

COMMUNITY PHARMACISTS' USE IN PRESENT CANCER CARE – LITERATURE
ANALYSIS AND QUESTIONNAIRE EVALUATION IN HUNGARY AND GERMANY

PhD thesis

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1. Introduction

Recently cancer has developed a globally expanding problem and is expected to escalate simply due to the growth and aging of population. The disease cancer presents national healthcare systems around the world a dramatic challenge. Despite of scientific progress the disease cancer is still fatal for many patients. There are almost only two reasons for natural death – cancer or cardiovascular diseases such as cardiac infarction or insult.

The intention of this PhD thesis developed in my pharmacy by the daily contact with cancer patients appearing with prescriptions of highly effective drugs and in the same manner insufficient knowledge about intake, effects and consequences. Patients felt unsafe with the handling and there was a great demand for consultancy. Therefore, in my mind from day to day the suggestion matured that usage of pharmaceutical expert knowledge is urgently needed in oncology care. With their knowledge about drugs, pharmacists may be able to contribute in different ways to improve cancer care and complement the multidisciplinary cancer care team.

Much effort and research have been presented over the past years about the future of practice of oncology as discussed in 2010 by Session. But the role of community pharmacists' support in cancer care is still an open issue.

2. Objectives

In my PhD thesis I analysed the use of community pharmacists' in present cancer care of Hungary and Germany. My target was to focus on the analysis of the following questions:

What is quantity and utility of outpatient models of pharmaceutical cancer care compared to existing interventions of pharmacists in hospital or ambulatory oncology settings?

Is there need for community pharmacists in the daily reality of cancer patients in Hungary and Germany?

What is the opinion of health experts regarding the use of community pharmacists in cancer care?

3. Methods

3.1 Literature research

I performed broad literature research to get an overview of existing models of pharmaceutical care in oncology. I focused on outpatient models of pharmacists' interventions and compared them with models in hospitals or ambulatory settings. Thereby I received a picture of quantity and utility of community pharmacists' interventions in literature

I created 4 key questions with the objective of comparing community pharmacists' approaches in outpatient care and interventions in inpatient and ambulatory care.

- What models exist in literature?
- What outcomes exist in literature?
- Are pharmacists' interventions efficient?
- Is there a disparity in quantity of scientific research regarding outpatient models of pharmacists' interventions and models in inpatient or medium care?

I defined inclusion criteria according to the PICOS tool. There was no restriction regarding the language of the analysed literature. If necessary, translation was performed. I only included peer reviewed studies. To maintain comprehensiveness there was no restriction referring to the article type.

Precondition for the inclusion of studies was the reporting on cancer patients. I only included studies discussing pharmacists' interventions in cancer care however formed. Subsequently I used studies comparing the results of pharmacists' intervention with standard care. This means the results of pharmacists' intervention was compared with the result occurred without pharmaceutical intervention. Referring to the outcome

measure of the studies I focused on items such as drug interactions, cancer patients' quality of life, nutritional support, pain management, social – mental health or cost reduction.

Literature search was based on the information sources PubMed and University of Illinois research guide. With the objective of maximizing the data pool and receiving comprehensive results it was important for me to use two databases for my research. PubMed database was used for the main research. Afterwards the University of Illinois research guide was used for checking the PubMed database search terms for coherency and completeness. I declared key words based on PICOS oriented key questions and classified them in 4 groups. Then I combined key words from each group to receive data preferably pertinent to the key questions.

Study selection was performed by reviewing titles and abstracts and then full text screening with application of inclusion criteria. The study selection was checked by three team members, independently from each other. The same procedure was exercised to extract the study data. With the objective of ensuring quality I appraised the quality of each individual study, took care of publication bias and selective outcome bias.

Data synthesis was performed by the allocation of received data to inpatient, medium and outpatient care. Subsequently I compared and estimated the results of scientific research concerning quantity and utility of community pharmacists' interventions.

