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Drug-Related Problems in Belgium: From community pharmacies to hospital

State of the situation and Impact

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Summary

Introduction

For many decades, pharmaceutical care has been subjected to many evolutions partly related to society evolution, research progress and introduction of new drugs on the market. The pharmacist practice evolved from product-focused to patient focused in particular by detecting, intervening and resolving Drug Related Problems (DRP).

Particular medical conditions of some patients, such as cancer, are related to heavy treatment needed and makes them more vulnerable to DRP occurrence.

Objectives

This thesis objective was to study DRP proportion in both community pharmacies and hospitals and to evaluate the potential issues related to them. This work was divided in two parts.

The first part was composed of two steps; 1) Translation and adaptation of the PCNE V6.2 classification to the Belgian pharmacy practice and legal setting; assessment of the content validity and inter-rater reliability of the adapted tool. 2) Evaluation of the DRP proportion related to the most frequently used pain drug classes in Belgium.

The second part of this thesis was composed of three phases. 1) Quantification and classification of DRP readmissions within 30 days for cancer patients and identification of risk factors potentially correlated to these readmissions; 2) Assessment of costs involved in DRP readmissions and potential savings; 3) Detection of drug-drug interactions in the cancer population readmitted in the first phase and assessment of impact on the survival rate.

Method

The PCNE V6.2 classification was adapted and translated to the Belgian setting. To evaluate the content validity, academic and community pharmacists evaluated criteria in the instruction manual and in the registration form. Pharmacists used the adapted PCNE tool in daily practice that led to evaluate compliance with the instructions and time needed to solve a DRP. To assess inter-rater reliability, pharmacist codings were used.

In a pilot study, DRP were coded by pharmacy students during their internship, with the adapted PCNE V6.2 tool. Pain DRP were extracted from the database and analyzed.

The second part was based on a 6-months observational retrospective study in two care facilities in Brussels: an academic hospital and a reference center in oncology. To evaluate DRP, an intermediate medication review type 2b was applied for each patient readmitted from the emergency or the medical consultation. To determine the probability of DRP implication on readmission, the World Health Organization-Uppsala Monitoring Center (WHO-UMC) system for a standardised case causality assessment was used. To estimate DRP readmission costs, cost databases from the two cares facilities were analysed. The preventability of DRP was assessed by Schumock et al.'s method in order to evaluate the potential avoidable costs. The last project evaluated potential Drug-Drug Interactions using Lexicomp® and Epocrates© databases. A Kaplan-Meier analysis and a Cox analysis were performed to evaluate the link between the interaction and death onset.

Results

The adaptation resulted on adding 16 items. A high content validity resulted from the academics and the community pharmacist's evaluation. A total of 109 DRP forms were coded, with an average resolution time of 5 min. Regarding inter-rater reliability, 74 tool items out of the set of 83 showed high consistency in coding. The pilot study resulted on 15 952 DRP collected, with 1 832 for non-cancerous chronic pain, 3 200 interventions were performed to solve them. The majority of DRP were fully or partially solved (77.2%).

Cancer patients' DRP analysis revealed that 123 patients were readmitted due to a certain (4.9%), probable (49.6%) or possible (45.5%) DRP. Risks factors detected were a low Charlson Score, polymedication and some chemotherapy (Platine, anthracycline, and vinca alkaloids preparations). A total amount of €495 869.10 were involved in DRP readmission, with a median length of stay of 7 days. The predominant cancers related to these readmissions were lung (19.5%) and breast (17.9%), and a large part (71.5%) of DRP readmissions was related to chemotherapy adverse drug effect (ADE) readmission, according to healthcare practitioners' diagnoses.

The final population readmitted 30 days after discharge for their cancer or their treatment included 299 patients. According to data sources, between 78.9% and 80.9% of patients had at least one interaction. The means were 1.6 and 2.3 interactions per patient for, respectively, Lexicomp® and Epocrates®. Opioids (29.9%) followed by anxiolytics (15.8%) were the drugs most often involved. The most predominant harm effects highlighted were central nervous system (CNS) and respiratory depressions. Kaplan-Meier analyses highlighted a significant difference between patients with and without interactions regarding death. Nevertheless, death seems not to be directly linked to the presence of an interaction.

Conclusion

The first project showed that the tool adaptation to a French-speaking Belgian context was reliable and has adequate validity for daily use. A large participation including 6 faculties allowed a national application that highlighted a large proportion of DRP (15 952); among them more than 10% concerned pain drugs that were mostly totally solved.

For the second project, approximately 10% of patient readmissions within 30 days were related to a DRP including 71.5% of DRP readmission related to adverse drug effect. The median cost per readmission evaluated was €2 406.10. Among these DRP 7.3% were considered as avoidable and amounted at €27 938.61 and was most often related to ADE. Interactions assessment highlighted a large proportion of potential interactions in cancer patient treatment however do not seem to be linked to death onset.

This work demonstrated the large presence of DRP in both community pharmacies and hospital. The first part of the thesis showed that community pharmacists are willing to improve their practice, nevertheless, a more specific tool for community pharmacies may be more efficient and may lead to a better practice. The second part of this work detailed some interesting risk factors and the large presence of interactions among cancer patients to consider, in order to decrease the potential DRP readmission and the costs related to them. However, an improvement of communication between healthcare professionals inside the hospital context and outside including community pharmacists and physicians may lead to a better follow up and a potential decrease of these readmissions in order to improve patient quality of life.

Résumé

Introduction

Depuis plusieurs décennies, la pratique et les soins pharmaceutiques sont soumis à plusieurs changements en partie en raison de l'évolution de la société, des progrès de la recherche et de la mise sur le marché de nouveaux médicaments. La pratique du pharmacien a passée d'une délivrance centrée sur le médicament vers la délivrance centrée sur le patient notamment par la détection, l'intervention et la résolution des Problèmes Liés aux Médicaments (PLM).

Certains patients atteints d'une condition médicale particulière, tels que les patients cancéreux, peuvent être soumis à des traitements lourds qui leurs sont nécessaires mais qui peuvent les rendre plus vulnérable à l'apparition d'un PLM

Objectifs

L'objectif de cette thèse était de mettre en évidence la proportion des PLM dans les pharmacies d'officines ainsi qu'à l'hôpital et d'évaluer les potentielles conséquences en milieu hospitalier.

La première partie était composée de deux projets ; 1) Traduction et adaptation de la classification du PCNE V6.2 à la pratique et au cadre juridique pharmaceutique belge en intégrant la validation du contenu et la fiabilité inter-évaluateur de la classification adaptée. 2) Étude pilote visant à évaluer la proportion de PLM des antidouleurs les plus utilisés en Belgique.

La deuxième partie de cette thèse était composée de trois projets. 1) Quantification et classification des réadmissions des PLM des patients cancéreux réadmis dans les 30 jours et mise en évidence des facteurs de risque liés à ces réadmissions ; 2) Évaluation des coûts liés aux réadmissions dues aux PLM et les potentielles économies de PLM évitables ; 3) Détection des interactions médicamenteuses à partir de différentes sources disponibles au sein de la population cancéreuse réadmise lors du premier projet et évaluation de l'impact de ces interactions sur la survie des patients.

Méthode

La classification du PCNE V6.2 a été adaptée et traduite pour le contexte belge. Afin d'évaluer la validité du contenu, les pharmaciens académiques et d'officines ont évalué six critères, deux qui ciblaient le mode d'emploi (compréhensibilité, utilité) et quatre le formulaire d'encodage (pertinence, logique d'agencement, exhaustivité et redondance). Lors de leur pratique quotidienne, les pharmaciens ont appliqué l'outil adapté du PCNE afin d'évaluer si les instructions avaient été respectées et de quantifier le temps nécessaire pour résoudre un PLM. Par la suite, l'analyse des encodages des pharmaciens a permis d'estimer la fiabilité inter-évaluateurs.

Le second projet était une étude pilote qui a permis aux étudiants de Master 2 d'encoder avec l'outil adapté du PCNE V6.2 les PLM détectés en officine par leur maître de stage. Les PLM impliquant les antidouleurs ont été extraits de la base de données initiale et ont été analysés.

La deuxième partie s'est basée sur une étude rétrospective observationnelle de six mois dans deux établissements de soins Bruxellois : un hôpital général universitaire et un centre de référence en oncologie. Afin d'évaluer les PLM, une revue de médication de type 2b a été appliquée pour chaque patient réadmis aux urgences ou suite à une consultation médicale. La probabilité d'implication d'un PLM dans la réadmission a été évaluée à l'aide du système du Centre de surveillance de l'organisation mondiale de la santé d'Uppsala (OMS-UMC). La réception de la base de données des différents coûts liés à ces réadmissions a permis une estimation des coûts de réadmission de ces PLM pour chacun des deux établissements impliqués. Le caractère évitable d'un PLM a pu être évalué par l'utilisation du questionnaire de Schumock et al. . Le dernier projet à évaluer les potentielles interactions médicamenteuses à l'aide des bases de données en ligne Lexicomp® et Epocrates®. Une analyse de survie de Kaplan-Meier et une analyse de Cox ont été effectuées pour évaluer le lien entre les variables interaction et survenue du décès.

Résultats

L'adaptation de l'outil a permis l'ajout de 16 items. Une bonne validation du contenue a été obtenue suite à l'évaluation des pharmaciens académiques et des pharmaciens d'officine. Un total de 109 PLM a été encodé, avec un temps de résolution moyen de 5

min. Concernant la fiabilité inter-évaluateur, 74 items sur un ensemble de 83 ont montré une fiabilité élevée. L'étude pilote a permis de recueillir 15 952 PLM, dont 1 832 pour les antidouleurs, 3 200 interventions ont été produites afin de résoudre les PLM. La majorité des PLM ont été totalement ou partiellement résolus (77,2%).

Lors de la seconde partie de la thèse, l'analyse des dossiers de patients cancéreux réadmis dans les 30 jours a révélé que 123 patients avaient été réadmis pour un PLM certain (4,9%), probable (49,6%) ou possible (45,5%). Les facteurs de risque mis en évidence étaient un faible score de Charlson, la polymédication et certaines chimiothérapies (préparations à base de Platine, les anthracyclines ou les vinca-alcaloides). Un montant total de 495 869,10 € a été mis en évidence pour les réadmissions dues aux PLM, avec une durée médiane d'hospitalisation de 7 jours. Les cancers prédominants liés à ces réadmissions étaient le poumon (19,5%) et le sein (17,9%). En se basant sur les diagnostiques des médecins, une part importante (71,5%) des réadmissions du aux PLM était liée aux effets indésirables de la chimiothérapie.

Le troisième projet de la seconde partie de ce travail a inclus une population finale de 299 patients réadmis 30 jours après la sortie de l'hôpital en raison d'un PLM. Selon les bases de données en ligne, entre 78,9% et 80,9% des patients étaient réadmis avec au moins une interaction. En moyenne entre 1,6 et 2,3 interactions par patient ont été détectés pour Lexicomp® et Epocrates®. Les opioïdes (29,9%) suivis des anxiolytiques (15,8%) étaient les médicaments les plus souvent impliqués. Les effets indésirables les plus prédominants étaient les dépressions du système nerveux central (SNC) et les dépressions respiratoires. Des analyses de Kaplan-Meier ont montré une différence statistiquement significative sur la survenue du décès, entre les patients avec et sans interactions. Néanmoins, le décès ne semble pas être directement lié à la présence d'une interaction.

Conclusion

La première partie a pu montrer que l'adaptation de l'outil au contexte francophone belge était fiable et avait une validité suffisante pour une utilisation quotidienne. La participation de 6 facultés belges a permis une implication nationale permettant d'obtenir une grande proportion de PLM (15 952) ; parmi eux, plus de 10% concernaient les

antidouleurs dont la quasi-totalité ont été complètement résolus.

Concernant la deuxième partie, environ 10% des réadmissions de patients cancéreux dans les 30 jours suivant leur dernier soin étaient liées à un PLM, parmi ces réadmissions 71,5% étaient liées à un effet indésirable. Le coût médian par réadmission était de 2 406,10 €. Les PLM évitables représentaient 7,3% dont le coût s'élevait à un total 27 938,61 €. L'évaluation des interactions a pu mettre en évidence une forte proportion de potentielles interactions liées aux traitements de patients cancéreux, néanmoins cela ne semble pas être lié à la survenue du décès.

Ce travail a pu mettre en évidence la présence importante de PLM en officine et la volonté des pharmaciens d'officines belges à améliorer leur pratique. Néanmoins l'intégration d'un outil plus spécifique à la pratique officinale sur le terrain permettrait une adhésion plus complète et potentiellement une meilleure détection. La deuxième partie de ce travail a montré quelques facteurs de risque intéressants et l'importante présence d'interactions, qui demandent une potentielle vigilance chez les patients cancéreux afin de réduire les risques de réadmission dues aux PLM et les coûts associés. Cependant, une meilleure communication entre les professionnels de santé au sein de l'hôpital mais également avec les prestataires extérieurs tels que les médecins de famille et les pharmaciens d'officine, pourrait permettre un meilleur suivi et une diminution de ces réadmissions avec pour objectif d'améliorer la qualité de vie des patients.

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Glossary and Abbreviations

ACCP : American college of clinical pharmacy

ADE : Adverse drug effect

ADR : Adverse drug reaction

ALK: Anaplasic lymphoma kinase

ANC: Absolute neutrophil count

APB : Association des pharmaciens belges

ASHSP : American society of health system pharmacists

BUM : Bon usage du médicament

CAM : Complementary and alternative medicines

CD-P-PH/PC : Committee of experts on quality and safety standards in pharmaceutical practices and pharmaceutical care

CMP : Consultation médico-pharmaceutique

CNS: Central nervous system

DDI : Drug-drug interaction

DRP : Drug related problem

EDQM : European directorate for the quality of medicines and healthcare

EGFR: Epidermal growth factor receptor

EORTC: European organization for research and treatment of cancer

G-CSF: Granulocyte colony stimulating growth factor

GP: General practitioner

GSASA: Association suisses des pharmaciens de l'administration et des hôpitaux

HER2 : Human epidermal growth factor receptor-2

I-CVI: Item content validity index

ICPS : International classification for patients safety

INN: International non propriety name

LABA: Long acting beta adrenoreceptors

LAMA: Long acting muscarinic agents

MUR : Medicine use review

NSAID: Non-steroidal anti-inflammatory drug

OTC : Over the counter

PCNE : Pharmaceutical care network europe

QALY: Quality adjusted life year

RDI: Relative dose intensity

S-CVI: Scale content validity index

SABA: Short acting beta adrenoreceptors

SAMA: Short acting muscarinic antagonists

SSMG : Société scientifique de médecine générale

SSPF : Société scientifique des pharmaciens francophones

VEGF : Vascular endothelial growth factor receptor

WHO : World health organization

WHO-UMC: World health organization- Uppsala monitoring center

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1. Introduction

1.1 Pharmaceutical care, drug-related problems and tools

1.1.1 Pharmaceutical care and drug-related problems: history and definitions

1.1.1.1 Pharmaceutical care development

Pharmaceutical care is a dynamic discipline that evolves with patients' needs and drugs newly introduced on the market. As a consequence of evolutions in pharmaceutical care, new terms and definitions appear or are modified to fit better to current society and pharmacists' work. Nonetheless, depending on country, languages, health care system or culture, a term or a concept can be applied differently[J. W. FOPPE VAN MIL, McELNAY (1), (2)].

Almost fifty years ago, in 1975, the first definition of "pharmaceutical care" was published by Mikeal and al., who defined it as: *"the provisions of any personal health service involving the decision whether to use, the use and the evaluation of the use of drug, including the range of services from prevention, diagnosis and treatment, to rehabilitation provided by physician, dentists, nurse, pharmacists and other health personnel. Pharmaceutical care includes the complex of personal relationships and organized arrangements through which the health service of a personal nature are made available to the population".* As defined by *Mikeal and al*., the pharmacist's tasks are not clearly highlighted and the pharmacist's background is not specifically stated. This definition stems from the hospital context and involves all hospital staff (physicians, nurses, etc.) and not specifically the pharmacist[(2)].

Since the 1990s, the pharmaceutical care concept has been extended from the hospital context to the community pharmacy context. It marks the evolution of pharmaceutical care and the different tasks that the pharmacist can provide in both hospital and community pharmacies. This progress was initiated following modern developments, with the inclusion of clinical care and knowledge from the literature, in the middle of the 1960s[(3, 4)].

In particular, *Hepler and Strand* largely contributed to this expansion. They defined, clearly and in greater detail, many terms related to pharmaceutical care and pharmacist

roles to improve patient follow up. They initiated the beginning of the international movement to highlight pharmaceutical care by implementing concepts in hospital and community pharmacies. In 1996, they started to adapt the definition of pharmaceutical care with a more pharmaceutical vision. They defined pharmaceutical care as *"the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve the patient's quality of life".* With this definition, they highlighted clearly the link between pharmaceutical care, adverse effects and patient harm[(2)]. They detailed the outcomes in four points. The first was the "cure of the disease", the second was " the reduction or elimination of the patient's symptomatology", the third aimed at the "arresting or the slowing of a disease process" and the last was "preventing a symptomatology or a disease". The definition highlighted the desire and need to create an effective care relationship between the patient, his pharmacist and other healthcare practitioners to improve the patient's quality of life[(5)]. They suggested a new vision of pharmacists' tasks, delivering care with a patient-centred philosophy, rather than simply drug delivery as provided before[(6)]. *Hepler* pictured pharmaceutical care with a cycle, as a quality-improvement cycle[(7)]. According to this representation, the main objective for each treatment was to care and was to assess by monitoring the treatment to reach the therapeutic objective and at the same time avoid unwanted effects that could occur during the treatment (**Figure 1**).

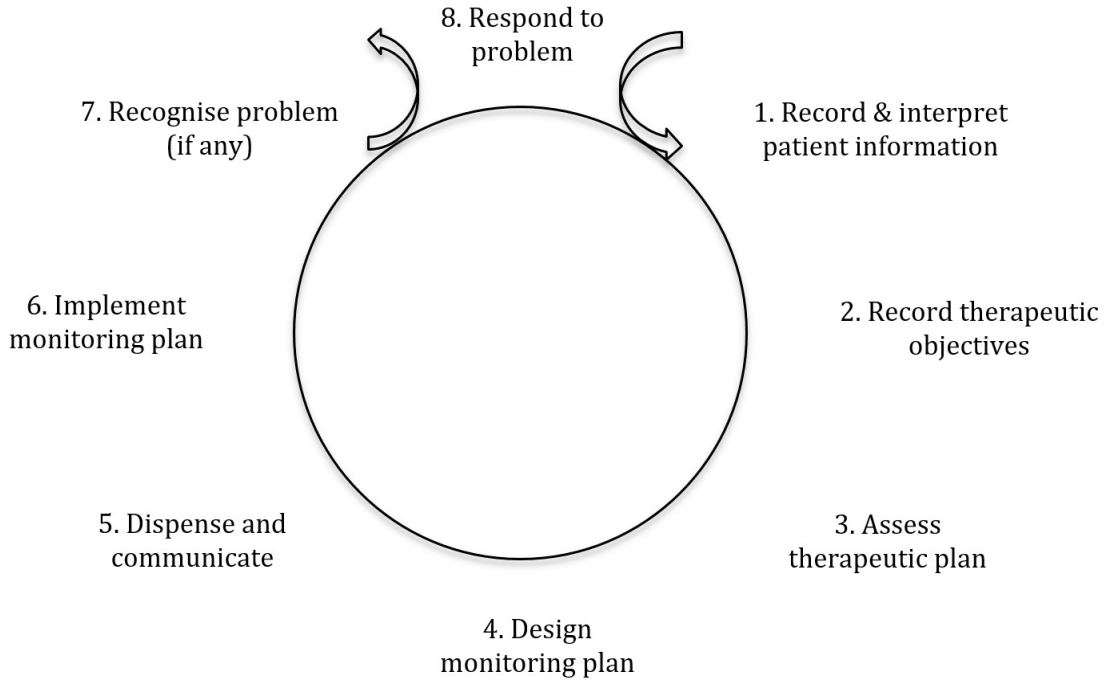

Figure 1: Hepler's pharmaceutical care cycle

Afterwards, in the late 1990s and early 2000s, Strand, Cipolle and Morley wanted to demonstrate a more humanistic vision of pharmaceutical care and adapted their definition as "*a practice for which the practitioner takes responsibility for a patient's drug therapy needs and is held accountable for his commitment*"[8]. For clarity, they defined a drug as *"any substance or product used by or administered to a patient for preventive or therapeutic purposes".* This definition included prescription medications, over-the-counter (OTC) products, herbal remedies, nutritional supplements, traditional medicines and all other products taken for a therapeutic objective[9]. The aim of their approach was to improve patient's quality of life. With this definition, the collaboration is put forward to look after the sharing of responsibilities of each practitioner[7]. The pharmacist must be able to communicate with his patient about the treatment and all the drugs taken. However, to have the opportunity to do this, the relationship between the pharmacist and his patient has to be good. Cipolle et al. discussed the relationship to create with the patient and raised the *"*therapeutic relationship*".* This concept represented the creation of a coordinated medication plan for the patient to reach the therapeutic objective while also taking into account the patient's personal-life context. Linked to the therapeutic

relationship, they introduced many concepts to define and refine pharmaceutical care. The “pharmacotherapy workup” is one of them. This can be defined as a systematic thought process to assess the patient’s need and to identify and resolve problems. The “patient care process” is another concept, composed of three steps: patient assessment, care plan development and follow-up evaluation[9].

1.1.1.2 Pharmaceutical care in Europe

In Europe, pharmaceutical care philosophy has been less systematic than the concept developed by Hepler and Strand, but takes great inspiration from their pharmaceutical care vision[10].

In 1994, a European organization, the Pharmaceutical Care Network Europe (PCNE), was created. This group was composed of a working group of European pharmaceutical care researchers and became an official organization in 2004. This working group aimed to improve pharmaceutical care in several European countries by stimulating pharmaceutical care research and organizing regular events to bring together several points of view from the different countries. They tried to impact pharmaceutical practice positively through their research experience by the development, evaluation and implementation of pharmaceutical care concepts[2, 11]. In addition to the PCNE researcher group, European governments decided to focus on these topics.

The European Directorate for the Quality of Medicines and HealthCare (EDQM) participated in the implementation of the pharmaceutical care concept and considered it as “*a quality philosophy and working method for the professionals within the medical chain. It is indispensable for helping to improve the good and safe use of medicines, thus realising the full potential of medicines available on the market to achieve the best possible outcome in patients. It contributes to the prevention or reduction of inappropriate medicine use by promoting (medication-related) health literacy, the involvement and participation of patients in their medication, greater equality in healthcare, and the balanced sharing of responsibilities. These factors serve to improve the quality of life of patients and their families and the cost effective utilisation of resources and to reduce inequalities in healthcare“.* With the objective to evaluate the current state of pharmaceutical care in Europe in 2009, a survey inspired by Hepler and

Strand's vision was sent to different European pharmacists. This survey was constructed by the EDQM and the Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC). It aimed to pay particular attention to patient concordance or involvement, monitoring (documentation) and multi-disciplinary co-operation between healthcare professionals within the medication process[10].

However, in Europe, variability in practice and legal frameworks may lead to standardization problems in pharmaceutical care implementation[11]. The PCNE helps to reduce this variability by regularly updating many definitions concerning pharmaceutical care. The last definition of pharmaceutical care provided by the PCNE was published in 2013, after discussions with pharmacists and researchers from many countries in Europe. It defined the concept as "*the pharmacist contribution to the care of individuals in order to optimize medicines use and improve health outcomes*"[12].

Nevertheless, many pharmaceutical services linked to the evolution of pharmacist practice are regularly reviewed in different European countries, which can improve the research in care implementation by highlighting the associated facilitators and barriers.

In the Netherlands, for example, a quality circle was evaluated to improve primary care. A group of pharmacists and physicians was organized for meetings, to discuss about patients they had in common. These meetings aimed to define every act that the care team could do to improve patient quality of life, for chronic patients or more specific patients[11].

In the United Kingdom, many pharmaceutical services were implemented, such as the Medicines Use Review (MUR) in 2005. This service aimed to provide a better control of polypharmacy and to evaluate patients' knowledge and use of their treatment[13]. The MUR involved a meeting between the pharmacist and his patient to discuss the medication and to address difficulties encountered during treatment. This service aimed to identify potential drug-related problems (DRP). It tried to look for a solution with the collaboration of the prescriber by providing him feedback on the situation for a potential resolution[11]. To be eligible for this pharmaceutical service, a patient had to receive two or more drugs and had to be followed for at least three months in the same pharmacy [14]. A study showed that 56% of pharmacists' recommendations given during the MUR

were applied. The greatest benefits of this service were observed with asthmatic patients[15, 16].

Another approach to bring more attention to polypharmacy is the Polymedication Check that was developed in Switzerland in 2010. This implemented service was independent of the prescriber and was included in the Swiss refund system. It was developed as "a pharmacist-led medication review", following the new PCNE definition of a medication review. The objective of this service was to "optimize medicine use and improve health outcomes". Patients eligible for this care were patients using more than four prescribed medicines for more than three months. The medication review was composed of a deep analysis of the current treatment, the history of the patient's complaints, the patient's feelings about his treatment and potential misunderstandings[17]. The objective was to build a strong basis with the patient to plan and implement the intervention to reach an optimal outcome[17, 18].

- **Belgium**

In Belgium, a Royal Decree (AR 21/01/2009)[19] defined "good pharmaceutical practice and acts" and calls Belgian pharmacists, from 2010, to implement pharmaceutical care in their practice. Since this period, many initiatives were created thanks to professional organizations such as the Belgian pharmacist association (APB), the scientific society of French speaking pharmacists (SSPF) or the scientific society of general medicine (SSMG). Among these initiatives, the medico-pharmaceutical consultation (CMP) was introduced and included pharmacists and physicians. The CMP aimed to discuss about difficulties related to daily practice in order to create practice recommendations[20].

Since 2013, a new medicine counselling service (NMC) was implemented in Belgian community pharmacies. This service is destined to asthmatic patients with a new inhaled corticosteroid treatment for the first time and can be at the request of the general practitioner (GP). This care aimed to help patients to better understand their treatment and to use more appropriately their inhaled corticoids. This care is composed of two interviews with the patient, the first at the beginning of the treatment and the second between 3 to 6 weeks after the first one[21].

Many initiatives are regularly undertaken in Belgian universities professional a in order to improve pharmaceutical care quality and patient safety.

These projects were mostly conducted by clinical pharmacists in hospital context.

From 2007 to 2014, some important pilot projects funded by Belgian Government were developed in clinical pharmacy and aimed to improve drug efficacy and to decrease DRP occurrence. Over the years of funding, the number of participating pharmacists and institutions increased from 20 pharmacists in 28 hospitals to 40 pharmacists in 54 hospitals. Most of these projects were focused on patient's related activities. These studies resulted on a report, in 2015, that exposed four essential areas to focus on:

- Providing optimal and safe pharmacotherapy to patients
- Ensuring seamless pharmaceutical care at transition moments
- Developing, maintaining, and increasing pharmacotherapeutic knowledge
- Developing adequate communication skills

From this report followed a plan of action concerning the five following years until 2020.:

- 2015: ensuring the basic conditions for the implementation of clinical pharmacy
- 2016: developing a structured method for drug history taking, registration, and communication of the medication scheme upon admission and at discharge
- 2017: applying clinical pharmacy for (a) specific patient group(s) and/or therapies
- 2018: performing risk assessment for patient groups
- 2019: performing risk assessment for pharmacotherapeutic classes/pathologies
- 2020: assessing the 5 years of structural clinical pharmacy

The realization of these projects highlighted the added-value of the hospital pharmacists and lead to clinical pharmacy financing [(22)].

Other studies in hospital context were performed in order to improve patient's quality of life.

Among them, one concerning hospitalized older patients aimed to implement a screening tool in geriatric routine in order to improve prescribing by reducing potential inappropriate medications (PIMs) and potential prescribing omissions (PPOs). The tool involved was based on START and STOPP criteria[(23)].

A similar project using the Ghe^{3}OP's tool was conducted in community pharmacies and in hospital, it aimed to identify potential inappropriate prescription among older patients with or without particular medical condition (renal problems)[(24-26)].

A hospital in Brussel, UZ Brussel, highlighted the value of a Drug-Drug Interaction (DDI)

Alert system that can improve alert acceptance among Healthcare team [27].

Other initiatives aimed to promote and to evaluate clinical pharmacy activities in hospital such as the development of a benchmarking tool by the Université Catholique de Louvain. The implementation at the national level of this tool can lead to improve patient's outcomes[28].

The latest initiative is an important study including several countries. The project evaluated the "OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people" and involved a European multicenter, cluster randomized, controlled trial. The objective was to assess the impact on a structured medication review on older patient admission (OPERAM). This study aims to improve older patient following and to avoid harm related to over or underprescribing. The second part of the study will be completed in the second semester of 2019 [29].

