for meaningful subgroups of interest, such as antithrombotic therapy usage patterns during the various phases of VTE treatment.

Survey

Patients indicated the number of VTE events they had experienced in their lifetimes, types of VTE experienced whether deep vein thrombosis (DVT) and/or pulmonary embolism (PE), and the type and timing of their most recent VTE event (within the past month, between 1 to 3 months ago, 3 to 12 months ago, and more than 12 months ago). The survey asked a comprehensive array of questions related to VTE treatment as described in detail previously.[11-13] However, the primary outcome for this study related to antithrombotic treatment pathways used during three phases of treatment for the most recent VTE episode. Antithrombotic medication use was categorized in the initial phase (days 0-7 since VTE diagnosis), long-term phase (days 8-90) and extended phase (90+ days). Patients indicated which oral and/or injectable antithrombotic medications they had been prescribed for their most recent VTE event in each of these time periods. Patients selected single or multiple agents from the following choices: injectable anticoagulants (unfractionated heparin, low-molecular-weight heparin, and fondaparinux); warfarin; DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban); and aspirin. Patients could also report if no antithrombotic medications were prescribed.

Table 1. Baseline characteristics of cohort of patients with recent VTE (N=907)

Characteristics	Result
Age (years), Mean (SD)	52.4 (14.4)
Female (%)	514 (56.7)
Race (%)	
Caucasian	804 (88.6)
African American	62 (6.8)
Asian/ Pacific Islander	28 (3.1)
Native American/ Alaskan Native	16 (1.8)
Other	20 (2.2)
Comorbidities (%)[a]	
Anxiety	242 (26.7)
Depression	258 (28.4)
Diabetes	156 (17.2)
Heart disease	249 (27.5)
High blood pressure	414 (45.6)
High cholesterol	347 (38.3)
Stroke or TIA	77 (8.5)
PE	306 (33.7)
DVT	769 (84.8)
Most recent VTE Type	
PE	164 (18.1)
DVT	579 (63.8)
PE + DVT	164 (18.1)
Number of VTE in lifetime, median (IQR)	2.0 (3.0)
Number of VTE in past 2 years, median (IQR)	2.0 (1.0)
VTE within past month (%)	77 (8.5)
Insurance	
Through employer	319 (35.2)
Medicare	308 (34.0)
Medicaid	128 (14.1)
Uninsured	24 (2.6)
Other	128 (14.1)
Household income, annual <$50,000 (%)	337 (37.2)

[a]Patients could select more than one comorbidity
SD-standard deviation, TIA-transient ischemic attack, PE-pulmonary embolism, DVT-distal venous thromboembolism, VTE-Venous thromboembolism, IQR-interquartile range.

Analysis

The proportions of patients corresponding to the various treatment pathways in each treatment phase were calculated by dividing the number of patients in each pathway by the total number of patients. Overall anticoagulant pathways were also assigned to each patient considering only anticoagulants used during days 8 to 90+. The proportions of patients who used injectable anticoagulants and/or aspirin in addition to other anticoagulants in each treatment phase were also calculated. Data was summarized using basic descriptive statistics, for example proportions for categorical variables and means and standard deviation (SD) or median and interquartile range (IQR) for continuous variables.

RESULTS

A total of 4,092 patients had access to the online survey. The data set included 971 who completed the survey and 64 patients were removed from the data set for reasons that included no VTE within past two years, choosing none of the medication options during most recent VTE treatment, and completing the survey in an unrealistically short amount of time (less than 6 minutes). A total of 907 patients were included in the final analysis (Table 1). The mean (SD) age of patients was 52.4 (14.4) years and 56.7

Table 2. Prevalence of self-reported anticoagulation use during various treatment phases

Anticoagulation medication pathway	Initial phase (First 7 days since diagnosis) (%)	Long-term phase (8 to 90 Days since diagnosis) (%)	Extended phase (90+ days since diagnosis) (%)	Overall (%)
Injectable anticoagulants only	355 (39.1)	47 (5.2)	14 (1.5)	35 (3.9)
Warfarin	244 (26.9)	349 (38.5)	239 (26.4)	351 (38.7)
DOAC	147 (16.2)	242 (26.7)	187 (20.6)	237 (26.1)
Switched between different DOACs	23 (2.5)	33 (3.6)	8 (0.88)	41 (4.5)
Switched between warfarin and DOACs	52 (5.7)	72 (7.9)	20 (2.2)	121 (13.3)
Aspirin only	46 (5.1)	80 (8.8)	128 (14.1)	79 (8.7)
No treatment	34 (3.7)	84 (9.3)	311 (34.3)	43 (4.7)

DOAC-direct oral anticoagulant

percent were women. In the overall population, the most common comorbidities were hypertension (45.6%), hyperlipidemia (38.3%), depression (28.4%), heart disease (27.5%), anxiety (26.7%), and diabetes (17.2%). The most recent VTE episode was deep vein thrombosis (DVT) in 63.8 percent, pulmonary embolism (PE) in 18.1 percent, or both DVT and PE in 18.1 percent of patients.

We identified the following antithrombotic usage patterns: injectable anticoagulants only, aspirin therapy only, warfarin, DOACs, patients who switched between warfarin and DOACs, patients who switched between different DOACs, and no treatment (Table 2). Overall, 38.7% of patients received warfarin-based treatment, 26.1% DOACs, 8.7% aspirin monotherapy and 3.9% injectable therapy only. 13.3% of patients switched between warfarin and DOACs, 4.5% switched between different types of DOACs, and 4.7% reported not receiving any of these treatments.

During the initial treatment phase, some responses were deemed implausible (e.g., respondent selected all types of anticoagulant therapy) and were excluded from the analysis for that phase. The proportion of patients receiving injectable anticoagulant monotherapy, mainly low-molecular-weight heparin, during the first 7 days of treatment was 39.1% declining to 5.2% and 1.5% during days 8-90 and 90+, respectively. During the first 7 days of treatment 48.4% of warfarin patients also received injectable anticoagulants, compared to 38.1% of DOAC patients (Table 3). 82.6% and 67.3% of patients who switched between different DOACs and between warfarin and DOACs also received injectable anticoagulants during the first 7 days of therapy, respectively. Concurrent injectable use dropped sharply after the first 7 days of therapy, but was still more common in patients who switched between warfarin and DOACs or between different DOACs. The proportion of patients receiving extended anticoagulant therapy beyond 90 days was 65.7%. Aspirin coadministration with anticoagulant therapy

Table 3. Prevalence of self-reported concurrent injectable anticoagulant and aspirin use during various treatment phases

	Injectable (%)	Aspirin (%)
Initial Phase (First 7 days since diagnosis)		
Injectable only (N= 355)	NA	59 (16.6)
Warfarin (N= 244)	118 (48.4)	75 (30.7)
DOAC (N= 147)	56 (38.1)	41 (27.9)
Switched between different DOACs (N= 23)	19 (82.6)	13 (56.5)
Switched between warfarin and DOAC (N= 52)	35 (67.3)	28 (53.8)
Aspirin only (N=46)	0	NA
No treatment (N=34)	0	0
Long-Term Phase (8 to 90 days since diagnosis)		
Injectable only (N= 47)	NA	9 (19.1)
Warfarin (N= 349)	49 (14.0)	80 (22.9)
DOAC (N= 242)	16 (6.6)	58 (24.0)
Switched between different DOACs (N= 33)	9 (27.3)	12 (36.4)
Switched between warfarin and DOAC (N= 72)	15 (20.8)	37 (51.4)
Aspirin only (N= 80)	0	NA
No treatment (N= 84)	0	0
Extended Phase (90+ days since diagnosis)		
Injectable only (N= 14)	NA	6 (42.9)
Warfarin (N= 239)	8 (3.4)	68 (28.5)
DOAC (N= 187)	4 (2.1)	56 (29.9)
Switched between different DOACs (N= 8)	1 (12.5)	3 (37.5)
Switched between warfarin and DOAC (N= 20)	5 (25.0)	8 (40.0)
Aspirin only (N= 128)	0	NA
No treatment (N= 311)	0	0
Overall		
Injectable only (N= 35)	NA	15 (42.9)
Warfarin (N= 351)	62 (17.7)	133 (37.9)
DOAC (N= 237)	17 (7.2)	84 (35.4)
Switched between different DOACs (N= 41)	9 (22)	14 (34.1)
Switched between warfarin and DOAC (N= 121)	22 (18.2)	60 (49.6)
Aspirin only (N= 79)	0	NA
No treatment (N= 43)	0	0

DOAC-direct oral anticoagulant

occurred in 33.7% of patients ranging from 34.1% (patients switching between different DOACs) to 49.6% (patients switching between warfarin and DOACs).

DISCUSSION

In this study, we identified self-reported antithrombotic utilization patterns during various VTE treatment periods (0-7, 8-90 and 90+days) in a large national sample of recent VTE patients who completed an online survey. We were able to discern seven distinct antithrombotic utilization patterns. The results revealed that warfarin-based therapy was the most prevalent overall anticoagulant used to treat VTE, followed by DOACs. These results differ from those reported in a retrospective cohort analysis of 12,390 commercially insured adults treated with oral anticoagulants for VTE diagnosed between 2010 and 2016.[7] The percentage of patients treated with warfarin decreased from 99.9% to 34.0% while the use of DOACs increased from <0.1% to 66.0%. Possible explanations for why DOACs had not overtaken warfarin in our study population include the fact that only a third of patients who took the survey indicated that they were commercially insured. Further approximately a third of our patient population reported an annual household income over USD50,000. Thus, affordability issues may have resulted in a greater proportion of patients in our study opting for warfarin as the less expense anticoagulant option. This may also explain why some patients switched between anticoagulants during the various VTE treatment phases.

Switching between anticoagulant types was common; both between warfarin and DOACs and between different types of DOACs. We were not able to discern the specific sequencing of anticoagulants nor the reasons for switching. We speculate that possible reasons for switching between anticoagulants could include cost, adverse events, health plan formulary considerations, and patient and/or provider preferences. Further study is needed to determine the specific reasons why patients switch between anticoagulants.

We also described the concurrent use of injectable anticoagulants during various phases of VTE treatment. The use of injectables in addition to oral anticoagulant therapy was most common during the first 7 days of treatment. The use of injectable anticoagulants is common with initiation of warfarin therapy. However, less than half of patients who reported taking warfarin during the first 7 days of therapy also reported receiving injectable anticoagulants while a high number of patients reported receiving only injectable anticoagulants during the initial 7 days of therapy. The reasons behind this finding are unknown but could be related to some patients receiving initial therapy in the hospital where it may not have been clear which anticoagulants were being administered. Injectable anticoagulant use was common in the initial 7 days even in patients who received DOAC therapy, a finding which requires further study as a potential advantage of DOACs (apixaban and rivaroxaban) over warfarin is no need for injectable anticoagulation. Injectable anticoagulant use decreased during days 8-90 and 90+ as would be expected. The use of injectable anticoagulants was higher in patients who switched between warfarin and DOACs and between different DOAC types in all phases of treatment. Reasons underlying this observation are unknown but could include the management of recurrent VTE or the use of bridge therapy during anticoagulant therapy transitions, especially from DOACs to warfarin. DOAC prescribing information suggests use of parenteral anticoagulants as one approach that can be used during transitions from DOACs to warfarin.[14-16]

We observed a high prevalence of combined anticoagulant and aspirin use that is similar to that reported in other observational studies.[17,18] Combined use of anticoagulants and aspirin has been associated with increased risk for major bleeding without concomitant benefit in terms of thromboembolic event prevention.[17] Anticoagulant providers should carefully watch for unnecessary aspirin use during the treatment of VTE and discontinue aspirin in patients without a valid indication for combined therapy.

This study was unique in the use of anticoagulant utilization data derived from patient self-reports instead of pharmacy claim data. Self-reported anticoagulant use may provide a more realistic snapshot of actual anticoagulant use than pharmacy claims data where whether the patient actually took the prescribed medication may not always be clear.[9,10] However, self-reported data is also subject to recall bias, by both over and under reporting of actual anticoagulant use. We were unable to determine the specific sequencing of switches between warfarin and DOACs and between specific DOACs and the rationale for switching between agents. We were also unable to determine the specific reasons why patients were receiving concurrent aspirin therapy or reported receiving no therapy. We included data from a large national sample of recent VTE sufferers which increase the generalizability of results. However, this study required access to an online survey which might introduce some selection bias where participation was limited to a population who had access to computers.

CONCLUSIONS

Overall, anticoagulant utilization in patients with recent VTE remained predominated by warfarin followed closely by DOACs. Given that DOACs are now recommended over warfarin by evidence-based guidelines, our results indicate that some patients and prescribers continue to prefer warfarin and that anticoagulant prescribing for VTE treatment needs to evolve to be more consistent with contemporary guideline recommendations. Switching between warfarin and DOACs and between different types of DOACs was common early in therapy which could indicate adverse events or affordability issues. Reasons for switching between anticoagulant therapies during VTE treatment requires additional study. Concurrent injectable anticoagulant use was common during the first 7 days of therapy even among patients prescribed DOACs which indicates prescribers may not be taking full advantage of the rapid onset of effect associated with DOAC therapy. Aspirin therapy was frequently coprescribed with all anticoagulant therapy types and is a potential target for medication safety interventions by anticoagulation providers as updated consensus guidelines no longer recommend indefinite aspirin following percutaneous coronary intervention and use of combined therapy of

aspirin with oral anticoagulant therapy has been shown to increase the risk of bleeding without providing additional protection against thromboembolic complications.[17,19]

CONFLICT OF INTEREST

Dr. Feehan has consulted to Pfizer previously. All other authors have no conflicts of interest to report.

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Original Research

Culture of antibiotic use in Kosovo - an interview study with patients and health professionals

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Abstract

Background: Kosovo is a new state and has a high consumption of antibiotics in relation to other European countries. Existing quantitative studies have shown that practices exist that is not optimal when it comes to antibiotic use in Kosovo, this includes citizens' use of antibiotics, pharmacy practices of selling antibiotics without prescriptions and physicians' prescribing behaviours. To address these problems, there is a need for a deeper understanding of why antibiotics are handled in a suboptimal way.

Objective: The objective was to explore antibiotic users', community pharmacists' and prescribers' attitudes towards, experiences of, and knowledge about antibiotics in Kosovo.

Methods: Semi-structured interviews were conducted with patients who recently received an antibiotic prescription for an upper respiratory tract infection (URTI), patients who recently received antibiotics for a URTI without a prescription, community pharmacists, and physicians. Interviews were recorded, translated into English, and analysed using deductive content analysis.

Results: In total, 16 interviews were conducted in the period from 2015-2016. Five themes were identified: Obtaining antibiotics, Choice of antibiotics, Patient information, Patients' knowledge and views on when to use antibiotics, and Professionals' knowledge and attitudes towards antimicrobial resistance. Antibiotics were sometimes obtained without a prescription, also by patients who currently had received one. The specific antibiotic could be chosen by a physician, a pharmacist or the patient him/herself. Former experience was one reason given by patients for their choice. Patients' knowledge on antibiotics was mixed, however health professionals were knowledgeable about e.g. antimicrobial resistance.

Conclusions: There is currently a culture of antibiotic use in Kosovo, including attitudes and behaviours, and hence also experiences, which is possibly underlying the high consumption of antibiotics in the country. The culture is reproduced by patients, pharmacists and physicians. There is, however, an awareness of the current problematic situation among practitioners and policy makers; and as Kosovo is a new country, opportunities to effectively tackle antimicrobial resistance exist.

Keywords

Drug Resistance, Bacterial; Anti-Bacterial Agents; Respiratory Tract Infections; Drug Misuse; Attitude; Pharmacists; Pharmacies; Qualitative Research; Kosovo

INTRODUCTION

Antimicrobial resistance is a global problem. The WHO states that "Antibiotic resistance is one of the biggest threats to global health, food security, and development today".[1] Inappropriate use and misuse of antibiotics play a large role in this accelerating problem. Suboptimal use of antibiotics is affected by many stakeholders involved in the different steps of the medicine use chain, i.e., prescribers and their practices, the actual availability of antibiotics, pharmacy dispensing practices and patients' behaviours. Inappropriate use is influenced by both attitudes towards and knowledge of antibiotics, which are factors on an individual level; however, these factors are affected by the context in which patients and health care professionals live and practice.[2-6] For example, it has been shown that social norms influence prescribing behaviours.[6]

Kosovo is a new state and has a high consumption of antibiotics in relation to other European countries.[3] Additionally, the health care system is still under development, e.g., there is no reimbursement system, and regulations are not always followed.[3,7] A survey conducted with citizens of Kosovo in 2014 showed that 58,7% of respondents had used antibiotics during the last year and that 25% of the respondents obtained these antibiotics without a prescription, despite prescriptions being mandatory by law. To a large extent, the antibiotics were used to treat conditions that were most likely caused by viruses, e.g., the common cold, a sore throat, and the flu.[3]

Hence, in Kosovo, there is a problem with citizens' use of antibiotics, pharmacy practices of selling antibiotics without prescriptions and physicians' prescribing behaviours. To address these problems, there is a need for a deeper understanding of why these situations occur. The aim of the study was therefore to explore the attitudes, experiences and knowledge of users, pharmacists and prescribers towards antibiotics in Kosovo.

METHODS

As the aim was to, more in-depth, explore attitudes, experiences, and knowledge, a qualitative approach was most appropriate.[7] The qualitative study is part of a larger project with the aim of understanding the reasons for inappropriate use of antibiotics in non-EU eastern European countries.[2,9,10]

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Semi-structured, individual, interviews were conducted with four groups of people; these were: Patients who recently received a prescription for one of the antibiotics (see below), patients who recently received one of the antibiotics without a prescription (i.e., bought it directly at a pharmacy), community pharmacists, and physicians with recent experience of dispensing or prescribing antibiotics and hence were key persons in the process of handling and using antibiotics.

In all cases, the focus was on certain antibiotics, i.e., amoxicillin-clavulanic acid, azithromycin, ciprofloxacin or ceftriazone, for an upper respiratory tract infection (URTI). The specific choice of these antibiotics was based on a consumption survey in the area of south-eastern Europe, indicating that these types of antibiotics were used in a non-rational manner.[11] The choice of URTI was in order to better compare participants' attitudes and experiences of using antibiotics due to more homogeneous data and because symptoms related to URTI are often treated with antibiotics. Hence, patients were enrolled if they both had suffered from an URTI and used one of the four specific antibiotics to cure it.

The interview guides were developed in a larger project (please see Online appendix 1).[9] Here, a recognized physician and researcher within use of antibiotics and an experienced community pharmacist and researcher in social pharmacy (specialized in qualitative methods) developed the interview guides based on their knowledge of the research field.

The patient interviews included questions about their last experience of antibiotic use, including consultation with a physician (where relevant), communication with and experience of the pharmacy/pharmacist, and knowledge about and attitudes towards antibiotics, e.g., when they should or should not be used. In the pharmacist version of the interview guide, pharmacists were asked to give examples of and describe three consultations involving antibiotics for a URTI during the last week, including information about whether they themselves had diagnosed the patients, the choice of antibiotic (if not a prescription), and patient communication. Pharmacists were also asked about the use of guidelines, satisfaction with the procedures, attitudes towards the use of antibiotics, antimicrobial resistance, and information sources. For physicians, questions included how often they prescribed antibiotics for a URTI, what were their general attitudes towards antibiotics, when should they be used, and what were their sources of information. Physicians were also asked to describe three recent consultations that included an antibiotics prescription for a URTI, e.g., diagnosis, patient expectations, instructions given, and if guidelines existed and were used to guide the prescription process.

An effort was made to obtain a heterogeneous sample in terms of age and sex, e.g. purposive sampling. Respondents in the patient groups were however recruited mainly via snowballing. Interviewers (authors 1 and 2) asked people they knew to find someone who had recently taken antibiotics and who was willing to participate in the study. Respondents in the health professional groups were recruited within the interviewers' professional networks – direct collaborators or colleagues of these – while avoiding interviewing people personally known by the interviewers. Eligible persons were then informed about the study before being asked to participate.

Interviewers were specifically trained by researchers from Copenhagen University to conduct the interviews. The interviews with patients were conducted in the Albanian language at the patient's workplace or in a café. Interviews with physicians and pharmacists were conducted at their workplace. Interviews were documented thoroughly during and immediately after the interviews. The documentation was then translated into English by the second author before analysis.

The analysis was based on the topics in the interview guide (i.e., deductive or directed content analysis), first within each of the four groups of interviewees, and was conducted separately by authors 1, 2 and 4 and then processed in a consensus meeting.[12] This was followed by an analysis that merged the four groups, also in a consensus meeting. The analysers had different professional (pharmacists/social scientists) and cultural (Balkan/ Nordic) backgrounds, thus giving supplementary perspectives in the analysis and allowing more nuances to be identified.[9] During the analysis not only the words used but also the context was discussed. This was necessary but also advanced the analysis since the researcher who was 'naïve' in the context asked other questions to the material, while the researchers from within the context could interpret findings from inside the context. The knowledge of pharmacists and prescribers were assessed according to whether they made explicit comments about the difference between viruses and bacteria (and that antibiotics don´t kill viruses), and if antimicrobial resistance was recognized.

Ethical approval was not required for this study in Kosovo. However, ethical requirements were fulfilled; respondents were informed about the study, including that interviewers were pharmacists and part of an international research project. Respondents were also given assurance about their anonymity, and told that they had the right to withdraw. All respondents gave verbal consent to be included in the study before the interview. In Denmark, a permit was obtained from the Faculty of Health and Medical Sciences, University of Copenhagen on behalf of the Danish Data Protection Agency to analyse and store the data (j. nr. SUND2016-30).

RESULTS

In total, 16 persons were interviewed in the period from 2015-2016: 4 users/patients with prescriptions for antibiotics (age 24-43, two female), 4 users/patients without a prescription (age 34-46, two female), 4 pharmacists (age 27-42, one female), and 4 physicians (3 GPs and 1 specialist, age 34-64, one female). Four patients had a university degree; two of the pharmacists were pharmacy owners. Interviews lasted for approximately 30-40 minutes.

Quotes are used to illustrate the results. Each interviewee was given a number. It is documented which of the four groups the interviewee belonged to.

Obtaining antibiotics

According to both patients and pharmacists, symptoms for which antibiotics were used were typically a cough, sore throat and/or fever – also described as cold or flu/flu-like symptoms.

Patients with a prescription had typically waited 2-3 days before going to see a physician. Their expectations were to obtain a cure from the physician, i.e., a prescription for antibiotics. Rationales for not consulting a physician given by patients without a prescription included previous positive experiences with specific antibiotics and that their choice of antibiotics at the time was based either on their own experience or on advice from a colleague or family member. Additionally, negative experiences were used as rationales, such as previously having taken an antibiotics that did not help (i.e., not trusting the physician), not thinking a consultation would add anything, or that they had already received enough information about how to use the antibiotics from the pharmacist.

> "Each time I visited the doctor he prescribed me these antibiotics/…/so that's why I thought it was unnecessary to visit the doctor, because he would prescribe me the same antibiotic." (Patient nonprescr 4).

> "These were flu-like symptoms and I did not want to wait too long. I don't always go to the doctor – it's the dynamics of life. The pharmacy is near where I live and the pharmacist is very professional." (Patient nonprescr 2)

Some of the patients with a prescription reported that even if they had consulted a physician this time, they sometimes went directly to the pharmacy to buy antibiotics.