On 12 July, 2015 I performed an update research and modified my original results. Almost 2 years after the first research my objective was to refresh the data pool and to avoid missing studies. Therefore, I performed the same research procedure and additionally tried to bring the search terms into a sharper focus. Thereby I was able to include studies published in the meantime since the first research. With the knowledge of the original data pool it was possible to search the received titles and abstracts systematic for missing content. As in the first research process the procedure was performed for the PubMed database and the Illinois research guide as well.

3.2 Questionnaire analysis

To approach the question of community pharmacists need in the daily reality of cancer patients a self - developed questionnaire was distributed to cancer patients in hospitals and pharmacies of Hungary and Germany to analyse cancer patients' attributes and their preferences regarding community pharmacists and cancer linked topics. Statistical evaluation of returned questionnaires provided an image of cancer patients' reality needs.

The questionnaire consisted of 22 closed - ended questions and one open question in the end. I considered, which information seemed to be important to analyze current status quo in cancer care of both countries and how to explore patients' preferences and expectations from community pharmacists. Based on these thoughts questions with the target of receiving preferably comprehensive information were contrived.

I performed a tripartite validation procedure. The prepared questionnaire firstly was checked by BH, secondly by RZ and thirdly by five physicians. My objective was to avoid inappropriate questions or ambiguity and maintain validity, suitability and comprehensibility. It was a conscious decision to choose five health experts and not the target group for the questionnaire validation. I accurately deliberated whether it was constructive to ask health experts or the targeted patient group. Both groups show benefits and disadvantages. Physicians certainly can assume the questionnaire from the medical and technical perspective. But in comparison to cancer patients' physicians probably aren't able to put themselves into patients' physical and emotional atmosphere. The targeted patient group certainly is able to examine the comprehensiveness from the perspective of an ordinary person in a better way than physicians.

Both groups include the hazard of false positive results. On the one hand physicians could imagine that the task is clear anyway - no need for occupation with the questionnaire in an intense way. On the other hand the targeted patient group could be ashamed of admitting that they do not understand parts of the questionnaire. The main factor deciding against the targeted patient group was the knowledge of a sensitive patient pool in exceptional circumstances with extraordinary physical and psychical strains.

With the knowledge of the benefits and disadvantages of both groups finally the ethical conscience predominated and I decided to ask the physicians for questionnaire validation to avoid unnecessary stress for the targeted patient group.

The validation of a questionnaire distributed in two countries also requires comparable questionnaire versions in both countries. I consciously developed the questionnaire together with BH in English language. I translated the English version to German and BH to Hungarian. I assumed that the translation of the well - established English language to the particular native languages is less fault-prone than the direct translation from German to Hungarian. Both developers of the questionnaire also were the translators to their particular native language. Therefore, there is little likelihood of differences regarding the comparability of both versions and hence the obtained data. The level of comparability of both versions and the content identity of obtained data is comprehensible at any time.

The questionnaire was distributed in 26 community pharmacies and 4 hospitals in Hungary and Germany from August 2013 to October 2014. Pharmacy selection was performed by reflecting on proper questionnaire randomization. I primarily classified the questionnaire distribution places into hospitals and community pharmacies. Then the community pharmacies were classified in town- (inhabitants > 20000) and village pharmacies (inhabitants < 20000).

Targeting valid and representative results there was a statistical calculation before questionnaire distribution referring to the required number of questionnaires. Presuming a confidence interval of 95% and a maximal tolerable sample error of 10%, the intention was to receive at least 100 questionnaires for evaluation. It was calculated with a basic population of 1,000,000 patients.

Due to the sensitive patient pool 25 % rate of response was calculated; Response rate was calculated by searching for a preferably comparable reference point and applying individual criteria of questionnaire composition, distribution proportions and target group attributes. Iversen et al. received in 2012 a questionnaire response rate of 52 % (Iversen et al., 2012). At the time of questionnaire distribution this reference was quite recent and exhibited similar setting conditions such as a paper based survey,

questionnaire development based on the findings of a literature review, cancer patients' assessment of hospital care, cancer patients suffering from all kinds of cancer and questionnaire distribution in inpatient and outpatient clinics. Our questionnaire comprised 9 pages and addressed a sensitive target group in extraordinary circumstances. It is known that the response rate decreases with increasing page number and sensitivity of the target group. The questionnaire was not mailed but distributed at the local distribution places. Therefore the target group did not receive the questionnaire directly. In each case of distribution there was either pharmacy or hospital staff between author and target group.