Several other studies are regularly performed in Belgian hospital and focus on specific medical condition such as detailed below but none focused on cancer patients DRP readmission.

In community pharmacies some studies are performed but much less than in hospital context. The collaboration between community pharmacist's organization (e.g. APB or Ophaco) and Universities can lead to improve cares in community pharmacies.

Besides, Pharmaceutical care in Belgium are continuously implemented, nevertheless, practitioner's and patient's adherence to these new concepts may takes time to be completely accepted. GPs involvement and opinions are sometimes mitigating and even critical.

Simultaneously with all these new definitions and services implemented in European countries, the PCNE developed a DRP classification that is updated regularly according to practice improvement and different legal contexts.

1.1.2 Drug-related problems characteristics, identification and tools

1.1.2.1 Drug-related problems: Terms and definitions

As highlighted by *Hepler and Strand*, the risks linked to treatments were not correctly monitored in most health care systems. To improve the management of these risks, they defined new functions attributed to the pharmacist. Among these functions, three were

considered as “major functions” and stand out from the others: the identification of a potential or actual DRP, its resolution and the prevention of an actual DRP. Strand et al. completed their vision of pharmaceutical care with their definition of a DRP as “*an event or a circumstance involving drug treatment that actually or potentially interferes with the patient’s experiencing an optimum outcome of medical care*”[30].

Hepler and Strand were interested in morbidity and costs linked to DRP and were looking for a way to reduce them. They identified different causes that could be linked to these costs, and explained them with eight categories detailed in **Table 1**[30, 31]. These causes served as a basis of the first DRP classification created by Strand et al.[31].

Classification or coding systems can be very useful to collect and record DRPs, as well as for research in pharmaceutical care implementation in community pharmacies[32].

Table 1: Hepler and Strand Classification

DRP category	Definition
Untreated indication	The patient has a medical problem that requires drug therapy (an indication for drug use) but is not receiving a drug for that indication
Improper Drug selection	The patient has a drug indication but is taking the wrong drug
Subtherapeutic dosage	The patient has a medical problem that is being treated with low dose of the correct drug
Failure to receive a drug	The patient has a medical problem that is the result of his or her not receiving a drug (e.g., for pharmaceutical, psychological, sociological, or economic reasons)
Overdosage	The patient has a medical problem that is being treated with high dose of the correct drug (toxicity)
Adverse Drug Reaction	The patient has a medical problem that is the result of an adverse drug reaction or effect

Drug Interaction	The patient has a medical problem that is the result of a drug-drug, drug-food, or drug-laboratory interaction
Drug use without indication	The patient is taking a drug for no medically valid indication

Consequently they defined the existence of a DRP "[…] when a patient experiences or is likely to experience either a disease or symptom having an actual or suspected relationship with drug therapy"[31].

These categories and definitions were the basis of the first DRP definitions and classifications that will be detailed below. These classifications aimed to prevent DRP morbidity and therefore to detect, solve and prevent DRP on time.

The DRP definition related to *Hepler and Strand* categories aims to incorporate all problems related to a drug event amenable, including the correct drug, dose, frequency, duration, route, and monitoring and not only the effect of the drug[31]. This definition included the process of drug use and the potential clinical outcome of drug use[33]. *Pinto et al.*[33] defined the process of drug use as the process involved in *"a set of activities or situations that occur before the outcome "*and the clinical outcome of the drug use as *"a change in the state of the patients health that was attributed to the prior health intervention"*[33].

The term DRP was largely discussed and many other definitions emerged depending on the aim of the classification or the local context[34, 35], at least seven different definitions for the same term were detected[33, 36]. Therefore, depending on the study definition, a DRP can be related to the drug process, the clinical outcome of the drug or both. For the most important part of studies using this term, a DRP is considered as related to both the process and the clinical outcome of the drug. Besides, *Pinto et al.*[23] also highlighted 13 different terms from the literature using the same definition than a DRP but not the same terms such as "drug therapy problems" or "drug related morbidity"[33].

The chosen definition for this work was the PCNE definition that defined a DRP as *"an event or circumstance involving drug therapy that actually or potentially interferes with*

desired health outcomes"[37]. This definition remains close to *Hepler and Strand* definition as it includes drug process and the clinical outcome of the drug.

Other terms related to the medication problems are also very heterogeneous. For a single term, definitions can vary widely between different authors. A term can be related to the process of medication use or the clinical outcome of medication use or both, such as DRP term detailed above [33]. These variabilities result on some difficulties to compare or interpret findings from studies and consequently to evaluate the magnitude of the problem and the interventions needed to decrease the occurrence (Masotti). Terms such as adverse drug reaction (ADR) or adverse drug event (ADE) are sometimes wrongly considered as equivalent[38]. These terms are sometimes confused in the literature.

The American Society of Health System Pharmacists (ASHSP) represented in a diagram (**Figure 2)** all the potentially confusing terms**.** This figure aimed to represent the correlation between all the medication problems. This representation exposed that a medication error can or not lead to an ADE and inversely an ADE can be or cannot be the consequence of a medication error[39]. A medication error in this case is defined as *"a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient"*. [40]. This definition considers a medication error as part of a DRP according to the PCNE definition.

The different letters expose a particular situation:

- **A**: This letter represents all the medication errors, for example the prescription of beta-blocker with a beta-2-mimetic.
- **B**: This situation involves an ADE resulting from this medication error that can lead to respiratory difficulties.
- **C**: The overlap between the medication errors and the ADR circle involves the decreasing effect of the beta-2-mimetic in combination with the beta-blocker.
- **D**: The section D represents an ADR not related with a medication error, for example an allergic reaction.
- **E:** The E section represents an ADE not related to a medication error such alopecia with chemotherapy.

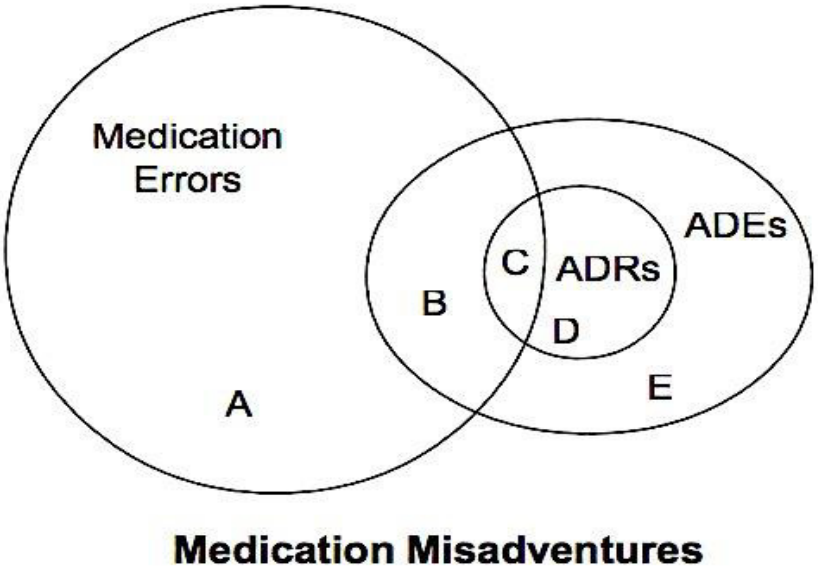

Figure 2: Relationships among medication misadventures: Inspired from ASHSP: Am J Health-Syst Pharm. 1998; 55:165-6

Since 2004, the World Health Organization (WHO) tried to constrain the problem by implementing a collaborative work between international experts from all around the world in order to " identify and agree upon safety concepts, definitions and preferred terms based on solid theoretical and analytical foundations"[41]. The objective of this collaboration was to have a better comprehension of the different risks that can impact patients in order to develop the appropriate strategy for patient safety. They tried to develop a framework for International Classification for Patient Safety (ICPS) with standardized concepts in order to improve a common understanding of terms and concepts [3]. These definitions were modified and improved that led to other definitions such as *Edwards et al.* who defined an ADR as "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product"[42].

For *Bates et al.* medication error is defined as errors occurring at any stage in the process of ordering or delivering a medication. The entire range of severity are included from trivial errors, to life-threatening errors [43].

The definition of an ADE differs in the sense that it is related to the clinical outcome[33] of the drug and is defined as " an adverse outcome that occurs while a patient is taking a drug, but is not or not necessarily attributable to it" [42]

However, these definitions remain sometimes confusing.

In 2009, WHO published their ICPS, it was developed using a Delphi method and tried to focus on a holistic approach to patient safety and not only on medications [33].

The WHO defined in details many terms as medication error, ADR or ADE considering some parameters such as temporality.

Three definitions will be developed on this chapter, medication error (**Table 2**), ADE (**Table 4**) and ADR (**Table 3**). Each definition includes between 6 to 11 different points.

Table 2: WHO Medication errors definition

Medication Errors	Definition
	1. Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer
	2. A deviation from the prescriber's handwritten or typed medication order or from the order that the prescriber has entered into the computer system. Medication errors are typically viewed as related to administration of a medication, but they can also include errors in ordering or delivering medication
	3. Any preventable event that may cause inappropriate medication use or jeopardize patient safety.
	4. An error in the processes of ordering, transcribing, dispensing, administering, or monitoring medications, irrespective of the outcome (i.e., injury to the patient).
	5. A failure of some kind in the process of medication administration.
	6. A discrepancy between what a physician orders and what is reported to occur. Types of medication errors include omission, unauthorized drug, extra dose, wrong dose, wrong dosage form, wrong rate, deteriorated drug, wrong administration technique, and wrong time. An omission medication error is the failure to give an ordered dose; a refused dose is not counted as an error if the nurse responsible for administering the dose tried but failed to persuade the patient to take it. Doses withheld according to written policies, such as for x-ray procedures, are not counted as omission errors. An unauthorized drug medication error is the administration of a dose of medication not authorized to be given to that patient. Instances of "brand or therapeutic substitution" are

	counted as unauthorized medication errors only when prohibited by organization policy. A wrong dose medication error occurs when a patient receives an amount of medicine that is greater or less than the amount ordered; the range of allowable deviation is based on each organization's definition.
	7. Any preventable event (i.e., professional practice, drug products, procedures, systems, prescribing, order communication, product labeling/packaging/nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use) that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer.
	8. A deviation from an interpretable written prescription or medication order, including written modification of the prescription made by a pharmacist following contact with the prescriber or in compliance with the pharmacy policy [or] any deviation from professional or regulatory references, or guidelines affecting dispensing procedures.
	9. Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding' dispensing; distribution; administration; education; monitoring; and use.

Table 3: WHO definition Adverse Drug Reaction

Adverse Drug Reaction	Definition
	1. Unintended, undesirable, or unexpected effects of prescribed medications or of medication errors that require discontinuing a medication or modifying the dose; require initial or prolonged hospitalization; result in disability; require treatment with a prescription medication; result in cognitive deterioration or impairment; are life-threatening; result in death; or result in congenital anomalies.
	2. An undesirable response associated with use of a drug that either compromises therapeutic efficacy, enhances toxicity, or both.
	3. An undesirable effect caused by a drug, usually excluding intentional or accidental poisoning and drug abuse.

	4. Any unexpected, unintended, undesired, or excessive response to a drug that requires discontinuing the drug (therapeutic or diagnostic); requires changing the drug therapy; requires modifying the dose (except for minor dosage adjustments); necessitates admission to a hospital; prolongs stay in a health care facility; necessitates supportive treatment; significantly complicates diagnosis; negatively affects prognosis; or results in temporary or permanent harm, disability, or death.
	5. An undesired side effect or toxicity caused by the administration of a drug.
	6. A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

Table 4: Adverse Drug Event definition from WHO

Adverse Drug Event	Definition
	1. A patient injury resulting from a medication, either because of a pharmacological reaction to a normal dose, or because of a preventable adverse reaction to a drug resulting from an error.
	2. Any incident in which the use of a medication (drug or biologic) at any dose, a medical device, or a special nutritional product (e.g., dietary supplement, infant formula, medical food) may have resulted in an adverse outcome in a patient.
	3. A generic term for any undesired or unintended response to a drug occurring at doses appropriate for a person's status, that can be divided based on the presence or absence of an immune mechanism; . . . ADEs are therapeutic reactions that are noxious, unintended, and occur at doses used in man for prophylaxis, diagnosis, therapy, or modification of physiologic functions; the definition of ADEs excludes therapeutic failures, poisoning, or intentional overdoses
	4. An injury from a drug-related intervention. These can include prescribing errors, dispensing errors, and medication administration errors.
	5. An injury or harm resulting from medical intervention related to a drug.
	6. Injury that results from the use of drugs. ADEs that are associated with a medication error are considered preventable, while those not

	associated with a medication error (e.g., known medication side effects) are considered non-preventable.
	7. As defined by the World Health Organization, an adverse drug event is an event that is “noxious and unintended and occurs at doses used in man for prophylaxis, diagnosis, therapy, or modification of physiologic functions.” Also, an injury resulting from medical intervention related to a drug. Note that this definition does not include mistakes in prescribing, providing, or administering drugs unless injury results.
	8. Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
	9. Administration [of a drug] outside a predefined time interval from its scheduled administration time, as defined by each health care facility.
	10. An injury from a medicine or lack of an intended medicine.
	11. A medication-related adverse event.

The WHO tried to be as complete as possible in order to help researchers to define precisely terms by including all of the different definitions to each term.

Moreover, over the past few decades, there was a growing interest in research or actions concerning patient safety and the intervention that led to the creation of many different terms and definitions [41].

1.1.2.2 Drug-related problems: Classifications

Strand et al. classification

This classification results from *Hepler and Strand* observations, as detailed above, is composed of 8 categories.

The wording of this classification implies that the DRP is the result of a drug intake. To classify an event as a DRP, at least two conditions must exist[31]:

- A patient must be experiencing, or must be likely to experience, disease or symptomatology.
- These conditions must have an identifiable or suspected relationship with pharmacotherapy.

This tool was applied in many studies. Following their results, it has undergone modifications leading to the inclusion of eight categories grouped into five domains. However, all results have been published. The major difference between the initial classification and the update was the distinction between the concept of "problem" and that of "cause" for a clearer classification. Thus, the interaction became a cause of a problem and not a problem[35]. Afterwards, a new modification was applied to results, the classification with seven categories grouped into four domains[44].

This tool was modified and adapted to hospital use in Norway. The objective of this study was to highlight more DRPs in hospitalized patients. They used this tool during an interview to find DRPs and to classify them thereafter[45].

From this innovative perspective in the 1990s, many projects and classification tools were developed to complete or improve the pharmaceutical care vision, according to the local pharmaceutical practice or the national legal context. Arising from this, a section on intervention and results of the intervention was included in some tools[36]. Thereafter; many tools were developed in different countries. For some of them, the objective of the tool use was different and resulted in a different construction of categories to include[36].

Westerlund classification system

In 1996, *Westerlund et al.* developed a classification on the basis of a different definition of a DRP, with the objective to be integrated into the nationwide Swedish community pharmacy software system in 2001[36]. They defined a DRP as "*a circumstance related to the patient's use of a drug that actually or potentially prevents the patient from gaining the intended benefit of the drug".* This classification system was intended to be applied daily in community pharmacies. A supplementary section for pharmacist's intervention

and a manual for better use completed this classification. The classification is composed of 14 types of problem and 11 types of intervention. Each category is clearly defined and organized, as in **Table 5**:

Table 5: Westerlund classification

Type of problem	Intervention
1. Uncertainty on aim of drug	1. No intervention
2. Underuse of medication	2. Patient medication counselling
3. Overuse of medication	3. Practical instruction to patient
4. Other dosage problem	4. Patient referred to prescriber
5. Drug duplication	5. Prescriber informed only
6. Drug-drug interaction	6. Prescriber asked for information
7. Therapy failure	7. Intervention approved by prescriber
8. Side effects	8. Intervention disapproved by prescriber
9. Difficulty swallowing tablet	9. Switch of drug
10. Difficulty opening container	10. Referral to a colleague
11. Other practical problem	11. Other Interventions
12. Language deficiency	
13. Prescribing error	
14. Other drug-related problems	

This classification is associated to questions for patients to gain a better understanding of the situation and for a better DRP codification. This classification was validated, and led to the creation of a database after a daily-use study[46].

PI-Doc: Problem-Intervention-Documentation

This system was created in Germany and is composed, like *Westerlund* system, of two sections. One concerns problems and the other concerns interventions. As the *Westerlund* classification, this system was implemented in most parts of the German community pharmacies software. It was constructed with a user-friendly interface to be easy for daily use practice[36]. This tool was constructed as a decision tree to facilitate computer use.

The construction was mainly based on three points:

1. The classification of drug-related problems
2. The intervention taken to solve the problem

3. The degree to which the problem was solved.

These three points led to six categories of DRP causes, as in **Table 6**:

Table 6: PI-Doc® categories

DRP category	DRP subcategories and number of items
A. Inappropriate drug choice	11 items
C. Inappropriate use by the patient, including compliance	8 items
D. Inappropriate dosage	5 items
E. Drug–drug interaction	3 items
F. Adverse drug reaction	3 items
G. Other problems	***a. Patient-related***: 6 items
	b. Physician-related: 1 item
	c. Communication-related: 3 items
	d. Technical and/or logistical: 5 items

With regard to the PI-Doc®, the interventions were created based on pharmacists' actions to intervene and to solve DRP[32]. Interventions were organized on two levels: The first level is named "general intervention" and the second named specific intervention, with more detailed interventions linked to the causal factors. The ideal situation will involve both kinds of interactions to introduce a maximum amount of information concerning a DRP resolution. The general interventions of the PI-Doc® are summarized in **Table 7**.

Each general intervention is presented with the number of items related to this part.

Table 7: General and specific interventions

General Intervention	Number of items
I0. Checking factual databases, books, etc.	0
I1. Interview and counselling	3
I2. Contacting the physician	0
I3. Referrals	4
I4. Filling out a medication box for the patient in the pharmacy	0
Specific Intervention	**Number of items and subcategories**
IA: Intervention: inappropriate drug choice	11
IC: Intervention: inappropriate drug use by the patient/compliance	8
ID: Intervention: inappropriate dosage	5
IE: Intervention: drug interactions	4
IF: Intervention: adverse drug reaction (ADR)	3
IG: Intervention: other problems	***a. Patient-related***: 6 items
	b. Physician-related: 1 item
	c. Communication-related: 3 items
	d. Technical and/or logistical: 5 items

The PI-Doc® was applied in many studies in Germany and in Denmark, where it has been adapted and used for research. One study in Bavaria differentiated DRP linked to prescribed treatments to those linked to OTC drugs. The main DRP found were “inappropriate drug choice” and ” inappropriate use by the patient/compliance”. The interventions performed by the pharmacists helped to solve them[32].

ABC of DRP

The ABC of DRPs created by *Meyboom et al* [47] was implemented for use in the WHO with a pharmacovigilance objective[36]. It was composed of only three categories. These categories were “dose unrelated problem”, “appropriate use problem” and “inappropriate

use problem" [47]. This classification was limited in terms of drug problems choice and it used the term "problem" instead of "DRP" because the term was defined clearly.

PCNE Classification Tool

In September 2009, the working group on DRP of the PCNE was officially created, even if members had started working on this topic unofficially since 2001. The working group was composed of leading researchers in the field of pharmaceutical care and DRP, such as Dr. Nina Griese and Dr. Tommy Westerlund. Until the official creation of the working group, they had worked for eight years on a DRP classification, which was upgraded several times, from version 1 to version 5.01[48]. During the PCNE symposium in 2009, a new definition of a DRP and an improvement of the DRP classification were widely discussed. The applied definition was *"a drug-related problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes."* [37]

The first version of the PCNE classification tool was composed of three categories: "problems", "causes" and "interventions". Each of these categories was divided into subcategories that included several items. For "intervention" there were five subcategories and six subcategories each for "problems" and "causes"[49]. From this first tool, many additions, deletions or reformulations were done, leading to PCNE classification v 6.2. This version was the first after the formalisation of the PCNE Network Group. This classification was composed of four categories, the first three were the same as in the PCNE Classification v1, with one more, "outcome of the intervention". This classification was associated with a manual explaining each part and the different subcategories and items linked to these parts[50]. This tool was validated and was one of the most used and translated DRP classification tools[34]. Indeed, it was translated into Croatian, Spanish and Turkish[37]. PCNE classification v6.2 was used and evaluated in many studies. One, a Swiss study, showed that it had a practical use in a hospital context and allowed the classification of DRP but that it seemed complicated to implement it for daily use, especially because it is time-consuming[51].

PCNE Classification v6.2 and the PCNE DRP definition were used as the basis of this thesis work because of the good validity of this classification and the clear definition associated with it.

Since v6.2 of the PCNE Classification tool, other modifications have led to other versions. The latest is v8.03, dated from February 2019, after the latest PCNE Working Conference.

Important changes were observed after the v6.2 that led to an incompatibility between the V6.2 and the following versions. Choices for “adverse drug events” domain (allergic and non-allergic) were removed and led to lesser details about the kind of ADE. Besides, the V6.2 included domain “cost of the DRP” in the “type of problem” whereas this domain moved to “causes” in the following versions.

The version 8.03 is composed of five parts that can explain the problem entirely and classify it correctly. Each part is composed of many categories that are detailed into subcategories. Each subcategory is associated with several items[52]. The different parts of v8.03 are summarized in **Table 8.**

Table 8: PCNE v8.03 organisation

Parts	Primary domain	Items (problems, causes, interventions, implementation, outcome of the intervention)
Problem	Treatment effectiveness	***3***
	Treatment safety	***1***
	Other	***3***
Causes		
Prescribing	Drug selection	***7***
	Drug form	***1***
	Dose selection	***5***
	Treatment duration	***2***
Dispensing	Dispensing	***4***
Use	Drug use process	***6***
	Patient-related	***9***
	Other	***3***
Planned intervention	No intervention	***0***

	At prescriber level	***4***
	At patient level	***4***
	At drug level	***6***
	Other	***2***
Acceptance of the intervention	Intervention accepted	***4***
	Intervention not accepted	***4***
	Other	***2***
Status of the DRP	Not known	***1***
	Solved	***1***
	Partially solved	***1***
	Not solved	***4***

The latest version of the tool V9 was just published in June 2019. In this version, the main change concerned a new domain in Causes section (the C.8) that was added. This domain involved DRP that can occur during transfer between care levels or departments and named “Seamless”. They defined the seamless care as the “uninterruption of care for the patient during every transfer in the healthcare system, within primary, secondary of tertiary care or between those care levels”. Another change appeared in C.7, the following subdomain was added: “Patient unable to understand instructions properly”, which is used when a language problem led to a DRP[53].

GSASA

The Swiss Society of Public Health Administration and Hospital Pharmacists (GSASA) suggested the implementation of a classification to record pharmacists’ interventions after DRP detection, with the aim to highlight their performance. An expert group, the GSASA working group, developed this tool, which was intended for hospital use. The group was composed of eight clinical pharmacists from eight different hospitals in Switzerland, including French and German speakers in equal proportion[54]. The construction of this tool was based on PCNE classification v6.2[50] and a tool from the

French Society of Clinical Pharmacy that documented clinical pharmacists' interventions[55]. To have a clear purpose for the creation of this tool, they defined an intervention as "*a recommendation initiated by a pharmacist in response to a DRP occurring in an individual patient in any phase of the medication process*"[54]. The researchers chose to follow the American College of Clinical Pharmacy (ACCP) for the objectives of an intervention. The ACCP defined that the objective of an intervention is to optimise pharmacotherapy, in terms of efficacy, safety, economic and humanistic aspects[56]. This tool was first validated as GSASA V1. After a 6-week period of use in a 427-bed teaching hospital by six experienced clinical pharmacists to classify the interventions they performed during their routine work, the pharmacists made some suggestions to improve the classification. These suggestions led to GSASA V2, which was published.

The tool is composed of five categories, which include a total of 41 subcategories[54]:

1. Detected problem: 5 subcategories
2. Type of problem: potential or manifest, 2 subcategories
3. Cause of intervention: 18 subcategories
4. Intervention: 11 subcategories
5. Outcome of intervention: 5 subcategories.

This tool showed the same reliability as PCNE v6.2 but had a larger choice of interventions than those found in the PCNE[54].

PharmDISC: Pharmacists' Documentation of Interventions in Seamless Care

From the GSASA, which was created for hospital use, the PharmDisc was adapted for community pharmacist practice[57]. The development process was structured in two parts, which included qualitative and quantitative approaches. The first part covered the tool development and the piloting stages, while the second part concerned the evaluation and implementation stages. The first part included the adaptation that was made on the basis of previous studies in Swiss community pharmacies, such as the study previously cited that used a modified version of the PCNE v6.2 classification[58]. It was also made by deleting some specific items related exclusively to hospital use. These modifications were done through expert panel discussions. The final version of

the classification included five categories[59], which included multiple items. For the "causes of intervention" part, there were subcategories with items. The different parts are summarized in **Table 9**.

Table 9: PharmDisc parts

Parts	Number of Items
Problem	5
Type of problem	2
Causes of intervention	*Therapy choice*: 7
	Drug choice: 1
	Dose choice: 4
	Drug use: 2
	Therapy duration: 2
	Logistics: 2
	Patient: 3
	Prescription quality: 6
Intervention	14
Outcome of the intervention	5

This tool was evaluated and tested twice in daily use practice. It showed substantial interrater reliability and an acceptable user satisfaction, which defined the tool as valid for pharmacists' daily use[59, 60]. One of these studies highlighted the important place of the direct interaction between patients and their pharmacists during the dispensation of the prescribed drug[60].

The principal tasks in pharmaceutical care are to identify, prevent and resolve a DRP occurrence. The various tools detailed above make it possible to help and to improve care by creating DRP databases for a better understanding of usual practice[34]. Considering the large number of diseases, each patient needs a different follow up and a different attention. It would be interesting to continue to study these tools with more specific patients or for conditions such as cancer or kidney diseases [61].

1.2 Drug-related problems impact

1.2.1 Drug-related problems impact

Since many decades, DRP occurrence remains a potential source of morbidity and mortality around the world. In 1987, *Manasse et al.*[62, 63] concluded that around 12 000 deaths and 15 000 hospitalizations were due to ADR in the United States. Besides the increase in morbidity and mortality, unplanned hospital readmissions may be highly impacted.

Studies on DRP detection in hospitals have been performed and published since the 1990s. The identified DRP were especially linked with the occurrence of medication errors and ADE. Such as represented above, a medication error can be present in different steps of the medication process and can be a risk for an ADE or an ADR[64]. In 1992, *Bond et al*. highlighted that 5.07% of patients readmitted suffered from a medication error, in the United States. Each participating hospital experienced a medication error every 19.73 readmissions, and 4.9% of these can adversely affect patient care outcomes[65]. These results were confirmed in a study performed, in Australia, between 1988 and 1996 by *Roughead et al.*[66]. They identified between 3.6% and 24% of drug-related readmissions among readmitted patients. More than 50% of these patients were over 65 y.o. and have been prescribed four to five different drugs on average[66]. Using the categorisation of *Strand et al.*, the main DRP identified were ADE, omitted or inadequate therapy, and excessive or unnecessary therapy. Some drugs were identified as often involved in these DRP, such as cytotoxic agents, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, cardiovascular and antihypertensive agents, anticoagulants, central nervous system depressants and corticosteroids[66].

This DRP burden has remained an important concern over the years. Indeed in 2018, *El Morabet et al.*[67] performed an international review and evaluated that between 3% and 64% of readmissions were linked to a DRP, with a median percentage of 21% depending on the country. The preventability of these readmissions presented the same variability, with a range of 5-87% of preventable readmissions and a median at 76% without the outliers. Two risk factors, a cancer condition and a high Charlson score, were highlighted for a DRP readmission. In the literature, other DRP readmission risk

factors have been cited, such as impaired cognition, comorbidity, renal function problems and patient non-adherence to the treatment[68]. The drugs most involved include antibiotics, diuretics, vitamin K antagonists, opioids, anti-diabetics, anticancer drugs, anti-hypertensive drugs, digitalis glycosides and psychotropics[67].

In comparison to the previous results cited above, both the proportion of DRP readmissions and the preventable nature of these DRP seem to increase, depending on the study method. Concerning the drugs involved, some categories remain strongly implicated in DRP leading to readmission.

As detailed in the part above, a DRP can appear at different steps of the medication process and lead to patient harm. Depending on the DRP classification, ADE and drug-drug interactions (DDI) seem to be the predominant source of DRP. This is particularly so in some categories of patients with a particular medical condition such as kidney failure, paediatric conditions or cancer[61, 69]. Some parameters, such as age, comorbidity or polypharmacy, seem related to DRP readmission[67, 70]. Besides the disease itself, ageing induces pathological and pharmacological changes that may cause modifications of drug pharmacokinetics'. Ageing can lead to modifications of drug absorption, distribution or metabolism and can result in an increase in DRP events or readmissions[70].

DRP readmissions stay important and have increased in recent decades[71]. Nevertheless a high variability of proportion exists, depending on the country, the kind of patient or the kind of medical condition. Besides, around 30 years have passed from the 1990s to now, and it is necessary to remain cautious about any increase in DRP readmissions. This increase may be related to better drug knowledge or better DRP tools available for more sensitive detection and classification.