> "While I think that antibiotics should not be used without a doctor consultation, the majority of my friends and colleagues are ready to use antibiotics on their own initiative. I always consult with a professional, at least with the pharmacist/…/ [pharmacies] are a good place to go before taking antibiotics, because pharmacists have sufficient knowledge about drugs and diseases." (Patient 3)

The pharmacists' view was in line with the patients' view, i.e., that patients go directly to the pharmacy to get antibiotics because they either trust the pharmacist to have the knowledge necessary or they themselves have had experience and know what they want. "…enough with a pharmacist who is half a doctor." (Pharmacist 1)

However, pharmacists reported in some cases having tried to convince the patients not to take antibiotics or to go to a physician. This sometimes succeeded but mostly did not. "The patient was determined to get his antibiotic and he didn't want any advice." (Pharmacist 4)

Choice of antibiotic

All interviewees with a prescription stated that the specific antibiotic was chosen by the physician alone, without any involvement or pressure from the patient. When asked how the physician knew how to choose the antibiotic, the patients believed that it was from experience or from test results. This was in line with physicians' reporting about choosing antibiotics based on symptoms, knowledge and experience, although factors such as known allergies and the patients' economic situation were also mentioned by physicians as possible bases for choosing among antibiotics.

In the cases presented by the pharmacists, most often the patient had chosen the antibiotics themselves. "…he said 'I know what I have and what I should use'." (Pharmacist 4). The patients without a prescription also reported that they chose the medicine themselves. Former experience with the AB and their perception that the antibiotic was "strong" were mentioned by the patients as reasons behind their choices.

> "I heard that it was stronger and cephalexin didn't have an effect."(Patient nonprescr 1)

> "I selected this antibiotic [amoxicillin] because I think it is stronger than ampicillin, based on my experience." (Patient nonprescr 4)

However, pharmacists also reported that they sometimes chose the antibiotic or that the antibiotic was, directly or indirectly, chosen by a physician: directly in the sense that, in one case, the physician had told the patient what to use but had not written a proper prescription; indirectly, as in cases where the patients used earlier experiences with antibiotic prescribing "Because his idea is that doctors always prescribe the same antibiotic so he suggests taking amoxicillin or amoxiclav." (Pharmacist 2). When the pharmacists chose the antibiotic, they said they either made a choice based on experience or looked for the presence of purulent discharge on tonsils.

Patient information

Almost all patients said they received instructions from the physician (those who had visited a physician) as well as the pharmacist on how to use the antibiotic. Patients with a prescription reported that those instructions were similar from both professionals; at least they had not experienced receiving conflicting instructions or information.

The patients stated that they had followed the instructions. However, one patient also reported having increased the dose when the antibiotic did not help.

> "Actually, I started with one capsule three times a day, but my throat pain became more severe, so I increased the dosage to two capsules three times a day to get faster results." (Patient nonpresc 4).

Physicians and pharmacists also reported always giving instructions on how to use the medicine, and many specifically mentioned instructions about dosage.

Patients' knowledge and views on when to use antibiotics

When asked about how ABs work, there were examples of respondents who were clear about this. "Antibiotics fight the disease and eliminate bacteria." (Patient 1) and examples of those who were not as lucid "Antibiotics cure you, but how – I don't know." (Patient 4). However, other factors, such as time, were also mentioned: "[Antibiotics] have a faster effect." (Patient nonprescr 2).

Those who were more knowledgeable mentioned "when infected with bacteria." (Patient 3). "Antibiotics are used when we have bacteria in our body, when the disease does not go away by itself or when drinking tea, taking vitamins or eating fruit doesn't help." (Patient nonpresc 1)

When asked about sources of information, answers typically referenced family, physicians, pharmacists, the internet, patient information leaflets, magazines or experience. A television campaign from the Kosovo medical agency was also mentioned by a few of the patient respondents.

Patients' attitudes towards when antibiotics should be used were typically focused on severe diseases: "More problematic diseases" (Patient 1) and "Internal fever" (Patient 2). However, other reasons were also given: "I have used antibiotics before/…/ I purchased them only for throat problems." (Patient nonprescr 4).

One respondent specifically said that she was hesitant to give antibiotics to her children, for whom she wanted tests conducted and a physician's advice. However, for herself, it was a different matter: "For myself, I use antibiotics more freely, and I don't do blood analyses." (Patient 4).

Professionals' knowledge and attitudes towards antimicrobial resistance

Pharmacists said they updated their knowledge mostly through the internet but also relied on other methods, e.g., continuing education and discussions with colleagues. Physicians reported getting knowledge from education, colleagues, and experience.

All pharmacists and all the physicians but one stated there were no national guidelines available in the country. However, one physician mentioned the standard therapeutic guideline for primary care from the Ministry of Health.

Both professions were knowledgeable about when antibiotics should be used and also knew that they were being used in a suboptimal way in the country. They were also aware of antimicrobial resistance and considered it to be a problem in Kosovo.

> "Patients are used to abusing antibiotics, and they purchase them by themselves. However, I try to discourage such behaviour." (Physician 3)

The physicians considered pharmacies selling antibiotics without prescriptions and people using antibiotics abundantly as the main causes of overuse. Likewise, physicians were identified by the pharmacists as a cause; here, the influence of marketing activities from the pharmaceutical industry was specifically mentioned. However, pharmacists also reported the possible influence of the pharmaceutical industry on pharmacists.

> "[Antibiotics are] sold freely in pharmacies, especially amoxicillin/…/used for mild tonsillitis and for allergic rhinitis, and they are given by unprofessional people in pharmacies. In addition, people use antibiotics for a day or two and then stop the treatment."(Physician 2)

> "Unfortunately, even doctors get influenced by certain pharmaceutical companies to prescribe different antibiotics even for mild cases." (Physician 4)

> "Every day, a medical [industry] representative visits our pharmacy, but I don't think they have the intention to foster good practices. They are only there for marketing purposes." (Pharmacist 4)

All the pharmacists thought that antibiotics should only be sold with a prescription. However, even though they chose to sell without a prescription, some added that they tried to have a conversation with the patients to ensure that the antibiotic was the right treatment.

> "I try to fully respect good professional service, but there are some cases/…/when patients insist on taking an antibiotic, and if I don't give them, they will simply go to another pharmacy." (Pharmacist 3).

> "This [selling without a prescription] is the culture in our society." (Pharmacists 2)

DISCUSSION

The aim of this study was to explore antibiotic users', community pharmacists' and prescribers' attitudes towards, experiences of, and knowledge about antibiotics in Kosovo. Five themes were identified: Obtaining antibiotics, Choice of antibiotics, Patient information, Patients' knowledge and views on when to use antibiotics, and Professionals' knowledge and attitudes towards antimicrobial resistance. Results are further discussed below.

Some of the reasons behind the identified high consumption of antibiotics in Kosovo, appears to be based in the current practices of antibiotic use, in which antibiotic are used a great deal, and sometimes, they also seem to be the first choice for minor ailments, such as colds, coughs and "flu-like" symptoms.[7] This can be interpreted as a suboptimal antibiotic culture, which, when it comes to patients, also has been confirmed by other studies.[3,7] and it is, to some extent, also supported by the behaviours of pharmacists and physicians as reported in this study. This culture is reproduced e.g. when patients seek advice from family and unspecified web sites, and when pharmacies are selling antibiotics without prescriptions. There is seemingly not enough, or not strong enough opposition to this culture.

Hence, this study relying on a qualitative methodological approach contributed to the existing literature in the field by showing not only that, but how a culture of suboptimal use of antibiotics works and is reproduced. This kind of culture has also been shown to exist in other countries in the area, e.g., Serbia and Albania.[2,5] In a survey conducted with patients in Serbia, almost 60% believed that antibiotics could treat common colds.[5] A quantitative study in Albania showed that of 259 pharmacies visited, 80% dispensed antibiotics without a prescription, and a qualitative study in the same country reported how both patients and health care professionals found that antibiotics were the best remedy to use in the case of colds and flus, and like in this

study, that antibiotic treatment was sought after only a few days of symptoms.[2,13] Even if the problem is regional, national interventions are needed to change the current practice. In Kosovo, a television campaign about the use of antibiotics from the Kosovo medicines agency was mentioned by a few patients, and while this can be a first step, more fundamental changes are necessary.

Another potential problem seen was that microbiological tests were mentioned only occasionally as a basis for antibiotic prescriptions, but all respondent groups mentioned former experience more frequently. This could be because there is a lack of resources in the country, and hence, tests are not always available. The consequence of not using microbiological tests when diagnosing infections is uncertainty of appropriateness of antibiotic use, as it will not be clear if the infection is caused by a virus, for which antibiotics are ineffective, or bacteria. However, antibiotics are not always effective even if bacteria are involved, because of the bacterial resistance, which can only be detected by microbiological tests.

Only one physician mentioned the existence of guidelines for prescribing antibiotics. At the time of the interviews, the Ministry of Health had developed a draft of guidelines; however, they have not been officially implemented. A first step from the government would be to implement and inform health care professionals about these guidelines. However, there is a question about how much guidelines will affect prescribing behaviour and practice in pharmacies. Earlier studies have shown that colleagues' perceptions and behaviours may have more impact on physicians' prescribing behaviours than guidelines.[6]

At the time of the study, pharmacists in Kosovo seemed to dispense antibiotics without prescriptions and without a proper indication. This practice occurred in spite of pharmacists' knowledge about antibiotics and their awareness of the problems associated with antimicrobial resistance. It is illegal to sell antibiotics this way.[7] The reason given by pharmacist interviewees for this behaviour was pressure from the patient, but it is also possible that it directly or indirectly was influenced by factors related to the financial turnover of the pharmacy. This has also been shown in other settings.[10] The financial incentives are hard to work against. Since 2017, i.e., after data collection for this study was conducted, the pharmaceutical inspectorate of Kosovo has been auditing pharmacies for sales of antibiotics for which pharmacies have to provide a valid copy of a prescription. The outcome of these inspections has yet to be studied.

In the interviews, both physicians and pharmacists were, according to some respondents, influenced by marketing activities from the pharmaceutical industry. Hence, there are several mechanisms leading to financial incentives being more influential than health aspects. In a young country with a restrained economy, both on the state level and for many individuals, this is not surprising.

The influence of contextual mechanisms on antibiotic prescribing and dispensing were recently also described in a report by the Antimicrobial Resistance Centre at the London School of Hygiene & Tropical Medicine for the WHO.[14] The aim of the report was to situate awareness of antimicrobial resistance and knowledge of antibiotics within the lived experience of prescribing and dispensing across a range of Low and Middle Income Countries settings. The results showed that despite high level of knowledge of health care professionals and great awareness of antimicrobial resistance (like in this study), prescribing and dispensing practices were influenced by challenges of access to information on resistance patterns, next line antibiotics, diagnostics and patient records. Further, health care professionals reported that they were influenced by visits of representatives from the pharmaceutical industry.

In addition, the lack of a reimbursement system for medicines in Kosovo as well as the lack of general health insurance can be a driver for patients and pharmacies to maintain the current practice. A reimbursement system for pharmacies that is connected to a prescription service fee, rather than the product margin, could be a way to ensure proper antibiotic dispensing that would require a prescription to get reimbursement.

On the positive side, patients claim to have been given instructions to follow from physicians (for those with prescriptions) and pharmacists. Additionally, all professionals seem to be concerned about antimicrobial resistance, even if they blame others for the current practices that may add to the problem. Blaming others (other health care professionals or other persons within their own profession) can also be seen as not taking responsibility for their own conduct. This has been observed in studies regarding antibiotics both for physicians and pharmacists.[4,15,16] Hence, these professionals are important keys to fostering change. Professional organizations should take the lead in both practice changes and in policy discussions to counteract the financial incentives that drive suboptimal prescribing and selling of antibiotics.

In Kosovo, a first strategy document named "Strategy and action plan to combat antimicrobial resistance 2011 - 2015" has been published.[17] This has been followed by a strategy covering 2019-2021. Included in these documents are strategies for dispensing information and education on antimicrobials both for the population and for medical staff as well as the training of all medical staff and primary school teachers on antimicrobials. Hence, the situation is being taken seriously, and measures are being taken to improve the use of antibiotics.

Limitations

Limitations of this study include that few respondents were interviewed in each group; hence saturation was possibly not achieved. However, the reported practices were similar between the groups. Further, some results were validated by findings from other studies in the country and area. Recruitment was to a large degree carried out by convenience sampling, even though heterogeneity was strived for, and the interviews were only carried out in the capital, which reduces the transferability of the results. Using a qualitative methodology gave new insights into how a culture of antibiotics is working and reproduced.

CONCLUSIONS

There is currently a culture of antibiotic use in Kosovo, including attitudes and behaviours, and hence also experiences, which is possibly underlying the high consumption of antibiotics in the country. The culture is reproduced by patients, pharmacists and physicians. There is, however, an awareness of the current problematic situation among practitioners and policy makers; and as Kosovo is a new country, opportunities to effectively tackle antimicrobial resistance exist.

CONFLICT OF INTEREST

The WHO was not involved in writing the manuscript; hence, we declare no conflict of interest.

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Original Research

Impact of an HIV-trained clinical pharmacist intervention on error rates of antiretroviral and opportunistic infection medications in the inpatient setting

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Abstract

Background: Based on a retrospective study performed at our institution, 38% of inpatients living with human immunodeficiency virus (HIV) were found to have a medication error involving their anti-retroviral (ARV) and/or opportunistic infection (OI) prophylaxis medications.

Objective: To determine the impact of a dedicated HIV-trained clinical pharmacist on the ARV and OI prophylaxis medication error rates at our institution.

Methods: A prospective quality improvement project was conducted over a six month period to assess the impact of a dedicated HIV-trained clinical pharmacist on the ARV and OI prophylaxis medication error rates. IRB approval received.

Results: There were 144 patients included in this analysis, who experienced a combined 76 medication errors. Compared to historical control study conducted at our institution, the percent of patients who experienced a medication error remained stable (38% vs. 39%, respectively) and the error rate per patient was similar (1.44 vs. 1.36, p=NS). The percent of medication errors that were corrected prior to discharge increased from 24% to 70% and the median time to error correction decreased from 42 hours to 11.5 hours (p<0.0001).

Conclusions: Errors relating to ARV or OI prophylaxis medications remain frequent in inpatient people living with HIV/AIDS. After multiple interventions were implemented, ARV and OI prophylaxis medication errors were corrected faster and with greater frequency prior to discharge, however, similar rates of errors for patients existed. Dedicated HIV clinicians with adequate training and credentialing are necessary to manage this specialized disease state and to reduce the overall number of medication errors associated with HIV/AIDS.

Keywords

Pharmacy Service, Hospital; Pharmacists; Medication Errors; Quality Improvement; Anti-Retroviral Agents; Acquired Immunodeficiency Syndrome; HIV Infections; Inpatients; Historically Controlled Study; Illinois

INTRODUCTION

Adopting recommendations by the U.S. Department of Health and Human Services to initiate antiretroviral therapy (ART) in all people living with the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) (PLWHA), regardless of CD4 count, increased the number of patients receiving ART for the management of HIV/AIDS.[1] Additionally, advances in treatment have prolonged the expected survival of PLWHA, effectively making HIV infection a chronic disease state. It was estimated that by 2015 half of the PLWHA population would be over the age of 50. While the use of anti-retrovirals (ARVs) have prolonged survival and improved the quality of life of these individuals, medication errors involving ARVs place PLWHA at significant risk for developing adverse events, clinically significant drug-drug interactions, and failure of ART. The incidence of ARV errors reported in the inpatient setting has been as high as 86% with an average of 1.16 - 2.70 medication errors per patient.[2,3] The most commonly identified errors were omission of an ARV, incorrect frequency of dosing, and drug-drug interactions.[2,4-8] Additionally, those with CD4 counts <200 cells/mm^3 and/or AIDS-defining illnesses require additional medications for prophylaxis against opportunistic infections (OIs), creating another potential source for medication errors.

In a retrospective, quality improvement (QI) study completed at our institution errors with ARV and OI prophylaxis medications were found in 38% of patients.[9] The estimated medication error rate was 35% in those receiving ART and 22% in those receiving OI prophylaxis. During this study period, the standard of care at our institution was not to have a dedicated, HIV-trained clinical pharmacist review any ARV or OI prophylaxis order. As a result of that study, a prospective QI project was implemented at our institution to evaluate the impact of having a dedicated HIV-trained clinical pharmacist on the ARV and OI prophylaxis medication error rates at our institution.

METHODS

In this prospective QI project, adult patients were included if they were admitted to the University of Illinois Hospital & Health Sciences System in Chicago, IL over a 6-month intervention period, had a diagnosis of HIV/AIDS, and were taking ARV or OI prophylaxis medications. Exclusion criteria included patients who were co-infected with hepatitis B or C virus (HBV or HCV), not taking ARV or OI prophylaxis

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Table 1. Baseline demographics and exclusion criteria		
	Pre-Data	**Post-Data**
Gender (N)		
Male	192	93
Female	152	51
Age (years [range])	46 [18-85]	50 [18-76]
Race (N)		
Black	259	116
Other	40	12
White	30	11
Hispanic	11	5
Asian/Pacific Islander	4	0
Followed at Institution Clinic (N)		
Yes	226	7
No	118	
CD4 (cells/mm^3)		
Mean	332	363
Median	255	325
(range)	(1-1,680)	(2-1,414)
patients >200	178	85
patients <200	166	43
HIV-RNA (copies/mL)		
Mean	76,541	65,272
Median	73	8,387
(range undetectable)	(4,259,831)	(537,171)
Undetectable (<48 copies/mL)	163	57
HIV-related admission (N)		
Yes	36	21
No	308	123
Length of stay (days)		
Median (range)	5 (1-61)	3 (1-30)
Total Excluded		
HBV, HCV	n/a	32
Not a confirmed HIV diagnosis	108	5
Not taking ARV/OI meds	9	4
<18 yo	24	10
Not admitted	218	4
Pregnant	n/a	6
HIV-Related Admissions		
Kaposi Sarcoma	4	1
HIV-associated B-cell lymphoma	n/a	7
AIDS-related failure to thrive	n/a	4
Suspected cryptococcus	3	1
Suspected toxoplasmosis	4	1
Other	21	7

medications, did not have a confirmed HIV diagnosis, were <18 years old, pregnant, or were not admitted to the hospital. An automated alert, created based on historical data, was generated upon admission of a PLWHA (based on ICD-10 coding) or if an inpatient order for ARV(s) was placed. The alert notified the investigators to review the patient's electronic medical record (EMR). All investigators were HIV-trained, whereas, staff and other clinical pharmacists were not HIV-trained. Specific HIV training included post-graduate residency year 2 education and training in HIV/infectious diseases (ID), ID fellowship training, and also those who have achieved certification as an American Academy of HIV Medicine Trained Pharmacist (AAHIVP). The investigators would evaluate if a medication error occurred and whether it was corrected by the clinical pharmacist, if present, on the admitting service within the first 24 hours of admission. In the event that no clinical pharmacist was present on the admitting service, the investigator would directly contact the medical team to make any recommendations regarding a HIV-related medication error. After 24 hours, the investigators would contact the clinical pharmacist or medical team managing the patient with any further recommendations.

Baseline demographic data collected included gender, age, race, most recent CD4 count and HIV-RNA viral load, renal and/or hepatic impairment (renal defined as estimated creatinine clearance <50 mL/min and hepatic defined as Child-Pugh Class C), and whether the patient was followed at an outpatient HIV clinic associated with our institution. Collected hospital admission data included whether the admission was HIV-related, admitting medical service, presence of a clinical pharmacist on the admitting service, presence of ID consult service, length of stay, and all ARV and OI prophylaxis medications ordered including dose, frequency, formulation, and formulary status.

All medication errors were documented and classified into one of the following categories: omitted order, missed dose(s), wrong medication, incorrect frequency, incorrect dose, renal adjustment not performed, duplicate order, drug-drug interaction, incorrect formulation, and known drug allergy. This classification and identification of errors was only done by the HIV-trained clinical pharmacist study investigators. At the time of the chart review, Micromedex 2.0® was available through the institution's intranet; therefore, this was used to check drug-drug interactions, which were documented if classified as 'major'.[10] All data was collected from the EMR system, recorded on a data collection form, and organized using REDCap.[11] Also collected was the type of medication error(s) and its associated specific ARV or OI, correction of the error prior to discharge, and how long it took to make the correction. The study received Institutional Review Board (IRB) approval.

For demographic data, the Chi-squared and Wilcoxon Mann-Whitney tests were utilized for categorical and continuous variables, respectively. Descriptive statistics were used to create tables of errors by medication. Statistical significance was set under a p-value of 0.05.

RESULTS

During the 6 month enrollment, 203 patient alerts were sent to the investigators through the EMR system, of which 144 patients were included in the study. Most of the excluded patients were either co-infected with HBV or HCV (N=32), were <18 years old (N=10), or pregnant (N=6). Baseline characteristics (Table 1) included a mean age of 50.6 years, 65% male, and 80.6% African-American. A CD4 count was documented for 128 patients, with a mean of 363 cells/mm^3 (range 1-1,414 cells/mm^3). Approximately 65% of these patients had a CD4 count >200 cells/mm^3. A viral load was documented for 81.3% of patients (N=117), and was detectable (>20 copies/mL) in 51.3% of those patients (N=60). The average daily pill burden was 3.7 tablets (range 1-9). Other baseline information included 53.5% (N=77) of patients following at one of our institution's outpatient HIV clinics. Infectious disease was on consult for 43.1% (N=62) of patients, and a PharmD was on service for 69.4% (N=100) of patients. Compared to the historical data, there were little differences found between pre- and post-data, with the exception of mean CD4 332 cells/mm^3 in pre and 363 cells/mm^3 in post (p = 0.004).

Table 2. Medication errors per patient pre- and post-interventions			
	Pre	**Post**	**p-value**
Total number of errors (N)	190	77	0.99
ARV errors (N, %)	151 (79%)	58 (75%)	
OI errors (N, %)	32 (21%)	19 (25%)	
Total number of patients with an error (N, %)	132/344 (38%)	56/144 (39%)	
ARV Error (N, %)	113/320 (35%)	47/144 (33%)	0.99
OI Error (N, %)	37/166 (22%	17/57 (30%)	0.74
Errors corrected (N, %)	45 (24%)	56 (73%)	
ARV errors corrected (N, %)	40 (26%)	42 (72%)	0.35
OI errors corrected (N, %)	5 (13%)	14 (74%)	0.69
Median time to corrected error (hours)	42	11.5	<0.0001
ARV: anti-retroviral; OI: opportunistic infection			

There were 76 medication errors identified, of these 56 (73.7%) were ARV medications and 20 (26.3%) were OI prophylaxis medications (Table 2). A total of 56 (38.9%) patients had at least one medication error occur during their admission, and 53 (69.7%) of the errors were corrected prior to discharge. Compared to the historical data, the percent of medication errors that were corrected prior to discharge increased from 24% to 70% and the median time to error correction decreased from 42 hours to 11.5 hours (p<0.0001).

The most common reasons a medication error occurred were drug-drug interaction (17.9%), incorrect timing (16.1%), omitted order (14.3%), incorrect dose (14.3%), and missed dose (12.5%). The drugs involved in the drug-drug interactions with ARVs were famotidine (N=5), fluticasone (N=4), and lansoprazole (N=1). A total of 27 non-formulary ARV orders were placed for 25 patients. Of the 56 ARV medication errors that occurred, 6 involved a non-formulary ARV.