The success of questionnaire distribution on the one hand largely depends on addressing the target group. Hence the level of staff motivation is essential. There were no monetary or other incentives either for the patients or for the staff. The questionnaires were handed out to one crew member. Hence there is the obstacle of information transfer to the residual crew members. Just in bigger hospitals or pharmacies there is the risk of confusion and questionnaire loss. Additionally there is the fact of crew changes. In the worst case the crew member the questionnaires handed out to had left the pharmacy two weeks later accompanying the loss of all distribution information. Furthermore the long list of agents with oncology indication as inclusion criteria exhibits the drug names. In many cases prescriptions only contain the trade names of the product. The mental transfer to pull trade name and inclusion criteria together and subsequently to address the target patient is a further obstacle restricting the response rate.

All above mentioned issues the author wasn't able to influence. Finally the entire comparison of Iversen et al.'s reference and my distributed questionnaire is difficult. Considering above mentioned points and the authors' intention to calculate the response rate carefully a response rate of 25 % was assessed suitable.

Hence 400 questionnaires were intended for distribution. To avoid bias and to achieve proper randomization, the distribution points of questionnaires were elected in all cardinal directions in the surroundings of Budapest in Hungary and Regensburg in Germany and deliberately excluded pharmacies within a radius of 5 km to oncologists. Without this condition there could have been for example 100 questionnaires from one

pharmacy next to an oncologist due to the convenient clientele visiting this pharmacy frequently. Subsequently this condition was necessary to ensure the objective of equal numbers of questionnaires in town and village pharmacies.

If the pharmacy or hospital agreed we left 10 - 15 questionnaires at each distribution place. The questionnaires were delivered face to face at the particular distribution places. The procedure was continued up to the distribution of 400 questionnaires. 234 questionnaires were distributed in Germany and 180 in Hungary making a total of 414. Finally, 73 questionnaires were received in hospitals, 40 questionnaires in town pharmacies and 35 questionnaires in village pharmacies, making a total of 148.

Patients were screened by hospital and pharmacy staff by application of inclusion and exclusion criteria and were informed about the aim of the study. Pharmacy and hospital staff was not allowed to help the patients if any question came up. The questionnaire was voluntary and anonymous. Participants could decide if they wanted to answer directly in the pharmacy, hospital or at home. The involvement of the patients was diverging and mostly dependent on the physical constitution of the particular patients. End stage cancer patients were rarely in the mood for answering the questionnaire. Questionnaires answered at home then returned to the particular distribution place. After a few months all filled questionnaires were collected personally from the particular distribution places. Data handling occurred in accordance with the law of Hungary and Germany.

Inclusion criteria

Voluntary patients were only asked to answer the questionnaire, if they were treated with an anticancer drug, which was mentioned in a defined list. I developed this list and submitted it to BH and RZ for checking. The list included all prescription drugs in German market containing an oncology indication up to the time of distribution in August 2013 and is attached in Appendix in the end of the original questionnaire. Interview partners were elected if they verified their professional license and agreed to answer the questions.

Exclusion criteria

If patients were not able to answer the questionnaire due to physical or psychical restrictions, they were excluded from the study. Patients who were reluctant to answer were also excluded.

Evaluation/Statistical methods

Statistical evaluation was performed by descriptive analysis. The statistical software and expert knowledge was provided by Andrea Meskó – Semmelweis University Budapest. If patients provided a rating on a scale analysis was performed by means of measure of central tendency and determination of standard deviation. The significance of differences among groups was evaluated with Bonferroni test. The level of significance was defined a priori at 5 %. Chi square test was used for categorical variables, Fischer exact test for border values. The one-sample Kolmogorov–Smirnov test method was used to identify the kind of distribution in two groups. The Mann–Whitney and Wilcoxon W-test methods were used to analyze group differences in the mean of an examined parameter.