However, DRP events have remained, over the years, an important health burden leading to patient harm[67, 70]. The growth in patient readmissions could be linked to a higher morbidity and consequently mortality. Besides the effects on the patient, a DRP can be an important source of high health costs.

Over the years, DRP readmission has become an international concern, especially at the government level. The European Commission has focused on this problem by

performing a study among European regulatory agencies combined with a public consultation leading to the publication of a report. The study had three objectives: to document the current EU pharmacovigilance system; to identify its strengths and weaknesses; and to make recommendations on how to strengthen the system. Interviews were conducted in the different agencies, and a survey was carried out among representatives of the different agencies. The public consultation was performed in two parts from March 2006 to February 2008 and involved stakeholder groups around Europe. The results demonstrated that around 5% of patients experienced a DRP and 197 000 deaths were related to a DRP event. This report resulted in a pharmacovigilance reform implemented in 2012[72, 73].

In the same way, the United States implemented the Hospital Reduction Readmission Program in 2012[67].

The pharmacist's involvement in a multidisciplinary team, combined with a specific training to improve patient follow-up, can lead to a decrease in DRP occurrence. It was already demonstrated around the 1990s that a lack of pharmacy training in patient support could be a DRP risk factor[65]. Already at this time, the necessity of better patient support by healthcare practitioners was recognised. Over the years, many studies have demonstrated the need for a clinical pharmacy contribution in DRP detection and resolution in the hospital or in community pharmacies[74-76]. The United States was one of the first countries to highlight the need for pharmacist clinical opinions in patient care, followed by the United Kingdom and the rest of Europe afterwards[77-80].

1.3 Drug-related problems and cancer

1.3.1 Cancer patients and treatments

1.3.1.1 Cancer burden in Belgium

Cancer remains an important cause of mortality and morbidity around the world. In 2012, it was recorded that there have been approximately 14 million new cases and 8 million cancer-related deaths. The most common cancer localisations were breast (25.2%), for women, lung (16.7%), and prostate (15%), for men, and colorectal, for both (10%). For men, lung cancer remains the most fatal cancer (11.9%) in Europe[81].

In 2014, in Belgium, 16 600 men and 13 000 women died from a cancer (**Figure 3**)[81]. Belgium remains one of the most impacted countries in Europe. The incidence rate evaluated for breast cancer was 100 cases per 100 000 persons and 56.3 per 100 000 for lung cancer. Among 14 countries in Europe, these recorded numbers put Belgium in the first place for women's breast cancer and second for men for lung cancer. Colorectal cancer in Belgium is in the fourth and fifth places, with 44.8 cases for men and 28.8 for women per 100 000 persons[81]. Belgium is in the first place for lung cancer mortality and in the top five for other cancers[82]. This health burden is increasing over time. There were estimated to be 3.91 million new cases of cancer in Europe in 2018[82] and 1.41 million cancer deaths in 2019 [83]. Due to the ageing of the population, the cancer proportion remains high and is not declining[83].

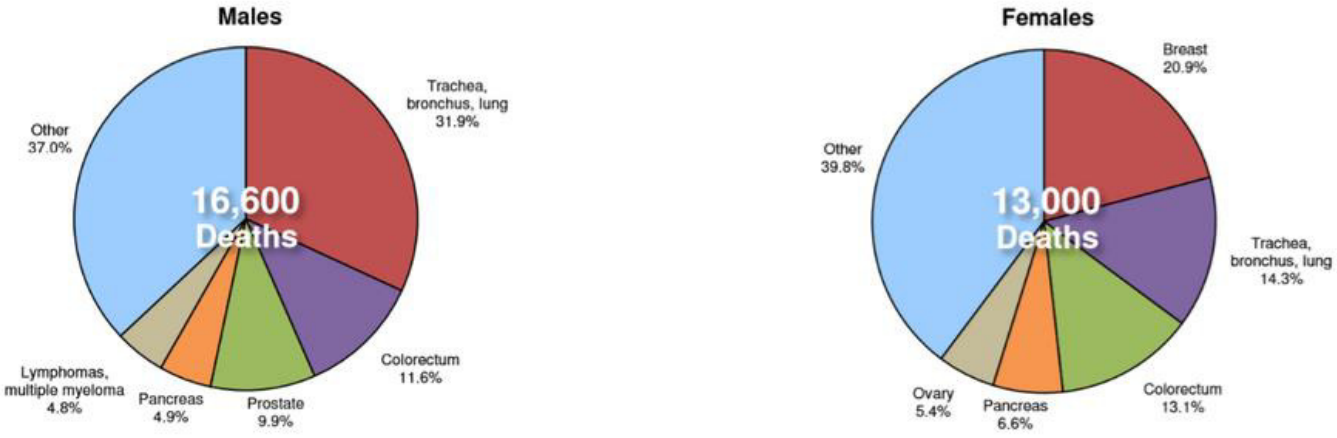

Figure 3: Cancer proportion In Belgium (From WHO report 2014)

The cancer population represents a vulnerable group of patients. This group has a higher risk of organ failure or altered metabolism due to the progression of their disease or the malnutrition that can occur with chemotherapy[84]. Combined with the narrow therapeutic windows of cancer treatments or other ancillary treatments (comforts; adjuvants), these modifications increase the risk of drug-related problems (DRP) and potentially lead to hospital readmission.

In spite of these high estimates, cancer mortality continues to decrease. Compared to 1988, around 5 million deaths have been avoided in Europe[83].

1.3.1.2 Cancer treatment

This high cancer variability is related to the large quantity of treatment plans that exists. To get an overview of the different types of cancer treatments, only the various kinds of treatments involved in the most prevalent cancers, such as lung, breast and colorectal cancers, will be presented.

Cancer stages can be describing by different nomenclatures: the tumor nodes metastasis (TNM) system; a staging including five stages (stages 0, I, II,III and IV), which is less detailed than the TNM system; and a staging related to the localisation of the tumor (in situ, localized, regional, distant)[85].

The second nomenclature has been used to present the different kinds of treatments.

The different stages represent different evolution of the tumor (**Table 10**).

Table 10: Cancer stages (inspired from the National Cancer Institute)

Stages	Details
Stage 0	Abnormal cells but have not spread to other tissue
Stages I, II and III	Cancer is present; the higher the stage, the larger the tumor is and the higher the risk of spread into nearby tissues
Stage IV	The cancer has spread to distant parts of the body

Breast cancer treatment

Breast cancer represents one of the most prevalent cancers in industrialized countries. Nevertheless, its prevalence increases in developed countries that have adopted Western lifestyles[86]. Breast cancer is composed of two major categories: ductal and lobular breast cancer. These categories can be at the different stages detailed above[86, 87].

The treatment protocol and composition depends on many parameters, such as tumor growth, cancer stage, patient age, the presence of human epidermal growth factor receptor-2 (HER2) receptors and other parameters for attention[88, 89].

Breast cancer treatment can combine surgery, radiotherapy, neo-adjuvant and adjuvant chemotherapies.

Surgery is used for local control of the tumor and for a histological diagnosis. It can be combined with radiotherapy sessions and/or neo-adjuvant chemotherapy[87]. The surgical procedure applied may be a lumpectomy or a total mastectomy[88].

For example, in the case of an invasive cancer, a total mastectomy or a lumpectomy can be applied. If some axillary nodes are diagnosed positive, radiotherapy can be used to treat them before adjuvant chemotherapy[88].

Radiotherapy treatment is applied to help to control tumor growth and to avoid the transition to the next stage of cancer[87, 90]. Since the 1990s, an improvement in the survival rate has been observed with the inclusion of radiotherapy in breast cancer treatment[91, 92].

Neo-adjuvant chemotherapy is a pre-operative treatment that aims to control and decrease tumor growth. It is usually considered for locally advanced cancers[86, 87]. The chemotherapies involved can be similar or not to adjuvant treatment[86].

After surgery, adjuvant treatment is administered. Its composition depends on the cancer recurrence, the death risk, the phenotype and the benefit/risk to the patient[86].

Adjuvant treatment includes endocrine therapy, an oral treatment usually administered for five years. This treatment is a targeted therapy and involves tamoxifen and aromatase inhibitors[86]. Tamoxifen is usually recommended for pre- and post-menopausal women but for post-menopausal women, aromatase inhibitors are preferred[86].

In breast cancer, endocrine therapy can lead to a significant decrease in death. Tamoxifen decreases the relative death risk in 34% of cases and decreases recurrence in 40%[93].

In the cases of a metastatic breast cancer, an endocrine therapy associated with the adjuvant treatment is recommended and can increase the survival rate[88].

Besides endocrine therapy, other effective therapies, such as monoclonal antibodies, are involved in breast cancer such as trastuzumab[86, 88]. For patients treated with trastuzumab, the relative risk of death for patients under 50 y.o. decreases by 50% and by 34% for patients between 50 and 69 y.o.[94, 95].

Lung cancer treatment

Lung cancer is composed of two categories: small cell and non-small lung cell cancer. These two categories, as in breast cancer, can be at different stages of evolution: 0, I, II, III and IV. The most prevalent cancer is non-small cell cancer and presents a higher survival rate than the small cell lung cancer. Nevertheless, the small cell lung cancer is on the decrease but leads to a fatal outcome, with five years survival rate lower than 7%[86, 96].

The treatment of lung cancer includes surgery, radiotherapy, neo-adjuvant and adjuvant chemotherapy treatments. The treatment is adapted to the cancer stage, as detailed above.

Surgery is the reference treatment for the first and the second stage if patients are eligible. A neo-adjuvant treatment if needed or radiotherapy if the tumor growth is over 4 cm can precede the surgery. The applied surgery can be a lobectomy associated with an axillary curettage, with mediastinal node sampling and dissection if needed[86, 97, 98].

In the case of ineligibility for surgical treatment, stereotactic radiotherapy or a radiofrequency treatment can be used. Adjuvant chemotherapy can be associated if needed and can include monoclonal antibody treatment (durvalumab)[97, 98] or other chemotherapies such as cisplatin or vinorelbine.

For the third stage, surgery is a subject of discussion between healthcare practitioners, particularly if nodules are affected. Depending on the invasiveness and the progression of the tumor, surgery can be applied or not. For a non-invasive third stage, if surgery is applicable, the protocol is the same as in the previous stages. A neo-adjuvant treatment can be associated to decrease the tumor growth before the surgery[86, 97, 98]. If surgery is not applicable, a chemoradiotherapy or a chemotherapy are directly applied[97, 98].

The therapeutic choice concerning the four stages of non-small cell cancer has to take into account the mutational statue of the tumor. Genes concerned with the mutation

code for the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK). Depending on the mutation status, a specific treatment plan can be introduced[97, 98]. The identification of mutations can lead to the introduction of targeted therapy such as crizotinib. Nevertheless, an important problem concerning these targeted therapies is that resistance can appear and lead to tumor progression[86]. The use of these targeted therapies is essential in the evolution of lung cancer treatment. However, patient education (e.g. explanation about who to take correctly the treatment) is needed to better benefit, considering the narrow therapeutic window[86].

If the tumor is metastatic, different treatments are associated depending on the metastasis localisations (e.g. cisplatin/pemetrexed or cisplatin/vinorelbine), and a palliative treatment can be started if metastasis are too extended[97, 98].

Colorectal cancer treatment

The lifestyle in Western countries is related to some risk factors that lead to a higher risk of colorectal cancer. Excessive body weight, a diet that includes alcohol consumption, high consumption of red meat, low consumption of vegetables/fruit, cigarette smoking and physical inactivity were evaluated as related to colorectal cancer onset[99, 100].

Colorectal cancer treatment depends on diverse parameters such as localisation (colon or rectum), the patient's condition and the presence and localisation of metastases. In the early stages, if treated appropriately, the survival rate and the healing prognosis are high[86]. Colorectal cancer is composed of five different stages, as detailed above, and two sub stages in stage II (IIa and IIb)[101].

Surgery can be applied at a primitive or a metastasis stage. For a local primitive cancer, surgery is usually applied, unless contraindicated. Any other treatment is usually associated with surgery (Stage I and IIa). Depending on the tumor localisation, the damaged part of the colon or rectum is removed and a lymph node curettage may be associated, followed by an adjuvant chemotherapy for stage IIb and III[86].

For more invasive cancers, particularly metastatic cancers, radiofrequency therapy can be integrated into the treatment plan. This aims to treat other damaged localisations such as the liver or pulmonary area[86, 102, 103]. This treatment aims to destroy small secondary tumors (< 3cm)[86].

The hyperthermic intraperitoneal chemotherapy technique is another kind of treatment and can be combined with cytoreductive surgery[103, 104] to treat the metastasis in these locations. This technique involves an intraperitoneal administration of a hyperthermic (42-43°C) chemotherapy solution (usually oxaliplatine), which is administered to the patient for 30-60 min[86].

For rectum unresecable tumors, radiotherapy can be applied to decrease the tumor size before a neo-adjuvant treatment or after surgery before an adjuvant treatment[86, 103]. Radiotherapy can also be used for a limited number of liver or lung metastasis[103].

As in lung and breast cancers, new targeted therapies have been introduced for colorectal cancer. Among these are aflibercept, which is designed to link to vascular endothelial growth factor (VEGF). This receptor is involved in the angiogenesis that is necessary for metastasis expansion and has become a new therapeutic target for metastasis colorectal cancer[86].

1.3.1.3 Anti-cancer drugs

Considering the large quantity of anticancer drugs and treatment plans, only the different drug categories involved in most prevalent cancers (lung, breast and colorectal) will be presented. Any dosage and treatment scheme will be provided to avoid confusion related to the complexity of the disease. The chemotherapies act in different phases of the cellular multiplication to slow down and potentially stop the tumor growth.

Covalent liaison with DNA

1.3.1.3.1.1 Platinum derivatives

Discovered in 1965, cisplatin has revolutionised cancer therapy. Since FDA approbation, in 1978, cisplatin has remained one of the most important chemotherapies and is still involved in many cancer treatments (e.g. lung, breast, ovarian or bladder).

After cisplatin, other platinum derivative components were developed to potentiate cytotoxic activity and decrease related ADE. These components are detailed below.

The carboplatin structure differs from cisplatin by the presence of a dicarboxylate group, which leads to less toxicity. However, more concentration is needed to reach the cisplatin effect[105]. The component was approved in 1989 for ovarian cancer[105]. Oxaliplatin differs from carboplatin by the replacement of two amine ligands[106]. Oxaliplatin is usually used for colorectal cancer and was approved in 2002. The last platinum derivative, which is currently in the final stages of approval, is satraplatin. This component does not yet have market authorisation but demonstrates added value for prostate cancer[107-109]. Considering the lipophilic composition of satraplatin, analyses are being performed to evaluate its possibilities for brain cancer[107].

These platinum derivatives are alkylating agents. Their activity blocks tumor development by creating covalent liaisons with DNA strands, which interfere with the mitosis division processes. They can be associated to other chemotherapies which target other steps of the cell cycle[105].

Nevertheless, platinum derivative treatments are not without patient harm and many ADE have been counted that can lead to interrupt treatment (**Table 11**). In addition, resistances to platin derivatives can appear, which may lead to treatment failure and relapse[105]. To decrease these effects, products for new administration methods are being developed, such as inhaled cisplatin[110].

Table 11: The most predominant platinum derivative ADE (CBIP)

ADE	
Hypersensitivity reaction	Nausea
Ototoxicity	Vomiting
Peripheral neuropathy	Neurotoxicity
QT interval prolonging	Nephrotoxicity

1.3.1.3.1.2Nitrogen mustard and derivatives

Around 1942, Gilman and Goodman were interested in the systemic effect of nitrogen mustard.

After observations on animals and clinical trials, nitrogen mustard became the precursor of current cancer treatments. It was the first alkylating agent to provide good results in cancer research and the first cytotoxic commonly used in cancer treatment. Considering its toxicity as a gas, Gilman and Goodman studied other administration methods than gas administration to obtain similar or better effects in fast-growing cancers. They finally

detected that there was less toxicity for the host and better outcomes with intravenous administration[111].

The compounds that compose nitrogen mustard and its derivatives are melphalan, cyclophosphamide, ifosfamide, busulfan and chlorambucil[112].

The main activity of these drugs is to provide a stable cross link with the intra and inter DNA strands, which inhibits DNA synthesis and may lead to cell death[113].

Nitrogen mustard and its derivatives are involved in many cancer treatments, such as breast, ovarian, lung, lymphoma and multiple myeloma[114].

Given the toxicity of these compounds, many ADE can occur. Some are summarized in **Table 12.**

Table 12: The most predominant nitrogen mustard and derivative ADE (CBIP)

ADE	
Hypersensitivity reaction	Nausea
Haemorrhagic cystitis	Vomiting
Inconstant alopecia	Respiratory difficulties
Amenorrhea	Azoospermia
Neuropathy	Allergic reactions
Increase in hepatic enzymes	Icterus
Pulmonary fibrosis	Dizziness

Microtubule inhibitors

1.3.1.3.1.3 Taxanes

Discovered in the 1960s by the National Cancer Institute, paclitaxel comes from a natural source, the Taxus brevifolia, located in the bark of the Pacific yew in the forests of the Northwestern United States. Its diterpenoid structure has presented an strong cytotoxic effect on mouse tumor cells, which generated great interest[115]. Nevertheless, Taxus brevifolia regenerates slowly. This motivated the researcher Potier and his team from the Institut de Chimie des Substances Naturelles of Rhone-Poulenc Santé to look for a semi-synthetic derivative. They isolated a natural compound from the Taxus baccata leaves, which regenerates faster than the brevifolia species. They used this

compound to realize a semi-synthetic derivate, docetaxel, which was slightly more active than the natural compound[116].

The last taxane derivate is cabazitaxel, which was synthetized to improve prostate cancer treatment by Sanofi-Aventis and was approved in 2010[117].

The activity of taxanes leads to strongly linked tubulin polymers, resulting in an abnormal and strongly stable structure that inhibits DNA replication[116, 118-120]. Taxanes are usually used in different cancers such as breast, lung, prostate, ovarian, head or neck[112, 121].

Due to their activity, taxanes provide some ADE that are related to the dose that is administered, among them neurotoxicity or hematologic toxicity (**Table 13**).

Table 13: Important taxane ADE (CBIP)

ADE	
Hypersensitivity reaction	Neutropenia
Cardiac toxicity: rhythm disturbance	Hypotension
Irregular alopecia	Dyspnoea
Myopathy	Flushing or rash
Neuropathy	Urticaria
Myelosuppression	Angioedema

1.3.1.3.1.4 Vinca alkaloids

Vinca alkaloid drugs were isolated from the Madagascar periwinkle plant (Catharentus roseus) by *Robert Noble and Charles Beer*. This drug category includes four different molecules: vinorelbine, vinblastine, vincristine and vindesine. All these molecules are approved in Europe for cancer treatment[122]. *Jacquesy et al.* synthetized another fluorinated vinca alkaloid, vinflunine, to treat urothelial cancer. This compound was approved in Europe in September 2009[123, 124].

Vinca alkaloids interact with tubulin, which composes microtubules. This avoids microtubule assembly at the end of a mitotic spindle, which leads to the arrest of the mitotic phase in the metaphase[122].

Vinca alkaloid drugs are involved in treatment plans for many cancers, such as testicular cancer, Hodgkin and non-Hodgkin lymphoma, breast cancer, lung cancer or bone cancer[112].

As with all other chemotherapies, they are related to many ADE, summarized in **Table 14**.

Table 14: Vinca alkaloid ADE (CBIP)

ADE	
Anaemia	Nausea
Infection	Vomiting
Hand-foot syndrome	Constipation
Fatigue	Dyspnoea
SIADH inappropriate secretion	Fever
White blood cell ADE	Neurotoxicity
Thrombopenia	Tumor pain

Topoisomerases I and II inhibitors

1.3.1.3.1.5 Topoisomerase I inhibitors

In 1958, *Wall et al.* isolated topoisomerase I inhibitors from a Chinese tree, *Camptotheca acuminata.* The isolated extract of *Camptotheca* presents a high toxicity, with haemorrhagic cystitis and severe myelosuppression that led to setting it aside in 1970.

Nevertheless a few years later in 1985, Liu et al. understood the cytotoxic mechanism related to the inhibition of topoisomerase I, which resulted in the synthesis of a large number of derivatives. Among these derivatives, two are usually involved in cancer treatments: irinotecan and topotecan. Irinotecan was one the first water-soluble compound. It was approved in 1994 in Japan for both types of lung cancer and in 1996 for advanced colorectal cancer. Topotecan aimed to be more water-soluble and was approved in 1996 by the FDA for ovarian and small cell lung cancer and in an oral form in 2007 for the relapse of small cell lung cancer[(125)].

Many other derivatives were synthetized, such as belotecan, which was approved in South Korea in 2004, or rubitecan, a more lipophilic orally-deliveredanalogue that showed some limitations and was not approved[(125)].

The main activity of these compounds is to damage DNA single strands and stall the replication fork[126]. However, these drugs are related to some resistance related to the cell efflux pump and severe ADE[125] (**Table 15**).

Table 15: Topoisomerase I ADE (CBIP)

ADE	
Bilirubin increase	Fever
Cholinergic symptoms	Diarrhoea
Decreased appetite	Leucopoenia
Hepatic enzyme increase	Fatigue

1.3.1.3.1.6 Topoisomerase II inhibitors

Topoisomerase II inhibitors have been derived from podophyllotoxin, which is isolated from plants belonging to the Berberidaceae family. In 1946, the antimitotic properties of podophyllotoxins were discovered. This was followed by the synthesis of a compound by a research team from Sandoz Pharmaceuticals: etoposide (1966) and teniposide (1967), which were approved in 1983. They act on topoisomerase II, leading to single DNA strand and double DNA strand breaks. Mitosis is inhibited in the prophase phase (phase S and G3). This mechanism results in cell lysis during the mitosis phase[127]. Topoisomerase II inhibitors are currently administered for both types of lung cancer, testicular cancer, leukaemia and Hodgkin lymphoma[112]. The ADE related to these compounds are usually neurotoxicity (central and peripheral), hematic toxicity (myelosuppression, neutropenia, thrombocytopenia, leukopenia) and alopecia[112].

Anthracyclines

Anthracyclines are antibiotics with anti-neoplastic activity. The first, daunorubicin, was isolated in 1963 from Streptomyces bacteria and was designed to treat leukaemia or lymphoma. Afterwards, doxorubicin was developed for adenocarcinoma or sarcoma. It aimed to be less cardiotoxic than daunorubicin but needed a longer administration time[128].

The anthracyclines seemed to be a good treatment to overcome acquired multiresistance in the cancer cells.

This antibiotic drug category includes daunorubicin, doxorubicin, epirubicin and idarubicin. Nevertheless, idarubicin was withdrawn from the Belgian market in July 2018[112].

The mechanism targets topoisomerase II. Anthracyclines inhibit topoisomerase activities, which leads to DNA breaking by avoiding its repair and resulting in cell death.

Anthracyclines are included in the treatment of many cancers, such as ovarian, breast, lung, bladder, gastric or thyroid cancer[112].

Nevertheless, some oxygenated free radicals are produced, which increases the toxicity of anthracyclines[129]. Cardiotoxicity is one of the most serious anthracycline toxicities of all the ADE (**Table 16**)[112, 128].

Table 16: Anthracycline ADE (CBIP)

ADE	
Cardiomyopathy	Nausea
Alopecia	Vomiting
Neutropenia	Stomatitis

Antimetabolites

1.3.1.3.1.7Pyrimidine analogues

Since 1953, 14 pyrimidine and purine analogues have been approved. The category of pyrimidine analogues is composed of six drugs or pro-drugs: fluorouracil, gemcitabine, decitabine, cytarabine, capecitabine and azacytidine. The first to be synthetized was fluorouracil[130].

These drugs act as pyrimidine molecules. They use a membrane transporter to go inside the cell. Afterwards, they are converted into nucleotide analogues. This leads to enzyme inhibition, resulting in DNA damage and apoptosis. Other new compounds are being synthetized, such as thiarabine, which has a better activity than gemcitabine and a half-life that is 10 times longer[131].

Pyrimidine analogues act on different cancers such as colorectal, breast, stomach, liver, pancreatic, head, neck or ovarian[112].

The ADE associated with them are most commonly stomatitis, diarrhoea, granulocytopaenia, thrombocytopaenia, alopecia or dermatitis.

1.3.1.3.1.8Methotrexate

Methotrexate was developed in 1947 by Bound Brook researchers[132]. It is a folic acid antagonist that leads to the inhibition of tissue proliferation. It enters the cells by active transport and acts during phase S of the cellular cycle, resulting in a decrease in proliferation. Methotrexate acts as an inhibitor of the folate way. It is included in the treatment of many cancers, such as ovarian, bladder, breast, leukaemia, bone sarcoma or non-small cell lung cancer[126].

Its use is related to some ADE, such as kidney or hepatic failure, anaemia, neutropenia, nausea or thrombocytopaenia[112].

Others

1.3.1.3.1.9Endocrine therapy

Endocrine therapy looks to block hormone action or production. Around 70-80% of breast cancers overexpress oestrogen or progestin receptors. To decrease this overexpression, endocrine therapy completes breast cancer treatment. This therapy includes tamoxifen or aromatase inhibitors.

1.3.1.3.1.9.1 Tamoxifen

Tamoxifen produces a competitive inhibition by binding the oestradiol receptor localized in different tissues such as endometria or bones. Tamoxifen is mandatory prescribed to pre-menopausal women and can be prescribed to post-menopausal[86]. Common ADE related to its administration are hot flushes, vaginal dryness, ovarian cysts, nausea, vomiting, thrombocytopenia and skin rashes[86, 112].

1.3.1.3.1.9.2 Aromatase inhibitors

Aromatase inhibitors concern postmenopausal women and include three molecules: anastrozole, letrozole and exemestane. Anastrozole and letrozole inhibit competitively the aromatase enzyme complex in the peripheral tissues that produce oestradiol. Exemestane makes a destructive covalent liaison with the aromatase, resulting in a decrease in oestradiol[86].

As with tamoxifen, aromatase inhibitors are associated with some ADE such as a decrease in bone density, joint pain, hot flashes, vaginal dryness and thromboembolic phenomena[86, 112].

1.3.1.3.1.10 Monoclonal antibodies

In 1975, *Köhler and Milsteine* developed the technique of monoclonal antibody production[133]. Afterwards, in 1988, a humanization method was introduced to allow medical use of the antibodies. The principle is to produce a hybridoma, with myeloma cells and B lymphocyte. Six steps compose this technique: immunization, fusion, propagation, selection of the antibodies, cloning and antibody production. Their mechanism is to fix a specific epitope in order to destroy specific cells and to treat the disease[134]. A large proportion of antibodies have been extended to different diseases, such asthma or cancer. Concerning cancer, a large panel of monoclonal anti bodies has been developed for many cancers, such as breast, lymphoma, lung, kidney or colorectal cancer.

Trastuzumab is a well-known monoclonal antibody for breast cancer and metastatic gastric cancer. It acts by binding to the extracellular domain of HER2, avoiding receptor activation, which inhibits tumor cell proliferation[126]. Nevertheless, these drugs are also related to ADE, such as cardiotoxicity, hepatotoxicity, pain, hand-foot syndrome, fever and neurotoxicity[112].

1.3.1.3.1.11 Protein kinase inhibitors

Protein kinases are a large set of proteins composed of two important groups: protein serine/threonine kinases and protein tyrosine kinases. A protein kinase inhibitor aims to block the activity of one or more protein kinases, e.g. VEGF, which is involved in angiogenesis[135]. Protein kinases control cell growth, metabolism, cell differentiation and the apoptosis phase. Inhibitors are used to block or decrease disease evolution by provoking abnormality, as wanted in cancer treatment[136]. The first approved molecule was imatinib in 2001 for leukaemia and gastric cancer. Many others followed, such as lapitinib (2007) and crizitinib (2011).

Lapatinib is a protein kinase inhibitor used in breast cancer treatment in association with trastuzumab. This inhibitor acts on the intracellular domain of the EGFR and HER2 to

slow and block tumor development. Crizitinib acts on the ALK receptor in lung cancer and provides an inhibition to tumor growth, leading to apoptosis[126].

Protein kinase inhibitors are related to many ADE, an important risk of prolongation of the QT interval and torsade de pointes. Other ADE include hepatotoxicity, visual troubles, gastric troubles, hand or feet cracks and neuropathy[112].

1.3.1.4 DRP in the cancer population

The increase in the cancer burden, in combination with large quantity of new cancer treatments, leads in more patients under heavy cancer treatments such as chemotherapies. Consequently, cancer patients need a deeper attention, which may include medication monitoring and a closer follow-up[84]. DRP occurrence in cancer patients is frequent and may result in patient harm that can consequently decrease the patient's quality of life. Patients can suffer from diverse DRP but some seem more prevalent. Among these are ADE related to cytotoxic effects or DDI (drug-drug interaction) because of the large number of drugs prescribed and contraindications. The presence of a DRP can result in a hospital readmission that can be related to the patient's weakening[84, 137-140]. In The United States, Lund et al. showed that among patients with readmissions within 30 days after treatment, 11.1% of 30 days readmission were related to the chemotherapy treatment[140].