We found no stastically significant difference between the pre- and post- medication error rates of either ARV (p=0.99) or OI prophylaxis medications (p=0.74). Likewise, we found no statistically significant difference in the rates of corrected ARV (p=0.35) or OI prophylaxis medication (p=0.69) errors.

DISCUSSION

PLWHA often present to the hospital on multiple medications, including ART and possibly OI prophylaxis medications depending on their CD4 count and past medical history. The combination of multiple medications, unfamiliarity with ARVs, and medications that may or may not be on the hospital formulary can create various avenues for the development of medication errors. This QI project demonstrated that the medication error rate for ARVs and OI prophylaxis medications has unfortunately not improved at our institution since the historical study was performed (38% vs. 39%, respectively), therefore indicating the need for a clinical pharmacist specialized in the area of HIV/AIDS. Medication errors predominantly occurred at the time of order entry by the admitting service. The most common medication errors were incorrect timing, omitted order, incorrect dose, missed dose, and drug-drug interactions. Incorrect timing had a high association with the most common ARV medications associated with an error, ritonavir and darunavir, because their administration was not timed together. Omitted orders mostly involved the omission of the third-most common ARV associated with an error, tenofovir disoproxil fumarate (TDF), or missing OI prophylaxis medications. In patients with end-stage renal disease, weekly dosing of TDF was often ordered or administered incorrectly. With the newer tenofovir alafenamide fumarate (TAF) formulation being used more often, this may no longer be a significant concern. Although combinations agents including TAF are not approved for hemodialysis, with the exception of elvitegravir/cobicistat/emtricitabine/TAF, these agents may still be used given that TAF itself has been shown to be safe and effective and the other agents appear to be safe as well. Importantly, the rate of medication errors due to incorrect dosing decreased compared to the historical control study performed at our institution (47% vs. 26%). We hypothesize that the addition of single tablet regimens to our hospital formulary was most likely responsible for this decrease.

In the case of drug-drug interactions, the most commonly observed interactions included protease inhibitors and either famotidine or fluticasone. In one case, the fluticasone interaction resulted in symptoms consistent with Cushing's syndrome. It was also observed that after being removed from our hospital formulary, etravirine was still ordered with regularity. As a result, the recommendation was made to add etravirine back to the formulary. The use of non-formulary ARVs resulted in six errors during the course of the study.

Although many previous studies have evaluated the presence of ARV errors in the inpatient setting, fewer have addressed the potential impact that a HIV-trained clinical pharmacist can make on ARV-related error rates. Heelon *et al*. showed that having a clinical pharmacist review an HIV patient's medication profile upon admission decreased the duration of prescribing errors from 84 hours to 15.5 hours.[12] Daniels et al. found that by implementing targeted interventions such as a small drug reference card, alerts in the pharmacy order-entry system, adding default orders into the computerized physician order entry (CPOE) system, and adding combination ARVs to the formulary, they were able to decrease medication errors from 72% to 15%.[13] Liedtke, *et al*. involved a dedicated HIV-trained pharmacist and found a 73.9% reduction in errors.[14] Eginger *et al*. reported 54.7% of patients on ART and/or OI prophylaxis experienced at least 1 medication error at their institution. In that study, the primary investigator was a post-graduate year 2 pharmacy resident, but it appears all incorrect regimens were reviewed by an AAHIVE-certified practitioner. Furthermore, they reported 94.7% of ART errors and 89.9% of combined ART and OI prophylaxis errors were corrected by a HIV-trained pharmacist.[15]

Additionally, Carcelero *et al*. expressed having a clinical HIV-trained pharmacist may reduce errors, which were found in 21.7% of patients with HIV at their institution.[16]

While overall medication error rates remained stable at our institution, the proportion of errors corrected prior to discharge, and the median time to error correction, both drastically improved. This improvement can be contributed to having a designated HIV-trained clinical pharmacist reviewing all inpatients living with HIV/AIDS on a daily basis, who notified the responsible services with recommendations to resolve any medication errors. Similar positive intervention results have been seen in the literature.[13-16] Initially, the intention of the project was to empower the clinical pharmacists on service to better evaluate the PLWHA admitted to their service. However, the investigators found medication error rates slightly rose due to a potential-perceived expectation that the HIV-trained investigators reviewing the patients would recognize any errors and contact the service directly to address any issues. Future directions of this QI data is to demonstrate the need for a dedicated, HIV-trained clinical pharmacist who can monitor these patients to eliminate potential medication errors. Additionally, with HIV guidelines receiving updates frequently, staff education by an HIV-trained clinical pharmacist should be reviewed and provided just as often.

Limitations

Limitations to our study include different investigators performing the historical retrospective study analysis and this prospective QI project. This could potentially create bias and/or the potential to interpret the same error differently. The implementation of multiple types of interventions following the retrospective QI project (in-services for the clinical and staff pharmacists, in-service for the internal medicine residents, a clinical pharmacist checklist for HIV patients based on the most common errors found at our institution, formulary updates, and order sentence changes to the CPOE system) could potentially confound the impact of the HIV-trained investigators each intervention type on ARV and OI prophylaxis medication error rates. However, the similar incidence of error rates between the pre- and post-implementation QI projects suggests these additional interventions had minimal impact on ARV and OI prophylaxis medication error rates at our institution. In some cases, the EMR alerts were sent to the investigators before the patient made it to the floor, in which case the clinical pharmacist on the admitting service may not have had the opportunity to make interventions prior to the investigators.

CONCLUSIONS

With the increased number of patients receiving ART and the growing number of ARVs and combinations on the market, this study helps demonstrate the importance and impact that a HIV-trained clinical pharmacist can have on the timeliness to resolution of medication errors in the inpatient setting. Although the accuracy of medication histories upon admission were not assessed, we believe placing an emphasis on obtaining accurate and complete medication histories at admission may play an important role to decrease ARV and OI medication errors in PLWHA. Additionally, continued and consistent staff pharmacist education may increase the likelihood that medication errors occurring during the ordering process would be identified and resolved prior to order verification. Based on our findings, we believe that a full-time HIV-trained clinical pharmacist should consistently provide review of admission, daily, and discharge medications to reduce errors in PLWHA which also may assist in improving effective transitions of care.

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CONFLICT OF INTEREST

No personal connections that could be perceived to bias the work are to report for any authors.

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Original Research

Mandatory continuing education for pharmacists in a developing country: assessment of a three-year cycle

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Abstract

Background: In Lebanon, mandatory continuing education (CE) for pharmacists was implemented in January 2014.
Objective: The objectives of this study are to assess 1) the overall adherence to the mandatory CE program, 2) pharmacists' preferences related to CE, and 3) barriers to adherence to CE.
Methods: By the end of October 2017, an evaluation of pharmacists' participation in the mandatory CE program was conducted using electronic reports available in the Learning Management System (LMS). Descriptive results were presented as frequencies and percentages. In addition, a cross-sectional survey was conducted among pharmacists to better understand their preferences and barriers to their participation to the CE program. Finally, a focus group was organized with pharmacists who did not start their CE.
Results: Out of all registered pharmacists in Lebanon, 68.30% started their CE and 25.6% already achieved their required credits. Among pharmacists enrolled in the CE system, the majority (69%) used the online courses at least once. Moreover, CE enrolment was similar among old and young pharmacists except for those newly registered. The majority of pharmacists preferred clinical and pharmacological topics, followed by preventive medicine and transferable skills. Barriers to engaging in CE were mainly work and family obligations, lack of interest, lack of time, and difficulties in commuting and technology use.
Conclusion: Although results of the present study are similar to those in developing countries, the resistance to change is higher. The Lebanese Pharmacists Association [Ordre des Pharmaciens du Liban] should develop strategies to motivate and enroll more pharmacists in the CE system, based on the barriers and preferences cited in the results, while continuing to offer high quality and cost-favorable CE programs to Lebanese pharmacists.

Keywords

Education, Pharmacy, Continuing; Pharmacists; Professional Practice; Motivation; Attitude of Health Personnel; Developing Countries; Focus Groups; Surveys and Questionnaires; Lebanon

INTRODUCTION

Continuing Education (CE) is an internationally recommended approach that allows pharmacists to acquire the knowledge, skills and ethical attitudes necessary to stay current and competent in their practice, as insufficient knowledge, limited skills, and inappropriate attitudes may be obstacles to achieving satisfactory health outcomes.[1-3] The educational strategies and competency-based approaches that are successfully used for pre-graduate training must be maintained and expanded throughout the practitioner's career, beyond the entry-to-practice level; this would define the characteristics of the pharmacy profession.[1,4-7]

A growing body of evidence demonstrates that not all health care workers actively participate in CE activities once they begin to practice, even in developed countries. In Japan, where CE is not mandatory, the major challenge is to involve pharmacists in CE cycles.[2,8,9] In low- and middle-income countries, some aspects of CE may not be adequately addressed, and accreditation or quality assurance systems may be lacking or have to be improved.[3,10]

Regarding the Middle East and North Africa region, CE was implemented in some countries such as the United Arab Emirates and Qatar, whereas it is still lacking in others. The current role of the Emirates Pharmacy Society is limited to providing certified CE credit hours required by the Emirates Ministry of Health to renew most of the medical practitioners' licenses on a yearly basis, while its initial role was to promote the pharmacy practice and the advancement of pharmaceutical sciences.[11] In Qatar, the established CE model reflects a wide spectrum of international approaches to life-long learning. In fact, almost half of pharmacists are in favor of the mandatory CE system for annual licensure.[12] On the other hand, in Yemen, pharmacists are not required to pursue additional training after graduation, nor is CE openly encouraged.[13] As for Egypt, no recertification for pharmacy licensure is mandated for registered pharmacists and community pharmacists are not interested in CE, owing to low salary incomes and the absence of motivating career pathway.[14]

In Lebanon, to be able to practice, pharmacists should register with the official pharmacists' association, the Lebanese Pharmacists Association [Ordre des Pharmaciens du Liban] (OPL). The OPL was established by law in 1950 and represented the commencement of a new era in

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pharmacy practice. Its main goal is to advance pharmacy practice and support pharmacists. Within OPL structure, an appointed Scientific Committee has the role of organizing educational activities including conferences, congresses and publishing newsletters. CE activities were started in the late nineties through conferences and selected articles published in an internal newsletter. As the CE was not mandatory, organized activities were not on a regular basis except for the annual 3-day congress and the annual pharmacists' day.

In November 18, 2011, the law 190 on the "Mandatory Continuing Education to Pharmacists" was enacted in the parliament (Table 1). According to this law, each pharmacist registered with the OPL has to complete 15 credits per year, of which at least 5 should be live (the remaining 10 may be done either live or through online courses), and all courses and activities organized by the OPL should be offered to pharmacists free of charge. It is noteworthy that the law does not distinguish between CE and Continuing Professional Development (CPD), pharmacists are therefore allowed to choose topics freely.[15]

To better serve the established CE system, a Learning Management System (LMS) that includes online courses of interest to the majority of pharmacy sub-specialties (including clinical, community and hospital topics, clinical laboratory, psychology, etc.) was adopted to manage the pharmacists' CE credits.[16] This system is available free of charge to all participants. To help pharmacists enroll in the system, the OPL offered live training sessions across Lebanese regions throughout 2014. The purpose of these sessions was to explain to pharmacists how to create their accounts and how to take online courses and tests available through the LMS platform. Furthermore, an explanatory manual was developed, printed and distributed to pharmacists who attended these sessions and a PDF version was made available online.

Because it was expected to be unpopular among pharmacists, law 190 was only enforced in January 2014, 3 years after its adoption, without any previous situation assessment to evaluate the readiness and willingness of pharmacists to join a CE program; therefore, it is hypothesized that a large number of pharmacists would show a resistance to change and/or have other issues that may be potential barriers (lack of time, lack of interest, logistic difficulties, etc.) as in other developing countries.[10,17] The extent to which pharmacists enrolled in OPL CE program and the potential barriers preventing them from doing so, have never been evaluated yet in Lebanon.

Therefore, the objectives of this study are to assess 1) the overall adherence to mandatory CE program, 2) pharmacists' preferences related to CE, and 3) barriers to adherence to CE.

METHODS

The current manuscript is divided into: the LMS data, the registered pharmacists' survey (quantitative on a sample), and the focus group on encountered barriers (qualitative on a sample).

Learning Management System data

The number of registered pharmacists and their date of registration were collected from the OPL database. At the end of October 2017, the number of registered pharmacists enrolled in the CE program was assessed through electronic reports generated using the LMS. These reports included credits earned by attending live activities, and those earned by taking online courses and tests through the LMS. Live activities are created and recorded manually in the LMS, which allows generating comprehensive reports on participants' activities.

Registered pharmacists' survey

A cross-sectional observational study was conducted between February and May 2017, using a random sample of 628 Lebanese pharmacists from all districts of Lebanon. All pharmacists were eligible to participate; the sample consisted of those who agreed to complete the questionnaire that was developed and reviewed by ten experienced academics and pharmacy practitioners and comprised four distinct sections. Section 1 clarified socio-demographic characteristics, including years of experience in pharmacy practice, the number of working hours per day, and the highest degree achieved. Section 2 was designed to obtain information about technology and computer literacy; questions included the ease of access to the LMS platform to take online courses. Section 3 was designed to assess the pharmacists' communication with OPL. Section 4 included questions about value and motivation regarding CE, and reasons for rarely/not adhering to OPL CE program. The questionnaire was then piloted on a sample of 10 pharmacists prior to its finalization and distribution. The pilot study revealed no need for modification; its results were thus included in the study. Further methodological details are available in another publication.[18] Statistical analyses were performed using SPSS version 23 (IBM SPSS Software, Chicago, IL, USA). Descriptive statistics were calculated using counts and percentages for categorical variables.

Focus group on encountered barriers

A focus group was organized by the authors to assess the reasons why several pharmacists are not adhering to CE.

Table 1. Overview of the Law 190 on the "Mandatory Continuing Education to Pharmacists"
This law applies to all registered pharmacists living on the Lebanese territory whether working or not. Pharmacists living abroad are exempted from the system after presenting the appropriate proofs.
The cycle is of 3 years during which pharmacists have to achieve a total of 45 credits of which 15 at least should be live. The counter is turned to zero after each cycle.
Pharmacists are allowed to achieve all their credits as live credits but they are not allowed to achieve them all online.
Pharmacists who fail to achieve their credits in due time, will be suspended until achieving the required credits.
Registered pharmacists should be provided with the necessary tools and opportunities to achieve their credits at no cost (online and live).
The CE Committee of the OPL has the role of supervising, managing and accrediting scientific and educational activities. It is nominated by the advisory board and has a yearly mandate.

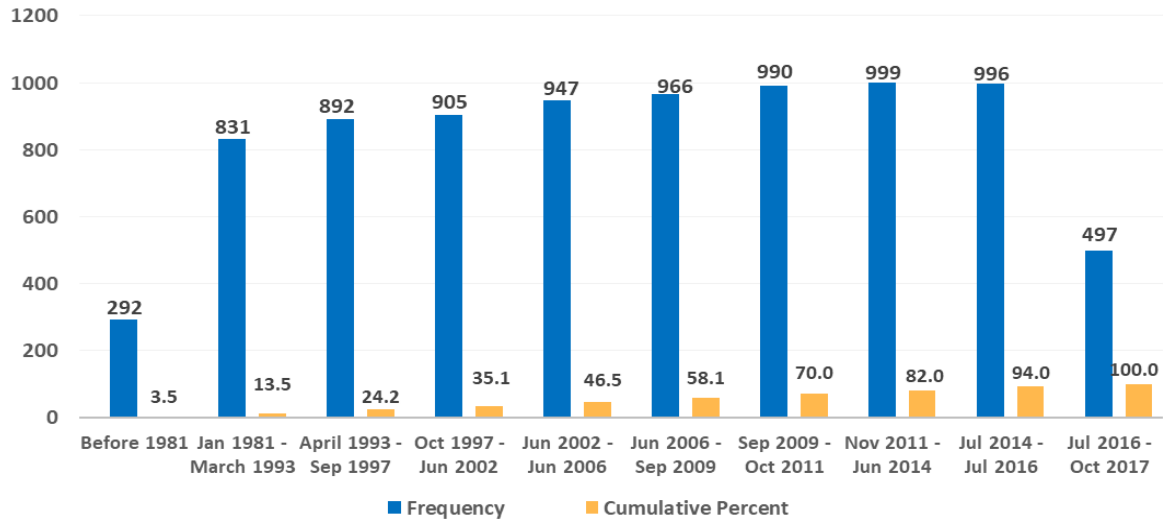

Figure 1. Date of Pharmacists' Registration with the Lebanese Pharmacists Association (n=8315)

Based on the official list of pharmacists, a random sample of 50 pharmacists who did not start their CE were called and conveyed to a focus group meeting; 30 of them attended the meeting that was held at the OPL premises. It was facilitated by pharmacists of the CE team at the OPL, and the chair of the scientific committee (pharmacist and academic professor). The latter developed the open-ended questions used in the discussion. After a general discussion, participants were divided into 3 groups and the discussion was prompted with each group through questions about the reasons why they did not start their CE yet, and their awareness of the mandatory aspect of the law 190. Facilitators wrote the minutes of the discussion and data transcription and analysis were performed using a written form. Triangulation of the results with those of the survey and their convergence showed that no additional focus groups are necessary.

Ethical Aspects

The Ethical committee at the Lebanese University waived the need for an ethical approval since this is an observational study that respects participants' confidentiality and autonomy.

RESULTS

A total of 8315 active members were registered with the OPL till October 2017. This number is steadily increasing as new members apply yearly, typically after graduation (Figure 1).

Learning Management System Data

Overall Adherence to the CE Program: Among 8315 registered pharmacists, 5679 (68.3%) have started their CE activity, but only 2129 (25.6%) completed their requirements or more.

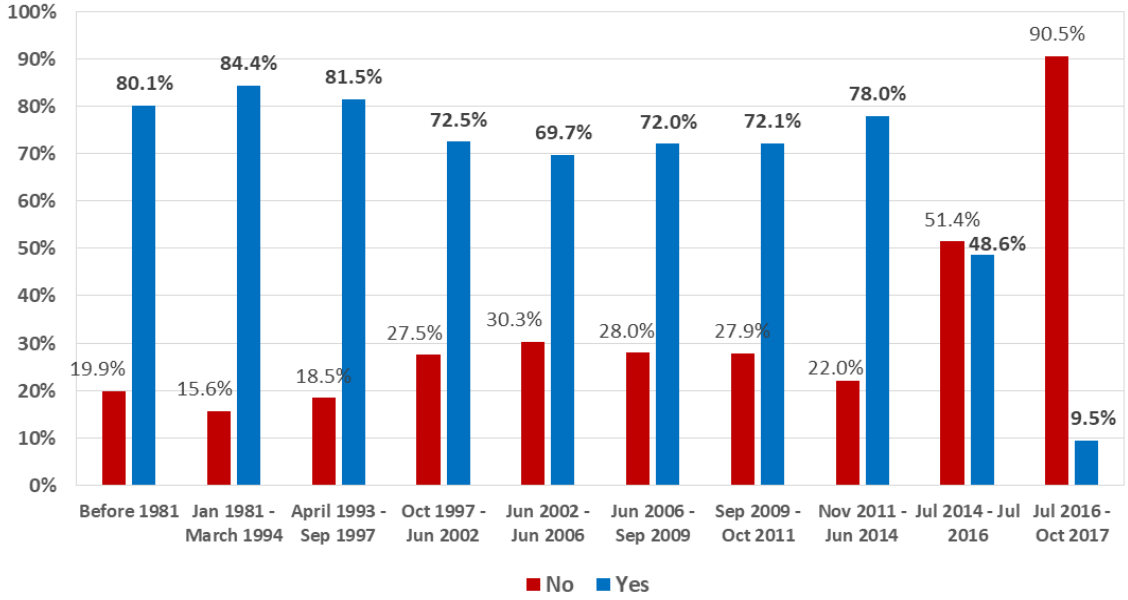

Figure 2. Percentage of 8315 pharmacists who started any continuing education according to registration date with the Lebanese Pharmacists Association

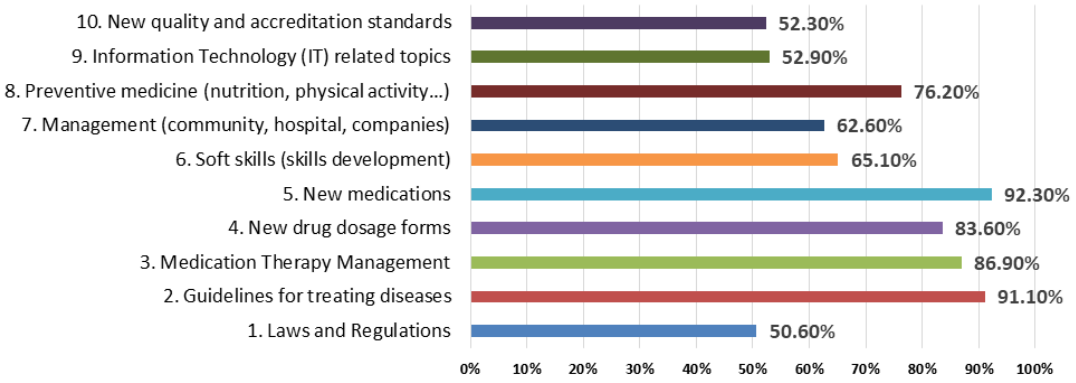

Figure 3. Preferred continuing education topics selected by pharmacists

Percentages of completed credits among registered pharmacists were found to be as follows: 19.9% completed 25% of their requirements or less, 22.3% completed 25.1-75% of their requirements, and 8.9% completed 75.1-100% of their requirements. Moreover, 17.1% of registered pharmacists completed more than what is required by the law.

The percentage of pharmacists who have started any type of CE activity after registering with the OPL is shown in Figure 2. Pharmacists registered before October 1997, had the highest percentage of CE activity (above 80%) followed by those registered between October 1997 and June 2014 (70-80%). As for newly registered members, their CE activity is below 50%.

Among pharmacists who started their CE activity, 31.1% use only live courses. Moreover, 18.7% completed less than 33% of their credits using online courses, 25.1% completed 33-68% of their credits using online courses, and 25% completed more than 68% of their credits using online courses.

Registered Pharmacists' Survey

Out of the 750 questionnaires distributed, 628 (83.73%) were filled out and returned to be analyzed. Among the 628 respondents, 567 (90.3%) have earned at least one CE credit. Of those, 5.4% declared taking mainly online courses, 15.4% mainly live courses and the remaining both types of CE. Only 12 (1.9%) declared not being interested in any type of CE.

Among surveyed pharmacists, 204 (32.5%) selected 1-hour long sessions, 129 (20.5%) sessions of 1 to 2-hour long, 82 (13.1%) sessions half a day (4-hour long), 15 (2.4%) all day long (7 hours), 52 (8.3%) preferred the weekend option (14 hours), 53 (8.4%) a 3-day option (Annual Congress), and 53 (8.4%) preferred long-term courses with certification (Masters, University Diploma...). As for the language, 372 (59.2%) preferred English, 155 (24.7%) preferred French, while other languages were mentioned (Arabic 44 (7.0%); Russian 2 (0.3%); and Spanish 1 (0.2%)).