Survey

The first part of questionnaire was aimed at investigating quite general questions, such as gender, age, the level of education, type of cancer or location, where the questionnaire has been received. The second part was targeted at evaluating patients' life style conditions such as smoking and collecting a picture of patients' attitude to cancer linked topics, such as information points, adverse drug reactions, reception of food supplements or mental support and assessment of pain or QoL. In the end patients had the possibility to state their wishes and expectations from community pharmacists to lift cancer patients QoL in future oncology care. The original questionnaire is attached in Appendix.

My research is in compliance with the 1964 Helsinki declaration and its latter amendments or comparable ethical standards. There is no ethics committee approval because this study is based on a questionnaire survey with anonymous and voluntary

participation. Due to the anonymous questionnaire survey there is no signing of informed consent. Instead the aim of the study was written at the top of the questionnaire and the purpose of this study was explained accurately to all volunteers orally.

3.3 Interview of professional health experts

To amplify the information pool for assessment of community pharmacists' use in present cancer care the process of opinion making was finalized by asking five practicing oncologists and five community pharmacists to give their opinion to four self developed questions. I called oncologists and pharmacists in the surroundings of Regensburg and explained my project in detail. In case of agreement I made an appointment and visited the interview partners at their workplace in Germany. After exhibiting the job license I conducted the interviews in a relaxed face to face atmosphere. I tried to create questions, which permitted reception of preferably comprehensive answers to achieve a diversified picture of community pharmacists' support in cancer care. These questions were likewise checked by BH and RZ. A provident check for validity was performed in the same manner as aforementioned.

Professional health experts were asked to consider possible supportive interventions of pharmacists in oncology care, advantages for patients, main obstacles and solution approaches to cross these obstacles in future. Professional health experts were accepted as interview partners if they were able to exhibit their job license. Analysis was performed by comparison of content and quality of mentioned answers.

4. Results

4.1 Literature analysis

Literature research was performed with the objective of analyzing quantity and utility of outpatient models of pharmaceutical cancer care compared to existing interventions of pharmacists in hospital or ambulatory oncology settings. In summary existing pharmacists' interventions are of highest quality and have proofed efficacy in all three fields of care. I compared the amount of research conducted on pharmacists'

intervention approaches in inpatient and medium settings with that in outpatient settings.

My results show that inpatient and medium models predominate in the literature. Nevertheless, a few studies also exist in outpatient fields. Unsurprisingly, there are more reported beneficial outcomes associated with inpatient and medium care compared with the results of pharmacists' interventions reportedly associated with outpatient oncology care. Altogether the majority of approaches focus on pharmacists' intervention in inpatient and medium care and the section of community pharmacists' interventions in outpatient care remains in big parts unexplored. Table 1 illustrates the results of literature search.

Table 1 Outcome of pharmacists' intervention in inpatient, medium and outpatient oncology care (Thoma et al., 2016)

type of care	outcome of interventions	significance	references	
inpatient care	improved quality of life		18, 32-34	
	improved nutritional status	yes	49	
	patient satisfaction after receiving MTM	yes	29	
	safe medication use, enhanced medication adherence		17, 33, 35-45	
	cost reduction for health care systems		31, 48	
	oncologists can focus on disease eradication		34	
	medium care	reduction of physicians workload		58
		improved understanding, patients agree with counseling services		33
		improved drug therapy management		16, 61-63
improved symptom control in palliative care, enhanced QoL			16, 64-66	
outpatient care		home care reduced costs of national health care systems		67
	essential support of medical team members in pain therapy		70, 72	
	home education leads to better understanding and correct intake		80	

Table 1 Pharmacists' interventions were beneficial and have proved efficacy in all three fields of pharmaceutical care.

4.2 Questionnaire analysis

The questionnaire research was conducted with the objective of analysing need for community pharmacists in the daily reality of cancer patients in Hungary and Germany.