The association between oncologic treatment, current treatment, OTC and herbal treatments may be another source of DRP to take in account, such as DDI[141].The use of complementary and alternative medicines (CAM) is increasing among cancer patients. A study in Italy performed a survey among 5 hospitals (468 patients). The results showed that 48% of patients were taking CAM at the same time as their cancer treatment. Only 11.4% of CAM taken were prescribed by a doctor and 86% of patients were not informed about the potential DRP related to these CAM[142].

Some patients do not consider that CAM can be related to important DDI or ADE when taken during a cancer condition or at the same time as chemotherapy. In Canada, two studies performed by *Riechelmann et al.* detected a large range of potential DDI among hospitalized cancer patients and ambulatory cancer patients. Among ambulatory cancer patients, 27% experienced a DDI, while DDIs concerned 63% of hospitalized cancer patients. Although the proportion of potential DDI was larger among hospitalized

patients than ambulatory patients, the presence of an interaction may be indirectly related to hospital readmission[137, 138]. Nevertheless, the presence of DDI did not appear as a risk factor for hospital readmission in cancer patients.

In the United States, a study investigated risk factors for hospital readmission among cancer patients. Major risk factors detected were age, metastatic status, haematologic cancer, being in the first cycle of chemotherapy and anthracycline administration. A large proportion of readmission diagnoses were related to ADE diagnoses, such as febrile neutropenia or diarrhoea[140].

As with DDI, ADE remain extensively reported in the literature and may be the source of patient harm.

A cohort study performed by *Culakova et al*.[143] in the United States estimated that 13.1% and 20.6% of cancer patients experienced febrile neutropenia after the first cycle and after 4 cumulative cycles of chemotherapy, respectively. Febrile neutropenia represents one of the most frequent ADE usually associated with cancer treatment[143].

It seems that DRP occurrence has remained a large burden over the years, in the United States as well as in Europe. DRP detection is one of the main concerns of pharmacy practice but rarely highlighted during the daily practice of pharmacists or doctors. Besides their large frequency, DRP can potentially be serious for patients. Nevertheless, it can be interesting to estimate a proportion and to identity DRP involved in hospital readmissions among Belgian cancer patients. The results can lead to avoiding DRP occurrence or to optimizing potential interventions.

Regardless, the presence of a clinical pharmacist or a community pharmacist in a multidisciplinary follow-up for patients and particularly patients at risk seems to improve potential DRP management and lead to better patient care. Cancer patient follow-up would be more effective by identifying the risk factors related to DRP readmission. A specific follow-up involving risk factors may result in a decrease in readmissions and an improvement of patient quality of life[78, 80, 144].

1.4 Drug-related problems cost

DRP may result in slight nuisances or at the extreme point, a lethal effect[145]. Besides the impact on patient health and quality of life, DRP occurrence affects health care

costs[75]. In 1995, *Johnson et al.* developed a model to evaluate the cost related to DRPs in the United States. They showed that the cost linked to DRP morbidity and mortality for society was around US$76.6 billion in the ambulatory population[146].

In the United States, between 2000 and 2010, hospital readmission remained an economic burden. Indeed, around 20% of patients under Medicare insurance were subject to a readmission 30 days after discharge. The annual costs estimated for these readmissions were US$17 billion. Among these readmissions it was reported that 4.5-24% were related to a DRP[67]. Regardless of the country, these readmissions strongly increase costs for patients and health care providers. Closer to Belgium, in Germany, a study estimated mean ADE readmission costs at €1 978 (± €2 036) per patient, with a mean length of stay of 6.8 days (± 8.7 days)[147].

Some health conditions may increase the risk of DRP readmissions. Having a cancer condition was detected as an important risk factor for DRP readmission. The heavy drugs usually involved during the treatment and ADE that can result after treatment sessions, such as neutropenia, increased the readmission risk[67, 145]. In Singapore, a study highlighted that more than 60% of DRP readmissions were related to myelosuppression or infection, with a mean length of stay of 6.1 days and a mean cost of S$4 747 (€3 109.52) per patient per readmission. The authors also made an estimation of the annual costs of S$16.2 (€10.61) million for cancer patients[145].

The magnitude of costs is related to the kind of DRP and the length of stay. A study in Australia evaluated the costs related to the mean length of stay depending on the type of DRP such as febrile neutropenia. The mean length of stay was 7-7.5 days, with an estimated neutropenia-related cost during the treatment cycle from A$16 291 (€10 113.29) to A$19 456 (€12 078.09). The mortality associated with these readmissions were ranged between 3.9% and 10.3%[148].

All costs detailed above included direct costs of DRP readmission for cancer and the general population. However, other costs need to be included in these costs, such as costs related to patients that experienced a DRP without a readmission, or indirect costs, such as productivity costs. In the Netherlands, researchers evaluated the indirect productivity costs. The average cost considered lost was evaluated at €1 712 per readmitted patient under 65 y.o.[149].

In response to this public health concern, some researchers evaluated potential solutions that may result in cost savings. Among these solutions, a multidisciplinary team that includes a clinical or community pharmacist for patient follow-up or the implementation of a primary prevention for the chemotherapy ADE may help to decrease these readmissions and their related costs.

2. Objectives

This thesis aimed to study DRP in community pharmacies and in the hospital.

The first goal of the project was to adapt and to validate the PCNE v6.2 DRP classification tool in Belgian community pharmacies. A pilot study was conducted with this tool to clarify the community pharmacist's involvement in the DRP detection with a special focus on pain DRP.

The second goal of the project was to evaluate the implication of DRP in cancer patient readmitted within 30 days after their last care, the costs related to these DRP readmissions and the analyses of potential drug-drug interactions among this population.

3. Method

This chapter will be devoted to detail some tools or concepts used during this thesis work, methodologies of the different studies will be developed in the Results part .

This work is divided in two parts. The first part involved two projects and the second three projects. Some explanations will be provided about the different programs, tools or scores used during the different parts of this project.

3.1 Drug-related problem in community pharmacies

3.1.1 Adaptation and validation of PCNE drug-related problem classification v6.2 in French-speaking Belgian community pharmacies

This first project of this part involved a tool validation study regarding the PCNE drug-related problem classification v6.2. The different parts that have not been approached in this chapter will be detailed in the Chapter IV part 4.1.1.

✓ Translation and adaptation of the PCNE V6.2 classification

The PCNE classification v6.2 was the basis for the development of the French validated classification. This classification results from workshop discussions with many experts from all over Europe, in 2009. The classification arrangement has been organized to classify and to describe the cases. The objective of this classification was to assist healthcare practitioners to record DRP data in order to improve research concerning nature, prevalence and incidence of DRP. This classification includes four primary domains in the “Problems” section, eight in the “Causes” section, five primary domains in the “Interventions” section and five primary domains in the “Outcome of the Intervention” section. Each primary domain includes between one to nine sub-domains for a deeper DRP analysis [50].

3.1.2 Pain DRP in Belgium Pharmacies

The second project of the first part involved a cross sectional observational study design.

During a cross-sectional study, all measurements on each case are made at the same time and the observation of the study population is done at a given moment. These studies are usually used to determine the prevalence of an event in a population. Knowledge of the prevalence is very useful in research to determine the association between variables. It reveals the likelihood of an event and the predictive value of it. [150, 151]

This second project presents the evaluation of the previous adapted PCNE tool in the Belgian daily use practice. This study involved the pharmacy students (second-year master's) with their community pharmacist's supervisors during their internship. A total of seven faculties of pharmacy around Belgium were invited to participate to this study.

To be included in the study, all the participating pharmacists had to be accredited as "internship supervisor pharmacist" by the commission organizing internships of each faculty.

The main objective of this study was to detect and to classify the daily practice Drug Related Problems (DRP), with the adapted PCNE classification during five complete days.

The adapted tool was available online on the Belgian Pharmacists Association (APB) website to make the coding easier.

The internship supervisor mission was to detect DRP. The student had to assist their supervisor, observe the detection of the DRP and the means provided to try to resolve it. Later, the student had to code the DRP on the online adapted tool in the APB website. The DRP detection could be done by two different ways. First during the usual drug delivery, the student had to stay next to his supervisor and to observe him detecting a potential DRP. The second way was "*a posteriori",* during all the prescription recheck at the end of the day. This step was realised by the internship supervisor and the student. When a DRP was detected, the student had to code with the online tool during the 5 months of the study period.

To be well prepared to the coding system the students had to take a training class and to code 5 fictive cases in the online tool. They could evaluate themselves by receiving a detailed correction of these cases in order to improve themselves and to get a deeper understanding of the coding.

For this research we chose to focus on pain drugs related problems that included the Anatomical Therapeutic Clinical (ATC) code M01 (including anti-inflammatory drugs and anti-rheumatics) and the N02 with the analgesics.

The patient DRP coding was done anonymously, and it was impossible to link a DRP to a specific patient or pharmacy. To ensure the confidentiality of the collected data, no information was collected concerning medical conditions of patients, students, pharmacists or pharmacies, aside from their location.

Data were analysed with descriptive statistics using the mean and the standard deviation for continuous variables, and the proportion for categorical variables.

3.2 Drug-related problem in hospital

The second part involved three projects; based on a retrospective cross-sectional study in two Belgian care facilities. The different tools and methods for the data collection and the data analysis will be presented in detail in chapter IV (part 4.2.1/ 4.2.2/ 4.2.3). This study reached to explore and to analyze cancer patient readmission due to a DRP and to highlight some risk factors to pay attention to. The applied method and the key steps of this study will be presented in the Chapter IV.

3.2.1 Evaluation and analysis of drug-related problems in cancer patients readmitted to two Belgian care facilities within 30 days after discharge

3.2.1.1 Data Collection: Epi Info™ 7.2

Epi Info™ 7.2 was the software that has been chosen for the data form creation. The Center for Disease Control and Prevention (CDC) created this program and provides it freely for the public health community practitioners and researchers. This software enables the researcher to create a form and to customize it according to the aim of the study. The data can be analyzed directly with the program or can be transferred to a Microsoft Office program for a deeper statistical analysis [(152)].

3.2.1.2 DRP detection and causality

WHO-UMC Causality System

The causality assessment was developed by the World Health Organization- the Uppsala Monitoring Centre (WHO-UMC) system through their "Program for International Drug Monitoring", in 1991. The program included at least 40 countries at this period. In order to create a practical tool they consulted all the countries that participated to the National Centres program. The causality assessment includes some necessary parameters to classify correctly the kind of causality [153].

During this study, this system was used by the expert group of practitioners to assess the potential causality between the readmission and a DRP. This system classifies the probability of a drug involvement in six categories representing causality: certain, probable/likely, possible, unlikely, conditional/unclassified, unassessable/ unclassifiable [153].

These categories tried to indicate the right way to classify a DRP by providing between two and five criteria in each category to assess. A **"certain"** DRP readmission was considered when a clinical event, including laboratory test abnormality, occurs in a plausible time relationship to drug administration, and which could not be explained by concurrent disease or other drugs or chemicals. A **"probable"** DRP considers a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which followed a clinically reasonable response. A **"possible"** DRP is considered when a clinical event appears, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals**.** An "**unlikely**" DRP is defined when a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration makes a causal relationship improbable, and in which case other drugs, chemicals or underlying disease provided plausible explanations. A DRP can be "**Conditional or Unclassified**" when an event or laboratory test abnormality occurs, and more data for proper assessment, or additional data under

examination are needed. The last category was a "**Unassessable or Unclassifiable**" DRP, it occurs when the report suggested an adverse reaction but cannot be judged because information was insufficient or contradictory and data cannot be supplemented or verified[153].

The WHO-UMC Causality system has been selected because it provides some advantages and was considered as an interesting and useful tool to classify drug relationship likelihood [153, 154].

Lexicomp

Lexicomp is an online database that provides a direct analysis of the interaction between drugs. Further details concerning this database will be detailed in the part (3.5.1.1) of this chapter.

3.2.1.3 Statistical analysis

Charlson Index

The cancer population remains linked to a high comorbidity [155, 156] and the study population has not been exempted to this general condition. In order to minimize the quantity of variables for the statistical analysis, the Age adjusted Charlson Index has been selected to assess patient level of comorbidity.

The Charlson Comorbidity Index is the most commonly used comorbidity measure of patient illness in contemporary clinical research. It includes a questionnaire about patient diseases, for each item a rating is assigned and the sum of all items results in an index [157] . This index aims to be predictive of survival and was validated with a population of 685 patients. A cut off has been defined and depending on the index, the probability of survival within 10 years can be assessed. For example, for an index of 2, the probability of survival at 10 years is 90 % and for an index of 6 or more, the probability decreases sharply between 2 and 0% [158].

To minimize the age cofounding bias this index was adjusted for age. Considering the extent of age difference in the study population, this index was applied.

The age-adjusted index has been used in several studies for survival prediction and treatment options concerning patients with colorectal cancer, bladder cancer, and early-stage endometrial cancer[159-162].

The medical history was analyzed for each patient to calculate the age adjusted Charlson Comorbidity Index. The aim was to integrate one comorbidity variable that takes into account medical history and may be included in the logistic regression.

Logistic Regression

The statistical analyses involved in this study were a logistic regression and the calculation of the odd ratio (OR).

The regression aims to explain a variable, the dependent variable, on the ground of other variables named independent variables that could be considered as predictive factors.

The aim of the logistic regression model is to highlight the association between one or more predictor factors (independent variable) with the variable of interest that is the dependent variable [163, 164].

The estimation could be direct with Risk Ratio (RR) or indirect with the Odd Ratio (OR). For this study the OR was calculated because of the cross-sectional study design and the low prevalence of DRP readmission (< 10%).

3.2.2 Drug Related Problems readmission cost in two Belgian hospitals: Is it avoidable?

The next project of this part aims to assess the costs linked to the DRP readmissions and to evaluate the proportion of avoidable DRP readmission.

To assess the preventability of a DRP, two independent evaluators reviewed all DRPs and classified them.

The agreement was evaluated with the Kappa coefficient. This coefficient measures the agreement between two evaluators. The Kappa is corrected for the chance to classify on the same way [165, 166]. Levels of agreement [166, 167] are summarized in the **Table 17.**

Table 17 Kappa's level

Kappa value	Agreement
< 0	Less than chance agreement
0.01–0.20	Slight agreement
0.21– 0.40	Fair agreement
0.41–0.60	Moderate agreement
0.61–0.80	Substantial agreement
0.81–0.99	Almost perfect agreement

The statistical analyses were mean (+/- SD), proportions, median and the interquartile square. All the analyses were performed via SAS 9.4 or Excel.

The details of this part will be exposed in the Chapter IV, part 4.2.2.

3.2.3 Drug-Drug interactions in Cancer Patients Readmitted 30 days after discharge

The last project of the second part consisted of a deeper analysis of the interactions found in the previously studied population. Interactions have been assessed by two

different databases and confirmed by another reference book, which are detailed below. The steps of the method will be presented in the next Chapter IV part 4.2.3.

3.2.3.1 Interaction Assessment

In order to provide a deep analysis of the interactions, three data sources were used for the interaction assessments.

Lexicomp®

Lexicomp® is an online database that provides information to strengthen medication decision making for health care practitioners particularly concerning drugs interactions.

Interaction levels are ranked in five degrees of severity; **X** indicates a combination to avoid, **D** implies a therapy to consider and maybe modify, **C** a therapy to monitor, **B** involves no action or modification to make in the treatment and finally **A** means "no interaction".

The online version provides some advantages such as a fast accessibility to a clear and updated drug information. The drug interactions module helps taking safer medication decisions[168].

Epocrates

The second evaluation of the interactions used Epocrates© MultiCheck. The free online Epocrates© version is a web service used by the health care professionals and is composed of various applications. These applications provide consistent information in different levels from the interaction check to the disease guidelines, according to the interaction severity. The drugs combination are classified in several categories (Therapeutic Advantages, no interaction, additional considerations, precautions for use, monitoring but not to avoid and contraindication)[169, 170].

Stockley's

The third evaluation used the Stockley's Tenth Edition, it remains one of the most known interaction references. It provides a complete information concerning Drug-Drug

interactions associated with practical information of the interactions management [171, 172]. However, the interactions have been developed without degree of severity. The interactions are only described in pharmacological terms [172].

3.2.3.2 Statistical Analysis

The statistical analyses involved in this part were the calculation of mean, median and proportion concerning the state of the situation of the interactions.

The second part of the third project analysed the impact of interactions on death and a survival analysis has been applied. The survival analysis begins from an event that leads to the inclusion in the study population until the end point, which is death. The survival analysis follows the same concept than the logistic regression but with the integration of a notion of time, from the event to the death.

A Kaplan-Meier model allows the estimation of the proportion surviving after an event during a precise period. This statistical analysis leads to a survival curve that presents the population proportion in abscissa and the Time To Death in the ordinate. The logRank can be calculated in order to compare the survival in two populations [173].

The Cox model was applied too, it estimates the risk of death depending on the time and covariates (or independent variables) [174]. The Cox analysis leads to an estimate that is represented by the Hazard Ratio (HR) [174, 175]. A HR greater than one involved that the event is more likely to occur and less than one, less likely to occur [175].

4. Results

4.1 Drug-related problem in community pharmacies

4.1.1 Adaptation and validation of PCNE drug-related problem classification v6.2 in French-speaking Belgian community pharmacies

Abstract

Background: Many tools exist to document DRP, such as the PCNE tool. However, none have been adapted and published for French-speaking Belgian community pharmacies.

Settings: French-speaking Belgian Community pharmacies

Objective: The objective was to translate and adapt the PCNE V6.2 classification to the Belgian pharmacy practice and legal setting and to assess the content validity, daily use and inter-rater reliability of this classification.

Main Outcome Measure: Validation of the French-language adapted PCNE 6.2 classification in Belgium.

Method: The first step translated and adapted the PCNE V6.2 classification to the Belgian setting. Thereafter academic and community pharmacists evaluated the content validity, which involved six criteria and concerned the instruction manual (clarity, helpfulness) and the registration form (representativeness, logical design, completeness and uniqueness). The next step was the DRP collection, using the PCNE tool daily. Compliance with the instructions and the time needed to solve a DRP were evaluated. Finally, the inter-rater reliability was evaluated by comparing DRP codings done by pharmacist volunteers.

Results: The classification was translated into French and adapted by adding 16 items. The classification showed a high content validity for the academics and the community pharmacists. A total of 109 DRP forms were coded, with an average resolution time of 5 min. Regarding the inter-rater reliability, 74 tool items out of the set of 83 showed high consistency in coding.

Conclusion: This study showed that the tool adaptation to a French-speaking Belgian context was reliable and has adequate validity for daily use.

4.1.1.1 Introduction

In Belgium as well as internationally, the community pharmacist's role has evolved from drug-focused to patient-focused activities, with an increased role in counselling and follow up of chronic patients.[176] Since the publication of the "Instructions for Pharmacists" in the Royal Decree of 21 January 2009, Belgian pharmacists have been legally responsible for the provision of pharmaceutical care. This care includes responsibility for medication delivery and counseling for the correct use of medicines[177]. The identification, prevention and resolution of drug-related problems (DRPs) are an integral part of pharmaceutical care, and also the pharmacist's role under Belgian law[30].

Different definitions of DRP exist. The Pharmaceutical Care Network Europe (PCNE) group defined a DRP as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"[50]. The definitions depend on the associated classification and the researcher's focus. To classify and document DRP, various tools exist, such as the PCNE classification, the *Hepler and Strand* classification, the PI-Doc or the *Westerlund* System[32, 178, 179]. These tools help to highlight the nature, incidence and prevalence of DRP, and generate a database for both researchers and practitioners[178, 180]. *Van Mil et al.* published an overview of existing DRP classifications and proposed recommendations for choosing the best tool, depending on the study aim[36]. The PCNE classification has several advantages. First, it includes a structured DRP classification with detailed sections and subsections, which allows each type of DRP to be coded. Second, a DRP can be classified by its type (e.g. treatment effectiveness), then its cause (e.g. patient forgets to use/take drug), the pharmacist intervention and the outcome. Third, the DRP and each category are clearly defined. Fourth, the tool has been validated through various studies in community pharmacies as well as in the hospital pharmacies context, and has been translated into different languages, such as Spanish, Turkish and Croatian[180]. However, the classification has never been validated and published in French or for the French-speaking Belgian community pharmacy setting and practice.

4.1.1.2 Objectives

The aim of this study was to translate and adapt the PCNE V6.2 classification to the Belgian pharmacy practice and legal setting, to assess the validity of its content, to evaluate its daily use practice in terms of time and instructions compliance, and to measure the inter-rater reliability of the adapted classification.

Ethics Approval: This study did not require ethics approval.

4.1.1.3 Method

Translation and adaptation of the PCNE V6.2 classification

The English version of the PCNE V6.2 classification includes a registration form and an instruction manual[181]. The adapted instruction manual followed the same classification structure and was completed by adding some examples to each section and primary domains to avoid misclassification. The adaptation was conducted by the research team in collaboration with academic and community pharmacists. The changes were introduced to fit better to the Belgian practise and legal context.

The adapted registration form is structured into five sections, allowing documentation of relevant information on documented DRPs. The five sections are:

- "General information": this part was added and helps to collect data about the patient, drug(s) involved in the DRP and the context of DRP classification;
- "Problem": to specify whether DRPs were potential or manifest, and to classify the DRP into four categories: “treatment effectiveness”, “adverse reactions”, “treatment costs”, “treatment accessibility” and “other”.
- "Causes": to classify the origin of the DRP in the following primary domains: “drug selection”, “drug form”, “dose selection”, “treatment duration”, “drug use process”, “logistics”, “patient” and “other”.
- "Interventions": to record the pharmacist’s initiatives to resolve the DRP;
- "Outcome": to explain the final result.

In the last part of the form, an area for comments was available to clarify a DRP description and/or DRP management.

To adapt the existing classification to the Belgian community pharmacy setting, the registration form and the instruction manual of PCNE V6.2 were translated into French and items were added or modified to fit legal and administrative regulations in Belgium. The translation was done by three investigators in the research team, each arriving at the same results. After the translation, the proposals by pharmacists were evaluated and added to the classification.

Content validity

The translated and adapted version of the tool, which includes the instruction manual and the registration form, was submitted to a group of 15 pharmacists (seven community pharmacists; eight researchers or academics). These reviewed the format and content of each item. The evaluation was done according to six criteria: “clarity” and “helpfulness” for the manual, and “representativeness”, “general structure”, “uniqueness” (avoidance of two items overlapping) and “completeness” for the registration form. In total, 30 elements (Item or tool part) were evaluated and scored using a 4-point Likert scale, from 1 (strongly disagree) to 4 (strongly agree). These scores were used to calculate the content validity index (CVI); which is determined by the item content validity index(I-CVI) and the scale content validity index (S-CVI). The content validity index (CVI) is a measure that indicates the proportion of members who endorsed an element (item or part) as valid content. The I-CVI highlights the ratio of satisfied evaluators, who considered the item as valid (i.e: evaluators who quoted the item at level 3 or 4 in their evaluations). It has been calculated for each item. The S-CVI is the mean of all I-CVI to evaluate the content validity of the entire tool. The I-CVI cut-off level was fixed at 0.8. This value, which was determined a priori from the literature, implies that the item was perceived as valid by respondents [182-184] and indicates whether an item was acceptable or not acceptable. A value under this cut-off level shows that evaluators’ opinions diverged and some items need modification to be more effective. However, it does not mean that the tool is not relevant. It was for this reason that the S-CVI was also calculated. This was measured as the mean value for all items for the

registration form and the manual. The S-CVI cut-off level was fixed at 0.9, above which level it is judged a relevant tool[184].

Daily use of registration form

For three months, 12 Belgian community pharmacists were invited to collect DRPs during their daily practice. They collected DRPs using the adapted form during their daily practice and send them back to the investigator. This registration was the first step of the inter-rater reliability evaluation. A self-completion questionnaire was then sent to these pharmacists to evaluate their experience, compliance with the instruction manual and the time needed for completion.

Inter-rater reliability

The aim of this part was to evaluate whether a DRP can be reported in one consistent way with the register form. The inter-rater reliability allows an investigator to assess the degree to which different data collectors give consistent estimates of the same phenomenon. In this study, it measured the extent to which data collectors (raters) assigned the same classification to one DRP. The method used in this study was similar to that used by *Conort et al.* to evaluate and validate an intervention codification tool in French clinical pharmacies[55]. The inter-rater reliability was conducted in two steps, and involved two or three pharmacists, depending on the workload at the pharmacy (X, Y and/or Z pharmacists). Following the first step, all DRPs coded by pharmacists in their daily practice (X pharmacists) were summarized by the investigator and reviewed by the research team. The 56 DRPs chosen were selected from 109 DRPs received for their clarity and comprehension. The DRPs were summarized as a case by the main investigator and reviewed by the research team. The summary included the patient description, the prescription content, the nature of the DRP and the type of intervention performed. All these DRP summaries were sent to Y and/or Z pharmacists to be coded again. All coding was then compared to calculate the inter-rater reliability (Fig.1). The analyses and calculation were done using Excel®.

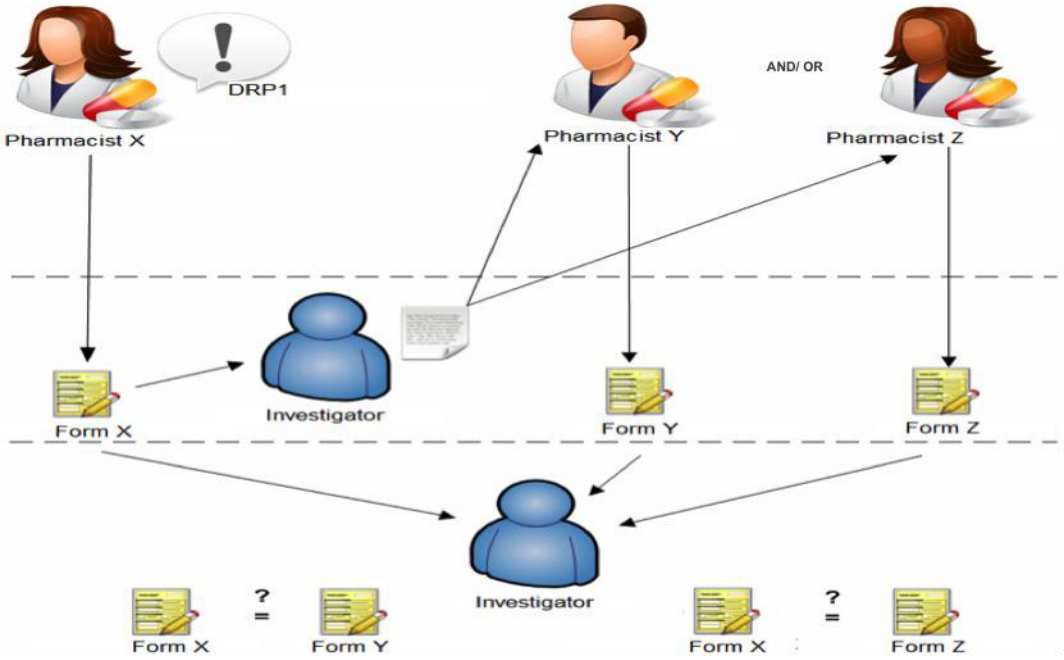

Figure 4: The process to test the inter-rater reliability of the adapted classification tool

In total, 56 DRP cases were selected from X pharmacists' registrations and divided between 10 other pharmacists (Y+Z). DRP were selected because of their comprehensibility and clarity . Consistent coding between two evaluators was marked as "1" and implies identical coding. Inconsistent coding was marked as "0". When too many items were coded, it was considered as inconsistent coding. The items were then classified according to their inter-rater reliability level. A consistency level higher than 85% represented "high consistency", a level between 66% and 85% "medium consistency" and a level lower than 66% "low consistency". The different levels were taken from the literature [182, 185].

4.1.1.4 Results

Translation and adaptation of PCNE drug-related problem classification v6.2"

The PCNE classification tool was adapted by adding one item to the "Problem" section and 12 to the "Causes" section. These new items were related to Belgian context, the dispensing process and patient behaviour. Two items were added to the "Interventions" section and one to the results section.

The details of these modifications are summarized in **Table 18**.