On weekdays, 73 (11.6%) preferred AM timing, 128 (20.4%) the PM, 194 (30.9%) preferred evenings. On weekends, 197 (31.7%) preferred AM timing, 115 (18.4%) preferred PM,

Table 2. Reasons that generally prevented pharmacists from attending live continuing education

Question	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Not Applicable
1. Cost of transportation (N=627; 99.84%)	124(19.7%)	185(29.5%)	165(26.3%)	54(8.6%)	30(4.8%)	69(11.0%)
2. Distance and traffic to venue (N=628; 100%)	26(4.1%)	40(6.4%)	68(10.8%)	246(39.2%)	221(35.2%)	27(4.3%)
3. Timing of the talk (N=628; 100%)	12(1.9%)	38(6.1%)	110(17.5%)	254(40.4%)	199(31.7%)	15(2.4%)
4. Interest in the topic (N=628; 100%)	34(5.4%)	92(14.6%)	181(28.8%)	238(37.9%)	66(10.5%)	17(2.7%)
5. Family commitments (N=627; 99.84%)	15(2.4%)	46(7.3%)	125(19.9%)	263(41.9%)	167(26.6%)	11(1.8%)
6. Work obligations (N=628; 100%)	6(1.0%)	20(3.2%)	57(9.1%)	250(39.8%)	286(45.5%)	9(1.4%)
7. Easier to do online courses (N=628; 100%)	13(2.1%)	64(10.2%)	137(21.8%)	232(36.9%)	174(27.7%)	8(1.3%)
8. Not finding adequate program to meet my practice needs (N=627; 99.84%)	28(4.5%)	135(21.5%)	240(38.2%)	144(22.9%)	55(8.8%)	25(4.0%)
9. Cost to be replaced at the pharmacy/Close the pharmacy during the CE session (pharmacy owners only) (N=625; 99.52%)	18(2.9%)	57(9.1%)	152(24.2%)	174(27.7%)	138(22.0%)	86(13.7%)
10. Language used for the presentation (N=628; 100%)	104(16.6%)	187(29.8%)	159(25.3%)	97(15.4%)	33(5.3%)	48(7.6%)
11. I learn very little during live CE (N=628; 100%)	78(12.4%)	200(31.8%)	183(29.1%)	107(17.0%)	28(4.5%)	32(5.1%)
12. I already attend CE organized by pharmaceutical companies/international congresses (N=627; 99.84%)	24(3.8%)	94(15.0%)	174(27.7%)	205(32.6%)	71(11.3%)	59(9.4%)
13. I am already accessing online CE courses (N=627; 99.84%)	23(3.7%)	110(17.5%)	147(23.4%)	222(35.4%)	90(14.3%)	35(5.6%)
14. I am exempted (teaching, registered abroad...) (N=627; 99.84%)	38(6.1%)	137(21.8%)	180(28.7%)	63(10.0%)	17(2.7%)	192(30.6%)
15. I am not interested in doing any live CE (N=628; 100%)	149(23.7%)	197(31.4%)	129(20.5%)	60(9.6%)	30(4.8%)	63(10.0%)

Table 3. Reasons that prevented pharmacists from doing online continuing education

Question	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Not Applicable
1. Difficulty accessing my OPL e-library account (N=628; 100%)	62(9.9%)	161(25.6%)	118(18.8%)	163(26.0%)	102(16.2%)	22(3.5%)
2. Difficulty using the OPL Swank platform (N=628; 100%)	63(10.0%)	168(26.8%)	131(20.9%)	157(25.0%)	86(13.7%)	23(3.7%)
3. Lack of interest in the topics available (N=628; 100%)	53(8.4%)	171(27.2%)	200(31.8%)	140(22.3%)	46(7.3%)	18(2.9%)
4. Not finding adequate program to meet my practice needs (N=628; 100%)	43(6.8%)	177(28.2%)	193(30.7%)	143(22.8%)	53(8.4%)	19(3.0%)
5. Family commitments (N=628; 100%)	39(6.2%)	116(18.5%)	140(22.3%)	219(34.9%)	96(15.3%)	18(2.9%)
6. Work obligations (N=628; 100%)	30(4.8%)	83(13.2%)	102(16.2%)	250(39.8%)	147(23.4%)	16(2.5%)
7. OPL staff not supportive/accessible to help with e-Library and Swank (N=628; 100%)	79(12.6%)	193(30.7%)	209(33.3%)	80(12.7%)	42(6.7%)	25(4.0%)
8. Courses only offered in English (N=628; 100%)	101(16.1%)	205(32.6%)	159(25.3%)	101(16.1%)	36(5.7%)	26(4.1%)
9. I am already attending live CE (N=628; 100%)	41(6.5%)	106(16.9%)	189(30.1%)	209(33.3%)	57(9.1%)	26(4.1%)
10. I am not interested in doing any online CE (N=628; 100%)	132(21.0%)	209(33.3%)	157(25.0%)	61(9.7%)	42(6.7%)	27(4.3%)

and 57 (9.0%) preferred evenings.

Preferred topics that pharmacists selected are summarized in Figure 3.

Reasons that prevented pharmacists from attending live CE: The reasons that prevented pharmacists from attending live CE sessions are presented in Table 2.

Reasons that prevented pharmacists from doing online CE: The reasons that prevented pharmacists from doing online CE are presented in Table 3.

Focus group on encountered barriers

The following issues were raised by pharmacists who have not started their CE yet:

- Resistance to change and lack of motivation: despite the law 190 that made the CE mandatory and conditional for re-licensure to all pharmacists living in Lebanon, many of them still hope that the system would be cancelled: "the new elected board will cancel this law" or "the new board will suspend the application of the CE law". The authors also noted that many pharmacists who are known to be knowledgeable in computer and technology and very active on social media, still did not start their CE because they did not perceive its added value to their daily professional activity: "it is a waste of time because nothing we learn is useful in our daily practice".

- Some pharmacists stated that they were not aware of CE sessions and online system, although a phone-based application was developed and used to communicate with pharmacists about professional issues including CE related information (available since 2009 and downloadable free of charge on Android and iOS phones). In fact, only 3579 pharmacists (43%) have downloaded this application to date while some of those claim to miss reading incoming messages whether through the application or by SMS (Short Message Service): "although I have the application, I don't read the messages", "I don't read any message from the OPL whether on the app or by SMS", "I don't have the mobile app and I don't want to download it"

- Although scientific sessions were organized by academic and other scientific entities in remote areas to give pharmacists in these regions the opportunity to attend and avoid long commutes, many pharmacists questioned the seriousness of the system and tried to find excuses to escape it; the majority stated lack of time and long distances as major barriers: "even if you are doing in remote areas, it is still not close enough to my work place and it takes me 30 minutes to get to the venue", "I have no one to replace me at the pharmacy even if the conference is presented in a region near my pharmacy".

- Another stated reason was language barrier. In fact, it is recognized that there are no online articles in French or in languages other than English: while in Lebanon the teaching languages of the pharmacy are exclusively French and English, pharmacists educated outside Lebanon (10% of total registered pharmacists) may have different languages i.e. Arabic, Russian, Persian, Italian, etc. and may thus find it hard to attend CE sessions in other languages: "I am a Saint Joseph University graduate and I prefer reading French articles", "English is hard for me to understand, why don't you have Arabic courses online", "why don't you seek Russian online courses".

- Pharmacists from remote Lebanese regions, blamed the lack or bad internet connection and others claimed not to be familiar with new technology for taking online courses: "why don't you come to Hermel region and check the Internet there? It would give you an idea of what we are going through", "I have no Internet nor 3G available in my region. To do online courses I would have to go to a friend or a relative at least 30 kilometers far". Although many introductory sessions to the CE program were organized, and a structured continuous support system was built along with the creation of a clear manual to help the pharmacists' login to their CE accounts, some pharmacists are still finding difficulties in using technology: "I'm not familiar with technology. I prefer live sessions".

DISCUSSION

Our results showed that among all registered pharmacists, 68% already started their CE and 25.6% completed their required credits. The relatively high number of enrollment

is due to the fact that in 2014, the OPL Council took a decision regarding the internships of pharmacy students in community pharmacies and hospitals: to accept trainees, registered pharmacists had to enroll in the CE program and complete at least 5 credits.

As for CE completion, our results are similar to those of some developing countries such as Namibia, and developed countries where the CE system is not yet "mature" such as Canada where provinces have not the same system or requirements. However, our results are in contrast with those of developed countries such as Australia, the United States, some provinces of Canada, and the UK where participation and completion rates are much higher.[2] For example, Canadian regions where the CE system is fully functional, such as Alberta, have better results than ours: most pharmacists exceeded the required number of education units and more than 70 percent of the total acquired were obtained by completing correspondence courses, and this more than 30 years ago.[19] In the UK, 32 to 49.6% completed the minimal requirements and all surveyed pharmacists agreed on the mandatory aspect of the CE.[20] In contrast, no information is available about the CE system implementation in neighboring countries, where the system has been adopted so far.

Among pharmacists enrolled in the CE system, the majority (69%) used the online courses at least once; this shows that computer literacy is not a barrier to most of these pharmacists. Our results show an opposite preference for online courses compared to Massachusetts pharmacists where 66% preferred live conferences.[21] This can be explained by the fact that most Lebanese pharmacists (74.4%) find commuting to attend live conferences more difficult than just taking online tests in-office or from home due to work or family constraints.

Moreover, age did not seem to be a limiting factor for pharmacists' involvement in the CE system, except for newly registered pharmacists; this might be explained by the fact that pharmacists registered before 2014, attended the training sessions offered at that time in various regions, while the newly graduated pharmacists believe that their scientific knowledge is still fresh and up-to-date. Thus, efforts should be done to motivate younger pharmacists to join the CE system by always offering new hot topics, in addition to live training sessions that would help them access the LMS.

The encountered barriers to starting the CE were family and work obligations, resistance to change, lack of interest, lack of time, difficulties in commuting and technology use. Some of these were similar to those found in developed and developing countries.[10,22] The top three barriers cited in a recently conducted study in Lebanon were lack of time, work constraints and distance to the venue for live events.[22] A study conducted in Kenya, showed that the main barriers for not attending local courses or workshops, were the distance to venue (21.6%), other commitments (20.9%) and lack of information on what CE activities are available (19.3%).[10] The most cited barriers by Flemish pharmacists were lack of time, uninteresting topics, and family obligations, while the most cited barriers by a sample of US pharmacists were work constraints, distance to venue, family obligations, and uninteresting topics.[23,24] Lack of time and work obligations were also cited by Egyptian pharmacists.[17]

Furthermore, some Lebanese pharmacists are still not convinced about the usefulness of CE, opposite to the attitude of US pharmacists who perceived mandatory CE as acceptable more than 30 years ago, and to the majority of Irish pharmacists (84%) who agreed that engaging in CE was essential for all practicing pharmacists.[19,25-27] Later on, a study conducted in Colorado in 2009 showed that only 10% of the pharmacists showed lack of interest in the live CE program while in Massachusetts (2012), all the surveyed pharmacists showed motivation for CE.[21,26] Efforts should be made to increase awareness of the CE system and familiarity with technology, as shown in other countries.[6,28]

The OPL should develop a strategy to motivate and increase the number of enrollments in the CE program by diversifying the topics to serve the interests of all pharmacy sub-specialty areas based on required competencies (particularly selected topics such as clinical topics, preventive medicine, and transferable skills), assessing the overall satisfaction of participants, evaluating the CE program to constantly improve the quality of the sessions presented, offering live sessions in languages other than English or French, offering sessions with various timings to cover all preferences, offering online courses in languages other than English, offering sessions to improve the computer literacy of pharmacists unfamiliar with computer technology, organizing hands-on teaching and workshops instead of theoretical sessions, and developing webinars that can be attended from home or the office to overcome difficulties of attending live conferences. Finally, it is recommended that a survey be conducted to assess the motivation factors among Lebanese pharmacists, and to develop a framework for CE, taking into consideration the recommendations provided by international examples.[2,29]

CONCLUSIONS

Although results of the present study are similar to those in developing countries, the resistance to change is higher. The Lebanese Pharmacists Association should develop strategies to motivate and enroll more pharmacists in the CE system, based on the barriers and preferences cited in the results, while continuing to offer high quality and cost-favorable CE programs to Lebanese pharmacists.

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CONFLICT OF INTEREST

We declare that the first two authors are full-time employees at the Lebanese Pharmacists Association, Drug Information Center Department. Georges Sili is the previous president of the Lebanese Pharmacists Association (non-profit position) and Pascale Salameh is a full-time Professor at the Lebanese University and the previous chair (non-profit position) of the scientific committee at the

Lebanese Pharmacists Association. We have no other conflict of interest to declare.

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Original Research

Pharmacist intervention to enhance postoperative fluid prescribing practice in an Iraqi hospital through implementation of NICE guideline

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Abstract

Objective: The objectives of this study were to evaluate the current practice of postoperative fluid prescribing and assess the effectiveness of pharmacist-led intervention in the implementation of the National Institute of Health and Care Excellence (NICE) fluid therapy guideline in an Iraqi hospital.

Methods: The prospective interventional study was conducted at AL-Hilla Teaching Hospital, Babylon, Iraq between November 2017 and July 2018. The study included two phases: The pre-intervention phase with 84 patients and the post-intervention phase with 112 patients. A pharmacist provided training and educational sessions for the hospital physicians and pharmacists about the NICE guideline of fluid therapy. The researcher calculated the amount of given post-operative fluids and compared to the NICE guideline and also measured the patients' body weight, serum Na, K and creatinine pre-and post-operatively.

Results: The pre-intervention phase showed no correlation between the amounts of prescribed fluids and body weight which caused increases in patients' body weight. In pre-intervention phase, 6% of patients experienced hyponatremia, 19% had hypernatremia and 7.1% had hypokalemia. In the post-intervention phase, abnormal level of electrolytes and patient weight gain decreased significantly. Additionally, the intervention led to a strong correlation between body weight and amount of prescribed fluids in addition to lowering the incidence of electrolyte disturbances.

Conclusions: A high proportion of patients in the pre-intervention phase experienced fluid overload, weight gain and electrolyte disturbances when fluid therapy was not prescribed in accordance with the NICE guidelines. The pharmacist-led intervention increased the surgeon awareness of the proper use of the NICE guideline which decreased the incidence of fluid-related complications and the inconsistency of fluid prescribing. Pharmacists can play a critical role to enhance post-operative fluid prescribing and minimize fluid-induced complications.

Keywords

Fluid Therapy; Body Weight; Electrolytes; Guideline Adherence; Professional Practice; Pharmacy Service, Hospital; Pharmacists; Prospective Studies; Iraq

INTRODUCTION

Perioperative fluid therapy is considered a fundamental part of any surgical procedure, and recently it has gained great attention because it is notably impacting post-operative outcomes.[1] The primary goals of postoperative intravenous (IV) fluid administration are to maintain or restore fluid and electrolyte balance, to correct the acid base imbalance and to maintain sufficient oxygen supply to organs.[2-4]

Despite the significance of the fluid therapy, there is no consensus about what kind of fluids should be prescribed or how much to be administered. This makes optimization of the fluid therapy a complex and challenging issue.[5,6] For this reason, many cases have been reported to have a suboptimum management of fluid therapy, causing many complications, such as fluid and electrolyte disturbances, edemas and organ dysfunctions.[3] Given such complications of improper fluid therapy, several studies have shed light on this problem.

The UK National Confidential Enquiry into Perioperative Deaths (NCEPOD) report has emphasized that giving too much or too little amount of fluids could cause serious postoperative morbidity and mortality. It was estimated that 20% of the participating patients in this report had either poor documentation of fluid balance or unrecognized and untreated fluid imbalance.[7] Furthermore, Walsh (2005) and Ferenczi *et al*., (2007) showed that patients' body weight, serum electrolyte, ongoing fluid loss and the fluid prescribed were not checked. Additionally, they found that 17% of patients showed significant fluid associated morbidity due to fluid overload.[6,8,9] Lobo (2006) also found that mortality increased by 30% in the patients who gained more than 10% of body weight and by 100% in patients who gained more than 20% of body weight.[10] Moreover, Walsh *et al*. (2008) showed that more than half of studied cases (54%) have experienced at least one fluid-associated complication.[6,11] A report in 2011, launched by NCEPOD showed that risk of death is amplified for patients within thirty days after surgery if they are prescribed inappropriate amount of IV fluid preoperatively.[6,12] Based on the evidence given above, inappropriate fluid therapy carries a significant risk during the peri-operative period.

In 2013, the National Institute for Health and Care Excellence (NICE) launched a new guideline for prescribing of IV fluid therapy to minimize fluid associated morbidity and mortality.[13] Several studies showed pharmacist involvement and intervention through auditing, education and training were effective to improve the medication

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prescribing practice and achieve better clinical outcomes.[6,14] Additionally, a review study in 2015 concluded that pharmacist intervention could improve IV fluid prescribing and enhance patient safety.[6] In the Middle East, there were limited data about this topic and post-operative fluid associated complications were overlooked. This study was designed to evaluate the current prescribing practice of IV fluid therapy in an Iraqi public hospital and to explore the pharmacist role in improving the prescribing practice of fluid therapy using the NICE guideline.

METHODS

The prospective interventional study was conducted at the general surgery ward of AL-Hilla Teaching Hospital, Babel governorate, Iraq between November 2017 and July 2018. Patients who were admitted for elective surgeries in AL-Hilla teaching hospital and received IV fluid therapy for at least 48 hours were enrolled in this study.

The inclusion criteria were patients who were admitted to elective surgery in the general surgical ward of the hospital, received post-operative fluid therapy and did not have any pre-surgical fluid or electrolyte disturbances.

The patients were interviewed after obtaining their consent to collect their demographic information (age, gender, weight, height, date of admission, length of stay in the hospital, presence of disease), medical history, diagnosis and type of surgery. Then the patients were assessed to be included or excluded according to the study's inclusion criteria.

This study included three phases: Pre-intervention (control group), intervention and post-intervention. In the pre-intervention phase which lasted for two months, we reviewed patient records (control group) who received postoperative fluid therapy. The researcher pharmacist measured blood electrolyte levels and serum creatinine level of each participant in addition to recording their weight and received fluids. The pharmacist intervention phase lasted for a month and included pharmacist (researcher)-led training and educational sessions for the hospital surgeons about the NICE guideline of fluid therapy. After the pharmacist-led intervention, we recruited other patients (post-intervention phase) who received postoperative fluid therapy. In summary, the pre-intervention (observation) phase lasted for two months; Intervention phase lasted for a month, while post-intervention phase lasted for two months.

The pharmacist-led intervention included seminars and posters to increase surgeon awareness about fluid prescribing according to the NICE, 2013. The pharmacist recommendations were according to the NICE guideline to maintain the amount of fluid prescribed post-operatively within 25-30 ml/kg/day of water in day 1 and day 2.

Subsequently, the participating patients were sorted into three groups according to the volume of fluid administered: Those who were administered fluid within the guideline recommended dose (25-30 ml/kg/day or 1 ml/kg/hr), those who received greater than the recommended dose and those who received less fluid than the recommended dose.

Patient weight was measured using a standard electronic scale. The weight was taken two times: At zero time (before surgery) and postoperatively (after administrating intravenous fluid). The pre-operative measures were conducted on the day before surgery (12-24 hours) when patients came to do required pre-operative lab tests (Hb and virology tests). On the other hand, the post-operative measures were conducted a couple of hours before discharging patient home which usually occurred 48-72 after surgery. In general, patients kept receiving post-operative IV fluids until they eat solid food and/or have a bowel movement which is usually extended to the last day of their hospital stay. In other words, post-operative measures were conducted a few hours after completing last fluid bottle. The measurement of serum electrolytes was conducted by the researcher using a fully automated electrolyte analyzer.

This study was approved by the Ethics and Scientific Committee of Kufa University Faculty of Pharmacy and the Ethical and Scientific Committee at Babel Health Directorate.

Table 1. The baseline demographic data and characters of patients.

Variable	Pre Intv. group N=84	Post Intv. group N=112	p-value between groups
Age	36.78 (SD 1.65)	36.57 (SD 1.28)	0.922
Gender			0.480
Male	26 (31.0%)	40 (35.7%)	
Female	58 (69.0%)	72 (64.3%)	
Weight	65.78 (SD 1.53)	71.77 (SD 1.43)	0.005*
Height	163.05 (SD 0.90)	164.13 (SD 0.59)	0.296
Type of surgery			0.470
Appendectomy	24 (28.6%)	20 (17.9%)	
Laparoscopic cholecystitis	25 (29.8%)	34 (30.4%)	
Hernia	11 (13.1%)	14 (12.5%)	
Thyroidectomy	6 (7.1%)	17 (15.2%)	
Intestinal and colonic surgery	8 (9.5%)	12 (10.7%)	
GUT surgery	7 (8.3%)	9 (8.0%)	
Others	3 (3.6%)	6 (5.4%)	
Systolic BP	124.47 (SEM 1.72)	128.82 (SEM 1.52)	0.061
Diastolic BP	77.23 (SEM 0.93)	77.56 (SEM 0.89)	0.081
Pulse Rate	90.69 (SEM 1.43)	87.13 (SEM 1.06)	0.043*

SEM=standard error mean. *Significant difference (p-value <0.05). Chi-square test was used for categorical variables, while independent t-Test was used for continuous variables. GUT=genitourinary tract.

Table 2. Comparison of proportions of the patients given fluid amount according to the guideline. N (%)

Parameter	Below the range	Within the range	Above the range	P-value
Fluid therapy (Day1)				0.0001 *
Pre-intervention	8 (9.5%)	24 (28.6%)	52 (61.9%)	
Post-intervention	22 (19.6%)	76 (67.9%)	14 (12.5%)	
Fluid therapy (Day 2)				0.0001*
Pre-intervention	9 (10.7%)	28 (33.3%)	47 (56.0%)	
Post-intervention	23 (20.5%)	75 (67.0%)	14 (12.5%)	
*significant according to chi-square test. The recommended range of routine maintenance is 25-30 ml/kg.				

Statistical analyses

The SPSS version 23 (IBM, Chicago, IL) was used for data analyses. The descriptive data including frequencies, ranges, means, and percentages were measured. A p-value of less than 0.05 was considered statistically significant. A paired T-test was conducted to compare variables of each group before and after fluid therapy (within the same group). To compare variables in pre-interventional group with those of the post-intervention group, a Chi-square test was performed for categorical variables and an independent t-Test was used for continuous variables. Bivariate analysis using Pearson correlation coefficient was also used to measure the correlation between body weight and received fluid.

RESULTS

During the pre-interventional phase, only 84 out of 108 patients met the inclusion criteria and were included in the analyses. In the post-interventional phase, only 112 out of 138 patients met the eligibility criteria and were included in the analyses. Due to pre-surgical electrolyte abnormalities, 21 patients (9 with hyponatremia, 11 with hypernatremia and one with hyperkalemia) were excluded in the pre-interventional phase and 16 patients (4 with hyponatremia, 10 with hypernatremia and 2 with hyperkalemia) were excluded in the post-interventional phase. The baseline characteristics of patients and types of elective surgeries are shown in Table 1. Our study results showed during both phases pulse rate (PR) and BP significantly reduced post-operatively compared to pre-operatively.

The amount of the postoperative fluid given to the pre-intervention group was significantly higher than the amount given to the post-intervention group (Table 2). More importantly, there was lack of correlation between the amount of fluid prescribed and the patients' body weight in the pre-intervention phase (Figure 1). However, in the post- intervention phase, there was positive correlation between body weight and the amount of fluid prescribed postoperatively (Figure 2).