Following investigated results underline need for community pharmacists' interventions in cancer care:

As human beings grow older and 41.9 % of people fall ill with cancer around the age of retirement between 61 and 75 years - shown in Figure 1 - there is need for specialised staff – including community pharmacists.

Figure 1 Age distribution of the examined cancer patient population (Thoma et al., 2018)

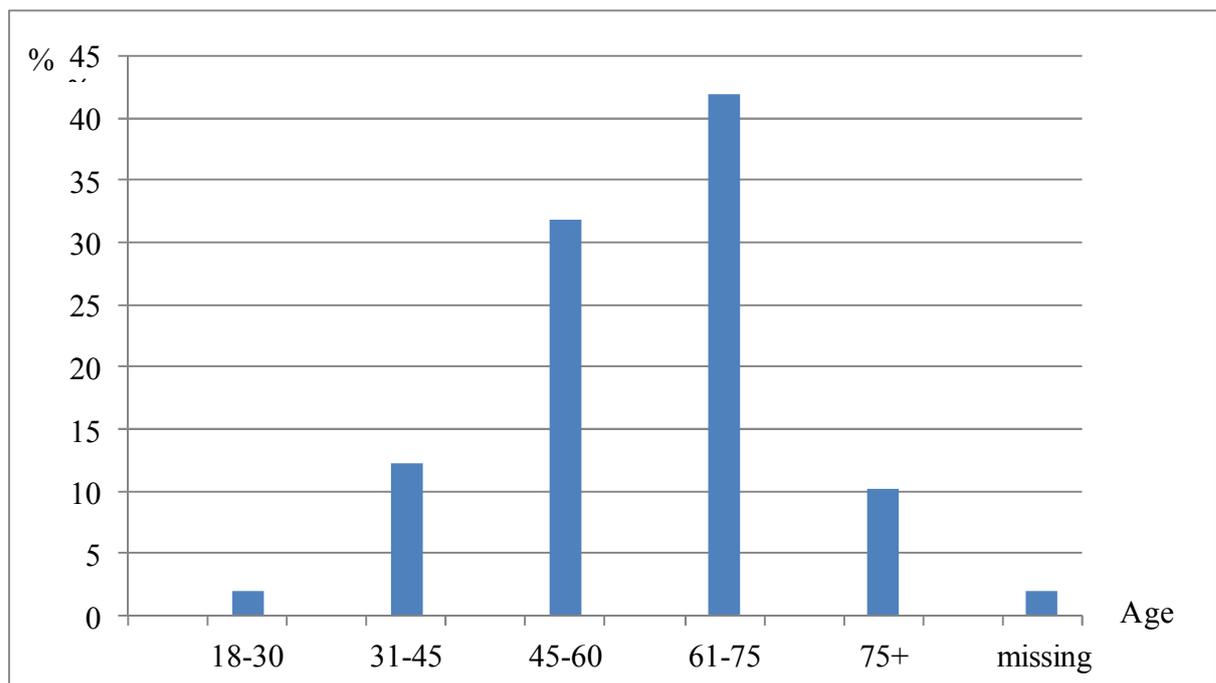


Figure 1 The predominating age of cancer patients is between 61 and 75 years.

My findings illustrate just if the severe topic is cancer the confidence of patients in specialized staff and experts is still high. Regarding the severe topic cancer patients want to receive qualified advice. Although internet information could be received faster

physicians and pharmacists still enjoy a good reputation in the population and therefore patients accept waiting times due to their confidence in professionals' qualified services. Table 2 illustrates significant difference $p < 0.001$ in seriousness assessment of internet (4.38 ± 2.32) and pharmacists' information (8.23 ± 1.81).

Table 2 Seriousness assessment of cancer patients referring internet and pharmacy information (Thoma et al., 2018)

location	seriousness assessment	confidence interval	significance	p value ^{c,d}
	information valid Mean \pm SD	95% CI	yes	<0.001
pharmacies n =114	8.23 \pm 1.81	7.88 - 8.55		
internet n =120	4.38 \pm 2.32	3.99 - 4.81		
^c Statistical evaluation by means of "measures of central tendency" and determination of SD				
^d Nonparametric bootstrap procedure used to obtain 95% CIs.				