Table 18: Belgian adaptation of the PCNE tool V6.2

Part	Section	Item(s)	Modifications	Other information
General information	/	/	**Added**	To collect patient descriptive information
The Problem	Treatment efficacy	Wrong drug effect	**Removed**	
	Adverse effect	Toxic adverse effect	**Removed**	
	Other problem	Non-classifiable DRP	**Added**	
The causes	Drug choice	No available alternative	**Added**	
	Drug use	Drug abuse/addiction	**Added**	
	Logistic and administrative causes	Medical device not available	**Added**	
		Reimbursement criteria not met	**Added**	
		Illegible prescription	**Added**	
		Incomplete prescription	**Added**	
		Forged prescription	**Added**	
		Drug to the wrong patient	**Added**	
	Cause linked to patient	Doubt, fear about the medication	**Added**	
		Drug intake influenced by perception and religion	**Added**	
		Life style conflicting with drug intake	**Added**	
		Many physicians consulted	**Added**	
Intervention	Prescriber level	An intervention was proposed and refused by the prescriber	**Divided into two items**	1: with a justification 2: without a justification
Results	Not solved	Not solved because no	**Added**	

Content validity

Most evaluators gave a score of 3 or 4 on the 4-level Likert scale, for both the instruction manual and the registration form. The I-CVI and the S-CVI also showed results between 0.9 and 1, indicating a high content validity (Table 2 and supplementary material 1).

The items related to the instruction manual had an I-CVI between 0.8 and 1 (**Table 19**). The S-CVI was calculated at 0.9. The lowest score was observed for the "clarity" criterion and concerned the definition of a "manifest problem" and "potential problem". Following this step, the definitions were made more detailed and some examples were added.

Table 19: Pharmacists' evaluation of the instruction manual

Criteria	Elements	Level 1	Level 2	Level 3	Level 4	Total %	ICV-I
Clarity	*Aim of the classification*	6.5 (1)	0	54 (8)	39.5 (6)	100 (15)	0.9
	DRP definition	0	0	39.5 (6)	60.5 (9)	100 (15)	1
	DRP registration formulary description	0	0	20 (3)	80 (12)	100 (15)	1
	Definition of "manifest problem"	0	20 (3)	33 (5)	46.7 (7)	100 (15)	0.8
	Definition of "potential problem"	0	6.5 (1)	46.7 (7)	46.7 (7)	100 (15)	0.8
	Elements in the chapter "DRP Classification"	0	0	85.7 (13)	14.3 (2)	100 (15)	1

	Elements in the section "DRP Cause(s)"	0	0	46.7 (7)	54 (8)	100 (15)	0.9
Helpfulness	*Elements in the section "Intervention Classification"*	0	0	39.5 (6)	60.5 (9)	100 (15)	1
	Examples in the section "DRP Classification"	0	0	39.5 (6)	60.5 (9)	100 (15)	1
	Examples in the section "DRP Cause(s)"	0	6.5 (1)	26.5 (4)	67 (10)	100 (15)	0.9
	Examples in the section "Intervention Classification"	0	0	39.5 (6)	60.5 (9)	100 (15)	1
	Examples in the section "DRP Classification"	0	0	33 (5)	67 (10)	100 (15)	1
	Examples in the "DRP Cause(s)"	0	0	33 (5)	67 (10)	100 (15)	0.9
	Examples in the section "Intervention Classification"	0	6.5 (1)	33 (5)	60.5 (9)	100 (15)	0.9
S-CVI							**0.9**

Concerning the registration form, the I-CVI varied between 0.9 and 1 and the S-CVI was at 0.99 (supplementary material 2).

All these modifications are summarized in material 1.

The final adapted tool included 83 items, classified in five sections (General information, Problem, Causes, Interventions and Outcome), and a modified definition of "potential problem" and "manifest problem".

Daily use of registration form

A total of 109 daily DRPs were returned to the research team from the X pharmacists. After their reception, each form was analyzed and 56 were summarized. Items judged as essential or unecessary were respectively added or removed.

The instructions related to the coding step were not completely effective and some pharmacists did not follow these. For example, pharmacists ticked more than one item in the "Problem" section, which was not allowed. In the "Causes" section, a maximum of three causes could be ticked but only 6% of pharmacists followed this instruction. Most pharmacists ticked more. Finally, 18% of DRP codings did not classify patients as a "regular" or "occasional" patient, while 9% of DRPs were not classified at all. This added part in the French-language adapted classification seems to have been overlooked by pharmacists.

Times to code and solve a DRP ranged between less than one minute to 2 hours, with 62% of DRPs in 5 minutes or less and 28% between 7 and 15 minutes. A long solving time for DRPs happened mostly when the prescriber was unreachable or when a drug was missing. Pharmacists then had to find a solution for a better resolution.

Inter-rater reliability

The 56 DRP cases were coded with the adapted tool. This tool includes 83 items, distributed in the five sections of the French-language adapted tool. The new items were added after daily experience evaluation and pharmacists' proposals.

The evaluation of these items showed 2 low-consistency items (with an inter-rater reliability under 65%), 7 with medium consistency (between 65 and 85% inter-rater reliability) and 74 with high consistency (over 85%) (**Table 20**). The items with low consistency were modified and the definitions of "potential" and "manifest" problem were adjusted a second time to avoid misclassification during tool use. The medium-consistency items were identified in three sections. The first is "Problem", with the items "Non-optimal efficacy" (insufficient or excessive drug effect), "Non-allergic adverse effect" and "Non-classifiable DRP" (unidentified or non-classifiable problem). The

second section, “Interventions”, concerned the items “Patient counselling” (provide oral information, advice or warning), “Patient referred to prescriber” and “Other intervention” (intervention made by the pharmacist was not included in the items list). The last was the “Results” section, with the item “Problem completely solved” (pharmacist's intervention was successful or could prevent a potential DRP).

The medium- and high-consistency items were considered as “consistent” and were not modified.

Table 20: Consistency results for the chapter "DRP Classification"

DRP Classification	Total of agreeing responses*	% of consistency
Potential problem	41	59
Manifest problem	43	61
Inefficacy	69	99
Non-optimal efficacy	48	69
Allergic adverse effect	69	99
Non-allergic adverse effect	59	84
Treatment too expensive	70	100
Undeliverable treatment	62	89
Unsatisfied patient	62	89
Treatment did not work	67	96
Not the good treatment	69	99
Non-classifiable DRP	56	80

*Total number of comparisons: 70 for 56 DRPs: (56 from Y pharmacists and 14 from Z pharmacists)

4.1.1.5 Discussion

The aim of this study was to adapt and validate the PCNE DRP classification tool (V6.2) for the Belgian community pharmacy setting. The adaptation of the PCNE V6.2 classification tool allowed it to be better understood by Belgian pharmacists. The validation of this adapted classification highlighted a good content validity and a high inter-rater reliability. In daily use, 62% of DRPs were coded in five minutes or less. However, for the inter-rater reliability, items such as “manifest problem” or “potential problem” were modified twice as they remained unclear despite the previous modifications. The medium consistency in the “Problem” section might be related to its multiple classification possibilities. For the “Interventions”, the consistency could be related to an omission by pharmacists. For example, counseling is a common practice and may have been forgotten in coding when any other intervention was applied, e.g. a change of drug. Clearer instructions on the number of items to tick in each section could be added to avoid a large number of items being ticked. This should be done in the manual as well as in the classication tool to decrease these discrepancies and make the tool more usable in daily practice.

The PCNE group tried to improve their classification and update it regularly. The last update was V8.02, in which different changes were noted. Many items were modified to be more understandable, with clearer items or sections, and easier to complete, by reducing the number of items. For example, “non allergic, allergic and toxic adverse effect” were grouped together in one item: “adverse drug effect (possibly) occurring”. Compared to our translated and validated tool, this change will avoid some discrepancies[181]. However, the new classification does not give more information about how to differentiate a manifest and a potential problem, which will result in the same kind of discrepancies[181]. A Swiss classification, the PharmDISC tool, was set up and helps to decrease this risk by defining a manifest problem as “reactive” and a potential problem as “preventive” in the registration tool[59]. This change could be added to the PCNE tool to improve its inter-rater reliability.

During this validation study, the adapted classification tool seemed to be suitable for community pharmacists to classify and document DRPs. Its validation has the

advantage of ensuring that each encountered DRP can be correctly described by pharmacists through the proposed items.

However, the main limitation of this classification tool was the time needed to code each DRP. As presented in the results, some sections were not completed at all, which might be due to a lack of time or the large number of items. In 18% of cases, the patient information section was not completed and for 9% of DPRs, the problem was not classified at all. These sections might have been considered as unnecessary for classifying a DRP and therefore not completed to save time. Most pharmacists took 5 minutes or less to code and solve a DRP but some DRPs might be more time consuming, according to their complexity. In Germany, a study evaluated the coding and resolution time for a DRP. DRPs were classified using a modified version of the problem-intervention-documentation (PI-Doc) classification system. The median time needed to solve a DRP was about 5 minutes[186], which is similar to our results. This limitation was also discussed by Krähenbühl and al, who proposed that the time barrier was the main limitation to the documentation process for pharmacists. They also highlighted the persistence of this limitation as pharmacies received no incentive programme, such as financial or human aid in documentation. This limitation can lead to the proportion of DRPs being underestimated, as the time needed to collect and code DRPs could discourage pharmacists in daily practice. However, this time might become shorter with more frequent use by pharmacists.

A backward-forward translation, which might have improved the reliability, was missing in this study, which could be seen as a limitation.

The inter-rater reliability evaluation was influenced by the DRP cases and description and could also be a limitation.

Although the time was a limitation, the integration of this tool into regular dispensing software might be informative for an optimal medication review, for better patient follow-up by pharmacists. Such a review could highlight pharmacists' knowledge, or improve research by creating a large database in Belgium for epidemiologic studies, as we can find in Sweden or Denmark[70, 75]. Some classifications are more appropriate for community pharmacy daily practice, such as the PharmDISC. Others are more suitable

for research, such as the PCNE classification [178, 179, 181, 187-191]. The French version of the latest adaptations of the PCNE 8.2 and PharmDISC tools could be considered for wider use in pharmacy practice and research. In addition, the introduction of an incentive programme could be evaluated as a strategy to increase DRP coding. Finally, the combination of this classification tool with patient health data collection could increase the relevance of the coded information and result in better DRP management.

4.1.1.6 Conclusion

This study allowed an international DRP classification to be adapted and validated for the Belgian community pharmacy setting. The results showed that the tool was reliable and had an adequate content validity to measure the frequency and nature of DRPs. However, some adaptations were still required to decrease the time needed to code a DRP in daily pharmacy practice and to include it in pharmacy workflows.

4.1.2 Pilot Study of PCNE v6.2 daily use: Focus on Pain DRP in Belgium Pharmacies

The pilot study involved 468 community pharmacists and their students from all areas of Belgium (**Figure 5**). In 2012, there were 16 426 community pharmacists in Belgium and 5 186 pharmacies[192] .

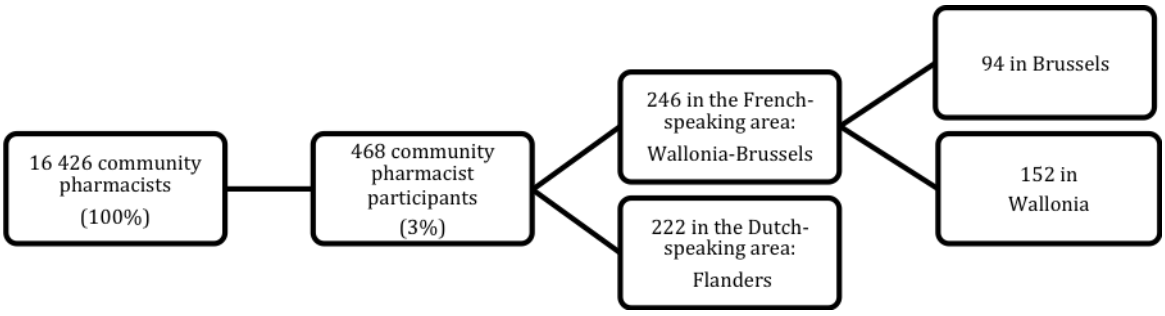

Figure 5: Study population PCNE v6.2 daily use

A total of 15 952 DRP were collected during the five-month study period. A mean of 6.81 DRP per pharmacist per coding day was calculated.

Concerning non-cancer-related chronic pain, more than 11% (1 832 DRP) of all encoded problems were encoded for analgesics (N02: 888 DRP= 5,6%) and anti-inflammatory drugs (M01: 944 DRP= 5,9%). The encoded pain DRP concerned more women (61%), and were more prevalent between 31-65 years (37%).

For non-cancer-related chronic pain drugs, the majority of the DRP concerned an "Incomplete prescription" or an "Interaction/Duplication" (62%). An incomplete prescription means that some information was missing (e.g. the dosage or the physician's signature) (**Table 21**).

Table 21: Categories of DRP

DRP categories Number of DRP (%)	M01	N02	TOTAL
Inappropriate administration time	109 (11.5%)	11 (1.2%)	120 (7%)
Incomplete prescription	334 (35.4%)	421 (47.5%)	755 (41%)
Interaction/ Duplication	234 (24.8%)	154 (17.3%)	388 (21%)
Others	302 (34%)	267 (28.3%)	569 (31%)
Total	944	888	1 832

	(100%, 51%)	(100%, 49%)	(100%)

For each DRP, the pharmacist had a choice between 27 types of intervention to manage and to solve it. Only the percentages of the main interventions are presented in **Table 22**. A total of 3 200 interventions performed by pharmacists were encoded concerning the 1832 DRP (**Table 22**). The interventions were performed by the pharmacist in two different ways, prospectively at the counter or "a posteriori" because some research was necessary and in this case the pharmacist called the patient to try to solve the DRP.

Table 22: Pharmacists intervention

Interventions*	M01	N02	TOTAL
Suggest medication change	122	142	264 (8.25%)
Provide verbal information	624	528	1 152 (32%)
Provide written information	324	220	544 (17%)
Suggest dosage modification	88	61	149 (4.6%)
Cooperate with other pharmacists	84	71	155 (4.8%)
No intervention	157	179	336 (11%)
Others	274	326	600 (19%)
TOTAL	1 673	1 527	3 200 (100%)

*Each DRP could have more than one intervention.

More than one intervention was possible for one DRP. Some interventions, such as "oral information" and "written information", were predominant. Nevertheless some DRP didn't need any intervention and pharmacists did nothing. The proportion of "no intervention" concerned 11% of the cases (**Table 23**).

Concerning the final result, DRP were fully or partially solved (77.2%) (**Table 20**). The category “Others” resolution represented an important part of 22.8% of all the resolutions.

Table 23: Results of the intervention

Resolution	M01	N02	TOTAL
Totally solved	654	605	1 259 (68.7%)
Partially solved	86	69	155 (8.5%)
Other	204	214	418 (22.8%)
TOTAL	988	888	1 832 (100%)

4.2 Drug-related problem in hospital

4.2.1 Evaluation and analysis of drug-related problems in cancer patients readmitted to two Belgian care facilities within 30 days after discharge

Abstract

Introduction

There are about 60 000 diagnoses of cancer per year in Belgium. After hospital care, about 12-13% of cancer patients are readmitted within 30 days after discharge. These readmissions are partly related to DRP, such as interactions or ADE.

Objectives

The aim of this study is to quantify and to classify DRP readmissions within 30 days for cancer patients and to highlight risk factors potentially correlated to readmissions.

Methods

This study is a 6-month observational retrospective study in two care facilities in Brussels: an academic general hospital and an academic oncology center. Patients readmitted within 30 days after their last hospital care for a potential DRP were included. Patient files evaluation was made with an intermediate medication review, and Lexicomp® database for interactions. The probability of DRP readmission was assessed using the WHO-UMC system.

Results

The final population included 299 patients, with 123 (41.1%) readmitted due to a certain (4.9%), probable (49.6%) or possible (45.5%) DRP. Risks factors linked to these DRP were a low Charlson Comorbidity Index, polypharmacy, the kind of hospital and some chemotherapies, such as platinum preparations. The most prevalent interaction involved was the D-type (44.8%), which suggests a possible therapy modification. However, it

was revealed that around 10% of interactions were X-type, which suggests a drug combination to avoid.

Conclusion

Almost 10% of patient readmissions within 30 days were related to a DRP, most of them from adverse drug effects. Four risk factors were highlighted to prevent these readmissions.

4.2.1.1 Introduction

Cancer remains at this time a global burden, with 14.1 million new cases worldwide and 8 million cancer-related deaths in 2012[81]. In Belgium, during the year 2011, 64 301 new cases were identified. Among them, 75% of patients were at least 60 years old (y.o.) at the moment of the diagnosis and the most common localization was prostate for men and breast for women[192].

The cancer population represents a vulnerable group of patients. This group has a higher risk of organ failure or altered metabolism due to the progression of their disease or the malnutrition that can occur with chemotherapy [84]. The combination of these modifications and the narrow therapeutic window of cancer treatments or other ancillary treatments (comforts, adjuvants) increase the risk of drug related problems (DRP) and potentially lead to hospital readmission. *Brown et al.* have reported that one-third of patients readmitted within 30 days came back 7 days after their discharge[193]. Chan et al. confirmed as well that approximately 12-13% of patients are readmitted one month after their discharge and some of these readmissions are related to DRP such as ADE or drug interactions[194].

A DRP is defined by the Pharmaceutical Care Network Europe (PCNE) as, “an event or circumstance involving drug therapy that actually or potentially interferes with desired outcomes”. Lau and al. have referenced a mean of 2.7 ADE per cancer patient per readmission. Among them, 48% were considered avoidable[195]. DRP severity is variable and may in some cases lead to patient deaths[196]. The anticancer treatment generally leads to an increase in the number of drugs used to limit ADE or to potentiate the therapeutic effect, which in return increases the risk of potential interactions[141]. The

drugs potentially related to these interactions are mostly analgesics, anti-infectious drugs or anti-emetics[197]. Chan et al. determined that approximately 5.4% of cancer patients could experience drug interactions, with a chemotherapy administration combined with another long-term treatment, over-the-counter products, herbs or nutritional products[141, 198]. These interactions could result in drug overdosing or under-dosing, leading to potentially avoidable clinical consequences[141].

4.2.1.2 Objectives

The aim of this study was to investigate the proportion, type and causality of DRP related to an unplanned hospital readmission among cancer patients in two Belgian care facilities and to highlight risk factors for an unplanned readmission.

4.2.1.3 Methods

Study design

This study was a retrospective, observational study of cancer patients readmitted into two Belgian care facilities between January 1 and June 30, 2016 within 30 days after discharge or after their last cancer treatment. This study involved two care facilities located in different area in Brussels: an academic center specialized in oncology (160 clinical beds) and an academic general hospital (864 clinical beds). An anonymization number was assigned to each patient to ensure data confidentiality.

Patients

All eligible cancer (solid tumors or hematological cancers) patients readmitted during this 6-month period for their cancer or their oncology treatment were included. Eligible patients were those readmitted from the emergency services or after physician consultation for at least 24 hours within 30 days after discharge or their last treatment, including cytotoxic agents, hormones and biological treatment. Patients were excluded if they were readmitted for reasons not related to cancer or its treatment (e.g. a car accident), when treated in two or more care facilities, when data were missing, when the readmission was programmed (e.g. for a chemotherapy session) and when they were

included in a clinical trial. Some patients were readmitted more than once during this 6-month period but only the first readmission was included.

Data collection

Lists of patients readmitted during the 6-month period were obtained from the two care facilities' informatics departments. In the academic general hospital, an initial screening process was developed to exclude non-cancer patients. Several additional screenings were applied in the two hospitals to exclude non-cancer or non-treatment readmissions and readmissions occurring more than 30 days after discharge.

Patient data were recorded in a form created in EpiInfo V7.2. The form was divided into five different parts **(Table 24)**.

Table 24: Data collected

Demographic data
Sex, age, death, alcohol, smoking status, geographical area
Cancer data
Cancer type, ICD[*] code, details about cancer type, stage, if evolution, medication, if surgery
Medical and drug data
Medical history, usual treatment, allergies, renal function[***], liver function[***], inflammatory marker (CRP) [***], neutrophils[***]
Readmission data
Length of hospital stay, symptoms on admission, final diagnosis, last cancer treatment administration (ATC classification[**])
DRP data
Presence of a DRP, causality, classification, interaction classification

[*] International Classification of Diseases

** Anatomical Therapeutic Chemical classification

*** Data collected before and after the readmission

DRP detection and causality

For each patient, the investigator made a medication review using patient files and an interactions evaluation with Lexicomp® database (between September 2017 and December 2017). An expert committee evaluated all patient files and medication reviews a second time. In each care facility, an expert committee was created and was composed of oncologists, emergency physicians or intensive care doctors and at least one clinical pharmacist. They had to meet to carry out a second review of medication and patient files to confirm, correct or detect more DRP. The medication review applied was the PCNE intermediate medication review type 2B that involved medical history, information from practitioners and drug interactions information[199]. Interactions measurement classifies into five degrees of severity: **X level** indicates a combination to avoid, **D level** a therapy to review for possible modification, **C level** a therapy to monitor, **B level** requires no action or modification in the treatment and finally **A level** means "no interaction". For the statistical analyses, the interactions were categorized into two categories, with A to C in the first category and D to X in the second one.

To evaluate the probability of drug involvement in the readmission, the causality assessment by the World Health Organization's Uppsala Monitoring Centre (WHO-UMC) system was used[153, 154]. This system classifies the probability of a drug's involvement into six categories. These categories were defined by between two and five criteria for each causality category to classify the DRP into the most likely category. A **"certain"** DRP readmission was considered when a clinical event, including a laboratory test abnormality, occurred in a plausible time relationship to drug administration and could not be explained by concurrent disease or other drugs or chemicals. A **"probable"** DRP considered a clinical event, including a laboratory test abnormality, within a reasonable time from administration of the drug and that was unlikely to be attributed to concurrent disease or other drugs or chemicals and followed a clinically reasonable response. A **"possible"** DRP was considered when a clinical event appeared, including a laboratory test abnormality, within a reasonable time from

administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals**.** An "**unlikely**" DRP was defined as when a clinical event, including a laboratory test abnormality, with a temporal relationship to drug administration made a causal relationship improbable and for which other drugs, chemicals or underlying disease provided plausible explanations. A DRP could be "**conditional"** or **"unclassified**" when an event or laboratory test abnormality occurred but more data for proper assessment or additional data under examination were needed. The last category was an "**unassessable"** or **"unclassifiable**" DRP. This occurred when the report suggested an ADE that cannot be judged because information was insufficient or contradictory and data cannot be supplemented or verified[153].

In order to classify the type of DRP, each DRP found was classified using a French-language adapted and validated version of the PCNE v6.2 classification tool. This tool classifies the DRP according to its type of "problem" (e.g. treatment effectiveness, treatment safety) and its "cause" (e.g. drug selection, drug form)[200].

The medical history was analyzed for each patient to calculate the age-adjusted Charlson Comorbidity Index[157, 158]. To minimize the age confounding bias, this index was adjusted for age, considering the extent of age difference, and was applied for our study[201, 202].

The patient's usual treatments were evaluated too. For each patient, the number of usual drugs was counted to highlight the polypharmacy. Considering the widely different definitions used for polypharmacy, the most common one was applied in this study, which considers the use of 5 or more drugs per patient as polypharmacy[203-205].

Statistical analyses

The statistical analyses performed were calculation of frequencies, Chi-square in univariate analyses and logistic regression. All these analyses were made using SAS version 9.4. Some independent variables were categorized into two or more categories.

4.2.1.4 Results

Patient characteristics

A total of 3 107 cancer patients were readmitted between January 1 and June 30, 2016 (**Figure 6**). Among them, 1 320 patients were readmitted within 30 days after discharge. Planned readmissions such as chemotherapy session were excluded. After review of their hospital files, 299 patients were included in the study population because of their cancer condition or their treatment. Among this population, 54% were men and almost 41% were 65 y.o or more. Almost 80% of the studied population was readmitted by the emergency department and the other 20% after their physician consultation.

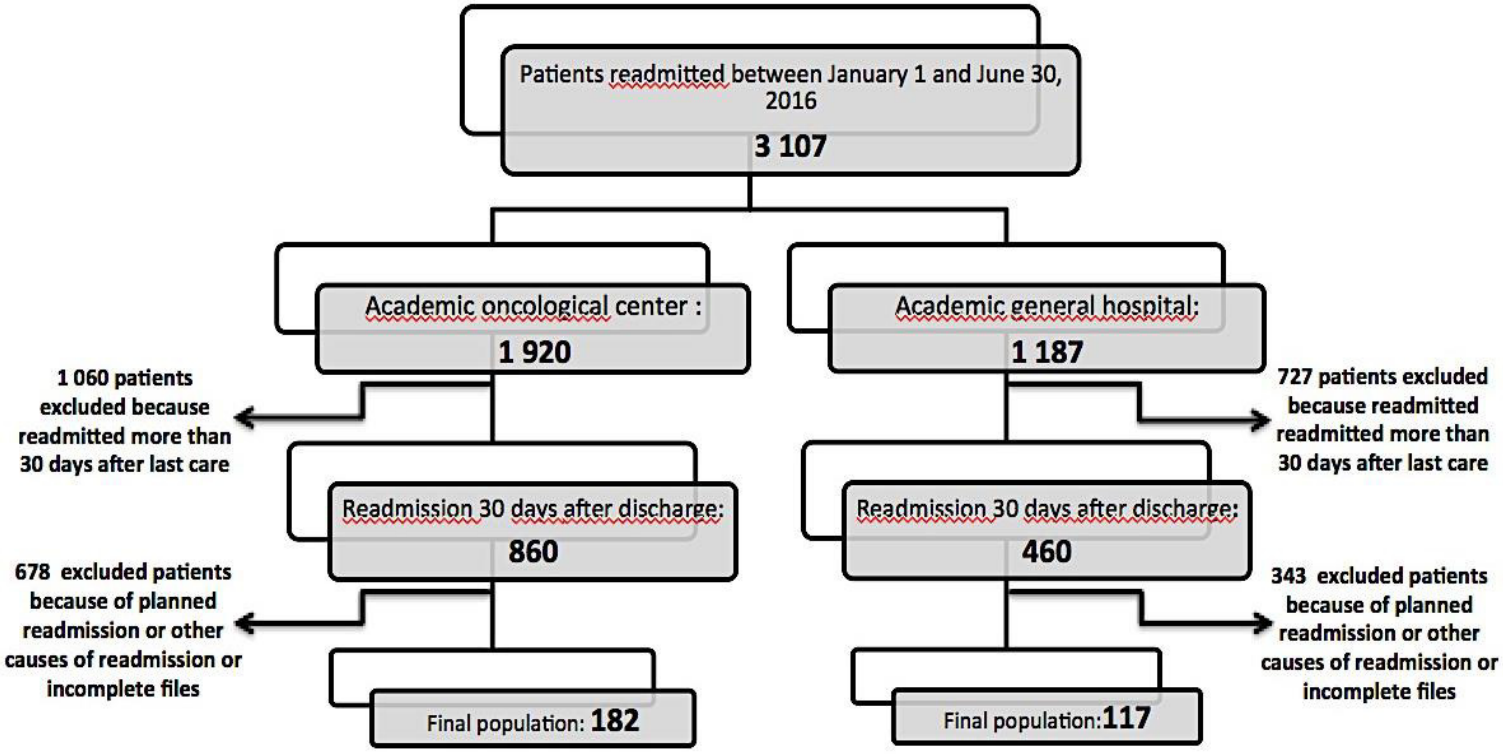

Figure 6: Study population readmitted 30 days after discharge

Concerning patients' medical condition, the majority of the studied population had a non-recurrent (73%) solid tumor (87%). The most prevalent cancers were lung and breast cancers, at 17.7% for each. Among lung cancer patients (50 patients), 94% were smokers or former smokers **(Table 25).**

Table 25: Study population characteristics

Variables	Proportion n (%)
Number of patients	299 (100%)
Academic general hospital	117 (39.1%)
Academic specialized center in oncology	182 (60.9%)
Readmitted by	
Emergency	235 (78.6%)
Medical consultation	55 (18.4%)
No information	9 (3%)
Sex	
Male	161 (54%)
Female	138 (46%)
Age categories	
≥ 65 y.o.	122 (40.9%)
50-64 y.o.	106 (35.6%)
36-49 y.o.	53 (17.8%)
18-35 y.o.	17 (5.7%)
Alcohol consumption	
Never	162 (54.2%)
Occasional	92 (30.8%)
Regular	27 (9.0%)
No information	18 (6.0%)

Smoking status	
No smoker	141 (49.1%)
Former smoker	95 (33.1%)
Smoker	51 (17.8%)
No information	12 (4.0%)
Solid tumor	262 (87%)
Hematological cancer	39 (13%)
Metastatic solid tumor	169 (59.3%)
Recurring cancer	
No	254 (73%)
Yes	27 (27%)
Surgery	
Yes	154 (51.5%)
No	145 (48.5%)
Type of cancer	
Lung	53 (17.7%)
Breast	53 (17.7%)
Gastrointestinal	42 (14%)
Lymphoma	21 (7%)
Leukemia	18 (6%)
Pancreas	15 (5%)

Bladder	11 (3.7%)
Prostate	8 (2.7%)
Uterine	8 (2.7%)
Cerebral	8 (2.7%)
*Other**	62 (20.7%)
Age adjusted Charlson Comorbidity Index	
0-3	30 (10%)
4-6	76 (25.4%)
≥ 7	193 (64.6%)
Polymedicated patients (> 5 drugs)	196 (65.6%)

*Other: All remaining cancers, hematological and solid tumor

The oncological treatments were mostly prescribed in combination that included different chemotherapy categories. The most commonly prescribed chemotherapy categories in this studied population were pyrimidine analogues (21.1%) and platinum preparations (19.9%) **(Table 26)**.