On top of that, the current practice (pre-intervention) of fluid therapy showed that 61.9% and 56% of the patients during the first and second day respectively were given higher doses of the postoperative fluid than those recommended by the guideline. These prescribed fluids primarily relied on clinical judgment of the clinicians. Approximately third of patients had been prescribed fluid doses according to the guideline (25-30ml/kg). Additionally, 9.5% of patients in first day and 10.7% of patients in second day were given fluid doses below the guideline range (Table 2).

Interestingly, after the pharmacist-led intervention, the percent of patients who were prescribed postoperative fluid according to the guideline dramatically increased to 67.9% and 67% in the first and second day respectively. On the other hand, the proportion of patients who received fluid doses above the guideline range dramatically decreased to 12.5% in both postoperative days. However, the proportion of patients who received postoperative fluid less than the guideline recommended dose significantly increased to 19.6% in first day and to 20.5% in the second post-operative day (Table 2).

The current practice of fluid therapy during the pre-intervention phase caused significant ($p<0.05$) increases in

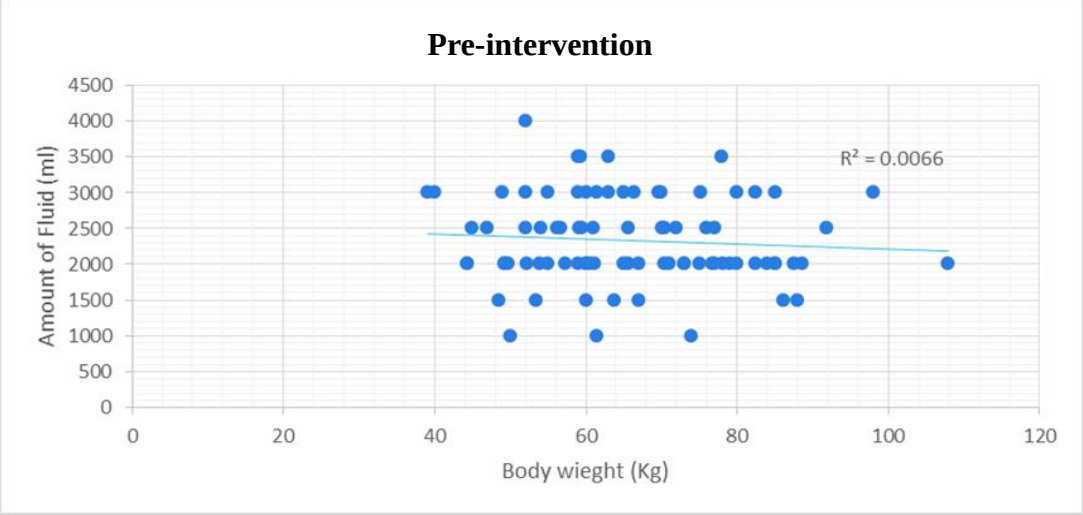

Figure 1. Correlation between body weight and amount of fluid prescribed in the pre intervention phase.

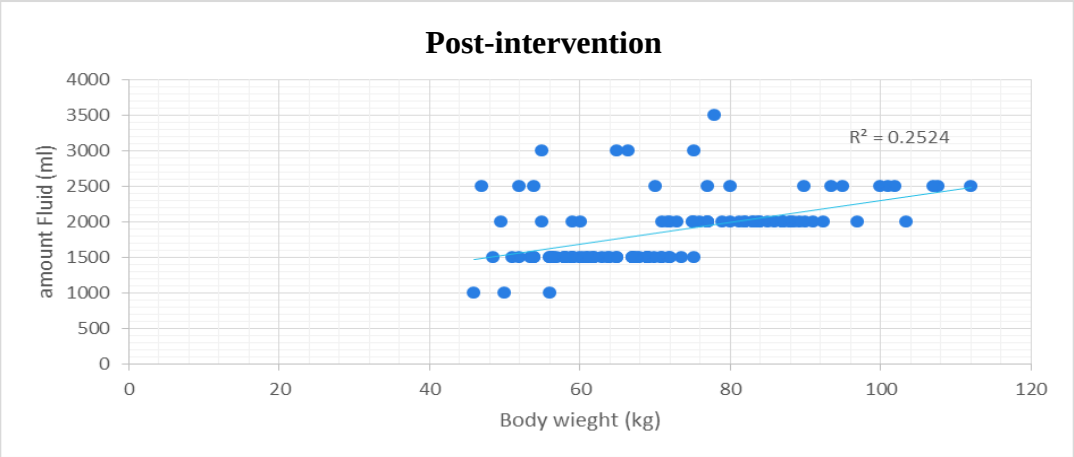

Figure 2. Correlation between body weight and amount of fluid prescribed in post-intervention phase.

patient body weight (average of 0.48 kilograms) after 2 days of fluid therapy compared to the baseline (before operation). On the other hand, in the post-intervention phase, there was no significant change in patient body weight compared to the baseline (Table 3).

In the pre-intervention phase, the surgeon prescribing practice of fluid therapy resulted in a large percentage of serum electrolyte abnormalities, including 19% of the patients experiencing hypernatremia and 6% of them having hyponatremia. In contrast, in the post-intervention phase, the incidence of electrolyte abnormalities significantly (p-value < 0.05) decreased to 7.1% for hypernatremia and 1.8% for hyponatremia (Table 4).

Regarding serum potassium, the pre-intervention prescribing practice caused several cases of hypokalemia (in 7.1% of the patients). In contrast, in the post-intervention group, only 0.9 % of the patients experienced hypokalemia which was significantly (p<0.05) lower than the pre-intervention phase (Table 4).

According to paired sample T-test, there was a significant (P-value < 0.05) increase in post-operative serum creatinine levels compared to pre-operative levels during the pre-intervention phase. In contrast, pharmacist-led intervention caused a significant decrease in post-operative serum creatine levels compared to pre-operative levels during the post-intervention phase (Table 5).

The fluid prescribing practice of pre-intervention phase revealed that the most commonly used post-operative IV fluids in the first and second day were saline containing fluids. Glucose saline (0.18% G/S) was prescribed in 53% of cases, while normal saline (0.9% N/S) was prescribed in 23% of cases. In contrast, Ringer lactate was rarely written in prescriptions with 3% in the first day and 5% in the second day. However, in the post-intervention phase, ringer lactate and glucose water were the most prescribed fluids, while the prescribing of saline containing fluids (N/S and G/S) decreased significantly (p<0.05) (by 10-15%) (Figure 3).

DISCUSSION

This study has not only focused on assessing the current prescribing practice, but has also showed how pharmacist educational intervention can enhance the prescribing and minimize post-operative fluid-associated complications.

The results of the pre-intervention phase showed the pattern of postoperative fluid prescribing was not consistent with the NICE guideline. The majority of patients were given higher doses of fluids compared to the amount recommended in the guideline. Furthermore, during the pre-intervention phase, there was no correlation between the prescribed amount of fluids and patients' body weight. This inappropriate prescribing pattern of the postoperative fluids has been reported in a previous study.[6] For instance, the data from a prospective audit in the UK showed that most patients receive an excess amount of the fluids and only few receive an insufficient amount of the fluids. Additionally, it found the volume of prescribed fluids is not correlated with preoperative body-weight.[11] Likewise, a multi-center observational audit found significant variability in the fluid prescribing pattern and that body weight was not considered in the fluid prescribing.[4]

More importantly, we found that the patients gained on average about 0.5 Kg of weight after two days of fluid therapy. A previous study in the UK reported a similar pattern of results when patients' weight notably increased due to perioperative extra-fluid volume.[15] Similarly, a blinded randomized trial found that body weight increased in patients receiving liberal fluid therapy.[16] Increases in the body weight due to excess amounts? of fluid directly associated with increased risk of morbidity and

Table 3. Effect of fluid therapy on body weight in pre and post-intervention groups

Body Weight (Kg)	Pre-intv. group (N=84) Mean (Standard error)	Post-intv. group (N=112) Mean (Standard error)
Before IV. therapy	65.77 (1.54)	71.68 (1.41)
After IV. therapy	66.24 (1.54)	71.46 (1.44)
Change in weight	0.48 (0.072)	-0.22 (0.2)
P-value within groups	0.0001	0.120
Data expressed in mean ± standard error mean and analyzed using paired T-test		

Table 4. Number of patients with electrolyte abnormalities before and after intervention

parameter	Normal	Below normal (hypo.)	Above normal (hyper.)
Sodium			
Pre-intervention	63 (75%)	5 (6.0%)	16 (19%)
Post- intervention	102 (91.1%)	2 (1.8%)	8 (7.1%)
p-value	0.009*	0.009*	0.004*
Potassium			
Pre-intervention	78 (92.9%)	6 (7.1%)	0 (0%)
Post- intervention	110 (98.2%)	1 (0.9%)	1 (0.9%)
p-value	0.046*	0.033*	0.184

Data were analyzed using chi-square test. Unites are frequency (N) and percent (%).
Electrolyte abnormalities (disturbances) include hypernatremia, hyponatremia, hyperkalemia and hypokalemia. Hypernatremia occurs when serum sodium ≥ 155 mmol/ l; Hyponatremia occurs when serum sodium is < 130 mmol/l. Hyperkalemia occurs when serum potassium is ≥ 5.5 mmol/l ; Hypokalemia occurs when potassium level is < 3 mmol/l.

mortality.[16,17] Previous studies reported that mortality increased by 30% to 100% in the patients who gained more than 10% or 20% of their body weight respectively.[16,17]

On top of that, the disturbances in the electrolyte levels were other complications during the pre-intervention phase due to improper prescribing of fluid electrolytes, namely sodium and potassium. The lack of potassium administration into postoperative fluids was noticed in almost all the participating cases. Accordingly, the patients' serum potassium level remarkably decreased after two days of fluid therapy compared to the baseline level. Consequently, about 7.1% of the patients developed hypokalemia mainly because of lack of prescribing potassium. Although the mean of serum sodium level did not change significantly after two days of fluid therapy, electrolyte abnormalities were reported in some patients. Nineteen percent of the participants experienced high serum sodium and 6% of them developed hyponatremia. These results were comparable with previous study findings which showed inappropriate fluid and electrolyte prescribing practices particularly ordering excess of fluids and sodium but subtherapeutic doses of potassium (8). Similarly, a previous prospective audit of the perioperative fluid management of 106 patients found more than half of the patients developed fluid and electrolyte related complications including 27 hypokalaemia, 17 hyponatraemia, 4 hypernatremia, 3 hyperkalaemia, 13 new dysrhythmia and 19 cases of fluid overload.[11]

It is worthy to mention that prescribing a higher volume of fluid, excess of sodium and suboptimal potassium doses in each postoperative day are associated with morbidity and mortality and prolong hospital stay time.[4,18] In the current study, two-thirds of the prescribed fluids were saline-containing solutions, and this might explain why the majority of patients received excess sodium and 19% of patients developed hypernatremia. Similarly, a previous study demonstrated that about one-quarter of surgeons prescribed more than four pints of 0.9% saline per day.[19] The traditional use of 0.9% saline in the majority of postoperative patients has been also reported by a study including two-year prospective audits.[20] This trend of high prescribing rate of 0.9% saline is associated with acid-base imbalance and electrolyte disturbances.[21] These disturbances could adversely affect patient's organ function and post-operative outcomes.[10]

The main reason behind these findings of inappropriate prescribing practices of fluid therapy is that firstly senior physicians may not pay as much attention to fluids as they do to other medicines. Physicians may think fluids do not cause as serious adverse effects as medications do. Secondly, the senior physicians delegate fluid prescribing to junior physicians. Korean and British studies confirmed that several errors in management of fluid and electrolyte therapy are due to inadequate knowledge and training of junior teams.[22-24] Principally, appropriate fluid prescribing necessitates complete understanding the physiology of fluid and electrolyte hemostasis as well as the composition and properties of each type of intravenous fluid. Therefore, there is urgent need for education and training of medical staff about these fundamentals and requirements for prescribing fluid therapy.[6,24]

The present study assessed the impact of pharmacist intervention on fluid prescribing practices by improving the knowledge and understanding of principles of fluid therapy and the guideline. Thus, the researcher pharmacist presented lectures to physicians about the prescribing guideline of fluid therapy, and electrolyte physiology as well as properties and composition of fluid types. On top of that, we also provided detailed explanation about the NICE guideline of postoperative IV fluid therapy. Several studies presented the importance of clinical pharmacists as key members of the medical multidisciplinary team that could improve prescribing practices of IV fluid therapy by providing training and educational programs to other healthcare practitioners as well as reviewing fluid prescriptions.[6,14]

After the intervention program, we found significant improvement in prescribing patterns of fluid therapy as reflected by amount of fluid prescribed according to the

Table 5. Paired Samples t-Test to compare pre and post-operative serum creatinine during both pre-& post-intervention phases

	N	Mean	SD	Difference mean	P-value
Pre-intervention phase					0.000*
Pre-operative blood Cr	105	0.587	0.181	0.037	
Post-operative blood Cr	105	0.625	0.255		
Post-intervention phase					0.000*
Pre-operative blood Cr	112	0.671	0.177	-0.02	
Post-operative blood Cr	112	0.65	0.166		

Significant difference < 0.05 according to paired t-test. Cr=creatinine. SD= Standard deviation

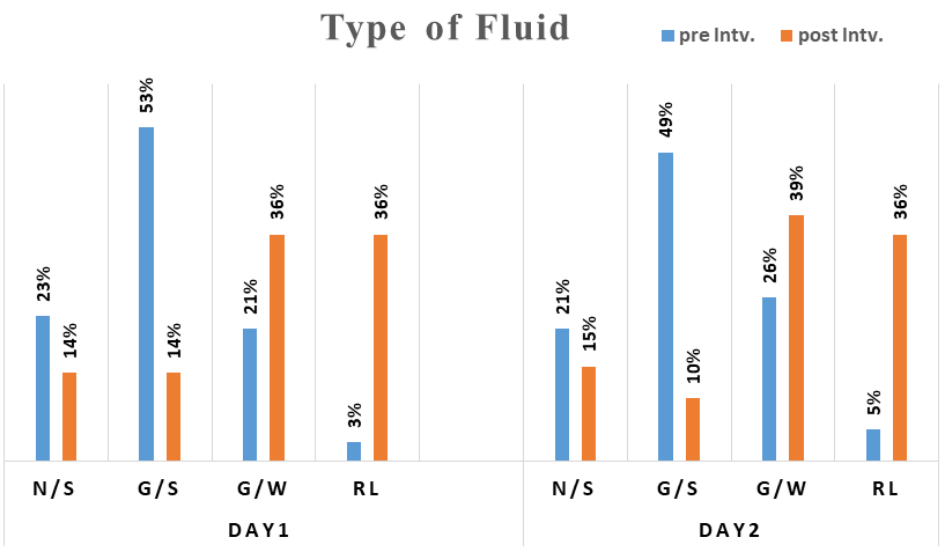

Figure 3. Types of fluids administered during the pre-intervention (control) and post-intervention phase.

recommended range of the guideline. We noted about 67% of patients received fluid doses according to the guideline (Table 2), which was remarkably higher than the percent reported in pre-intervention group (28.6-33.3%). Interestingly, the amount of fluid prescribed was significantly lower in the post-intervention group compared to the pre-intervention group (Table 2). This may be because physicians were overcautious about overloading patients following the intervention. Besides that, the prescribed volume of fluids showed a strong correlation with patients' body weight (Figure 2). This finding reflected the effectiveness of the pharmacist-led intervention program through convincing the prescribers to consider patient body weight in prescribing fluid therapy. Additionally, in the post-interventional group, body weight notably did not change after fluid therapy compared to pre-operative weight. This might attribute to prescribed IV fluids based on body weight according to the NICE guideline.

More importantly, the incidence of electrolyte abnormalities was significantly lower after intervention compared to those in the pre-intervention group as reflected by lower percent of hypernatremia, hyponatremia and hypokalemia (Table 4). Reduction in electrolyte disturbance means minimizing potential serious adverse effects including heart and brain problems. This reduction in the incidence of electrolyte abnormalities is mainly attributed to the improvement in prescribing practice of fluids and electrolytes. In addition to reduction in electrolyte disturbances and weight gain, the intervention helped to lower post-operative serum creatinine level. However, the reduction in creatine level may be not clinically significant. All these positive influences of the intervention may improve patient clinical outcomes after minimizing fluid-induced adverse effects.

Additionally, pharmacist-led intervention led to reductions? in use of 0.9% saline solution. This reduction in use of 0.9% saline and favoring use of balance crystalloid solutions (ringer lactate and glucose water 5%) in surgical wards? is also noted after an educational program in teaching hospitals in the UK.[20] A previous pilot study involved replacing 0.9% saline with balanced crystalloid through educational programs for nurses and junior doctors in order to achieve appropriate fluid prescription.[25] Balanced fluids including Hartmann's solution are considered more physiological and safer solutions. Hence, they are preferred for perioperative fluid.[26,27] On top of that, the use of ringer lactate over saline is recommended by British guidelines? (26). Interestingly, the reduction in prescribed volume of fluids and shifting from saline-containing fluids to balanced solutions for postoperative patients is associated with better outcomes reflected by less fluid overload and edema, quicker bowel movement and less hospital stay time.[20] Furthermore, recent randomized trials showed that the use of balanced crystalloid resulted in fewer mortality cases compared to saline in critically ill patients.[28,29] Importantly, following the intervention, we demonstrated a trend of increasing the use of D5W alongside with ringer solutions which provided the largest amount of free water which might explain the considerable reduction in the incidence of hypernatremia in post-intervention group. In summary, the pharmacist-led intervention enhanced fluid prescribing practice which minimized the increase in body weight, electrolyte disturbances, and fluid overload.

The analyses of vital signs were not included in the study results because PR and BP may be affected (reduced) by anesthesia medications and may not reflect patient fluid volume. The study strength was the researcher had no obligatory impact on physician decision, but the collaboration was totally optional.

This study had a number of limitations. The study included a relatively small number of patients and was conducted in one hospital. However, it is a typical example of Iraqi general public hospitals. Number of participants before and after the pharmacist-led intervention was not equal. Although we measured vital signs (PR and BP), we did not include the analyses of vital signs in the study results. Finally, the study was neither randomized nor blinded.

CONCLUSIONS

The current practice of postoperative fluid prescribing in the Iraqi hospitals showed variability and suboptimal practice which resulted in fluid-associated complications such as fluid overload and increase incidence of iatrogenic-induced electrolyte abnormalities. The pharmacist-led intervention to implement the NICE guideline of fluid therapy was effective in improving prescribing practice by increasing consistency with the guideline in amount of fluid prescribed and decreasing the incidence of fluid associated complications including fluid overload, increased creatinine levels and electrolyte disturbances. It is essential that healthcare authorities implement a universal fluid prescribing guideline in Iraqi hospitals to minimize variability in prescribing practices and reduce fluid associated complications.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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None.

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Original Research

Impact of select risk factors on treatment outcome in adults with candidemia

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Abstract

Background: Studies examining relationships between patient-related factors and treatment outcome in patients with candidemia are limited and often based on all-cause mortality.

Objective: Our purpose was to examine the impact of concurrent renal replacement therapy (RRT) and other pre-specified factors on treatment outcome among adults with candidemia.

Methods: This Institutional Review Board (IRB)-approved, single-center, case-cohort study included patients over 18 years of age admitted to Duke University Hospital between Jun 1, 2013 and Jun 1, 2017 with a blood culture positive for *Candida* spp. Treatment-, patient-, and disease-specific data were collected, and outcome (success/failure) determined 90 days after the index culture. An odds ratio (OR) and 95% confidence interval (95%CI) were calculated for the following during therapy: receipt of RRT, fluconazole monotherapy regimen, intensive care unit (ICU) stay, and neutropenia.

Results: Among the 112 encounters (from 110 unique patients) included, treatment failure occurred in 8/112 (7.1%). Demographics were comparable between outcome groups. Among 12 patients receiving concomitant RRT, only 1 patient failed therapy. With regard to treatment failure, no significant differences were observed with RRT (OR, 1.21; 95%CI, 0.14 – 10.75), fluconazole monotherapy regimen (OR, 1.59; 95%CI, 0.3-8.27), ICU stay (OR, 1.43; 95%CI, 0.32-6.29), and neutropenia (0 treatment failures).

Conclusions: Treatment failure, receipt of concomitant RRT, and neutropenia were infrequent in patients undergoing treatment for candidemia. In our cohort, exposure to RRT, a fluconazole monotherapy regimen, ICU stay, or neutropenia during treatment did not impact treatment outcome.

Keywords

Candidemia; Candida; Renal Replacement Therapy; Neutropenia; Fluconazole; Treatment Outcome; Treatment Failure; Intensive Care Units; Hospitals, University; Cohort Studies; North Carolina

INTRODUCTION

Invasive infections due to *Candida* spp., generally referred to as invasive candidiasis, is recognized as a major cause of morbidity and mortality in hospitalized patients.[1] According to the Centers for Disease Control and Prevention (CDC) it is estimated that approximately 46,000 cases of healthcare-associated candidiasis occur each year in the United States.[2] In patients with invasive candidiasis, all-cause mortality rates range from 10-49.8% while attributable mortality has been reported in 10-20%.[1,3,4] While there are at least 15 distinct *Candida* species that can cause human disease, >90% of invasive infections are caused by 5 pathogens: *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis*, and *C. krusei*.[2] Of these, *C. krusei* is inherently resistant to fluconazole and *C. glabrata* possesses low-level intrinsic resistance that may be overcome by increased doses of fluconazole.[2] In contrast to previous trends in rates of candidemia increasing over 20 years, declines have been observed in the past 5-7 years.[5] Despite this favorable trend, fluconazole-resistant *Candida* infections are becoming more prevalent.[2]

In December 2015, the Infectious Diseases Society of America (IDSA) published an updated clinical practice guideline for the management of candidiasis.[1] Recommended management of candidemia includes initial (empiric) therapy with an intravenous echinocandin, followed by oral or intravenous fluconazole after azole susceptibility has been confirmed (approximately 5-7 days). Per IDSA, fluconazole is also an acceptable alternative to an echinocandin as initial therapy in select patients who are not critically ill and unlikely to have a fluconazole-resistant *Candida* species. The pharmacokinetics of fluconazole, a drug extensively eliminated by the kidneys but metabolized in the liver, are altered in patients with renal impairment and reduction in maintenance doses should be made according to established recommendations in previously published literature and prescribing information.[6] In addition to drug treatment, patient- and disease-specific factors may impact treatment outcomes in patients with invasive candidiasis. Among these are the presence of immunosuppression, severe or life-threatening comorbidities, and the need for supportive therapies (such as mechanical ventilation and renal replacement therapy [RRT]).[1] Prior studies have identified that the risk of death from candidemia is predicted by increasing age, higher severity of illness, immunosuppression, renal dysfunction, *Candida* spp., presence of central venous catheter, and inappropriate or delayed antifungal therapy.[1,3,7,8] Factors positively affecting patient outcomes include early initiation of appropriate antifungal therapy and attainment of source control (i.e., removal of indwelling urinary or

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central venous catheters).[1] A recent retrospective surveillance study of patients over 21 years of age with candidemia identified RRT as independent predictor of all-cause mortality.[3] However, treatment outcome in these patients may have been impacted by treatment selection, and detailed information pertaining to the type and duration of concurrent RRT was not included. In addition, the study's endpoint (all-cause mortality) may have been influenced by factors other than candidemia treatment response. Among these factors, the data regarding the impact of RRT on treatment outcomes in this patient population is especially sparse. Our purpose was to examine the impact of select risk factors, most notably concurrent RRT on treatment outcomes among adults with candidemia.