^{Table 2} On a non - percentage scale from 1 to 10 cancer patients assessed pharmacists' information by far more serious than internet information.

Only 48.6 % of the targeted patient group was able to assess their pain level as shown in Figure 2. Probably it is difficult for patients to distinguish between unsustainable pain and lighter shapes of pain which impedes right intake of pain killer medications. The fact that 39.2 % stated to have difficulties with the right pain killer dosage shows the insecurity of patients in this point illustrated in Figure 2. In many cases cancer patients receive pain killer treatment in hospital and are discharged with a general medication plan. At home standing on their own it is difficult for many patients to adapt pain killer dosage to their temporary requirement. In other cases patients visit several physicians and receive several pain killer prescriptions without the knowledge of one physician about the prescription of his colleague. This compulsory leads to confusion and subsequently a worse adjusted pain level of cancer patients. It is one of community pharmacists' ordinary tasks to help patients reducing their pain level by giving professional advice referring adequate drug intake. Additionally, it is not enforceable to

meet oncologists or physicians weekly and not to mention daily. Therefore, community pharmacists' skills appear as promising alternative to help patients adjusting their pain killer dosage.

Figure 2 Cancer patients' assessment regarding pain killer use and the coordination of right pain killer dosage (Thoma et al., 2018)

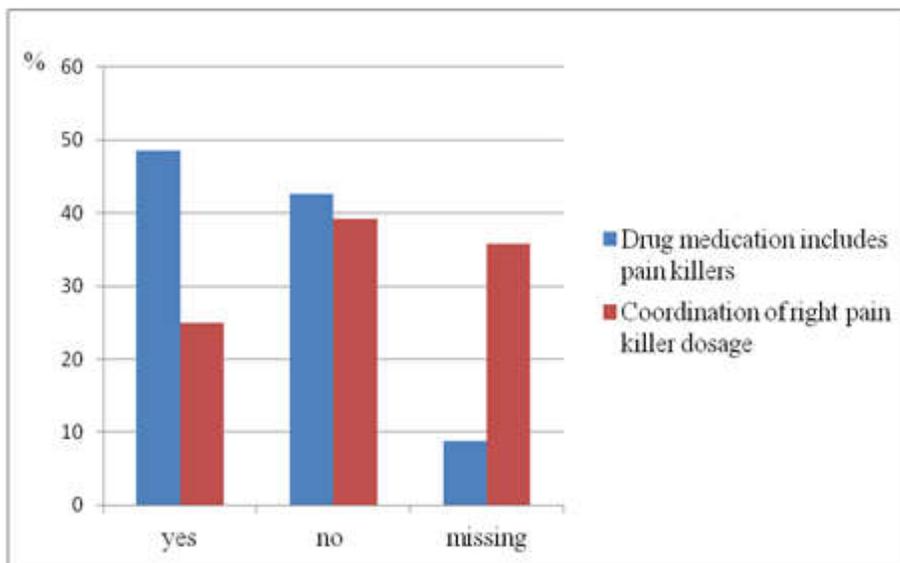


Figure 2 About half of the cancer patients took pain killer and almost half of the patients was not able to coordinate pain level and pain killer dosage.

On a non - percentage scale from 1 to 100 the investigated level of quality of life was in Hungary 65.91 ± 19.24 and in Germany 57.35 ± 23.44 as illustrated in Tables 3 and 4.

Table 3 Estimated level of quality of life of Hungarian cancer patients (Thoma et al., 2018)

statistic		bootstrap ^b		95% confidence interval		
		bias	std. error	lower	upper	
n	valid	49		38	60	
	missing	0	0	0	0	0
mean		65.9184	-0.0215	2.7222	60	71.0701
median		70	-0.26	3.0971	60	80
mode		70,00 ^a				
SD		19.2482	-0.18589	1.98193	15.24921	23.06492
percentiles	25	50	1.615	4.4468	45	60
	50	70	-0.26	3.0971	60	80
	75	80	-0.245	2.0449	70	80

^a Multiple modes exist. The smallest value is shown.