Table 26: Proportion of anti-neoplasic

Anti-neoplasic treatment	Proportion
Pyrimidine analogues	63 (21.1%)
Platinum specialties	59 (19.9%)
Monoclonal antibodies	33 (11.1%)
Other anti-neoplastics	28 (9.4%)
Vinca alkaloids and analogues	28 (9.4%)

Taxanes	24 (8.1%)
Anthracyclines and related substances	22 (7.4%)
Folic acid analogues	15 (5%)
Podophyllotoxin derivatives	8 (2.7%)

The evaluation of interactions included all drugs prescribed, usual treatments and anti-neoplastic treatments. The most prevalent interaction involved was the D-type (44.8%), which should lead to consideration of a modification of treatment. However, about 10% of interactions were X-type, which should be avoided **(Table 27).** These interactions concerned mostly β-blockers, β_2-adrenergic agonists, opioids, anticholinergics or gastroprokinetic agents**.**

Table 27: Interaction level proportion

Interaction Level	Proportion (%)
D	134 (44.8%)
C	74 (24.8%)
X	29 (9.7%)
B	14 (4.7%)
A	3 (1%)

DRP data

In a population of 299 patients, more than 40% (123 patients) were readmitted for a potential DRP. Among them, 6 (4.9%) were considered as “certain” DRP, 61 (49.6%) as “likely or probable” and 56 (45.5%) as “possible”. About 96% were related to ADE and about 4% concerned a “non-optimal drug effect” problem. The ADE DRP were mostly classified as a “non-allergic adverse effect”, with more than 81% involving the oncological treatment and more than 7% involving the current treatment. More than 32% of non-allergic adverse effects concerned direct chemotherapy ADE such as nausea,

vomiting, diarrhea or pyrexia. Febrile and non-febrile neutropenia represented more than 27% of total DRP. About 14% concerned infections (i.e. pneumonia, sepsis) that could arise after chemotherapy treatment. Concerning the ADE for the current treatment, antiplatelet and anti-coagulants drugs were mostly involved. The non-optimal drug effect represented interactions and involved painkillers, bisphosphonates, calcium complements or anti-platelets.

Statistical analyses

The collected variables were analyzed using a univariate analysis with a chi-square analysis. All variables with a $p < 0.1$ were included to the logistic regression. Variables included were: age, care facilities, kind of cancer, type of tumor, smoking status, alcohol status, if the tumor was metastatic or not, type of oncological drug (characterized by ATC code), polypharmacy status and Charlson Comorbidity Index. Statistically significant variables in the univariate analysis are summarized in **Table 28**.

Table 28: Univariate and Multivariate analysis

Statistically significant variables in univariate analysis	Odd ratio	Confidence interval 95%	p-value
Kind of care facility	1.7	[1-2.7]	$p < 0.05$
Solid tumor/hematologic tumor	2.6	[1.3-5.1]	$p < 0.01$
Metastatic tumor	1.7	[1.1-2.8]	$p < 0.05$
Polypharmacy (more than 5 drugs)	2.1	[1.2-5.3]	$p = 0.005$
Age-adjusted Charlson Comorbidity Index	2.3	[1.4-3.9]	$p < 0.005$
Type of chemotherapy		[1.4-3.9]	$p < 0.0001$
L01XA: Platine preparations	2.4	[1.3-4.2]	$p < 0.005$
L01BC: Pyrimidine analogues	1.9	[1.1-3.5]	$p = 0.01$

L01CA: Alkaloids and vinca alkaloid analogues	6.1	[2.4-15.5]	p < 0.0001
L01DB: Anthracyclines and related substances	3.3	[1.3-8.4]	p < 0.01
L01CB: Podophyllotoxin derivatives	10.4	[1.3-86]	p < 0.01
Multivariate analysis: Risk factors for readmission	**Odd Ratio**	**Confidence interval at 95%**	**p-value**
Kind of hospital	1.8	[1.1-3.1]	≤ 0.05
Age-adjusted Charlson Comorbidity Index	2.7	[1.4-5.1]	≤ 0.005
Polypharmacy	2.6	[1.4-4.8]	≤ 0.005
Chemotherapy			
Vinca alkaloid preparations	5.1	[1.9-13.7]	≤ 0.005
Platin preparations	2.5	[1.4-4.7]	≤ 0.005
Anthracycline preparations	2.9	[1.5- 8.3]	≤ 0.05
Podophyllotoxin derivatives	8.9	[1-77.6]	≤ 0.05

A backwards elimination procedure was performed. For the whole studied population, the highlighted risk factor variables following the regression were the kind of care facility, the polypharmacy status, the age-adjusted Charlson Comorbidity Index and the chemotherapy treatments (**Table 25**). Regarding the care facilities, a patient was almost two times less likely to be readmitted for a DRP when followed in the specialized oncology care facility, with a 95% CI [1.1-3.1]. Concerning the Charlson Comorbidity Index, a patient with an index under 6 was almost three times less likely to be readmitted for a DRP than a patient with an index higher than 6. A polymedicated patient has 2.6 times more chances to be readmitted than a patient with less than 5 drugs prescribed. Depending on the chemotherapy included in the treatment plan, a patient was 2.5 times more likely to be readmitted for a DRP, with a 95% CI [1.4-4.7],

and almost 9 times more likely, with a 95% CI [1-77.6], with platinum preparations and podophyllotoxin derivatives preparations respectively (**Table 25**).

4.2.1.5 Discussion

During the six months of the study period, 1 320 cancer patients were readmitted into the two care facilities 30 days after discharge. Among these patients, almost 10% were readmitted for a certain, probable or possible DRP. These DRP involved some ADE, interactions, prescription problems or the wrong intake of medication by the patient. The results showed that 96% of DRP readmissions were classified in the ADE category. These ADE were mostly related to chemotherapy treatments such as vinca-alkaloid preparations (e.g. vinblastine, vincristine), platinum preparations (e.g. cisplatin, carboplatin), anthracycline preparations (e.g. doxorubicin, epirubicin), podophyllotoxin derivatives (e.g. etoposide) and pyrimidine analogues (e.g. fluorouracil, gemcitabine). This study highlighted 4 of the 5 previously cited chemotherapy categories as risk factors for DRP readmission. It seems that these “old” chemotherapies such as vincristine or cisplatine had more readmissions linked to their ADE than the newest ones, such as biological treatment or immunotherapy. In our studied population, the proportion of patients over 50 y.o. (76.5%) is high. It has been shown that this population is known to suffer more from ADE from these treatments[206, 207]. It can also be related to the high toxicity[208, 209] of each of these “old” chemotherapies, which are involved in many chemotherapy combinations to improve efficacy. To solve this problem, researchers are looking for new drug delivery systems to minimize this toxicity. Developments of controlled-release cisplatin dry powders for inhalation or the emergence of nanomedicines can be a future opportunity to develop new combinations with less patient harm[110, 210].

It appears that many new treatments, in view of cancer burden around the world, have obtained marketing authorization faster than the “older” chemotherapies[211]. Consequently, many ADE are hard to recognize or not yet known due to their absence from drug leaflets. To prevent these possible DRP, some studies and reviews have summarized and highlighted them to help with their detection[212-214].

Besides DPR related to chemotherapy, seven DRP (8.6%) involved antiplatelet and anti-coagulant drugs. Due to the higher risk of thrombosis during cancer and/or related to some cancer treatments (lenalidomide, thalidomide)[215], more than 30% of the population with cancer in Europe[216] is treated with these types of drug. Their use helps to avoid thrombosis but can lead to harmful effects. Our study found that the ADE associated with these drugs were usually tumor bleeding or hemorrhage, as reported by Bulsink et al.[84] and Letarte et al.[217]. They also highlighted other commonly prescribed drug categories that are potentially linked to ADE and/or readmissions. Among others, these categories include corticosteroids, opioids, bisphosphonates and non-steroid anti-inflammatories. In our study, a small proportion of patient readmissions (4%) was linked to these drugs. Furthermore bisphosphonates were linked to hypocalcaemia readmission and opioids to constipation and/or feeding problem readmissions. These drug categories were rarely linked to a DRP readmission. However, it is not excluded that these drugs are linked to further DRP that affect the quality of life without leading to a readmission.

This study highlighted other risk factors for a DRP readmission, such as the kind of hospital. The care organization of the two care facilities involved in the study is substantially related to the number of patients they treat. The emergency unit of a general academic hospital usually accommodates more patients than an academic cancer center. Indeed, during the study period, in the general academic hospital, 18 953 patients (cancer and non-cancer) went to the emergency service and 4 275 (22.5%) of them were readmitted. Considering the various pathologies, less than a quarter of these readmissions concerned cancer patients, whereas 98.3% of the 2 920 patients coming into the cancer specialized center during the study period were cancer patients. The size of the care facility and the variety of medical specialties could increase the number of readmissions, which was confirmed by *Brown and al*.[193]. They highlighted that a large care facility associated with an increase in medical fields, leading to an increase in physicians and drug prescriptions, could be related to a higher readmission[193].

Moreover, the difference in management can inevitably increase significantly patient readmissions. Corresponding to the large difference in the number of patients visiting the emergency service, the care on arrival of patients is conducted differently. In the

specialized cancer center, all incoming patients with a neutropenia were not directly readmitted, while they usually were in the general academic hospital. A study by Legramante and al.[218] highlighted this difference in care by implementing an emergency department with a cancer pathway for three months. They observed a significant decrease in patient readmissions after the implementation of this new cancer pathway.

The next highlighted risk factor was the age-adjusted Charlson Comorbidity Index. A low one seemed to be related to DRP readmission. The Charlson Comobidity Index is widely used to evaluate survival depending on the comorbidity, and the usual end point studied is the death that can be an unfortunate consequence after a DRP readmission. Concerning the study population, an index between 1 and 2 was mostly related to DRP readmission. This risk factor can be interpreted as a warning to pay more attention to this population, which has less comorbidity but not necessary fewer drugs. These patients are potentially under less surveillance than those with higher index and more subject to a DRP readmission.

The highest Charlson Comorbidity Index calculated in our study was 15, meaning that the comorbidity was very high. Therefore, it could be more complicated to highlight a DRP among all the comorbidities. It seems complicated to attribute a symptom to comorbidity or a drug as this can lead to an underestimation of DRP when the index is high.

The last highlighted risk factor was the polypharmacy that increasing DRP readmission[203, 204]. This can be explained by the increase in comorbidities, especially in elderly patients (≥ 65 y.o.), leading to many drug prescriptions[219]. Self-medication or CAM used by cancer patients[220] can also be a cause of DRP[221].

Strengths and limitations

This study identified some risk factors for a DRP readmission of cancer patients with the aim of giving particular attention to patients who present some of these factors. This study presented some strengths, such as a large group of patients with different age groups, different kinds of cancers and oncology treatments, which allowed the highlighting of risk factors for a large population and not only a specific cancer or age

group. All patients readmitted for their cancer or treatment within 30 days after their discharge during the 6-month study period were included in the study population, which decreased the selection bias. Furthermore, the inclusion of two care facilities allowed the inclusion of patients who were nearly all from the Brussels area but also from all the towns around, including in Flanders and Wallonia. This led to a better external validity of the study concerning the variability of patients (age, type of cancer, severity…) . The patient medication review type 2B involving several physicians from different fields, associated with access to medical files, permitted a complete evaluation of each patient.

However, the evaluation by a local expert committee can include a bias, with an overestimation or underestimation of DRP detection because of differences in clinical judgment. Besides, true blinding was not possible and can also induced a bias. To limit this bias, the participating practitioners usually had similar backgrounds and for each DRP categorization, a consensus from all members was necessary. The study had known weaknesses in retrospective studies, such as incomplete files associated with an incomplete medical and medication history or wrong coding due to the different users of the patient files[222, 223]. We excluded patient files judged to be incomplete, leading to a potential underestimation of DRP readmissions.

This study can bring about reflection on the collaboration between different care practitioners (physicians from different fields, clinical pharmacists, community pharmacists, etc.) to improve cancer patient care and pharmacovigilance around these “old” and “new” drugs. It appeared that the notification of a possible ADE was not so effective. It could be interesting to include more pharmacists (community and clinical) during the follow up to notify ADE more regularly[224]. The establishment of interventions to improve health literacy, such as patient education, patient medication reconciliation and regular follow-up, could help to reduce DRP.

4.2.1.6 Conclusion

This study showed that about 10% of cancer patients were readmitted during the 30 days after their last treatment or discharge. Some of them were readmitted for a potential avoidable DRP. Some risk factors were found, making it possible to give more attention to some patients at risk (e.g. a low Charlson Comorbidity Index, platinum

preparations). This study brought forward some interesting information concerning some factors requiring care, but future prospective studies are needed to complete some necessary missing data and to identify more risk factors for DRP readmission. It could also be interesting to highlight the healthcare team interventions that could prevent DRP and the resulting readmissions.

4.2.2 Drug-related problems readmission cost in two Belgian care facilities: Is it avoidable?

Abstract

Introduction

There are about 60 000 diagnoses of cancer per year in Belgium. About 12-13% of cancer patients are subject to readmission within 30 days after discharge. These readmissions can be related in part to DRP such as drug interactions or ADE that can considerably increase hospitalization costs.

Objectives

The aim of this study was to quantify the cost of DRP readmissions within 30 days for cancer inpatient stays and to detect the avoidable DRP costs in Belgium

Methods

This study was a 6-month observational retrospective study in two hospitals in Brussels: an academic general hospital and an academic oncology centre. Patients readmitted within 30 days after their last hospital care for a potential DRP were included. The probability of DRP readmission was assessed using the World Health Organization's Uppsala Monitoring Centre (WHO-UMC) system and the preventability was assessed by Schumock et al.'s method.

Results

The population included 123 potential DRP readmissions and represented a total amount of €495 869.10, with a median length of stay of 7 days. The predominant cancers related to these readmissions were lung (19.5%) and breast (17.9%), and large share (71.5%) of DRP readmission was related to chemotherapy ADE readmission, according to healthcare practitioners' diagnoses.

Conclusion

A total of 71.5% of DRP readmission were related to ADE, with the median cost per readmission evaluated at €2 406.10. Avoidable DRP represented 7.3% of all DRP readmissions and amounted to €27 938.61. Neutropenia direct costs remain high and require more attention to decrease healthcosts.

Keywords

Belgium, drug related problems, oncology, costs, hospital readmission.

Key points

This study can help healthcare practitioners, such as physicians, pharmacists or nurses, to communicate better and regularly to decrease DRP readmission and costs related to it.

The highlighted results can help practitioners to be aware concerning parameters linked to avoidable DRP.

The amounts set out can increase patients' awareness of health costs that are usually unknown and only partly reimbursed in Belgium.

4.2.2.1 Introduction

Cancer remains at this time a global burden, with 14.1 million new cases worldwide and 8 million cancer-related deaths in 2012[81]. In Belgium, during the year 2011, 64 301 new cases were identified[225]. The cancer population has a higher risk of organ dysfonction or altered metabolism due to the progression of their disease or the malnutrition that can occur with anti-cancer treatments[84]. The combination of these parameters and a narrow therapeutic window for cancer treatments or other ancillary treatments (comforts, adjuvants) increases the risk of drug-related problems (DRP) and potentially leads to hospital readmission. A DRP is defined as *"an event or circumstance involving drug therapy that actually or potentially interferes with desired outcomes"*[50]. Chan et al.[194] assessed that around 12-13% of patients were readmitted one month after their discharge. Some of these readmissions were linked to a DRP[194]. In cancer population's, DRP are generally linked to drug interactions[84, 137, 194, 197, 226] or adverse drug effects (ADE) [69, 145, 195, 227]. Drugs potentially involved in the interactions were mostly analgesics, anti-infectious drugs or anti-emetics[197]. These interactions can lead to drug overdosing or under-dosing and potentially clinical harm[141]. ADE, which are particularly related to chemotherapy, remain some of the most prevalent kinds of DRP in

the cancer population[69, 145, 227, 228]. Among the predominant ADE, nausea, vomiting, thromboembolism, diarrhea, infections and neutropenia (febrile or not) are the principal ADE after chemotherapy[145, 208]. Neutropenia is particularly present, with chemotherapy-induced neutropenia (CIN). Among chemotherapies, platinum, taxanes[229] and even biological therapies such as bevacizumab[230] can be involved and result in a hospital readmission[231].

In Netherland a total cost of €355 million for all ADE and € 61 million for preventable ADE were evaluated in 2004. This amount included all medical costs related to the readmission such as care costs, diagnosis costs or treatment costs[232]. In Germany, the economical study by Rottenkolber et al. in 2012 compared the inpatient stays for patients with and whitout ADE. Considering the hospital perpective the ADE readmission amount was at €5,113±€10,059 comparativly to the non-ADE readmission at €4,143 ± €6,968 that was significantly lower ($p<0.0001$)[147].

Considering the treatment complexity, a cancer patient's risk of DRP readmission can significantly increase hospitalization costs, which are already high in cancer treatment. In Singapore Ko et al. assessed a mean readmission per patient cost at S$4 747 (€3 109.52) among 151 DRP readmissions and estimated an annual cost at S$16.2 (€10.61) million for cancer patients[145]. In Western countries, the mean cost per hospitalisation for a febrile neutropenia readmission was evaluated at approximately €13 500[233].

This study aimed to quantify DRP readmission to set out the stratified costs associated with these readmissions, using rates dated from 2016 in two Belgian hospitals , to present the current situation concerning cancer patient readmission.

4.2.2.2 Objectives

The aim of this study was to evaluate the direct cost of DRP readmission in a Belgian oncologic population, from two Belgian hospitals ,30 days after discharge to detect avoidable DRP and to estimate the potential savings.

4.2.2.3 Methods

Study design

The study was based on a previous study that evaluated the proportion of DRP readmissions 30 days after discharge[234]. It was a retrospective, observational study of cancer patients readmitted into two Belgian hospitals from 1 January to 30 June 2016 within 30 days after discharge or after their last cancer treatment. This study involved two hospitals from Brussels: an academic centre specialized in oncology (160 clinical beds) and an academic general hospital (864 clinical beds). An anonymization number was assigned to each patient to ensure data confidentiality. The protocol was reviewed and approved by the local ethics committees from both hospitals.

Patients

The study population included patients with cancer (solid tumours or haematological cancers) who were concerned about unplanned readmission during this 6-month period for their cancer or their oncology treatment. Eligible patients were those readmitted from the emergency services or after physician consultation for at least 24 hours within 30 days after discharge or their last treatment, including cytotoxic agents, hormones and biological treatment. Patients were excluded if they were readmitted for reasons not related to cancer or treatment (e.g. a car accident), when treated in two or more hospitals, when data were missing, when the readmission was programmed (e.g. for a chemotherapy session) or when they were included in a clinical trial. Some patients were readmitted more than once during this 6-month period but only the first readmission was included.

DRP detection and causality

The previous study[234]tried to highlight patients readmitted for a potential DRP and followed these steps.

For each patient, the investigator made a type 2B medication review from the Pharmaceutical Care Network Europe (PCNE)[199] using patient files and an interaction

evaluation with the Lexicomp® database[168]. An expert committee composed by oncologists, emergency doctor or doctor in intensive care and at least one clinical pharmacist evaluated all patient files and medication reviews a second time. Each care facility had his own expert committee.

To evaluate the probability of drug involvement in the readmission, the causality assessment by the World Health Organization's Uppsala Monitoring Centre (WHO-UMC) system was applied[153, 154].

Costs database

Databases including the different costs of each readmission for a potential DRP 30 days after discharge were obtained from the accounting departments (billing information) of each care facility. The society perspective was applied for this study and only the direct costs were analysed. Different costs such as pharmaceutical costs or medical care costs were extracted from the initial database to create a new database in an Excel file. The different costs were classified into categories, summarized in **Table 29.**

Table 29: Collected costs

Costs categories	Cares
Medical and paramedical care	- Medical care fees - Emergency services fees - Hospitalization fees - Surgery fees - Examination fees (e.g. ECG) - Blood transfusion costs
Pharmaceutical	- Drug fees - Medical device fees
Medical imagery	- Radiography fees - Tomography fees - Echography fees - ...
Laboratory analysis	- All blood laboratory test (Glucose,

triglycerides,…) - Virus search

All patient refined diagnosis related groups (APR-DRG) codes were used to associate the different costs to a specific category of patient. The APR-DRG is a special codification that includes the clinical severity, the mortality risk and the amount of resources used by the hospital services in patient diagnosis (primary and secondary diagnosis). This code corresponds to an international nomenclature[235].

DRP preventability

Two independent evaluators (two doctors from different specialties) evaluated the preventability of a DRP. Each evaluator had a list that included the most commonly-involved drugs in DRP readmission and the algorithm from Schumock et al.[236] for evaluating the preventability of a DRP. Each DRP was evaluated independently and classified into one of the following three categories: “avoidable”, “non avoidable”, “more information needed”.
The agreement between the two evaluators was calculated by the Kappa coefficient[167]. A DRP was considered as avoidable only when the two independent evaluators agreed on an “avoidable” classification.

Statistical analyses

Data were analysed with descriptive statistics using the mean and the standard deviation for the different costs or the median and the different quartiles. All analyses were performed using Excel® or SAS version 9.4.

4.2.2.4 Results

Patients

A total of 3 107 cancer patients were recorded between 1 January and 30 June 2016 (**Figure 8**). Among them, 1 320 patients were readmitted within 30 days after discharge in both hospitals. After review of their hospital files, 299 patients were included in the

study population because of their cancer condition or their treatment. Among this population, 54% were men and almost 41% were 65 y.o. or more[237].

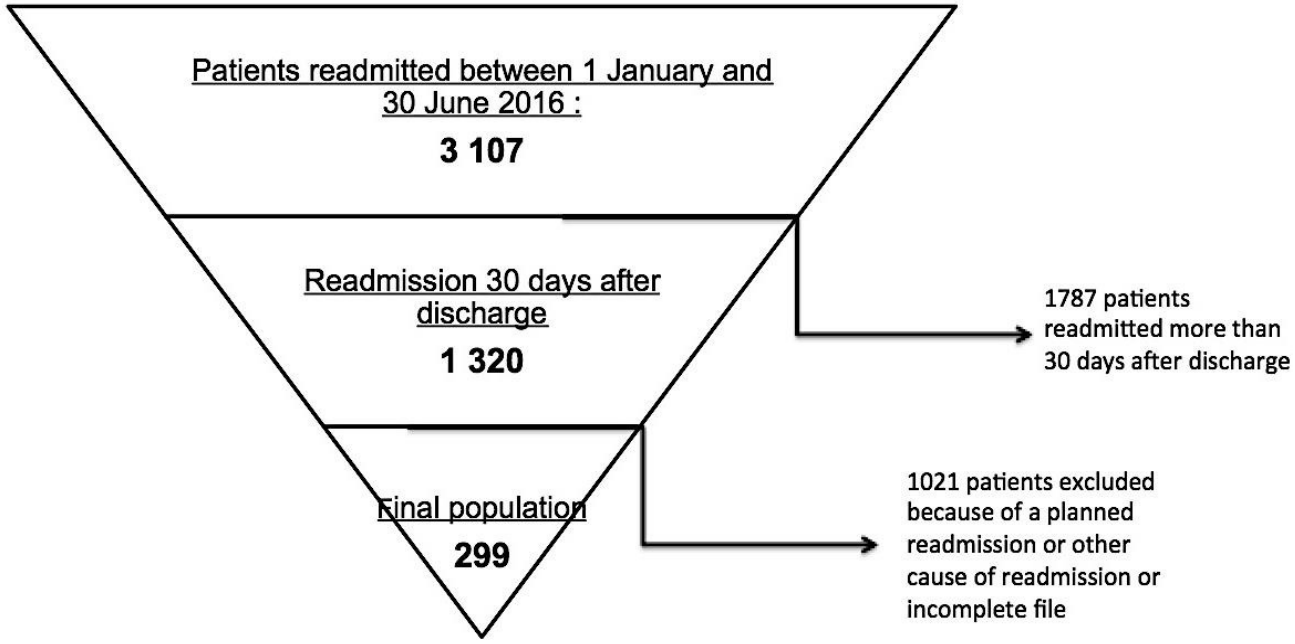

Figure 8: Study population

DRP detection and causality

After the two evaluations (by an investigator and the expert committee) of each file, a total of 123 patients were readmitted for what was at least a possible DRP. Within this DRP population, 55% were women, with a median age of 62 years old (y.o). The predominant cancers were lung (19.5%) and breast (17.9%). The age-adjusted Charlson comorbidity index score was calculated and ranged between 2 and 15, with a median score at 7. Patient had between 1 and 17 drugs drugs prescribed with a median at 6 drugs. According to the health practitioners' diagnoses, a large part of the DRP readmissions (71.5%) (ref 2) was related to chemotherapy ADE readmission. Among these, neutropenia, febrile or not, was the most common diagnosis (40.9%). The APR-DRG code most often associated to neutropenia was the code "660", for a "major hematologic/immunologic diagnosis, excluded sickle cell crisis and coagulation"[238]. This code correlated to the practitioners' diagnosis of neutropenia readmission (febrile or not) in 80.0% of cases. Considering the inclusion of primary and secondary diagnosis, the practitioners' diagnosis was preferred.

The total costs of the 123 DRP readmissions represented an amount of €495 869.10. Under the Belgian medical care reimbursement system, approximately 88% of this amount was paid by the patient insurance company (Belgian health care system), 6.8% by the patient and 3% concerned supplements (e.g. for a single room) that could be charged to the patient or the insurance company, depending on the health care contract subscribed to. The costs ranged between €754.56 for a one-day readmission to €41 983.42 for 43 days of readmission, with the average at €4 031.46 (± €4 967.85). Considering the large variability of the costs, the median and the interquartile range were calculated in order to be more representative of the study population. The median cost was preferred and was assessed at €2 406.10. The first and the third quartiles were respectively evaluated at €1 580.48 and €4 320.59.

The costs requested were stratified into four different parts, which represented 95.6% of the total costs. These costs are summarized in **Table 30**.

Table 30: Costs stratification per readmission per patient (€)

	Mean	Median	First quartile	Third quartile	% of the total costs
Medical and paramedical cares	2 199.08	1 213.19	763.52	1 949.00	**55.7%**
Medical Imagery	251.81	185.69	82.94	341.85	**6.4%**
Laboratory analysis	420.46	310.23	194.39	581.08	**10.7%**
Pharmaceutical	901.35	254.70	163.18	548.53	**22.8%**

The largest part of these 123 DRP costs concerned the medical and paramedical care costs. This part represented €270 486.33, or 55.7% of the total cost. These costs included medical acts, physiotherapy, emergency costs and all other costs linked to the hospitalization. The pharmaceutical costs were the second largest cost and represented €110 865.97, or 22.8% of the total cost.

ADE readmissions cost €371 188.95, which represented 74.9% of the total cost of 123 DRP readmissions. The median cost for these ADE readmissions was evaluated at €2 504.65. Concerning neutropenia, readmissions involved €181 053.83, or 37.3% of all

readmissions costs, and ranged between €1 049.2 and €43 983.4, with a median cost at €2 388.46. The first and the third quartile were respectively €1 922.80 and €4 469.95.

DRP preventability

The 123 DRP readmissions were analysed by the two independent evaluators. The analysis showed a good agreement between evaluators, with an observed kappa at 0.76 ± 0.056 (SD) (95% CI: 0.65-087).

After the analysis, nine DRP (7.3% of the total DRP) were considered as "avoidable" by both evaluators (**Table 31**), 56 "non-avoidable" and 35 "more information needed". Concerning the 23 remaining DRP, the evaluators did not agree about the classification.

"Non-avoidable" DRP included patients readmitted for pneumonia, infections and pulmonary embolism. The DRP classified in the category "more information needed" concerned, for the majority, neutropenia readmission.

Table 31: Avoidable DRP

Avoidable DRP	
DRP 1	Patient with renal failure readmitted for severe dehydration after Cisplatin toxicity
DRP 8	Patient readmitted for dehydration and acute renal failure related to drug toxicity
DRP 49	Type 1 diabetes readmitted for diabetic decompensation because of insulin pump problem
DRP 56	PAC infection after chemotherapy
DRP 57	Thrombosis
DRP 58	Stomach haemorrhage with tumour bleeding
DRP 59	Hypokalemia related to diuretics over-taking
DRP 89	Nausea and vomiting after chemotherapy session
DRP 96	Hyponatremia chronic renal failure because of furosemide and Aldactone combination

Concerning avoidable DRP detected, the major part involved drugs ADE. Medication review related to these DRP excluded comfort treatments such as prescribed anti-emetic agents or anti-diarrhoea drugs.