METHODS

This Institutional Review Board (IRB)-exempted, retrospective, case-cohort study was conducted at Duke University Hospital (DUH), a 938-bed academic medical center located in Durham, NC. Patients were identified and data were extracted utilizing the Duke Enterprise Data Unified Content Explorer (a web-based query tool providing direct access from Duke Medicine Enterprise Data Warehouse) and Maestro Care (DUH's electronic medical record). Patients over 18 years of age admitted to DUH between June 1, 2013 and June 1, 2017 and had at least one positive blood culture for *Candida* spp., received a minimum of 3 doses of appropriate antifungal therapy (was defined as therapy concordant with IDSA guidelines for empiric and definitive treatment of invasive candidiasis) and had a follow-up encounter (defined as readmission or outpatient visit) over 7 days and within 90 days from completion of antifungal therapy were included. Patients were excluded if medical records were incomplete for the primary endpoint, received additional antifungal therapy for treatment of non-candidemia infection, and/or received subsequent prophylactic or suppressive antifungal therapy.

Data collected included patient demographics, hospitalization (admission date/time, discharge date/time, status at discharge, intensive care unit (ICU) dates of stay and date(s) of follow up), fungal blood cultures (date, time, results and susceptibility), antifungal therapy (drug name, dose, frequency, and route of administration), description of RRT (method and dates identified via ICD-9 and ICD-10 codes), and absolute neutrophil count (ANC) at time of candidemia diagnosis.

The primary objective of this study was to compare the incidence of treatment failure among adult patients with candidemia and concurrent RRT. Secondary objectives were to compare the incidence of treatment failure among adult patients with candidemia and at least one of the following risk factors: treatment with fluconazole monotherapy, ICU stay, and neutropenia (ANC<500).

For all outcomes, treatment failure was defined as meeting any of the following criteria: 1) death prior to blood culture clearance (from any cause); 2) blood culture following index blood culture and within 14 days after completion of antifungal therapy positive for same *Candida* spp.; or 3) escalation of antifungal therapy secondary to clinical decompensation thought due to persistent or worsening fungal infection (i.e., persistent fever or hypotension). Cases absent of criteria meeting treatment failure definitions were categorized as treatment success.

An odds ratio (OR) and 95% confidence interval (95%CI) were calculated for the following during therapy: receipt of RRT, fluconazole monotherapy regimen, ICU stay at any point during treatment of candidemia, and neutropenia. Based on an alpha level of 0.05 and effect size of 20% a sample size of 76 would be required for 80% power, for the primary endpoint. For the primary endpoint, the use of concomitant RRT was compared between outcome groups using chi-square or Fisher's exact test, as appropriate. Secondary endpoints were compared using Chi-square or Fisher's exact test, as appropriate. For any characteristics(s) deemed to have a p-value≤0.20 between outcome groups,

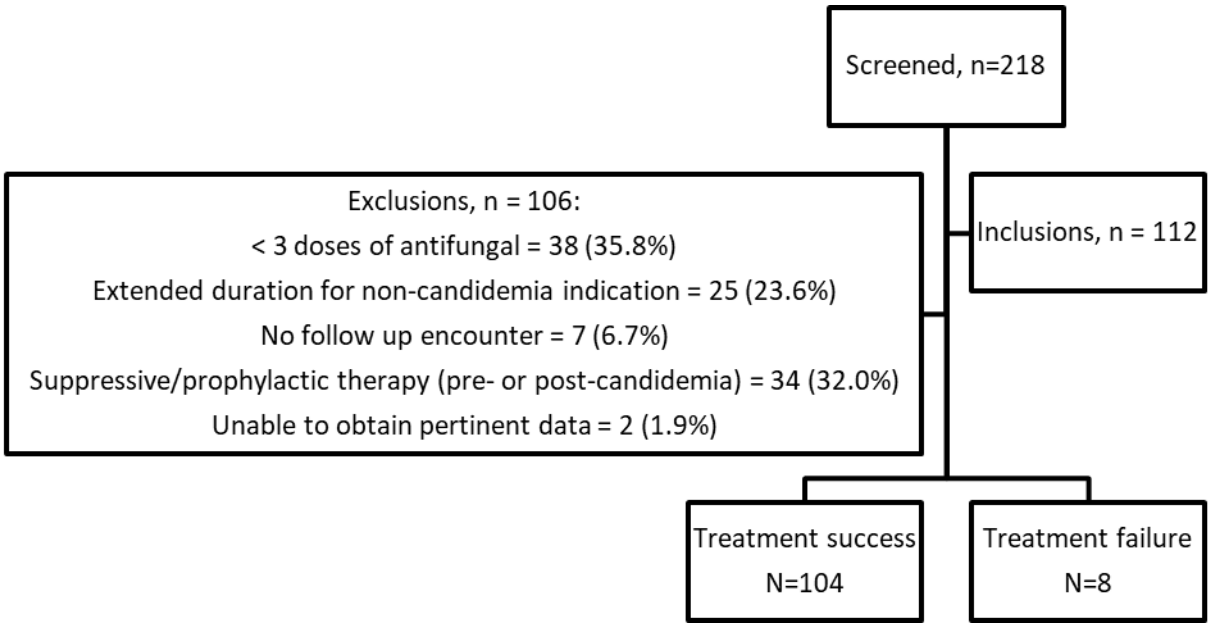

Figure 1. Subject encounters screened for inclusion and outcome assignment.

Table 1. Patient demographics among patients with candidemia by treatment outcome

Parameter	Treatment Success N = 104, n (%)	Treatment failure N = 8, n (%)	All encounters N = 112, n (%)
Age at arrival, years			
Median (range)	56.8 (1.7 – 91.7)	52.8 (20.3 – 61.5)	56.0 (18.0 – 91.7)
Male	60 (57.7)	4 (50.0)	64 (57.1)
Race			
Caucasian	66 (63.4)	3 (37.5)	69 (61.6)
African American	33 (31.7)	4 (50.0)	37 (33.0)
Other/not reported	2 (2.0)	1 (12.5)	3 (2.7)
Multiracial	2 (1.9)	0 (0.0)	2 (1.8)
American Indian or Alaskan Native	1 (1.0)	0 (0.0)	1 (0.9)
Discharge disposition			
Expired	25 (24.0)	2 (25.0)	27 (24.1)
Home health service	23 (22.1)	3 (37.5)	26 (23.2)
Home or self-care	22 (21.2)	1 (12.5)	23 (20.5)
Skilled nursing facility	14 (13.5)	1 (12.5)	15 (13.4)
Long term acute care	8 (7.7)	0 (0.0)	8 (7.1)
Hospice (inpatient)	6 (5.8)	1 (12.5)	7 (6.3)
Hospice (home)	3 (2.9)	0 (0.0)	3 (2.7)
Federal hospital	1 (0.9)	0 (0.0)	1 (0.9)
Left against medical advice	1 (0.9)	0 (0.0)	1 (0.9)
Rehabilitation facility	1 (0.9)	0 (0.0)	1 (0.9)
Characteristic of interest			
Receipt of RRT	11 (10.6)	1 (12.5)	12 (10.7)
Fluconazole monotherapy regimen	66 (63.5)	6 (75.0)	72 (64.3)
ICU stay	56 (53.8)	5 (62.5)	61 (54.5)
Neutropenia	2 (1.9)	0 (0.0)	2 (1.8)

RRT: renal replacement therapy; ICU: intensive care unit

a multivariable logistic regression model would be used to identify association of those characteristics with treatment failure. All data were entered into Microsoft Access™, version 16.0.4549.1000 (Microsoft Corp., Redmond, WA). JMP©, version 13 (SAS Institute, Cary, NC), was used for all statistical calculations.

RESULTS

Of the 218 encounters screened for eligibility, 112 encounters (from 110 unique patients) were included (Figure 1). The most common reasons for exclusion were receipt of < 3 doses of an antifungal agent (n = 38), receipt of subsequent suppressive or prophylactic antifungal therapy (n = 34), and extended duration of antifungal therapy for non-candidemia indication (n = 25). Overall, patients evaluated were primarily male (57.1%), Caucasian (61.6%) or African American (33.0%), and ranged in age from 18.0 to 91.7 years of age (median 56 years) upon arrival to DUH. Treatment failure was observed in 8 (7.1%) of the 112 encounters. Baseline characteristics regarding race, sex, age at arrival, and discharge disposition were comparable between outcome groups (Table 1). *C. albicans* and *C. glabrata* were the two most common organisms, isolated in 36.5% (n=42) and 38.3% (n=44) of all patients, respectively. These were the only organisms isolated in patients with treatment failure (Table 2).

Among 12 patients receiving concomitant RRT, only 1 patient failed therapy. No significant differences were observed with regards to secondary outcomes related to treatment failure with a fluconazole monotherapy regimen (OR, 1.59; 95%CI, 0.3 - 8.27), ICU stay (OR, 1.43; 95%CI, 0.32 - 6.29), and neutropenia (0 treatment failures) (Table 3). No characteristic met the pre-specified p-value for performance of the multivariable logistic regression.

DISCUSSION

The overall treatment failure rate in our study (7.1%) was substantially lower than that reported in the published literature of 30 to 40%.[1,3,9,10] Enrollment criteria requiring follow-up encounter over 7 days and within 90 days from completion of antifungal therapy may have significantly limited inclusion of patients with advanced malignancies or severe comorbidities. Patients were also excluded for receipt of subsequent antifungals as preventative or suppressive therapy. Fifty-nine of 106 (55.7%) encounters were excluded from our study due to meeting these criteria. These excluded patients may represent those at

Table 2. Causative organisms among patients with candidemia by treatment outcome

Organism	Treatment Success, n[a] (%)	Treatment Failure n (%)	All Encounters n[a] (%)
C. glabrata	41 (38.4)	3 (37.5)	44 (38.3)
C. albicans	37 (34.6)	5 (62.5)	42 (36.5)
C. parapsilosis	12 (11.2)	0 (0.0)	12 (10.4)
C. tropicalis	12 (11.2)	0 (0.0)	12 (10.4)
C. dubliniensis	2 (1.9)	0 (0.0)	2 (1.7)
C. krusei	1 (0.9)	0 (0.0)	1 (0.9)
C. lusitaniae	1 (0.9)	0 (0.0)	1 (0.9)
C. pelliculosa	1 (0.9)	0 (0.0)	1 (0.9)

[a:] 3 patients had > 1 organism isolated

Table 3. Univariate analysis of risk of treatment failure among select subgroups in patients with candidemia			
Characteristic	**Failure #failed/#exposed (%)**	**cOR**	**95% CI**
Renal replacement therapy	1/12 (8.3)	1.21	0.14 – 10.75
Fluconazole monotherapy regimen	6/72 (8.3)	1.72	0.33 – 8.99
ICU stay	5/61 (8.2)	1.43	0.32 – 6.29
Neutropenia	0/2 (0.0)	---	---
ICU: intensive care unit; CI: Confidence Interval; cOR: Crude odds ratio			

highest risk for treatment failure or relapse explaining their need for continuing therapy. Our study also required all patients to have received 3 or more doses of appropriate antifungal therapy prior to inclusion, thus resembling more of a "per protocol" analysis compared to other studies where no minimal treatment duration was specified.[3] Our institution is a tertiary-care, academic medical center employing mandatory consultation after identification of a positive blood culture for yeast, the primary team is required to place an infectious diseases consult to aid in management of invasive candidiasis. Such consultation has been shown previously at our institution to improve adherence to quality of care indicators for such infections.[11]

In the present study, the rate of concomitant RRT in the overall study population (10.7%) was lower than the 12% to 33% described in previously published literature.[3,9,10] Differences may be due to composite patient characteristic categories (i.e., "renal dysfunction") including patients requiring hemodialysis, patients diagnosed with chronic renal failure based on serum creatinine, and patients with diagnosed chronic renal failure or non-specific categories (i.e., "renal insufficiency" or "renal failure") with no further delineation. The current study relied on ICD-9 and -10 codes in addition to EMR records for receipt of RRT. Only 1 of the 12 patients receiving RRT failed therapy for candidemia. Reasons for differences in treatment outcomes likely parallel the reasons for differences between our study and others relative to overall success rates.

The impact of treatment selection on treatment outcome has been examined in prior studies.[1,4,9,10] A patient-level review of randomized trials for treatment outcomes of invasive candidiasis found a significant association with receipt of an echinocandin pertaining to improved survival and greater clinical success.[9] Two recent studies discuss the impact of initial antifungal strategy on outcomes of critically-ill patients after propensity-score matching was performed.[10,11] One retrospective, propensity-score adjusted, analysis reported empirical use of an echinocandin was found to be a protective factor of 30- and 90-day mortality while de-escalation to fluconazole was not associated with a higher mortality.[10] In contrast, a prospective, propensity-score derived analysis found targeted or empirical use of fluconazole was not associated with higher 30-day mortality compared to echinocandins among adult patients.[12] Among the 72 patients in the present study whose treatment regimen contained fluconazole, 6/8 (75%) experienced treatment failure, and 6/6 (100%) of failures received fluconazole as initial therapy. In comparison, 66 among the 104 (63.5%) of patients receiving fluconazole as step-down therapy were successfully treated. Such observations are consistent with studies (and the basis for current treatment guidelines) which support the use of an echinocandin as initial empiric therapy followed by de-escalation to azole therapy when the patient is clinically stable and an azole-susceptible organism is identified.[1,10]

Neutropenia and severity of underlying illness may also impact treatment outcomes in patients with candidemia. In prior reports, the low numbers of patients with neutropenia (5 – 12% of study populations) has led to the inability to extrapolate results from retro- or prospective studies of outcomes in candidemia patients.[7,10,11,12] In the present study, only 2 (1.7%) of the patients were neutropenic during treatment, both of whom were treated successfully. Severity of underlying illness also has been shown to influence treatment outcomes.[1,3,7,9,10,12] All-cause mortality rates in critically ill patients with candidemia range from 18.7 % to 33.9%.[3,10,11,12] ICU stay and increasing APACHE II, sepsis-related organ failure assessment (SOFA) scores on admission have both been demonstrated to be predictive of a higher risk of death in patients with invasive candidiasis.[3,9,10,12] In the present study, of those patients requiring an ICU stay, 5/61 (8.2%) experienced treatment failure.

There are limitations to our study worth noting. The study was retrospective in nature, and therefore dependent upon the availability and accuracy of the medical records (most notably reliance on accuracy of ICD-9 and ICD-10 codes and administration of antifungal agents). Because of this, several factors which have been associated with treatment failure were not evaluated (e.g. timing of initiation of appropriate antifungal therapy and attainment of source control). While risk adjustment was not employed to create comparable outcome groups seen in some other studies, our high success rate was not likely to be impacted by such adjustments.[10,12] Due to the specific nature of our patient population and characteristics studied, a small sample size is also a limitation of the study. Stringent inclusion criteria likely pre-screened for healthier patients to be evaluated leading to a limited number of patients requiring RRT and subsequent low rate of mortality. Lastly, dosages of fluconazole were difficult to assess for each patient as the dosage strategy was adjusted based on renal function, RRT flow rates and modality.

CONCLUSIONS

In the present study we were unable to detect an impact of RRT on treatment outcomes in adult patients with candidemia. This finding is likely impacted by the high treatment success rates reflective of a population receiving appropriate antifungal therapy and for whom adequate clinical and microbiologic data can be collected to more specifically measure impact of candidemia. No other characteristic investigated (receipt of fluconazole monotherapy regimen, ICU stay, and neutropenia) demonstrated statistical significance between outcome groups.

CONFLICT OF INTEREST

No conflicts of interest to disclose related to this study.

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Original Research

Medication dispensing, additional therapeutic recommendations, and pricing practices for acute diarrhoea by community pharmacies in Germany: a simulated patient study

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Abstract

Background: In Germany over-the-counter medications (OTC) – which since 2004 are no longer subject to binding prices – can only be purchased in pharmacies. Pharmacy owners and their staff therefore have a special responsibility when dispensing, advising on and setting the prices of medications.

Objective: The aim of this study was to assess medication dispensing, additional therapeutic recommendations and pricing practices for acute diarrhoea in adults and to evaluate the role of the patient's approach (symptom-based versus medication-based request) in determining the outcome of these aspects.

Methods: A cross-sectional study was conducted from 1 May to 31 July 2017 in all 21 community pharmacies in a medium-sized German city. Symptom-based and medication-based scenarios related to self-medication of acute diarrhoea were developed and used by five simulated patients (SPs) in all of the pharmacies (a total of 84 visits). Differentiating between the different test scenarios in terms of the commercial and active ingredient names and also the prices of the medications dispensed, the SPs recorded on collection forms whether the scenario involved generic products or original preparations as well as whether recommendations were made during the test purchases regarding an additional intake of fluids.

Results: In each of the 84 test purchases one preparation was dispensed. However, a preparation for oral rehydration was not sold in a single test purchase. On the other hand, in 74/84 (88%) of test purchases, medications with the active ingredient loperamide were dispensed. In only 35/84 (42%) of test purchases, the patient was also recommended to ensure an 'adequate intake of fluids' in addition to being dispensed a medication. In symptom-based scenarios significantly more expensive medications were dispensed compared to the medication-based scenarios (Wilcoxon signed rank test: $z = -4.784$, $p < 0.001$, $r = 0.738$). Also within the different scenarios there were enormous price differences identified – for example, in the medication-based scenarios, even for comparable loperamide generics the cheapest preparation cost EUR 1.99 and the most expensive preparation cost EUR 4.53.

Conclusions: Oral rehydration was not dispensed and only occasionally was an adequate intake of fluids recommended. There were also enormous price differences both between and within the scenarios investigated.

Keywords

Diarrhea; Loperamide; Self Medication; Professional Practice; Pharmacies; Pharmaceutical Services; Pharmacists; Quality of Health Care; Costs and Cost Analysis; Patient Simulation; Germany

INTRODUCTION

Acute diarrhoea is one of the most common diseases worldwide, including in Germany.[1,2] Thus, Germany with a population of about 83 million people records about 42 million cases of acute diarrhoea each year with no medical consultation in about two-thirds of cases.[2,3] For pharmacotherapy of acute diarrhoea in Germany there are medications available that require a medical prescription. These are primarily antibiotics (such as ciprofloxacin, azithromycin and metronidazole) for the treatment of bacterially induced diarrhoea along with the active ingredient combination diphenoxylate/atropine.[4] In addition to oral rehydration solutions, the active ingredients loperamide, racecadotril, Lactobacillus rhamnosus GG, Saccharomyces boulardii, medical charcoal, pectin, tannin albuminate/ethacridine lactate and uzara root extract are also available as over-the-counter medications (OTC) available for self-treatment.[5] The four preparations with the highest sales are the original preparation IMODIUM® (active ingredient: loperamide) with 23% market share, the generic Lopedium® (active ingredient: loperamide) with 18% market share, PERENTEROL® (active ingredient: Saccharomyces boulardii) with 18% market share and the generic Loperamid-ratiopharm® (active ingredient: loperamide) with 5% market share.[6]

Both prescription and non-prescription medicines are purchased exclusively in pharmacies in Germany.[7] In addition to pharmacists, pharmacy technicians and pharmaceutical technical assistants are also permitted to advise on and sell medications but only under the supervision of pharmacists. So that the advice dispensed is as comprehensive as possible, the Ordinance on the Operation of Pharmacies in Germany considers pharmacies obliged to introduce a quality management system. The German Federal Chamber of Pharmacists (BAK) has drafted a range of guidelines for the implementation of such

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systems, including the guideline 'Information and advice as part of self-medication using the example of self-diagnosed diarrhoea'.[8]

If the diarrhoea is self-medicated using OTC preparations, good advice should be provided by the pharmacies because acute diarrhoea can be a symptom of a wide range of diseases.[9,10] An important prerequisite for that is an appropriate assessment of the patient. However, good advice is an important criterion not only in regards to the patients.[11] In terms of competition between the pharmacies it also plays an important role. In particular, the removal of resale price maintenance in 2004 exacerbated the competitive situation in German pharmacies.[12] Good advice can therefore provide an important competitive advantage.[13] According to Hepler and Strand and the shift in the role of the pharmacist, good advice covers aspects such as safety, clinical effectiveness and cost-effectiveness of medications.[14] On one hand, according to the guidelines published by the BAK this includes whether relevant questions (for example, how long the symptoms have been present) are asked during the consultation or whether relevant information (for example, regarding the dosage) is provided after dispensing the medication.[8] In this regard, the simulated patient (SP) studies available to date for Germany on acute diarrhoea in adults – analogous to the international literature – have identified serious deficiencies.[15-21] On the other hand, this also includes the following aspects, which have not yet been investigated in Germany for this indication:

- Whether, and if so, which medications are dispensed as well as whether they appear indicated in regards to the test scenarios presented.
- Whether, and if so, how the additional information on 'adequate intake of fluids' for patients that is specified in the BAK guidelines is implemented by the pharmacies.[8]
- The economic aspects of providing good advice, because dispensing comparably expensive medications (without appropriate additional benefits) constitutes poor advice from the customer's perspective. This practice can be considered unethical and a poor business practice as it does not facilitate the building of good relationships that would create repeat customers.
- Whether the issues indicated differ based on the patient's approach (medication-based versus symptom-based query) because to date it has only been reported anecdotally that more expensive medications were dispensed more often in symptom-based scenarios than in medication-based scenarios.[19]

To close these gaps in the research, it was the primary aim of this study to investigate the dispensing and additional therapeutic recommendation practices of community pharmacies for acute diarrhoea and the costs charged to the patients. The secondary objective was to evaluate the role of the patient's approach in determining the aspects indicated above.

METHODS

Design

A cross-sectional study design was chosen in accordance with the 'STROBE Statement – Checklist of items that should be included in reports of cross-sectional studies' using the SP method as a form of participatory observation.[22,23] An SP here is an individual who visits a pharmacy with the aim of evaluating the quality of advice dispensed. Scenarios developed prior to the test purchase that define in particular which indications (for example, acute diarrhoea) will be investigated and which information will be given to the pharmacy personnel by the SP are used for this purpose. After leaving the pharmacy, the SP evaluates the quality of advice dispensed by the pharmacy personnel using an assessment form that was also developed prior to the test purchase. The drawbacks of this method specifically include the relatively high collection costs as well as any variation in the evaluations (both between different SPs and between different test purchases made by the same SP). The main benefit, however, is that a realistic (advisory) situation can be portrayed.[24] In a comparison of many data collection methods, the superiority of the SP method has been demonstrated, making it no wonder that this method has frequently been used internationally in pharmacy practice-based research.[25-27]

Setting and participation

Because of time constraints of the SPs, the test purchases were carried out over summer between 1 May 2017 and 31 July 2017 in the city of Neubrandenburg (31 December 2017: 64,259 residents; Federal State of Mecklenburg-Vorpommern) on different days of the week and at different times.[28] In the municipal area of Neubrandenburg there were 21 community pharmacies on the reference date of 1 May 2017.[29] Each of these 21 pharmacies was visited four times with one different scenario each time, yielding a total of 84 test purchases. To carry out the test purchases, a total of EUR 353.01 was required which was financed from the primary author's own resources.

Scenarios

Two of the test scenarios were designed as medication-based scenarios (test scenarios 1 and 3: request for the active ingredient loperamide without explicitly requesting a specific brand or generic preparation) while the two other test scenarios were symptom-based (test scenarios 2 and 4: request for a medication to treat acute diarrhoea without explicitly requesting a specific active ingredient). The particular scenarios were also differentiated by different user groups (test scenarios 1 and 2: purchase for the 74-year-old grandmother with the underlying conditions diabetes and hypertension; test scenarios 3 and 4: purchase for the 30-year-old partner with no underlying conditions). Each of the four test scenarios otherwise had an identical design in terms of the information provided in response to questions from the pharmacy staff (Table 1).