^b Unless otherwise noted bootstrap results are based on 1000 bootstrap samples.

Table 3 On a non - percentage scale from 1 to 100 Hungarian cancer patients' level of quality of life was at 65.92 ± 19.25 .

Table 4 Estimated level of quality of life of German cancer patients (Thoma et al., 2018)

statistic		bootstrap ^b		95% confidence interval		
		bias	std. error	lower	upper	
n	valid	79		68	89	
	missing	0	0	0	0	0
mean		57.3544	0.148	2.6455	52.1291	62.5
median		60	1.28	4.3509	50	70
mode		70				
SD		23.44609	-0.34246	1.48849	20.14988	25.97786
percentiles	25	40	0.04	7.608	30	50
	50	60	1.28	4.3509	50	70
	75	70	3.5625	4.677	70	80

^b Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples.

Table 4 On a non - percentage scale from 1 to 100 German cancer patients' level of quality of life was at 57.35 ± 23.45 . These results show there is still room for improvement.

There is the hope that pharmacists' interventions will lead to an increased level of QoL of cancer patients. Of course this hypothesis still has to prove final evidence.

In the introduction part I described that the incentive of this PhD thesis was the meeting of cancer patients in my pharmacy with insufficient knowledge about their medication. The considerations of these results highlight the need for community pharmacists in the daily reality of cancer patients. Providing integration and collaboration with community pharmacists as basic condition, pharmaceutical care can have an important share in future cancer care

4.3 Professional health experts' interviews

Both pharmacists and oncologists thought that in many cases patients could take profit from better coordination between health experts but there is a communication problem between pharmacists and physicians. Pharmacists mentioned home visitation offers and food supplement advice as important approaches. Oncologists emphasized the check of cytotoxic treatments. Both expert groups considered detailed schooling of pharmacists in special fields of oncology as the most important point to maintain expert knowledge. Nevertheless, physicians still want to avoid limitations of their own skills and their therapeutic freedom. In contrast pharmacists battle the fame of the small brother besides physicians to be accepted as equated professional in health care.

5. Conclusions

- Considering community pharmacists' support in oncology care I am the first who matched a comprehensive research of existing pharmacists' interventions in literature, a patient reported questionnaire analysis in Hungary and Germany and a professional directed health experts' interview.
- This is the first approach who evaluated the little ratio of existing community pharmacists' contributions in outpatient oncology care compared to an excess of approaches of pharmacists' interventions in inpatient and medium oncology care.

- There is no other approach in this modality which discovered a reverse correlation of a shortage of investigation efforts into community pharmacists' interventions in literature and rising demand and usefulness of community pharmacists' interventions in cancer patients' reality.

To contain the expansion of cancer it will be necessary to focus all disposable human and technical forces of the human race. To give powerful guidance for the future equal communication between physicians and pharmacists on eye level, integration of community pharmacists in oncology outpatient assistance and of capital importance schooling of community pharmacists in special fields of oncology care have to be mentioned as only three possibilities to maintain expert knowledge, reduce physicians' workload, limit costs of national health systems and in conclusion enhance cancer patients supply.

This PhD thesis could be the basis for further approaches. It remains to be seen if and to what extent community pharmacists' contribution will find a way into oncology care.

6. Bibliography

All publications are related to the thesis.

1. Thoma J, Hankó B, Zelkó R. (2016) The need for community pharmacists in oncology outpatient care: a systematic review. *Int J Clin Pharm*, 38: 855-862.
2. Thoma J, Zelkó R, Hankó B. (2018) Community pharmacists' use in cancer care of Hungary and Germany – a comprehensive evaluation of a patient intended questionnaire complemented with estimations of professional health experts. *Acta Pol Pharm – Drug Research*, 75: 229-240.
3. Thoma J, Zelkó R, Hankó B. (2018) Comparison of cancer patients' quality of life in Hungary and Germany – a cross national questionnaire analysis. *Acta Pol Pharm – Drug Research*, accepted for publication (APPDR-00186-2018-02), ahead of print.