Avoidable readmission costs represented 5.6% (€27 938.61) of the total costs. The median amount for these readmissions was calculated at €1 823.86, with the first and the third quartiles at €1 344.04 and €3 753.08, respectively. The mutuality intervention amounted to €20 674.63, which represented 74% of the total amount. The median amount engaged by the mutuality was €1 560.40.

Among the total avoidable costs, the largest one concerned medical care costs. For this, the calculated amount was €15 696.23, which accounted for 56.2% of the total amount of these avoidable readmissions. The pharmaceutical cost was €4 166.79 and represented 14.9% of avoidable DRP readmission costs.

4.2.2.5 Discussion

DRP readmission, in this study, concerned a population over 60 y.o, who had a high comorbidity with a median Charslon Score at 7 and were polymedicated, with a median number of six drugs prescribed. In some studies, such as one described by Hauviller et al.[239] in France, a higher readmission for elderly cancer patients with a high Charlson score was found. They estimated that a cancer patient over 65 had a more than 7.69 risk of being readmitted for an ADE than a non-cancer patient. Our study detected that a large proportion of readmissions were linked to ADE (71.5%), particularly neutropenia, which represented 29.3% of all DRP readmissions. The average cost of all DRP readmissions was €4 031.46. However, considering the different health care amounts between different countries, a comparison requires prudence. Nevertheless, it can be interesting to evaluate the magnitude of the amounts. A study performed in United-States with breast cancer patients between 2009 and 2011 evaluated a mean cost of readmission at US$37,087[240]. In Netherland, a study from Leenderste et al.[149] amounted an average cost of €5461 related to medication-related hospital admission. The medical costs comprised all direct medical costs included in a readmission[149].

Even if range of amounts are different these costs related to ADE remain important and need to be reduced.

The high proportion of DRP readmission is well listed in the literature particularly ADE readmission, as in our study. Gallagher et al.[69, 227] targeted a paediatric population and included 847 readmissions whereas Carrasco Garrido et al.[228] targeted adults and included 350,835 readmissions. Both evaluated the ADE readmission in the general population, not only cancer patients[69, 227, 228]. Both studies highlighted that the largest proportion of ADE was linked to anti-neoplastic agents, even in the general population. These ADE represented a high proportion, 37% in the paediatric population and 75.8% for adults. As in our study, neutropenia, vomiting and diarrhoea were the most common causes of readmission. Gallagher et al. also exposed that 33% of ADE readmissions were avoidable, as in other studies[145, 241],which also showed a large part of avoidable readmissions (between 15% and 20%). In our study, 7.3% of DRP readmissions were considered as avoidable. The lowest proportion of preventability was probably linked to the neutropenia DRP classification. During the preventability analyses, to consider a neutropenia readmission as unavoidable, the patient's drug history had to contain a granulocyte-colony-stimulating growth factor (G-CSF). Under the reimbursement criteria in Belgium, only some patients were eligible in 2016 for a primary prophylaxis by G-CSF administration. This is because the eligibility was subject to specific criteria[233]. Eligibility depended on the type of cancer, the kind of chemotherapy, the dosage, the frequency of the treatment and the risk of having a neutropenia[233]. Nevertheless, the probability that the drug history was incomplete was not excluded. To avoid a misclassification attributing an avoidable readmission to an unavoidable cause, and the contrary, the evaluators preferred to classify a large proportion of neutropenia readmissions as "more information needed" when G-CSFs were absent in the drug history. The European Organisation for Research and Treatment of Cancer (EORTC) defined a neutropenia as when the absolute neutrophil count (ANC) is under 0.5 x 10^9/L or is a count of < 1.0 x 10^9/L that is predicted to fall to < 0.5 × 10^9/L within 48h, with fever or clinical signs of sepsis[242]. A "high risk" of neutropenia is defined as a 20% or more risk of neutropenia, and an "intermediate risk" is defined as a neutropenia risk between 10 and 20%[242]. The EORTC guidelines[242] in 2010 recommended a G-CSF prescription when a patient was at high risk. Considering that the information concerning patient risk of neutropenia was not available during data collection, it was complicated to determine whether studied

patients were at high risk or not and whether a G-CSF was necessary or not. The efficacy of G-CSFs is well known and has appeared in many studies[243-246] for many years. However, although administration of a G-CSF reduces risk of neutropenia, it does not do so not totally and some patients can still experience a neutropenia. Altwairgi et al.[247] evaluated primary prophylaxis with a G-CSF administration in an early-stage breast cancer. A significant difference was highlighted. Only 14% of patients suffered from neutropenia with a primary prophylaxis, which represented a 50% decrease in febrile neutropenia in comparison to the control group with a secondary prophylaxis (31%). In our study, neutropenia represented by 29.3% of readmissions and amounted to €181 053.83. Among these neutropenia readmissions, 86.1% were classified as "more information needed". The cost of these neutropenia readmissions was evaluated at €155 698.54, with a median amount at €2 388.46, and the first and the third quartiles at €1 922.80 and €4 469.95, respectively. It cannot be excluded that some of these patients could have avoided a neutropenia readmission with a G-CSF administration as a prophylaxis but it seemed complicated to quantify the savings considering the missing eligibility data. However, a cost-effectiveness study using a Markov model evaluated the different prophylaxes (primary and secondary) with different types of G-CSF. The evaluation concerned the early stages of breast cancer or non-Hodgkin lymphoma within the Belgian health care system[248]. The analyses were performed from the payer's perspective and integrated the direct costs as in our study. The different costs presented in this study dated from 2014 using the Belgian health index[248]. The results showed that a primary prophylaxis with pegfilgrastim could save €7 700 per febrile neutropenia avoided, and €7 800 per quality-adjusted life-year (QALY) for stage II breast cancer[248]. The costs could not be transposed to our study because our study included all cancer patients and the costs used dated from 2016 and a two-year costs update would be needed. Nevertheless, the presented saved costs[248] may be a good indicator of possible future savings per neutropenia in Belgium after a more usual prophylaxis.

Another recent Belgian study (2019), performed by *Van Ryckeghem et al*.[233], aimed to document the primary prophylaxis of G-CSF and to evaluate the adherence to EORTC guidelines of Belgian reimbursement criteria for breast cancer and non-Hodgkin lymphoma. The results showed that there is still a high need to continue to treat breast

cancer patients by primary prophylaxis. Moreover, it seems that about one quarter of their patients did not receive a primary prophylaxis even though they should have received one[233]. With our study population, it is possible that some patients should have received a prophylaxis but did not, resulting in a febrile or not febrile neutropenia readmission. Moreover, a neutropenia could be indirectly linked to other reasons of readmission, such as fever or signs of sepsis[233, 242]. Such a readmission might cost more than the evaluated amount. Apart the harm effects linked directly to a neutropenia, the relative dose intensity (RDI) could also be impacted by a suboptimal delivery of chemotherapy, which could affect long-term outcomes of the cancer and survival[248].

Strengths and limitations

The study was able to evaluate recent direct costs of DRP readmissions in two hospitals in Belgium. All cancers were included in the study, with a large share being lung, breast and haematological cancers. The largest costs concerned medical and paramedical care costs, followed by pharmaceutical costs, with different stratifications. The society perspective applied highlighted the impact of health care costs for cancer patients in Belgium. The inclusion of two hospitals with different care practices might be a good representation of Belgian care. Considering the different area of specialization, they did not follow the same patient management processes and the costs related are different[234].

Nonetheless, the study was subject to a disadvantage of all retrospective studies. Some data was missing in the patient files. Moreover, the patient risk of neutropenia was missing, which would have been useful information for evaluating the potential savings. Finally, considering the specific health care reimbursement system in Belgium, the different costs cannot be generalized.

It could be interesting to evaluate prospectively the costs and the improvement that could be linked to an increase in G-CSF prescription. An inter-professional collaboration of healthcare practitioners composed of doctors, nurses and pharmacists (clinical and community) could create a closer follow up with the patient to be aware concerning the possible ADE that could occur.

4.2.2.6 Conclusion

This study highlights an important health cost linked to DRP readmissions, particularly ADE readmissions such as neutropenia. Neutropenia direct costs remain high and require more attention to avoid supplementary costs, particularly concerning avoidable readmissions. Better adherence to EORTC guidelines could help to avoid these patient readmissions. However, more research is needed to evaluate the costs impact of cancer DRP readmission.

4.2.3 Drug-drug interactions in cancer patients readmitted 30 days after discharge

Abstract

Introduction

Cancer patients usually undergo heavy treatment and are consequently at a high risk of polypharmacy. This explains why drug-drug interactions remain a constant concern, although their clinical effects can be hard to evaluate since they might be masked by disease progression or disease symptoms. Besides chemotherapy interactions, other interactions can also be linked to patient weakening during cancer treatment.

Objectives

The aim of this study was to detect the drug-drug interactions in the cancer population from different sources, which were compared to highlight the prevalent interactions and assess the impact on the survival rate.

Methods

This study followed a 6-month observational retrospective study in two major care facilities in Brussels. Patients readmitted within 30 days after their last hospital care for a potential drug-related problem (DRP) were included. Interactions were analysed using Lexicomp® and Epocrates© databases. A Kaplan-Meier analysis and a Cox analysis were performed to evaluate the link between the interaction and death onset.

Results

The final population included 299 patients. According to data sources, between 78.9% and 80.9% of patients had at least one interaction. The means were 1.6 and 2.3 interactions per patient for respectively Lexicomp® and Epocrates®. Opioids (29.9%)

followed by anxiolytics (15.8%) were the drugs most often involved. The most predominant harm effects were central nervous system (CNS) and respiratory depressions. Kaplan-Meier analyses highlighted a difference between patients with and without interactions regarding death. Nevertheless, death seems not to be linked directly to the presence of an interaction.

Conclusion

Interactions are predominant in cancer patient treatment but do not seem to be linked to the onset of death.

Keywords

Belgium, Drug-Drug Interactions, Oncology, Hospital readmission, drug related problems.

Key points

- This study can help healthcare practitioners, such as physicians, pharmacists or nurses, to communicate better and to take care with potential drug-drug interactions.
- The highlighted interactions could help prescribers to pay more attention about usual treatment, and to pay more attention to herbs or other complementary substances combined with the chemotherapy.
- This study highlights the potential impact of interactions on the patient survival rate.

4.2.3.1 Introduction

The cancer population represents a vulnerable group of patients. This group has a higher risk of organ failure or altered metabolism due to the progression of their disease or malnutrition that can occur with chemotherapy. Some pharmacokinetic parameters are modified and can result in a reduced level of serum-binding proteins, oedema or hepatic and/or renal dysfunction[84]. The combination of these modifications and the narrow therapeutic window of cancer treatments or other ancillary treatments (comforts, adjuvants) can increase the risk of drug-related problems (DRP) such as adverse drug effects (ADE) or interactions[84]. Between 20-30% of all DRP are linked to drug interactions. In an elderly cancer population Yeoh et al. highlighted that more than 30%

of all DRP readmissions were related to ADE[249]. The occurrence of both kind of DRP can be clinically relevant, particularly in an elderly population[141, 250].

A drug interaction can be defined as "*when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or by some environmental chemical agent*". Drug-drug interactions (DDI) usually involve not just one mechanism but two or more acting at the same time. A DDI can occur during various steps, such as during drug absorption, distribution, metabolisation or drug elimination. In the same way, herbs or dietary supplements may also interact with drugs[172].To help healthcare providers some DDI screening systems report potential DDI detected in patient's medication with a different specificity and sensitivity (e.g. Lexicomp®, Epocrates® or Micromedex®)[251].

Cancer patients usually undergo heavy treatment (ancillary treatment, chemotherapy, support treatment) and are treated by many healthcare providers, consequently they are at a high risk of polypharmacy [226]. An increase in prescribed and taken drugs has resulted in a higher probability of drug interactions[252, 253]. In elderly patients, an estimate average of 11.5 drugs per patient was identified[254].This explains why drug interactions remain a constant concern, although their clinical impacts can be hard to evaluate since they might be masked by disease progression or disease symptoms[141].

Some studies have highlighted the interactions in cancer patients with a focus on chemotherapies interactions but without usual treatment evaluation. This study aimed to analyse all treatments taken by the patient (cancer treatments and other treatments such as ancillary or support treatment) to evaluate all the interactions that could harm or weaken patients.

4.2.3.2 Objectives

This study seeks to highlight the DDI in a cancer population, detected by different sources, to compare these sources, highlight prevalent interactions and assess the impact on survival rates.

4.2.3.3 Method

Study design

This study follows a previous study that aimed at identifying DRP readmissions 30 days after patient discharge (ref Article 2). The study was a retrospective, observational study of cancer patients readmitted into two Belgian care facilities between 1 January and 30 June 2016 within 30 days after discharge or after their last cancer treatment. This study involved two care facilities located in Brussels: an academic specialized oncology centre (160 clinical beds); and an academic general hospital (864 clinical beds). The protocol was reviewed and approved by the local ethics committees from both care facilities. An anonymization number was assigned to each patient to ensure confidentiality.

Patients

All eligible cancer (solid tumours or haematological cancers) patients readmitted for an unplanned event regarding their cancer or their oncology treatment during this 6-month period were included. Eligible patients were those readmitted from the emergency services or after physician consultation for at least 24 hours within 30 days after discharge or their last treatment, including cytotoxic agents, hormones and biological treatment. Patients were excluded when they were readmitted for reasons not related to cancer or its treatment (e.g. a car accident), when treated in two or more care facilities, when data were missing and if the patients were included in a clinical trial. Some patients were readmitted more than once during this 6-month period but only the first readmission was included[(234)].

Data collection

A patient list was transmitted to the investigator from the information technology (IT) department of the two care facilities[(234)]. In the general academic hospital, an initial screening process was carried out to exclude non-cancer patients. Several additional screenings were applied in the two hospitals and aimed to exclude non-cancer or non-treatment readmissions and readmissions occurring more than 30 days after discharge.

Patient data were registered in a form created in EpiInfo V 7.2. The form was composed of four different parts (demographic data, cancer data, medical and drug data, readmission data).

Medical history was analysed for each patient to calculate the age adjusted Charlson comorbidity index score[158, 161, 201, 202]. Patient's usual treatments were also evaluated. Usual treatment was numbered in order to evaluate the polypharmacy. According to the literature, polypharmacy can be defined in different manners. For this study, we considered polypharmacy when five or more drugs are prescribed.

DDI assessment

DDI evaluation was measured in two different manners, with Lexicomp®, Epocrates® and the interaction confirmation was performed with the Stockley's Drug Interactions book. Lexicomp® is an online database that classifies interaction levels using five degrees of severity. The **X** level indicates a combination to avoid, **D** suggests a therapy to consider and maybe to modify, **C** describes a therapy to monitor, **B** involves no action or modification in the treatment and finally **A** means "no interaction". For the statistical analysis, interaction levels were categorized into two categories, from A to B for the first category and from C to X for the second[168]. An interaction was considered as one to requiring care of from **C** to **X** levels.

The second evaluation used Epocrates© MultiCheck. The free online Epocrates© version is a web service used by healthcare professionals[169, 170]. Interactions are classified into five categories: "no interaction", "caution advised", "monitor/modify treatment", "avoid/use alternative" and "contraindication". Regarding Epocrates©, a DDI to consider was defined as one from the categories "monitor/modify treatment" to "contraindication".

The DDI were confirmed using the Stockley's, which can be considered as one of the best-known drug interaction information books (Pharmaceutical Press, 2013). For this study, the tenth edition was used to evaluate the different interactions found as it presents interactions in a more pharmacological way than previous versions[172]. The Stockley's enabled the detection of interactions between two drugs but did not enable a whole prescription to be checked with a severity level. Some interactions could not be found due to the indexing by drug classes and sub-classes that did not mention all the

drugs. The Stockley's also gives a reduced list of substrates, inductors and inhibitors of cytochromes, resulting in a limited range of evaluation of pharmacokinetic interactions[255]. Nevertheless, the Stockley's may often be helpful in confirming some interactions[171].

The two sources previously detailed were selected because they are well-known and well-positioned in terms of drug interaction categorization[256-258].

When a patient presented many interactions with several severities, only the highest severity was evaluated for the assessment of interactions.

Interaction sources comparison

Epocrates© was compared to Lexicomp® using a 0/1 rating (0 for disagreement, 1 for agreement). Each interaction was evaluated by both databases. The **C** level in Lexicomp® was associated with "monitor/modify treatment" in Epocrates©. The **D** level was compared to "avoid/use an alternative" and the **X** level to "contraindication". The **A** and **B** levels were considered as "non-interaction" levels and were compared respectively to the "no interaction" and "caution advised" levels in the Epocrates© database. The comparison included only the interaction of the highest severity when a patient presented more than one interaction.

Statistical and survival analysis

The statistical analyses performed were means, medians with quartiles and proportions for the identification of the interactions with the different sources. A Kaplan-Meier analysis was performed to evaluate the link between the type of interaction and death. A Cox analysis was also applied to evaluate the link between interactions and death, adjusted to some parameters.

For the statistical analysis, a patient was defined as having an interaction when Lexicomp® reported an interaction from C to X or when Epocrates© reported an interaction from "monitor/modify treatment" to "contraindication".

All analysis were made using SAS software version 9.4.

4.2.3.4 Results

Study population

A total of 3 107 patients were readmitted during the 6-month study period in both care facilities(234).

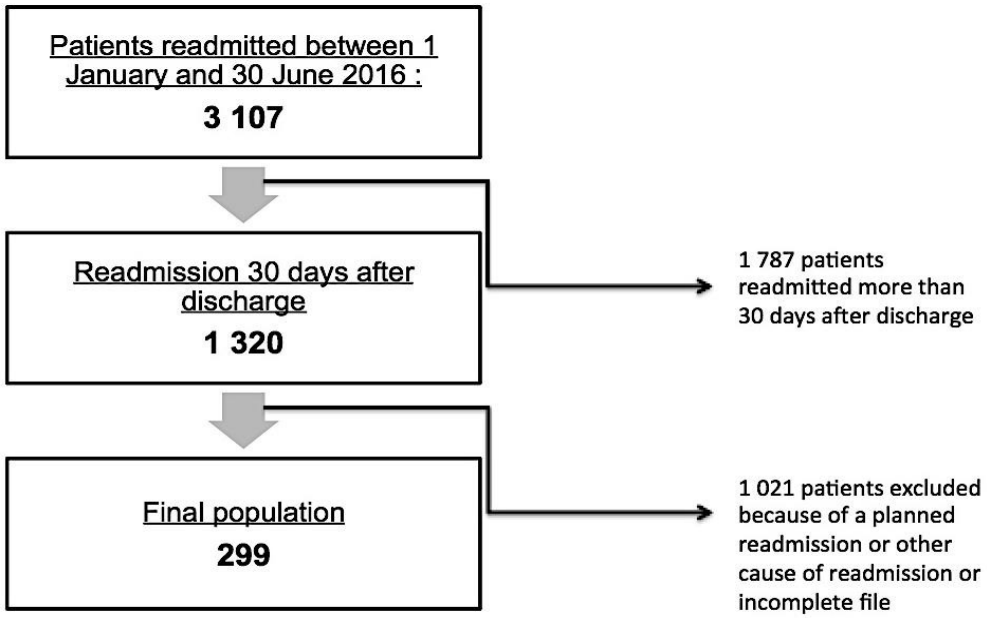

Figure 9: Cancer population readmitted 30 days after discharge

Several file reviews were carried out to exclude patients who did not present the inclusion criteria (**Figure 9**). The final study population included 299 patients. These patients were readmitted 30 days after discharge for their cancer or their treatment and were included in the study population. Patients aged from 50 or more composed a high share of the population (76.5%). The predominant cancers were lung and breast, both assessed at 17.7%. Polymedicated patients represented 65.5% of all the study population. All characteristics of the final population are summarized in **Table 32**.

Table 32: Characteritics of the studied population

Variables	Proportions
Number of patients	299 (100%)
Sex	
Male	161 (54%)
Female	138 (46%)
Age categories	
≥ 65 y.o.	122 (40.9%)
50-64 y.o.	106 (35.6%)
36-49 y.o.	53 (17.8%)
18-35 y.o.	17 (5.7%)
Alcohol consumption	
Never	162 (54.2%)
Occasional	92 (30.8%)
Regular	27 (9.0%)
No information	18 (6.0%)
Smoking status	
Non smoker	141 (49.1%)
Former smoker	95 (33.1%)
Smoker	51 (17.8%)
No information	12 (4.0%)
Solid tumour	262 (87%)
Haematological cancer	39 (13%)
Metastatic solid tumour	169 (59.3%)
Recurring cancer	
No	272 (91%)
Yes	27 (9%)

Surgery	
Yes	154 (51.5%)
No	145 (48.5%)
Type of cancer	
Lung	53 (17.7%)
Breast	53 (17.7%)
Gastrointestinal	42 (14%)
Lymphoma	21 (7%)
Leukaemia	18 (6%)
Pancreas	15 (5%)
Bladder	11 (3.7%)
Prostate	8 (2.7%)
Uterine	8 (2.7%)
Cerebral	8 (2.7%)
Other*	62 (20.7%)
Charlson index	
0-3	30 (10%)
4-6	76 (25.4%)
≥ *7*	193 (64.6%)
Polymedicated patients (> 5 drugs)	196 (65.6%)

DDI assessment

The Lexicomp® analysis highlighted a total of 488 DDI. Among the 299 patients included in the study population, 236 (78.9%) were concerned by these interactions. The proportions of interactions among the population are presented in **Table 33**.

The range of DDI was between 0 and 14 and included C, D and X interactions. A mean of 1.6 and a median of 1 DDI per patient were calculated. The first quartile and third

quartile were evaluated respectively at 1 and 2 DDI. The proportions and percentages of each kind of interaction are summarized in **Table 33.**

The predominant DDI level (59.6%) was **D**, which involved a therapy to consider or maybe modify. The interaction **X** represented 7.2% of DDI and involved a drug combination to avoid.

Table 33: Proportion of interactions for both data sources

Sources	Kind of Interaction	Proportion	Number of patients (%)
Lexicomp	**C**	162 (33.2%)	79 (26.4%)
	D	291 (59.6%)	129 (43.1%)
	X	35 (7.2%)	28 (9.4%)
	Total	**488 (100%)**	**236 (78.9%)**
Epocrates	**Monitor/modify treatment**	340 (49.3%)	110 (36.8%)
	Avoid/use an alternative	346 (50.1%)	129 (43.1%)
	Contraindication	4 (0.6%)	3 (1%)
	Total	**690 (100%)**	**242 (80.9%)**

Concerning the Epocrates© assessment, a total of 690 DDI were detected in 242 (80.9%) patients among the study population, with 0-19 DDI per patient.

A mean of 2.3 and a median of 1 DDI per patient were calculated. The first and the third quartiles were respectively 1 and 3 DDI per patient. The category “avoid/use an alternative” was the largest category of DDI (50.1%) in the Epocrates© evaluation. The next category, “monitor/modify treatment”, was shown to be a large proportion, with a percentage of 49.3%. For 3 patients, a total of 4 DDI were found for a “contraindicated” association.

A deeper analysis of recurrent interactions selected from the 488 interactions in Lexicomp® highlighted drug categories frequently involved, such as opioids. A total of 326 interactions (**D** and **X** interactions in Lexicomp®) were analysed and compared with the Epocrates© analysis. Some of these interactions are summarized in **Table 34.**

Table 34: Predominant and important interactions detected by Lexicomp® and compared Epocrates© levels

Drug-drug Interactions	Indications	Interaction	Lexicomp®	Epocrates©
Benzodiazepines	Cancer-related anxiety and depression	Additive CNS and respiratory system depressant effects	D	Avoid/use alternative
Anti-depressant drugs	Pain			
Opioids				
Beta-blockers	Anxiety related symptoms	Bronchodilatary depressant effects	X	Avoid/use alternative
Beta-2-mimetics	Respiratory symptoms of cancer			
Domperidone (gastroprokinetic) -	Nausea	Inhibition of CYP3A4 by aprepitant, leading to increased blood levels of domperidone and associated side effects	X	Avoid/use alternative
Aprepitant (NK1 receptor antagoniste)				
SSRI	Anxiety/depression	Increased QT interval	D	Monitor/modify
Metoclopramide	Nausea			
Aprepitant	Nausea	Inhibition of CYP3A4 by aprepitant, which increases corticosteroid blood levels and associated side effects	D	Monitor/modify
Corticosteroids	Anti-inflammatory			
SSRI[a]	Anxiety Depression	Additive anti-coagulant effects	D	Avoid/use alternative
NSAID[b]	Pain			
Calcium	Bone demineralization	Decrease in corticoid activity	D	Monitor/modify
Corticosteroids	Anti-inflammatory			
Opioids	Pain	Additive CNS depressant effects	D	Avoid/use alternative
Anti-H1 drugs	Allergy			
SSRI	Anxiety/depression	Inhibition of CYP2C19 by PPIs, leading to increase in blood SSRI levels and risk of QT prolongation	D	Monitor/modify
PPI[c]	Acid reflux			
Neurokinin (NK) 1 receptor antagonist	Nausea	CYP 3A4 inhibition by NK1 receptor antagonist, leading to increase in blood doxorubicin levels (and hepatic toxicity)	D	Avoid/use alternative
Doxorubicin	Cancer therapy			

[a] SSRI : Selective serotonin reuptake inhibitor
[b] NSAIDs : Nonsteroidal Anti-inflammatory Drugs
[c] PPI : Pomp proton inhibitor

Opioids represented 29.9% of the drugs involved in these interactions. The effects regularly linked to these drug combinations were central nervous system (CNS) and respiratory system depressions or a decrease of the analgesic effect. Anxiolytics (15.8%), anti-depressants (6.4%) and anti-epileptics (6.3%) represented, with opioids, the largest share of drugs linked to the interactions analysed. Other combinations to avoid were highlighted, such as the prescription of beta-2-mimetics and beta-blockers, which represented 1.8% of the interactions. The association between long-acting muscarinic agents (LAMA) or long-acting beta-adrenoceptor agonists (LABA) and short-acting muscarinic antagonists (SAMA) or short-acting beta-agonists (SABA) was classified as an **X** interaction by Lexicomp® and was detected in 1.5%.

Interaction sources comparison

The comparison did not evaluate the number of interactions per patient but only the capability to detect the DDI and its severity to classify it. Consequently, the difference in number of interactions between Epocrates© (690) and Lexicomp® (488) was not included in the analysis and only the strongest interaction per patient was considered.

Epocrates© agreed with the Lexicomp® classification in 57.2% of cases, including interactions and non-interactions. There was agreement on 171 patients among the studied population of 299 patients. The distribution of agreement is presented in **Table 35**.

Table 35: Interaction levels agreement between both sources

Interactions	Number of patients	%
A/B - No interaction/caution	30	10.0%
C - Monitor/modify treatment	48	16.1%
D - Avoid/use alternative	91	30.4%
X – Contraindication	2	0.7%
Total	**171**	**57.2%**

Disagreements were observed between both sources for severities of interactions, for 36 patients, who were classified at **D** level with Lexicomp® and "monitor/modify" with Epocrates©.

Nevertheless, a substantial quantity of disagreement between Epocrates© and Lexicomp® was observed between the "no interaction" and the "interaction" levels. A total of 21 patients were classified as having no interactions with Lexicomp® and interactions in Epocrates©. Conversely, Lexicomp® classified 15 patients as patients with an interaction that Epocrates© did not detect.

Survival analysis

A Kaplan-Meier analysis was performed to assess the impact of the interactions on death. For this analysis, the Lexicomp® assessment was selected, because of its better evaluation in the literature. The "interaction" group included patients with interactions type **C, D** or **X** and the "non-interaction" group the other patients, with **A** and **B** levels. For each patient, only one of the interactions was included in the analysis. Considering that some patients had different levels of interaction detected, if a patient had five interactions **C** and two **D**, the patient was considered as a patient **D**.

The analysis assessed the impact of interactions one year after the detection. Results showed that the presence of an interaction is statistically significant ($p < 0.05$) for the onset of death over time, using the log-rank test. The Kaplan-Meier curves highlighted that the “interaction” patient group had a higher risk of death than the “non-interaction” patient group **(Figure 10)**. Time to death at the first quartile was at 25 days post interaction-detection for the “interaction” group and 150 days for the “non-interaction” group. Consequently, the median time to death for a patient with an interaction was evaluated at 128 days post detection while the median time to death for a patient without an interaction was assessed at 260 days.