Data collection

To avoid the Hawthorne effect and to ensure the most realistic possible consultation situation, the test purchases took place without first informing the pharmacies included

Table 1. Simulated patient scenarios
Scenario 1
The SP enters the pharmacy and asks for a pack of loperamide. If the pharmacist offers a substitute preparation, the SP is willing to accept it. This is regardless of whether a medication with a different active substance or a homeopathic preparation is offered.
If the pharmacist asks, the following information is supplied:
- Preparation is for the SP's 74-year-old grandmother - Acute diarrhoea present for 24 h and has occurred several times up to now - No vomiting, no blood in the stool, no fever - Has not yet visited a doctor - Underlying conditions: Diabetes and high blood pressure
Scenario 2
The SP enters the pharmacy and asks for a preparation to treat diarrhoea. The SP does not have any particular product in mind.
If the pharmacist asks, the following information is supplied:
- Preparation is for the SP's 74-year-old grandmother - Acute diarrhoea present for 24 h and has occurred several times up to now - No vomiting, no blood in the stool, no fever - Has not yet visited a doctor - Underlying conditions: Diabetes and high blood pressure
Scenario 3
The SP enters the pharmacy and asks for a pack of loperamide. If the pharmacist offers a substitute preparation, the SP is willing to accept it. This is regardless of whether a medication with a different active substance or a homeopathic preparation is offered.
If the pharmacist asks, the following information is supplied:
- Preparation is for the SP's 30-year-old partner - Acute diarrhoea present for 24 h and has occurred several times up to now - No vomiting, no blood in the stool, no fever - Has not yet visited a doctor - No underlying conditions
Scenario 4
The SP enters the pharmacy and asks for a preparation to treat diarrhoea. The SP does not have any particular product in mind.
If the pharmacist asks, the following information is supplied:
- Preparation is for the SP's 30-year-old partner - Acute diarrhoea present for 24 h and has occurred several times up to now - No vomiting, no blood in the stool, no fever - Has not yet visited a doctor - No underlying conditions

in the investigation in accordance with other national and international studies.[19-21,30-33]

Three female and two male Master students from the Department of Health, Nursing, Management of the Neubrandenburg University of Applied Sciences acted as SPs. They were selected on the basis of their participation in a 3-semester student research project, the results of which are in part incorporated in this publication.

The test purchases for each scenario were always carried out over a two-week period. There was one week between the individual scenarios (with 21 test purchases for each). The pharmacies to be tested were distributed randomly among the particular SPs so that each SP was allocated to a total of 16–18 test purchases overall (SP 1: 16 test purchases; SP 2: 17 test purchases; SP 3: 16 test purchases; SP 4: 17 test purchases; SP 5: 18 test purchases). The allocation was subsequently checked to ensure that no pharmacy was visited repeatedly by a SP to minimise the risk of discovery. A summary was generated to indicate which SPs visited which pharmacies with which scenario and at what time point.

The SPs noted on the collection forms firstly as open-ended questions the commercial and active ingredient names as well as the prices of the medication dispensed differentiated by the test scenarios. Secondly, in the form of closed questions, the SPs recorded the medication category (brand vs. generic medication) of the dispensed preparation, the recommendations regarding additional intake of fluid (yes vs. no) as well as pharmacy and pharmacy staff characteristics such as the gender (female vs. male) of the particular pharmacy staff who provided the advice and the busyness of the particular pharmacy (staff < customers vs. staff > customers) at the time of the test purchase. Furthermore, during the test purchases the SPs also attempted to identify the professional group (pharmacist vs. non-pharmacist vs. not able to be determined) of the particular pharmacy staff who advised them using the name tag worn, the information on the sales receipt and by means of a telephone survey conducted once the study was completed (so as not to endanger the covert study design). Whether relevant questions (for example, about the medical history) were asked during the consultation and whether relevant information (for example, about any side effects) was provided after dispensing the medication by the pharmacy staff was also documented for each scenario but these issues were not the objectives of this study and are therefore published elsewhere.[21]

Before the data collection was started, each SP first familiarised themselves with the theoretical principles of the methodology as well as the contents of the collection form. A pilot study with 20 test purchases (five SPs × four visits) was then carried out by the SPs outside Neubrandenburg to train the SPs in the use of the methodology and to verify the functionality of the collection form and the four test scenarios. No changes to the test scenarios and the collection form were required after testing the scenarios.

Table 2. Pharmacy and pharmacy staff characteristics by patient's approach

Characteristics; n (%)	Medication-based test purchases (n=42)	Symptom-based test purchases (n=42)	P value
Staff gender			0.125#
Female	40 (95)	35 (83)	
Male	2 (5)	7 (17)	
Staff position			0.211*
Pharmacist	12 (29)	10 (24)	
Non-pharmacist	27 (64)	26 (62)	
Not able to be determined	3 (7)	6 (14)	
Pharmacy busyness			0.388#
Staff < customers	9 (21)	5 (12)	
Staff ≥ customers	33 (79)	37 (88)	

#McNemar Test; *McNemar-Bowker-Test; significant P values are indicated by characters in bold

The SPs made their request to the pharmacy staff who first approached them. The SPs only provided additional information when asked by the dispenser to ensure that the information provided by the SPs is consistent. The collection forms were filled out by the SPs immediately after visiting the pharmacies to minimise distortions in the study results due to faulty recall by the SPs.

Data management and analysis

Data were double entered into and analysed using SPSS software (IBM, Armonk, NY, USA) version 25 for Windows. This study is part of a larger research project. Unlike previously published research results, differentiating by different user groups does not play a role due to the objectives of this study, and for this reason the scenarios were only differentiated by the patient's approach.[19-21] This means that in the analysis the test purchases were differentiated into 42 medication-based (test scenarios 1 and 3) or 42 symptom-based (test scenarios 2 and 4) test purchases. Because the 74-year-old grandmother with diabetes and hypertension in scenarios 1 and 2 was clinically at greater risk of harm from dehydration, a subanalysis of an additional intake of fluids was conducted and therefore the test purchases were differentiated into 21 medication-based (test scenario 1) or 21 symptom-based (test scenario 2) test purchases. Categorical variables were reported as frequencies and percentages, whereas continuous variables were expressed as median, interquartile range [IQR], min and max. The application of the Shapiro-Wilk tests indicated that the data do not have a normal distribution. Due to the repeated measurements (4 test purchases in the same pharmacy), the samples are also related. Therefore, the McNemar test and the McNemar-Bowker-Test were performed on categorical variables and the Wilcoxon signed rank test was used to assess differences in the continuous variables between the groups. A p-value of less than 0.05 was considered to be statistically significant. The effect size of the Wilcoxon signed rank test was measured using the Pearson correlation coefficient r, whereby according to Cohen, from 0.10 onwards there is a small effect, from 0.30 onwards there is a medium effect and from 0.50 onwards there is a large effect.[34]

Research ethics approval

The study was approved by the ethics committee of the Neubrandenburg University of Applied Sciences. Due to the covert study design, neither the pharmacies nor the Federal Chamber of Pharmacists were informed about the study in advance. Following the 'Guideline for the use of mystery research in market and social research, the information obtained was recorded in such a way that the pharmacies involved could not be identified and the results were reported anonymously.[35] This ensures that participating pharmacists are not at any risk of criminal or civil liability nor does their participation harm their employability or reputation. Recruited students provided their verbal informed consent to act as SPs.

RESULTS

All the 84 test purchases planned were carried out. Pharmacy and pharmacy staff characteristics were not significantly different by patient's approach (Table 2).

A total of 84 medications (1 preparation per test purchase) were sold by the pharmacies. In 74/84 (88%) of test purchases, medications with the active ingredient loperamide were dispensed and these were sold significantly more often in medication-based scenarios than in the symptom-based scenarios (p=0.002). Aside from this, only a few preparations with the active ingredients racecadotril, Saccharomyces boulardii, medical charcoal and the combination of active ingredients tannin albuminate/ethacridine lactate were dispensed but these preparations did not show any significant differences in terms of the patient's approach. Generic formulations made up 61/84 (73%) of dispensed medications and only included loperamide. Generics were sold significantly more often in the medication-based scenarios than in the symptom-based scenarios (p<0.001). For 35/84 (42%) of test purchases, in addition to dispensing a medication, it was recommended to the patient to pay attention to an 'adequate intake of fluid', whereby such a recommendation was made significantly more often in symptom-based scenarios than in medication-based scenarios (p=0.011). For the 74-year-old grandmother with diabetes and hypertension such a recommendation was also given more often in symptom-based scenarios than in medication-based scenarios, whereby this difference was not significant (p=0.267) (Table 3).

In terms of the medication prices, there were significant differences seen when comparing the medication-based scenarios and the symptom-based scenarios (Wilcoxon signed rank test: z=-4.784, p<0.001, r=0.738). In the medication-based test scenarios considerably cheaper preparations were dispensed with a median score of EUR 2.36 (IQR EUR 1.94) compared to the symptom-based test scenarios with a median score of EUR 5.28 (IQR EUR 2.60). In the medication-based test scenarios the cheapest

Table 3. Medications dispensed and additional therapeutic recommendations by patient's approach

Active ingredients dispensed [n (%)]	Medication-based test purchases (n=42)	Symptom-based test purchases (n=42)	p-value
Loperamide	42 (100)	32 (76)	0.002#
Racecadotril	0 (0)	4 (10)	0.125#
Saccharomyces boulardii	0 (0)	3 (7)	0.250#
Medical charcoal	0 (0)	2 (5)	0.500#
Tannin albuminate/ethacridine lactate	0 (0)	1 (2)	1.000#
Of which total generics	42 (100)	19 (45)	<0.001#
Additional recommendation 'adequate intake of fluid'	11 (26)	24 (57)	0.011#
	Medication-based test purchases (n=21)	**Symptom-based test purchases (n=21)**	
Of which for the 74-year-old grandmother with diabetes and hypertension	6 (29)	11 (52)	0.267#
#McNemar Test; significant P values are indicated with characters in bold			

preparation cost EUR 1.99 (loperamide generic, 10 units hard capsules, 2 mg) and the most expensive preparation cost EUR 4.53 (loperamide generic, 10 units hard capsules, 2 mg). In the symptom-based test scenarios the cheapest preparation cost EUR 2.28 (loperamide generic, 10 units hard capsules, 2 mg) and the most expensive preparation cost EUR 10.98 (IMODIUM® akut lingual, 12 units, quick dissolve tablets, 2 mg). Referring only to hard capsules and across the four different scenarios and all 84 interactions, preparations with the active ingredient loperamide cost EUR 1.99 in the cheapest case for a pack of loperamide generic (10 units hard capsules, 2 mg) while up to EUR 5.28 had to be paid for a pack of the comparable original preparation IMODIUM® akut (12 units hard capsules, 2 mg).

DISCUSSION

The treatment of first choice for acute diarrhoea in adults is oral rehydration.[36] However, in this study – analogous to a comparable SP study conducted in Turkey – not a single preparation of this type was dispensed.[15] Very low dispensing quotas of preparations for oral rehydration of about 1%, about 4% and about 12% respectively were also seen in comparable SP studies from Iraq, Qatar and Pakistan.[16-18] This contrasts with a study from Trinidad and Tobago based on self-assessment in which about 64% of the pharmacists surveyed nevertheless indicated that they recommended oral rehydration for acute diarrhoea in adults.[37] Such differences are not surprising, and the international literature specifically investigated possible differences between SP results and the results based on self-assessment also shows similar discrepancies for indications other than acute diarrhoea in adults.[38-41] Quite obviously, the pharmacy staff are lacking less in basic knowledge than its daily implementation in direct customer contact.[39]

An additional intake of fluids, analogous to the BAK guidelines, was recommended considerably more often in this study with 42% of all test purchases but this value still indicates there is an enormous potential for improvement.[8] The significantly more common recommendation of an additional intake of fluids in symptom-based test scenarios of 57% is not surprising and differences in the advice given were also seen in the national and international literature between medication-based and symptom-based queries.[19,20,42] In the comparable symptom-based SP study from Iraq, however, a somewhat lower value of 44% was reported for the recommendation for fluid intake compared to this study.[16]

Along with oral rehydration, loperamide is the agent of choice to control faecal incontinence and frequent bowel movements but it should not be used in diarrhoea with bloody stool.[10,36] As the results of this study have shown, preparations with the active ingredient loperamide were by far the most commonly dispensed. In the cases with a medication-based request, loperamide was always sold, which is no great wonder given that it was explicitly requested by the SPs. Although there were significant differences between the medication-based and the symptom-based requests, a considerable proportion of preparations (76%) that were issued contained the active ingredient loperamide for symptom-based requests as well.[20,42] Studies from Trinidad and Tobago as well as the United Kingdom suggest that the desire for the patients to stop the diarrhoea is a key reason for the frequent dispensing of such preparations.[37,43] In the SP study from Qatar, which also investigated the dispensing of medications for acute diarrhoea in adults using a symptom-based scenario, loperamide was again the most commonly dispensed active ingredient.[17] However, the proportion of about 38% was considerably lower than in this study. Even lower proportions for loperamide or general peristalsis inhibitors (antimotility agents) of about 21%, 6% and 2% respectively are seen for comparable scenarios in the SP studies from Turkey, Iraq, and Pakistan.[15,16,18] Because only loperamide generics were sold in the medication-based scenarios, the pharmacy staff quite obviously equate the request from patients for 'loperamide' with the desire for a generic product since many generics contain the word 'loperamide' (for example, 'Loperamid akut' from 1A Pharma®) in their trade names while the original preparation IMODIUM® does not. The significantly lower rate for dispensing generics in the symptom-based scenarios – in which no active ingredient was explicitly specified – may therefore be due less to possible scepticism on behalf of the pharmacy personnel regarding the quality of generics as reported in the international literature because in the medication-based scenarios generics were dispensed in all cases by the same pharmacies.[44,45] Rather, it can be presumed that dispensing more expensive original preparations results from a deliberate profit maximisation by the pharmacies.[46,47] In this study, for example, the cheapest loperamide generic (10 units hard capsules, 2 mg) cost 62% less than the comparable original preparation (12 units hard capsules, 2 mg). Even taking into account the 2

additional hard capsules in the original preparation, there are still enormous price differences. Estimates by the US Food and Drug Authority (FDA) typically assume a saving potential with generics of up to 85%.[48] Similar values are reported in studies from Malaysia and Kenya with savings of up to 90% or even over 90%.[49,50] The large difference in prices for loperamide generic products and the comparable original preparation IMODIUM® akut reported in this study are also a reason for the considerable price differences between the medication-based and the symptom-based scenarios.

Furthermore, in the symptom-based scenarios only a few other active ingredients were dispensed apart from loperamide and these are likewise much more expensive than loperamide generics. Although the active ingredients Saccharomyces boulardii and racecadotril, which were dispensed in very small quantities, are therapeutic alternatives to loperamide, they do come at substantially higher prices.[36,51,52] Medical charcoal and the combination of active ingredients tannin albuminate/ethacridine lactate are not alternatives to loperamide for treating acute diarrhoea from a therapeutic perspective and likewise have considerably higher costs.[5,36] The opioid diphenoxylate/atropine, which requires a prescription in Germany due to its potential for abuse, was correctly not dispensed at all for the treatment of acute diarrhoea in this study, unlike a comparable SP study from Iraq.[16,53] Likewise, antibiotics that require a prescription were not dispensed at all, whereas in SP studies in Saudi Arabia and Jordan for acute diarrhoea an antibiotic was unlawfully sold without a prescription in 97% and 83% of test purchases respectively.[54,55]

What was noticeable were the enormous price differences within the medication-based scenarios for comparable loperamide generics – between pharmacies that are located in the same city and in some cases are located only a few hundred metres away from each other. The cheapest preparation cost 56% less than the most expensive. Drastic price differences for comparable generics are not an exclusively German phenomenon. Thus a few recent US studies – likewise for pharmacies in close proximity and even for different indications (heart failure, erectile dysfunction, benign prostatic hyperplasia) – in some cases revealed considerably more drastic price differences for comparable generic preparations.[56-59]

As reported in the international literature, the cost of medicines is a perceived or actual barrier to accessing treatment.[50,60-63] Therefore, in light of the enormous price differences, patients should be informed by public campaigns and community sensitisation to compare prices more thoroughly in future and to also be able to access this information.[58,59,64] The success of such measures would, however, be rather limited in view of the lack of transparency of market conditions in Germany. There is no obligation for price labelling for OTC medications and prices are not stated by the pharmacy staff as a rule during the consultation.[65-67] Therefore, patients usually do not have any price information during the consultation. They usually receive price information from the pharmacy staff only at the time of purchase, when the purchase decision has already been made and a purchase withdrawal for cost reasons is a major emotional barrier. The government is therefore prompted to ensure greater price transparency for OTC medications for all pharmacies. Innovative and up-to-date voluntary pharmacy concepts in which customers can inform themselves about OTC medications and their prices using interactive touch screens or cards in the sales area are possible options.[68,69]

Strengths and limitations

The study presented here investigated in Germany for the first time which preparations for self-medication of acute diarrhoea in adults are dispensed and whether these medications appear indicated in regards to the test scenarios presented. As far as the authors are aware, it may well be the first SP study worldwide that investigates possible price differences for dispensed medications depending on the patient's approach (symptom-based versus medication-based request). Another strength is that the SP method used means that the prices currently paid by patients in the pharmacies are used in the studies rather than the prices that are recorded in the official standard price list (Lauer-Taxe). The method is also well suited to reflect real interactions between providers and consumers because they reduce the observation bias of studies based on self-assessment, especially as only very few SP studies in the pharmacy setting exist to date in Germany.[21] Furthermore, the different patient approaches (symptom-based versus medication-based request) were each used twice in all 21 pharmacies (42 test purchases for each), which may increase the accuracy of the study results.

Some of the limitations of this study are that the investigation was carried out only in a medium-sized German city and only referred to the indication acute diarrhoea in adults. The individual pharmacies also did not receive any feedback about the study results, which prevents the pharmacies initiating appropriate measures for improvement. Furthermore, audio recordings must be omitted for data privacy reasons because all pharmacies would have to be informed about this in advance, which would jeopardise the covert study design. On the other hand, data collected was not subject to interpretation but could be verified at any time after the test purchases (for example, the prices of the medications using the sales receipt), thus minimising the risk of recall bias. For greater quality assurance, future SP studies could always carry out and evaluate test purchases by a second observer. Although the comparison between the symptom-based and product-based requests was carried out in the same pharmacies, it could not be ensured that the same pharmacy staff was always encountered for the four test purchases in each pharmacy. On the other hand, this aspect should not play a role because the owner of the pharmacy should ensure that the staff members providing advice deliver a consistent level of advice. Possible reasons that the dispensing and recommendation behaviour of the pharmacy staff was not, in many cases, in accordance with the guidelines should be identified in future studies using a survey or interviews because this could not be determined by the SP approach used.

CONCLUSIONS

Oral rehydration was not dispensed and only occasionally was an adequate intake of fluids recommended. Further relevant education (pharmacists) and training (pharmacy technicians) as well as ongoing appropriate continuing education are needed. There were also enormous price differences both between and within the scenarios investigated. Political measures to improve price transparency of OTC medications should therefore be implemented. Along with this, patients should be encouraged by public campaigns and community sensitisation to compare prices more thoroughly.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Original Research

Evaluation of an interprofessional naloxone didactic and skills session with medical residents and physician assistant learners

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Abstract

Background: The CDC has reported 399,230 opioid-related deaths from 1999-2017. In 2018, the US surgeon general issued a public health advisory, advising all Americans to carry naloxone. Studies show that enhanced naloxone access directly reduces death from opioid overdose. Despite this, health care professional learners report low knowledge and confidence surrounding naloxone. Therefore, it becomes critical that medical education programs incorporate didactic and experiential sessions improving knowledge, skills and attitudes regarding harm reduction through naloxone.

Objectives: 1. Describe the components and evaluation of a replicable and adaptable naloxone didactic and skills session model for medical providers; 2. Report the results of the evaluation from a pilot session with family medicine residents and physician assistant students; and 3. Share the session toolkit, including evaluation surveys and list of materials used.

Methods: In July 2017, a literature search was completed for naloxone skill training examining best practices on instruction and evaluation. A training session for family medicine residents and physician assistant learners was designed and led by University of Cincinnati College of Medicine and College of Pharmacy faculty. The same faculty designed a pre and post session evaluation form through internal review on elements targeting naloxone knowledge, attitude, and self-efficacy.

Results: The training session included one hour for a didactic and one hour for small group live skills demonstration in four methods of naloxone administration (syringe and ampule, nasal atomizer, branded nasal spray and auto injector). Forty-eight participants showed statistically significant ($p<0.05$) improvement in knowledge (67.5% to 95.9%), attitudes (71.2% to 91.2%), and self-efficacy (62.1% to 97.8%) from pre to post assessment. Forty-four of 48 participants agreed that the pace of the training was appropriate and that the information will be of use in their respective primary care practices. Supply costs for the session were USD 1,200, with the majority being reusable on subsequent trainings.

Conclusions: Our study of a naloxone didactic and skills session for primary care trainees demonstrated significant improvements in knowledge, self-efficacy, and attitudes. It provides an adaptable and efficient model for delivery of knowledge and skills in naloxone administration training. The pilot data suggest that the training was efficacious.

Keywords

Naloxone; Analgesics, Opioid; Education, Medical; Physician Assistants; Health Knowledge, Attitudes, Practice; Attitude of Health Personnel; Self Efficacy; Controlled Before-After Studies; United States

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INTRODUCTION

Despite legislative, medical, and educational efforts of the past decade, the opioid epidemic continues expanding its reach across America. According to data from the Centers for Disease Control and Prevention (CDC), there were 702,568 drug overdose deaths from 1999-2017 with 399,230 of those deaths related to opioids.[1] From 2016-2017, the rate of drug overdose deaths increased by 9.6%.[2] A large attributing factor to this increase is the rise of fentanyl co-ingestion and other highly potent synthetic opioids, especially in Cincinnati, Ohio which resides near the epicenter of the nation's opioid crisis. The greater Cincinnati area has seen an increase in fentanyl related overdose deaths by 1,000% since 2013.[3] Overall, Ohio ranks second in the country for highest rates of opioid related overdose deaths with studies reporting 3,613 deaths in 2016, which is more than double the nation's average.[4] For three consecutive months in 2016, Hamilton County, alone, experienced an average of over 16 ER visits and one death everyday due to overdose.[5] The harm reduction effect of naloxone distribution has been demonstrated regionally, with the number of doses distributed increasing nearly eightfold from 2015 to 2018.[6] This in part has contributed

to a 21% reduction in the number of deaths due to opioids from 2017 to 2018.[6]

Given the persistence of opioid related morbidity and mortality and the demonstrated positive impact of harm reduction efforts in the community, never has there been a more crucial time to focus on distribution and training about the opioid reversal agent, naloxone. Naloxone has been recognized for more than two decades as a safe agent to reverse the effects of overdose through its mechanism of action as an opioid antagonist.[7,8] The practice of co-prescribing naloxone to primary care patients with chronic pain is recommended by the CDC.[9] In 2018, the US surgeon general issued the first public health advisory in a decade, advising all Americans to carry naloxone and learn how to use it.[10] With no serious side effects known, naloxone has been distributed not only to first responders, including law enforcement, but also to community members as part of a larger harm reduction methodology. It has been shown to be effective in decreasing the mortality rate associated with opioid overdose by as much as 11%.[11-13] When coupled with education on overdose recognition and response, the provision of naloxone to both those with opioid use disorder and their friends and family has been associated with substantial reductions in opioid overdose mortality at the community level.[13] The regulations for prescribing naloxone vary from state to state. In 2015, a new law aimed at facilitating the distribution of naloxone in Ohio allowed for pharmacists to provide naloxone without a prescription.[14] Thus, pharmacists now play an expanded role in direct patient/caregiver training in the administration of naloxone. Furthermore, state legislatures have also adopted myriad Good Samaritan Laws as a means to facilitate use of naloxone by shielding individuals from adverse legal consequences surrounding emergency aide, such as naloxone administration, for those suffering from an overdose.[15] Therefore, as states direct policy measures to increase access to naloxone and remove potential barriers to its use, it becomes essential that all health care team members are available to address gaps in training and foster efficacy in the safe and proper administration of naloxone by patients and families.

Despite these enhanced legislative policies for increased access to naloxone, training programs have been slow to incorporate naloxone training into their respective curriculums. Physicians continue to report high levels of discomfort in prescribing naloxone, including the concern of enabling risky behavior and fear of liability for prescribing policies and protocols for both patients and family members.[16,17] Many physicians describe having not used naloxone since their training program, citing a lack of self-efficacy in use as a barrier to furnishing it to patients.[17] Additionally, clinicians have also reported doubts about properly identifying those patients at elevated risk for dependence.[18,19] Medical training programs have found health care professional learners reporting limited knowledge and low confidence in educating patients on naloxone and overdose risks, as well as discomfort with the patchwork quilt of laws and policies surrounding naloxone administration across the country.[16,20]

While many factors might contribute to low rates of naloxone prescription practice, training programs are where the process of integration for knowledge, attitudes, and efficacy begins. It has been strongly recommended that graduate level medical education programs incorporate trained and experienced faculty, adequate didactic and experiential sessions, and clinical exposure to care for patients with opioid dependence in the effort to introduce engaging platforms to support desired behaviors and skills.[21] Professional society guidance and primary care behavioral educators often recommend curricular domains in substance use disorders, including the risk assessment and provision of naloxone for treating overdose.[22] However, the currently mandated accreditation governing body family medicine residency components from the Accreditation Council for Graduate Medical Education (ACGME) are unfortunately silent on any explicit required training on substance use as it pertains to patient care. Interestingly, the only time substance use disorder training is mentioned in the more than sixty pages of requirements is in terms of self-care and identifying use in peers and other providers.[23] Opioids, naloxone, or other components in care and treatment for those with substance use are not mentioned explicitly in the required educational curricula. Thus, without expanding beyond the minimum required opioid objectives, recent primary care training program graduates experience inadequate preparation to meet the needs of the opioid epidemic. While some training programs that have integrated components of opioid use disorders and overdose treatment report increase in knowledge, efficacy, and attitudes for health care professional trainees, the current climate of practicing physicians' low comfort and confidence in educating patients in and prescribing life-saving naloxone suggests that further programming is necessary.[16,20,24-27]

After critical observation of existing training within our health system, a gap was identified in meeting the needs of patients with a substance use disorder. The objectives of this paper are to: (1) Describe the components and evaluation of a replicable and adaptable naloxone didactic and skills session model for medical providers; (2) Report the results of the evaluation from a pilot session with family medicine residents and physician assistant students; and (3) Share the session toolkit, including evaluation surveys and list of materials used, to enable other medical training programs to implement a similar educational session.

METHODS

In response to the lack of patient and family member access to and leaderships' desire to develop efficacious training for prescribing and administering of naloxone, The Christ Hospital/ University of Cincinnati Department of Family and Community Medicine Residency implemented a naloxone skills and education session for all of its first-year residents in Fall 2017. The session was developed and delivered with faculty and staff supported time from a Health Resources and Services Administration (HRSA) Primary Care Training Enhancement grant. An interprofessional team conducted a literature search for

primary care naloxone training programs in July and August 2017. From a review of this literature, the core components of an intervention were developed to include both didactic and skills training. This same group through an internal iterative process developed an evaluation form that could be administered both pre and post training. The evaluation form was designed through consensus to include items targeting knowledge, attitudes, and self-efficacy in the administration of naloxone. The evaluation form was reviewed by practitioners with substance use disorder experience for face validity and iteratively modified based on their feedback.

The 2017 pilot program with 7 family medicine trainees was then expanded to include interprofessional learners by partnering with a physician assistant training program in Fall 2018. Both iterations of the session were delivered by the same faculty members and lasted two hours; one hour for the didactic, and one hour for live skills demonstration in four methods of naloxone administration (syringe and ampule, nasal atomizer, branded nasal spray, and auto injector). Prior to the beginning of each session, learners completed a pre-session evaluation form that included knowledge, attitude, and self-efficacy questions regarding comfort level in the prescription of naloxone, care of patients with opioid use disorder and local practices and policy in surrounding county municipalities (Online appendix).

The didactic portion was led by a family medicine faculty member with a dual appointment in psychiatry. Content included: (1) a description of the recent national and regional background statistics of the opioid epidemic, (2) the function of naloxone, (3) identifying an opioid overdose, (4) an in-depth analysis of the advantages, functionality, and practicality of four widely used formulations of naloxone administration (auto-injector, syringe and ampule, nasal atomizer, and branded nasal spray), (5) representative naloxone access laws and Good Samaritan Laws, and (6) recommended indications for providing naloxone. Also, pharmacy faculty members were able to provide detailed instruction on writing a prescription for naloxone in the different methods described, demonstrated, and practiced during the session as described in Figure 1.

	Prescription	Sig*	Cost (average wholesale price per Lexi-Drugs)**
Intramuscular naloxone	Naloxone 0.4 mg/ml, single dose vial, # 2 vials (NDC No. 0409-1215-01) Syringe 3 ml 25Gx1 inch No. 2	-Call 911 -Uncap naloxone vial and uncap syringe -Insert needle through rubber membrane on naloxone vial. Turn vial upside down, draw up 1 mL of naloxone and withdraw the needle -Insert the needle into muscle of upper arm or thigh of victim, through clothing if needed -Push the plunger to inject the naloxone -Repeat injection if no response after 3 minutes	USD 23.72
Intranasal naloxone (Narcan Brand Nasal Spray)	Naloxone 4mg/0.1 ml nasal spray device, (Contains 2 devices) (NDC No. 69547-353-02)	-Call 911 -Peel back package to remove device -Hold nasal spray with thumb on bottom of plunger and first and middle fingers on either side of nozzle -Support neck and tilt patient's head back -Place the tip of the nozzle in either nostril until your fingers touch the bottom of the patient's nose -Press the plunger firmly to release the dose into the patient's nose -Repeat if no response after 2-3 minutes, give in the other nostril	USD 75
Intranasal naloxone (Nasal atomizer)	Naloxone 2mg/2 ml prefilled syringe, #2 syringes (NDC No. 76329-3469-01) Two mucosal atomization devices, #2 (MAD300)	-Call 911 -Remove colored caps from delivery syringe and naloxone vial -Screw the mucosal atomizer device onto top of syringe -Screw naloxone vial into delivery syringe -Spray one-half of syringe into each nostril -Repeat if no response after 3 minutes	USD 19.80
Auto-injector (Evzio intramuscular naloxone)	Naloxone 0.4 mg/0.4 ml (NDC No. 60842-030-01) No. 1 twin pack	-Call 911 -Pull auto-injector from outer case -Pull off red safety guard -Place black end of auto-injector against outer thigh (through clothing if needed) -Press firmly and hold in place for 5 seconds -Repeat if no response after 3 minutes	USD 2,460

Figure 1. Prescribing information

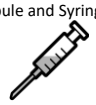
	Cost per Unit	Where Accessed	Timeline for Delivery
Ampule and Syringe 	USD 4.65 per syringe USD 74.95 per 100, 2ml ampule USD 36.95 per 100 safety breakers	http://www.wallcur.com/	2-3 weeks
Narcan Brand Nasal Spray 	Demo spray devices can be requested at no cost	https://www.narcan.com/	Did not receive; Out of stock. Sample devices were provided by College of Pharmacy faculty
Nasal atomizer 	USD 9.21 per complete kit	http://www.pocketnurse.com/	2-3 weeks
Evzio auto-injector 	Demo devices can be requested at no cost	https://www.evzio.com/patient/	6-8 weeks
CPR Manikin 	USD 88.50 per CPR Prompt Training Manikin	https://www.enasco.com/	2-3 weeks

Figure 2. Supplies for naloxone skills training session

The autoinjector and branded nasal spray have training units available from the respective pharmaceutical companies. These were requested and received in advance of the training. The syringe and ampule and nasal atomizer supplies were purchased from medical training supply companies and consisted of inert saline in otherwise medically accurate devices. Sufficient supplies were purchased for each learner to have their own training materials including CPR-style mannequin heads for each small group to provide an avenue to demonstrate naloxone administration. Additionally, oranges were purchased to provide a practice model for intramuscular administration of naloxone. Figure 2 details a complete list of the supplies acquired for the session.

The skills portion of the session included the assembly and active demonstration of four modes of naloxone: syringe and ampule, auto-injector, branded nasal spray, and nasal atomizer. This experiential portion of the training was led by a College of Pharmacy faculty member and two fourth-year pharmacy students. Each primary care learner practiced with their own complete demo kit for each method of administration in a small group setting. Stepped instructions were provided on assembly and administration of each within each small group to facilitate individual experiential learning.

Immediately following the didactic and skills portions of the session, all participants completed a post-session evaluation that included the same knowledge, attitude and self-efficacy questions as the pre-session evaluation. The post-session survey included four additional indirect assessment questions regarding usefulness of the information, effectiveness of the instructors, clarity of the session objectives, and pace of the training. The seven knowledge questions were multiple choice, with the remaining five statements on attitudes, four statements on efficacy, and six statements evaluating the session content and instructors having a four-point Likert scale response key (1=Strongly Agree to 4=Strongly Disagree). Descriptive and bivariate analysis was performed using IBM SPSS Version 25. These sessions were approved by the University of Cincinnati IRB under a larger primary care training enhancement training grant.

RESULTS

The naloxone didactic and skills session described occurred two times: The first was in October 2017 with seven family medicine intern participants who were required to attend the session during a behavioral science month rotation. The second session occurred in October 2018 and again included seven family medicine interns and 34 physician assistant learners.

Thus, a total population of 48 learners participated between the two training sessions. For the skills portion of the training, four methods of administration were initially planned. However, the October 2017 session included only the nasal atomizer, auto-injector, and syringe and ampule due to the branded nasal spray demo training devices being out of stock. Therefore, existing third party video was used to demonstrate appropriate use of the branded nasal spray device. All four methods were available for use during the

Table 1. Results from knowledge questions

Questions	Participants answered correctly/n respondents (%)	Participants answered correctly/n respondents (%)	p-value
	Pre	Post	
Which of the following is a sign of opioid intoxication?	41/45 (91%)	46/46 (100%)	0.125
What is the mechanism of action of naloxone?	37/44 (84%)	42/45 (93%)	0.372
True/False. Narcan can precipitate acute opioid withdrawal.	36/45 (80%)	41/42 (98%)	0.008
Which of the following symptoms is generally NOT seen in opioid withdrawal?	24/45 (53%)	42/46 (91%)	<0.001
In Ohio, Narcan is available by prescription via standing order, which means that…(correct response) a patient without a prescription can buy Narcan at a pharmacy.	14/45 (31%)	42/46 (91%)	<0.001
True/False. The naloxone nasal atomizer is more expensive and convenient than the EVZIO device.	16/45 (36%)	46/46 (100%)	<0.001
True/False. The state of Ohio has a Good Samaritan Law that will protect a person who seeks out help for someone who is experiencing a drug overdose.	44/45 (98%)	45/46 (98%)	1.00

October 2018 session. Faculty effort included time for two family medicine faculty members, one pharmacy faculty member, a research assistant, and a social scientist which amounted to just over USD 26,000. Material costs, including the demonstration devices, for both sessions totaled roughly USD 1,200.

Table 1 shows results of pre- and post-session evaluation knowledge questions. Table 2 displays results from the attitude and efficacy questions. Scores on all three domains improved from pre- to post-session assessment. Participants showed statistically significant ($p<0.05$) improvement from pre-knowledge evaluation to post assessment, with an average score of 5.6 correct answers on the seven knowledge questions. Statistically significant ($p<0.05$) differences were also measured in attitudes from pre-session evaluation to post-assessment. The greatest amount of attitude change was seen in responses to the statements, "I'm comfortable prescribing naloxone to a patient with opioid addiction" ($p<0.001$); and, "I'm comfortable prescribing naloxone to a family member of a patient with opioid addiction" ($p<0.001$). All participants after the session agreed that they felt comfortable prescribing naloxone to the patient, with only one participant disagreeing with feeling comfortable prescribing naloxone directly to family members of a patient under their care. The average percentage of those responding "agree" or "strongly agree" that they felt comfortable administering the four demonstrated naloxone devices increased from 53% to 97% ($p<0.05$).

Responding to the four additional post-survey indirect assessment questions, 44 of 48 (91.7%) participants agreed that the didactic and skills session met the expectations of the learners, objectives were clear, the pace of the training was appropriate, and that the information will be of use in their clinical practices.

Table 2. Results from the self-efficacy and attitudes questions

	Pre		Post		p-values
	Participants responding Strongly Disagree & Disagree/n respondents (%)	Participants responding Agree & Strongly Agree/n respondents (%)	Participants responding Strongly Disagree & Disagree/n respondents (%)	Participants responding Agree & Strongly Agree/n respondents (%)	
I can recognize signs and symptoms of opioid overdose.	5/45 (11%)	40/45 (89%)	0	46/46 (100%)	<0.001
I would feel comfortable having opioid dependent patients come to my practice.	13/45 (29%)	32/45 (71%)	0	46/46 (100%)	<0.001
I would feel comfortable prescribing naloxone to a patient with opioid addiction.	10/45 (22%)	35/45 (78%)	0	46/46 (100%)	<0.001
I would feel comfortable prescribing naloxone to a family member of a patient with opioid addiction.	12/44 (27%)	32/44 (73%)	1/45 (2%)	44/45 (98%)	<0.001
I am comfortable administering the intramuscular formulation of naloxone.	20/43 (47%)	23/43 (53%)	4/46 (9%)	42/46 (91%)	<0.001
I am comfortable administering the intranasal formulation of naloxone.	18/43 (42%)	25/43 (58%)	0	46/46 (100%)	<0.001
I am comfortable administering the auto injector formulation of naloxone.	23/43 (53%)	20/43 (47%)	0	46/46 (100%)	<0.001
It is reasonable for a local government policy, based on available public resources, to not provide naloxone for repeat overdosers.	29/43 (67%)	14/43 (33%)	33/46 (72%)	13/46 (28%)	0.096
Increased public access to naloxone will *increase* risky opioid use.	28/42 (67%)	14/42 (33%)	38/44 (86%)	6/44 (14%)	0.048

DISCUSSION

Our study is one of the first to assess naloxone training methods in medical residents consisting of both a didactic and skills station. However, there have been several previous studies that have analyzed naloxone training in other types of trainees including emergency medical technicians, pharmacy students, medical students, and others that only included didactic type interventions.[32-36] Our pilot of a naloxone didactic and skills session for primary care learners demonstrated substantial improvements in the domains of knowledge, self-efficacy, and attitudes. Prior studies have reported several barriers to practicing physicians incorporating naloxone into care of patients with substance use disorders including knowledge gaps in use and proper administration with those who have never received naloxone training.[28] Given that the ACGME currently does not specifically require any education or curricular activities regarding opioid use disorder treatment, our training model provides a unique opportunity to address a critical gap in knowledge and skills for primary care providers who will encounter this epidemic in many dimensions in practice. This program was developed with less than USD 28,000 of grant support for faculty time and supplies. The workshop component and evaluation form were created over 3 months. However, once created, such a program can be used for ongoing training without significant time or costs to training programs looking to enhance their learners' preparation to meet the need of patients with opioid use disorder. During our training, participants were not provided with personal active naloxone kits in an effort to keep costs low. Naloxone can be obtained without any prescription authorization and some community health centers have federal funds to provide free naloxone kits to community members. Participants who were interested in carrying a personal kit were provided this information as a source of free naloxone kits.

The results from the pre-post survey assessment suggests significant gains are possible in both knowledge and self-efficacy when implementing such a training program and this was true across both sessions. Based on similar improvement in pre and post session attitude and knowledge scores, we found this session format to be successful with both a smaller group of seven participants and a larger group of 41 participants. Increasing knowledge and comfort with naloxone amongst primary care providers outside of specific substance use disorder treatment settings is particularly encouraging considering where the reach of opioids has been found and persists, both in legitimate and illicit formulations. For example, a primary care physician at a community health center might provide a prescription for naloxone to a patient challenged with heroin use disorder; or they might facilitate naloxone access to a son or daughter caregiver of an elderly patient who has been prescribed opioids for pain. The pilot results of our training model demonstrated improvement in comfort levels administering four different methods of naloxone. Exposure to training, as suggested by others, in addition to personal experiences with patients and/or family members can impact necessary changes in behaviors and attitudes toward providing access to naloxone for patients who would benefit most.[28,29]

Evaluation of the pilot also suggests that an investment in a didactic and skills session exploring policy, access laws, identification of overdose symptoms, and the advantages and function of differing methods of naloxone administration may mitigate some of the stigma and treatment myths that persist at the practicing provider level. For example, despite the lack of any supporting evidence, many providers who report never having naloxone training still posit that facilitating naloxone access will enable risky drug behaviors.[18,30] Our training content described evidence countering these claims and, based on participant responses to the evaluation question directly targeting this belief, appears to mitigate such attitudes by primary care trainees.

The multidisciplinary approach with a College of Pharmacy faculty member also proved advantageous and enriched the perspectives of the training session based on informal feedback from participants and facilitators. Specifically, studies have identified primary care providers have knowledge gaps in how to prescribe naloxone and materials required for use as well as cost issues from commercial insurance. Furthermore, recent reports support the efficacy of naloxone access laws for pharmacists in reducing opioid-related deaths.[31] Pharmacists will be doing more direct patient/caregiver training on the use of naloxone, thus including pharmacy learners as skill station trainers under the supervision of pharmacy faculty for the primary care learners anecdotally enhanced their comfort in providing medication use counseling. Given the expanded roles for health care providers in the provision of naloxone it makes efforts in pharmacy and primary care training programs timely and more critical for the care of those who experience opioid overdose.

Limitations

Though the study provides initial support for targeted training to improve knowledge, attitudes, and efficacy in naloxone administration, there are several limitations with respect to our design and its broader generalizability. First, although we offer a readily available, adaptable, and financially accessible training model, the authors acknowledge that materials and faculty and staff resources were grant-supported and may vary across programs. However, the supplies listed are economical, the evaluation survey in the pilot session can be used and/or adapted, and the literature describing naloxone training in various environments is considerable; all are qualities facilitating access. The cost limitation can impact sustainability of the intervention as supplies are consumed through training sessions. Second, content for the pilot session regarding policies and laws around naloxone access and administration were unique to our region in Cincinnati, Ohio. While local policies reflect a growing number of state and local policies, it is advised to consult local and state laws to update content and evaluation as needed. Third, interprofessional training was used in the pilot session, however, the training could be facilitated by any one professional health care faculty including pharmacy,

primary care, or behavioral health. We included pharmacy learners as skill station trainers to foster their counseling skills surrounding naloxone, but did not formally evaluate the impact of their participation. Although our results suggest concurrent training of family medicine and physician assistants can be efficacious we are not able to specifically measure how having interprofessional faculty and pharmacy learners as trainers might have impacted these results. Furthermore, our evaluation approach did not include an assessment of actual learner skill in administering naloxone. The groups were designed to be small enough to allow individual instruction and observation, but there was not a specific competency assessment of learner skill in naloxone administration. Thus, it is possible that learners made gains in knowledge, attitudes, and self-efficacy while maintaining gaps in competency related to physical administration of naloxone. This could be addressed through the use of an OSCE type evaluation in addition to the survey instrument used in this intervention. Fourth, the training does not and is not intended to address the larger opioid issue in terms of overprescribing or diversion. It also is not intended to fulfill all recommendations for substance use disorder treatment training, such as medication assisted treatment. However, it is a critical piece in specifically targeting a harm reduction approach to acute and life-threatening conditions as a result of opioid misuse. Finally, there could be issues of subject bias given the pre and post surveys were administered at a single group session required as part of the training program. Additionally, although the training included 48 learners the number of complete survey responses was less than this indicating some participants did not answer all questions. Although the number of missing responses was very small, this coupled with our smaller sample size could have artificially elevated the findings of improvement on the post test, which can be mitigated through serial confidential administration to successive groups of learners over time to increase the number of completed responses analyzed. No follow-up survey has yet been designed or administered for those who participated in the training programs and thus we can't comment on permanence of the effect on knowledge and attitudes towards furnishing naloxone found in our work. An additional goal at project conception was to measure the association between participating in such training and the actual provision of naloxone at the patient level. Assessment of this goal was complicated because all trainees in a given year were required to participate in the training program so any comparison would have been between different years of trainees. Therefore, we are confidently able to describe gains in knowledge and attitudes, but not patient level changes in practice which could be done if this training was bundled as part of a QI project in a particular clinic location using naloxone prescription as an outcome pre-post.

Future Work

A few of the prior naloxone studies utilized patients in recovery to share their personal stories prior to the training workshop.[20] We believe this could be a great way to capture participants' attention by augmenting the urgency feel of satisfactorily completing training. Moreover, incorporating patient voice into future trainings to foster development of a more positive provider attitude towards patients struggling with substance use disorders represents a logical augmentation of this intervention. Perhaps a readily accessible manner of infusing patient voice would be to bring this training to existing Patient and Family Advisory Council (PFAC) meetings. Another prior study, focused on training student pharmacists to administer naloxone, utilized the objective structured clinical exam, commonly known as the OSCE, to assess skill and confidence level after training.[33] Using the OSCE or some other formal skill competency station as another post-training assessment could serve a dual purpose: (1) provide additional information towards gains in skill level and attitudes and (2) further solidify participant's knowledge in naloxone training by providing a direct case to practice their new skill set. Finally, having developed the naloxone didactic and skills session with an eye towards broad adoption, future work should aim to replicate our positive findings across additional classes of health care team members including medical students, community providers, and additional graduate medical education learners.

CONCLUSIONS

Our study provides a piloted, adaptable, and efficient model for delivery of a naloxone didactic and skills session. This is critical given the positioning of the primary care provider at the front line of managing their patient's potential substance use disorder and being in the best position to facilitate enhanced use of harm reduction approaches such as naloxone to both their patients, family members of patients, and community members at large. The pilot data suggest that the training was efficacious in enhancing knowledge, attitudes, and self-efficacy of learners. Material costs are minimal and the entire intervention was completed in two hours of classroom time. Implementing naloxone training is a critical and timely component of education that should be integrated into curriculums to fill a current gap in ACGME education requirements.

CONFLICT OF INTEREST

The authors of this work have no financial, commercial, legal, or professional relationship with other organizations, or with people working with them, that could in any way influence the research presented.

The views expressed in the submitted article are the authors' own and are not an official position of any affiliated institution or funder.

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