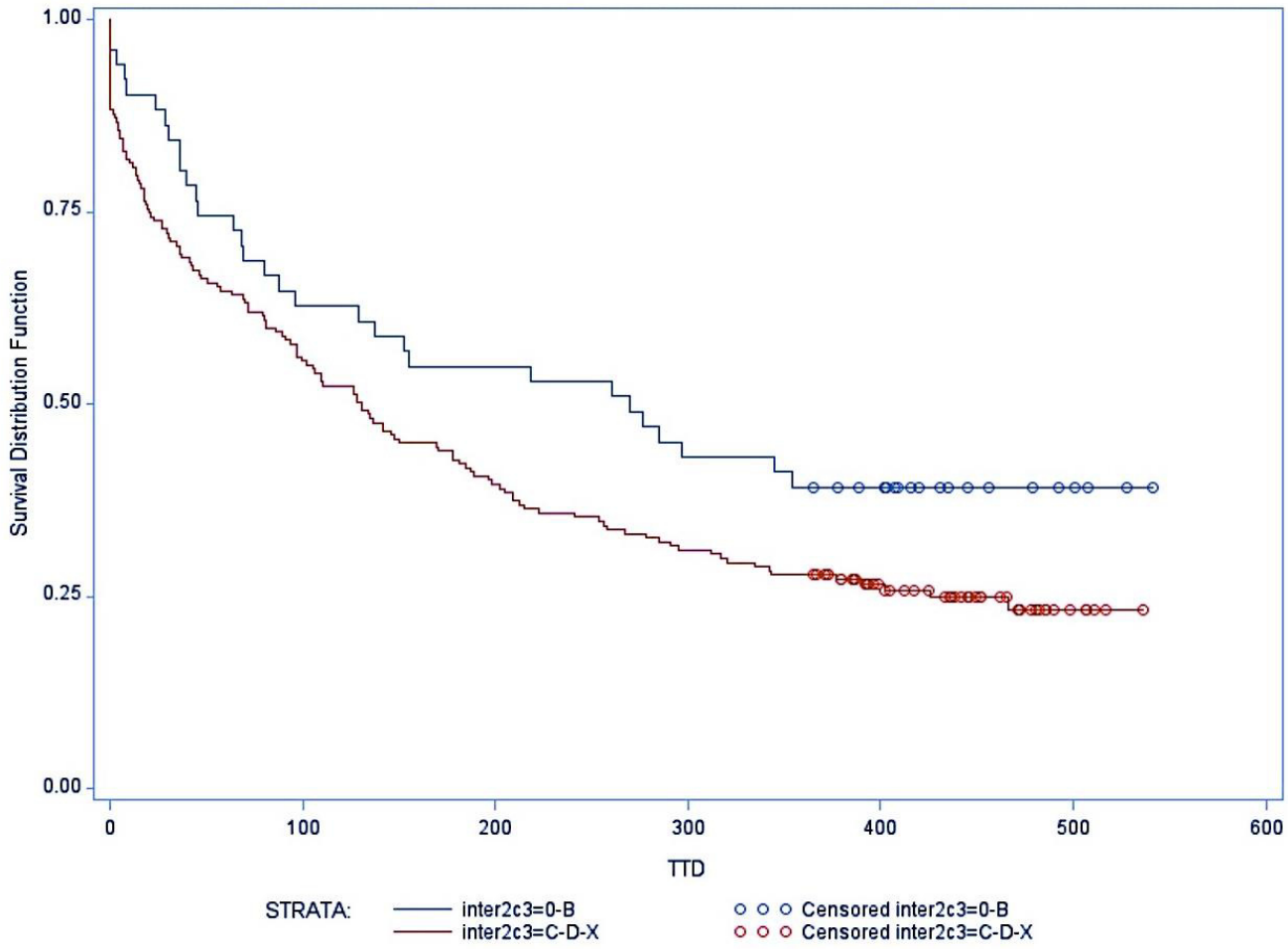

Figure 10: Kaplan-Meier Kurves[4]

Another analysis was carried out, with long-term follow up (three years after the interaction detection). This revealed that this difference strongly decreased over long-term follow-up. Interactions were no longer significant after long-term follow-up.

A Cox analysis was performed to evaluate the impact of some parameters on the relation between interactions and death. Parameters that were included in the analysis were age, gender, kind of chemotherapies, number of chemotherapies included in the treatment and the age adjusted Charlson Score. Only the comorbidity parameter was

[4] TTD : Time to death

significant and eliminated the significance of the interaction variable in the regression model **(Table 36)**.

Table 36:Cox model significance

Variable	Chi-square	P	Hazard ratio	Confidence interval at 95%
Interactions	**3.2511**	**0.0714**	**1.43**	**0.97-2.12**
age adjusted Charlson Score	5.0189	0.0251	1.59	1.06-2.39

The age adjusted Charlson Score remained the only statistically significant (<0.05) variable in the model. Analyses to check the interaction between these two variables were performed and no interaction was detected.

4.2.3.5 Discussion

Study population

The final population included 299 patients and was composed essentially of polymedicated patients (65.5%) aged 50 and over with an age adjusted Charlson Score of 7 or more (64.6%). Between 78.9% to 80.9% of the population suffered from at least one interaction. As found in our study, some studies highlighted that polypharmacy associated with a higher comorbidity and patient age are highly linked to potential DDI[259, 260].

DDI Assessment

DDI had to be evaluated using two sources, detailed above. The analyses with Lexicomp® and Epocrates© revealed, respectively, 488 and 690 interactions, which represented the presence of an interaction in 78.9% to 80.9% of the study population, respectively. This high percentage of interaction has been regularly found in the literature for many years. A 1996 study highlighted 82% of DDI in 205 patients with 7 or more drugs taken[261]. Another study confirmed the high proportion of DDI and detected

63% of DDI in hospitalized cancer patients[138]. A more recent study, including 525 patients in Slovenia, detected a DDI in about 84% of patients with cardiovascular disease. The cardiovascular system was the most affected by DDI[262].

In our study, the major share of detected DDI concerned drugs that affect the CNS, such as opioids, anxiolytics, anti-epileptics or anti-depressants. Most of these drugs are usually prescribed to cancer patients to support them during the disease period. This is because cancer patients are usually subject to multiple symptoms such as depression, anorexia, weight loss, insomnia and anxiety[263]. Opioids are usually prescribed to relieve moderate to severe pain[264], such as psychotropic drugs (antidepressant and anxiolytics)[265] in some cases. Besides the effect on pain, psychotropics are prescribed to cancer patients for major emotional distress linked to the disease[266, 267]. However, these drug category interactions can lead to CNS depression when two or more of these drugs acting in the CNS are prescribed together. CNS and respiratory system depressions were the most recurrent effects from the detected interactions. They represented 55.8% of all interactions. This high proportion of DDI leading to CNS and respiratory depressions was highlighted in different studies in the Netherlands[139, 268, 269], with some DDI defined as potentially relevant[268]. The analysis revealed other kinds of combination that can affect patients. Among these are the combination of beta-2-mimetics with beta-blockers, which produces a decrease in the bronchodilatory effect[170]. This DDI was not quantitatively important (1.8%) but should not be associated because of the total contraindication in patients where beta-2-mimetic are indicated[257] .

Interaction sources comparison

A high proportion of interactions/non-interactions was detected by Lexicomp® and Epocrates©. Nevertheless, some pharmaceutical products were not found in both sources despite the use of International Nonproprietary Names (INN). Only a few drugs were not included in Lexicomp® but more than 20 drugs or drugs combination were not included in Epocrates©. Moreover, in a study that compared many interaction detection sources[251], Lexicomp® showed better results in term of sensitivity and negative predictive value than Epocrates©. Besides Epocrates© seems to be more alarmist than Lexicomp® considering some interaction detection. These findings combined to the

findings of the other studies[251, 270] led to the use of the Lexicomp® results for the survival analyses.

Survival analysis

The Kaplan-Meier model highlighted a potential link between the presence of an interaction and death. Nevertheless, this impact seemed to be short-term. Indeed in a long-term follow-up, the difference between populations with an interaction and without an interaction decreased and was no longer significant. It might be related to a direct effect of the interaction and not a long term effect.

A Cox analysis was performed to evaluate the potential impact of other variables on death potentially related to the interactions. The other variables included the age, the type of cancer, the stage of cancer, the kind chemotherapy or the age adjusted Charlson Score. Only the age adjusted Charlson Score excluded the interaction variable from the model. This can be explained by the aim of the score to be able to predict patient survival. It can also be explained by the fact that it includes all comorbidity evaluation parameters that are directly linked to death onset. This possibility implies that the interaction could be a confusion bias. The interaction variable may be indirectly related to death in this population, especially because a high comorbidity is directly linked to polypharmacy that could lead to a DDI[47].

Strengths and limitations of the study

This study seems to be the first study that evaluates interactions between cancer treatments and all other prescribed or over the counter (OTC) drugs in cancer patients at their hospital readmission in Belgium. The participation of two large care facilities in Brussels allowed the analysis of a large number of patient files. Interactions were evaluated with well-known sources with good specificity and sensitivity. This evaluation highlighted an important proportion of interactions, such as CNS interactions, that can be considered as potentially relevant to avoid patient harm. The statistical analysis revealed the potential indirect link between interactions and death onset.

Nevertheless, the retrospective study design had some limitations, such as missing drugs from patient files (all OTC and herbal drugs) or incomplete prescribed drug history, which could be linked to an underestimation of interactions. Moreover, the time of taking the drugs was not always mentioned and could have led to an overestimation

of some interactions. Furthermore, some drugs might have been missing during the analysis, which could have led to an underestimation of the proportion of DDI.

4.2.3.6 Conclusion

This study highlighted some interactions and the potential link to death. However, more studies are necessary to establish a clear link between these factors, including the impact of comorbidities. It could be interesting to evaluate the context prospectively with a regular follow-up in cancer patients with a healthcare team, such as therapeutic drug monitoring (TDM) in cancer patients [(268)], to prevent or avoid these interactions. Nonetheless, the creation of an international database that could evaluate the interactions with a large number of OTC, herbs and food would be highly helpful for patient safety.

5. Discussion

5.1 Drug-related problem in community pharmacies

5.1.1 Summary of major results and literature comparison

The aim of this first part was to adapt, validate and use the PCNE DRP classification tool (V6.2) for the Belgian community pharmacy setting.

The adaptation allowed the inclusion of specific criteria and the clarification of some criteria that were poorly understood. These modifications led to a better understanding of DRP by Belgian pharmacists.

Concerning the performed content validation, a good content validity and a high inter-rater reliability were highlighted. Indeed, a good agreement between evaluators was observed, with more than 80% agreement. Nevertheless, some notions remained unclear despite the previous modifications and sometimes led to wrong coding of DRP during the daily use step.

The daily use step highlighted that pharmacists were not fully compliant with the instruction manual. This led to unclear DRP, which were eliminated for the inter-rater reliability step. As presented in the results, some sections were not completed at all. This might be due to a lack of time or the large number of items and possibly the lack of supplementary information in the tool. In 18% of cases, the patient information section was not completed and for 9% of DRP, the problem was not classified at all. These sections might have been considered as unnecessary for classifying a DRP and therefore not completed to save time. The time needed to code a DRP was, for 62% of cases, five minutes or less as showed in the literature with Pi-Doc tool[186]. This can be considered as acceptable in some conditions but not necessarily when the pharmacist has many patients in the pharmacy. This limitation was also discussed by Krähenbühl and al., who proposed that time barrier was the main limitation to the documentation process for pharmacists. They also highlighted the persistence of this limitation as pharmacies received no incentive programme, such as financial or human aid in documentation.

The inter-rater reliability step exposed different levels of consistency. Consequently, adding clearer instructions for the number of items to tick in each section could be

added to avoid a large number of items being ticked. This should be explained in the manual as well as in the classification tool to decrease these discrepancies and make the tool more usable in daily practice. Moreover, the “Interventions” had a medium consistency, which could be the result of an omission by pharmacists. Indeed, counselling is a common practice but some pharmacists may not consider it as a real intervention when a more important intervention is applied (e.g. drug change) and might forget to code it.

The next project was the application of the Belgian adapted classification PCNE v6.2 tool in Belgian community pharmacies. It allowed to a total of 15 952 DRP coded during the five-month study period. The non-cancer-related chronic pain DRP collected concerned more than 10% (1 832) of all DRP collected. The most frequent DRP collected was “incomplete prescription” and represented 41% of all DRP. This DRP was related for the major part to a missing time to take medication, posology or dosage. The drugs most involved were analgesics, including opioids, other analgesics and anti-migraine preparations. The “incomplete prescription” item also included prescriptions without a physician signature or other administrative data and was sometimes related to the identification of a false prescription. Pain drugs remain a societal problem, particularly opioids. Currently, in the United States, an opioid epidemic is observed, with an increase in opioid abuse, misuse and death related to opioid consumption that has required government action[271, 272].

The other important share of DRP (21%) concerned drug interactions or drug duplication. The most involved ATC code was M01 (NSAIDS and anti-rheumatics), at 60.3%. Even if the anti-inflammatories are, for the most part, under prescription, some are delivered without prescription and are easy to obtain because they are OTC drugs. This easy access is not without harmful effects for patients, such as DDI, drug-disease interactions or ADE[273-275]. These DRP are usually related to the patient condition, such as with kidney problems or heart problems, and the medication associated with these health problems[275, 276]. The involvement of M01 drugs in DRP has been presented in many studies, such as the study by Wu et al.[277]. They presented the potential issues related to this drug category in a cohort of 308 patients treated for kidney disease. They highlighted the relation between the DRP and the high medication intake that may result

from severe pain. A patient suffering from severe chronic pain was more than 3 times at risk of a DRP than one suffering mild pain[277]. NSAID drugs (M01) could be related to serious patient harm such as severe gastric and kidney ADE, as previously cited. This is particularly so in the absence of drug intake advice and if management practices are not applied correctly[278-280]. Even if the predominant proportion involved M01 drugs in these DRP, the N02 drugs remain important too and strongly involved in DRP. Currently, these drug categories are involved in many ADE. Paracetamol (N02) is the most frequently used drug in different stages of pain, but can nevertheless be the source of extensive liver damage when treatments are not supervised[281, 282].

After detection, pharmacists performed a total of 2 864 interventions that aimed to solve the DRP. On average, 1.6 interventions were provided. A Swiss study highlighted community pharmacists' intervention with the PharmDISC system and evaluated a mean of 1.2 interventions per pharmacist. The difference in number of interventions may be related to the type of interventions listed on the PharmDISC system tool. The Belgium-adapted PCNE v6.2 treated oral complementary information as separate from written information, as in the original version of the PCNE v6.2, whereas the PharmDISC considered these two interventions as one intervention (clarify/complete information), which could have decreased the number of interventions. The most important intervention performed was "providing verbal information" (32%) followed by "providing written information" (17%). These two interventions aimed to complete information about drug intake but were not necessarily provided together. Another study, by Schneider et al.[283] used the original version of the PCNE classification, in Germany, and also highlighted an important proportion (22%) of "written information" interventions but few (1.5%) for "oral information". Pharmacists solved a larger share of DRP (78.6%) than in our study. The pharmacists considered that a total of 68.7% of DRP were totally solved and 22.5% had an "other" issue. The "other" issues were generally related to problems such as administrative problems or those that needed the physician, who was unreachable up to the end of the day, and resulted in more time being needed to investigate and to solve the DRP.

To keep a daily use application, the PCNE group worked regularly on the classification to improve it and update it. The latest published update was V8.03[284], in which various

changes were integrated. Many items were modified to be more understandable, with clearer items or sections, and easier to complete, by reducing the number of items. Compared to our translated and validated tool, this change will avoid some discrepancies[181]. However, this new classification does not give more information about how to differentiate a manifest and a potential problem, which will result in the same kind of discrepancies[181].

Compared to the previous classifications, a Swiss tool, the Pharmacists' Documentation of Interventions in Seamless Care (PharmDISC)[57], was developed for community pharmacists. This has a special focus on the pharmacist's interventions. This tool construction helps to decrease the risk of misclassification in the "problem" category by defining a manifest problem as "reactive" and a potential problem as "preventive" in the registration tool[59]. Addition of this supplementary information in the classification could be a solution to avoid some misclassifications. It could help to improve the inter-rater reliability of the classification.

5.1.2 Strengths and limitations

During this validation study, the adapted classification tool seemed to be suitable for community pharmacists to classify and document DRP. The French translation and the adaptation to the Belgian context make it more accessible. Its validation had the advantage of ensuring that each encountered DRP can be correctly described by pharmacists through the proposed items. This validated classification tool had a good acceptance by pharmacists and seemed useful to highlight the involvement of pharmacists in their patients' treatment.

However, there were some limitations in the tool application and the study design detailed above in the Chapter IV.

The second project involved a study population who was spread around Belgium, including Wallonia and Flanders, which was representative of the population in Belgium and increased the external validity of the study. The study included a large sample of pharmacies with different practices, which highlighted the usability of the classification.

Moreover, validation over the counter and a posteriori allowed double-checking to avoid any potential omission of a DRP. Indeed, more information could be accessed a posteriori compared to over the counter.

As already demonstrated, this tool could be a very useful tool for better clinical practice in community pharmacies[189].

However, the main limitation of this study was the unit of measurement, the DRP. Consequently, no data about patient medical condition or patient treatment were included. Hence it was impossible to evaluate each DRP according to the patient medical condition or the treatment type. It could be relevant to document DRP according to the patient condition instead of only documenting the DRP unit.

5.2 Drug-related problem in hospital

5.2.1 Summary of major results and literature comparison

5.2.1.1 Evaluation and analysis of drug-related problems in cancer patients readmitted to two Belgian care facilities within 30 days after discharge

This 6-month retrospective study identified 1 320 cancer patients readmitted into two care facilities within 30 days after discharge. About 10% of these patients were potentially readmitted for a DRP. These DRP were related to ADE, for the major part (96%) for interactions, prescription problems or wrong drug intake. These ADE were mostly related to “old” chemotherapy treatments such as vinca-alkaloid preparations (e.g. vinblastine, vincristine), platinum preparations (e.g. cisplatin, carboplatin), anthracycline preparations (e.g. doxorubicin, epirubicin), podophyllotoxin derivatives (e.g. etoposide) and pyrimidine analogues (e.g. fluorouracil, gemcitabine).

A logistic regression allowed researchers to highlight 4 of the 5 previously cited chemotherapy categories as risk factors for DRP readmission. These “old” oncologic treatments, such as vincristine or cisplatin, seemed to be related to more DRP readmissions, particularly ADE readmission, than the “newest” treatments, such as biological treatments or immunotherapy. Moreover, the proportion of patients over 50

y.o. was high (76.5%) and this population is known to suffer more from ADE in these treatments than younger patients[206, 207]. The DRP rate can also be related to the high toxicity[208, 209] of each of these "old" chemotherapies, which are involved in many chemotherapy combinations in order to improve efficacy. To solve this problem, researchers are looking for new drug delivery systems to minimize their toxicity. Developments of controlled-release cisplatin dry powders for inhalation or the emergence of nanomedicines can be a future opportunity to develop new combinations with less patient harm[110, 210]. Furthermore, new treatments are not totally without ADE. In fact, a meta-analysis in 2012 highlighted that, depending on the patient's health condition, the balance between toxicity and efficacy seemed less favourable for some patients. These treatments seemed to increase the patient morbidity and the treatment-related mortality[285]. This could explain why a large proportion of our study patients were still being treated with "old" oncologic treatment. Considering the high burden of cancer around the world, some new oncological treatments, such as biological treatments, seemed to have obtained marketing authorization faster than the "older" chemotherapies[211]. Consequently, many ADE are presently hard to recognize or not yet well known due to their absence from drug leaflets. Some studies and reviews focusing on these "new" treatments have highlighted and summarized the ADE related to these treatments to help DRP detection and prevention[212-214].

While chemotherapy DRP represented the largest part of the evaluated readmissions, a small part involved other drugs included in the patient's usual treatment, to which it would be interesting to pay attention. A total of seven DRP (8.6%) involved antiplatelet and anti-coagulant drugs. Cancer patients are more at risk of thrombosis, which could be related directly to the cancer condition or related to some cancer treatments (lenalidomide, thalidomide)[215]. They also highlighted other commonly prescribed drug categories that are potentially linked to ADE and/or readmissions.

The next highlighted risk factor was the kind of hospital. The care organization of the two care facilities involved in the study is substantially related to the number of patients they treat. The emergency unit of a general academic hospital usually accommodates more patients than an academic cancer centre. Indeed, during the study period, in the general academic hospital, 18 953 patients (cancer and non-cancer) went to the emergency

service and 4 275 (22.5%) of them were readmitted. Considering the various pathologies, less than a quarter of these readmissions concerned cancer patients, whereas they concerned 98.3% of the 2 920 patients who came into the specialized cancer centre during the study period. The size of the care facility and the variety of medical specialties are related to the number of readmissions and may increase this number, which was confirmed by *Brown et al*.[193]. They highlighted that a large care facility, associated with an increase in medical fields, can lead to an increase in physicians and drug prescriptions, which can result in higher readmissions[193].

Moreover, the difference in patient management can inevitably increase patient readmissions significantly. Corresponding to the large difference in the number of patients visiting the emergency service and the cancer centre, the care of patients on arrival is conducted differently. In the specialized cancer centre, all incoming patients with a neutropenia were not readmitted directly. They usually were readmitted directly in the general academic hospital, which may have increased significantly the number of readmissions. *Legramante et al*.[218] highlighted this difference in care by implementing an emergency department with a cancer pathway for three months in an academic hospital. They observed a significant decrease in patient readmissions after the implementation of this new cancer pathway.

The age-adjusted Charlson comorbidity index score was another highlighted risk factor. A low score seemed to be related to DRP readmission. Concerning the study population, an index between 1 and 2 was mostly related to DRP readmission. These patients may be under less surveillance than those with higher score and are more subject to a DRP readmission.

Polypharmacy was the last risk factor highlighted as related to a DRP readmission. The presence of a large quantity of drugs is obviously related to more drug problems and the increase in DRP readmission[203, 204]. The increase in comorbidities, especially in elderly patients (≥ 65 y.o.), is leading to many drug prescriptions[219]. Self-medication or CAM taken by cancer patients [220] can also be a source of DRP sometimes unknown[221].

5.2.1.2 Drug-related problems readmission cost in two Belgian hospitals: Is it avoidable?

Most of the final population analysed were over 60 y.o., with a high comorbidity (median Charlson score at 7) and polypharmacy (median 6 drugs prescribed). *Hauviller et al.*[239], estimated that a cancer patient over 65 had more than 7.69 greater risk of being readmitted for an ADE than a non-cancer patient. Our study showed that a large proportion of readmissions were linked to ADE (71.5%), particularly neutropenia, which represented 29.3% of all DRP readmissions. The average cost of DRP readmission was €4 031.46. In the Netherlands, *Leenderste et al*.[149] evaluated that an average amount of €5 461 was related to each preventable medication-related hospital admission[149]. In the United States, health care costs are completely different and are higher than in Europe. Nevertheless, it is interesting to estimate an amount or DRP cost. An average cost for a patient with a breast cancer DRP readmission amounted to US$37 087[240]. Even though the ranges of amount are different and must be interpreted with caution, these ADE-related costs remain high and could be reduced.

In our study, the ADE appeared higher than the other DRP. Among them, neutropenia was highly involved. Neutropenia remains one of the severe complications of cancer treatment and can result in other DRP, such as pneumonia, infection, fever or sepsis[233, 242, 286].

Large shares of avoidable readmissions were listed in different studies and were ranged between 15% and 20%[145, 241]. Concerning our study, only 7.3% of DRP readmissions were considered as avoidable. This lowest proportion was probably related to the neutropenia preventability classification. To consider a neutropenia readmission as unavoidable, the patient's drug history had to contain a granulocyte-colony-stimulating growth factor (G-CSF). Under the Belgian reimbursement system, only a few patients were eligible in 2016 for a primary prophylaxis by G-CSF administration [233]. The probability that the drug history was incomplete was not excluded. To be cautious, the evaluators preferred to classify a large proportion of neutropenia readmissions as "more information needed" when G-CSFs were absent in the drug history. The efficacy of G-CSFs is well known and has appeared in many studies[243-246] for many years.

However, although administration of a G-CSF reduces risk of neutropenia, it may be insufficient and some patients can still experience a neutropenia. Nevertheless, only 14% of patients suffered from neutropenia with a primary prophylaxis. In our study, neutropenia was represented by 29.3% of readmissions and amounted to €181 053.83 of costs. Among these neutropenia readmissions, 86.1% were classified as "more information needed". The cost of these neutropenia readmissions was evaluated at €155 698.54, with a median amount at €2 388.46 and the first and the third quartiles at €1 922.80 and €4 469.95, respectively. It cannot be excluded that some of these patients could have avoided a neutropenia readmission with a G-CSF administration as a prophylaxis, but it seemed complicated to quantify the savings considering the missing eligibility data.

Moreover, *Cupp et al.* [286] evaluated that more than 50% of neutropenic patients may be subject to an infection and more than 13% to a sepsis. Consequently, it is not excluded that some infections or sepsis were misclassified as non-avoidable, leading to an under estimation of avoidable DRP readmissions and the costs related to them.

However, a cost-effectiveness study using a Markov model evaluated the different prophylaxis (primary and secondary) with different types of G-CSF. The results showed that a primary prophylaxis with pegfilgrastim could save €7 700 per febrile neutropenia avoided and €7 800 per quality-adjusted life-year (QALY) for stage II breast cancer[248]. The costs could not be transposed to our study because of it included all cancers and because the costs applied in our study dated from 2016 and a two-year costs update would be needed. Nevertheless, the presented saved costs[248] may be a good indicator of possible future savings per neutropenia in Belgium after a more usual prophylaxis.

According to a recent study performed by *Van Ryckeghem et al.*[233], it is not excluded that some patients in our study population should have received a prophylaxis but did not, resulting in a febrile or non-febrile neutropenia readmission.

5.2.1.3 Potential drug-drug interactions in cancer patients readmitted 30 days after discharge

The aim of this study was to evaluate the potential DDI among the cancer population from a previous part. The population included 299 patients and was composed

essentially of polymedicated patients (65.5%) aged 50 and over with an age adjusted Charlson score of 7 or more (64.6%). Between 78.9% and 80.9% of the population suffered from at least one interaction. As found in our study, some studies highlighted that polypharmacy associated with a higher comorbidity and patient age are highly linked to potential DDI[259, 260].

DDI had to be evaluated using two of the sources detailed above. The analyses with Lexicomp® and Epocrates© revealed, respectively, 488 and 690 interactions. This high percentage of interaction has been regularly found in the literature concerning cancer patients for many years [84, 141].

The major share of potential DDI in our study concerned drugs that affect the CNS, such as opioids, anxiolytics, anti-epileptics or anti-depressants. Most of these drugs are usually prescribed to cancer patients to support them during the disease period. This is because cancer patients are usually subject to multiple symptoms such as depression, anorexia, weight loss, insomnia and anxiety[263]. Opioids are usually prescribed to relieve moderate to severe pain[264], such as psychotropics (antidepressant and anxiolytics)[265] in some cases. Besides the effect on pain, psychotropics are prescribed to cancer patients for major emotional distress linked to the disease[266, 267]. However, these drug category interactions can lead to CNS depression when two or more of these drugs acting in the CNS are prescribed together. CNS and respiratory system depressions were the most recurrent effects from the detected interactions. They represented 55.8% of all interactions. This high proportion of DDI leading to CNS and respiratory depressions was highlighted in different studies in the Netherlands[139, 268, 269], with some DDI defined as potentially relevant[268]. The analysis revealed other kind of combinations that can affect patients. Among these, was the combination of beta-2-mimetics with beta-blockers, which produces a decrease in the bronchodilatory effect[170]. This DDI was not quantitatively important (1.8%) but should not be associated because of the total contraindication in patients where beta-2-mimetic are indicated[257].

The exponential increase in oncology treatments may likely be related to a growth in DDI that can result in patient readmissions[287]. Some drugs regularly prescribed in cancer treatments may interact directly with tumors, such as anti-coagulants, which can lead to tumor bleeding or prolongation of a QT segment[288].

Others kind of interactions that may lead to patient harm were detailed in the literature but not analysed in our study, considering its retrospective nature. Nevertheless, these interactions, such as drug-disease, drug-food or drug-herbal interactions, deserve particular attention.

A potential link was identified between DDI presence and death by the Kaplan-Meier analysis. Nevertheless, this relation decreased in the Cox analysis due to the inclusion of the Charlson score. Considering the relation between the Charlson score and death, it appears obvious that it has more influence than the DDI. Nevertheless a high comorbidity is usually related to a large polypharmacy, which can lead to DDI and an increase in death risk[289].

5.2.2 Strengths and limitations

5.2.2.1 Evaluation and analysis of drug-related problems in cancer patients readmitted to two Belgian care facilities within 30 days after discharge

This study allowed the identification of some risk factors concerning a DRP readmission in cancer patients. The aim was to give particular attention to patients who presented some of these factors. The large group of patients, with different age groups, different kinds of cancers and oncology treatments, allowed the highlighting of risk factors for a large population and not only a specific cancer or age group. The analysis of the files of all patients readmitted for their cancer or treatment within 30 days after their discharge during the 6-month study period decreased the selection bias. Moreover, the inclusion of two care facilities allowed the inclusion of patients who, while nearly all from the Brussels area, were also from all towns around, including patients from Flanders and Wallonia. This resulted in a better external validity of the study. The type 2B patient medication review involving several physicians from different fields, associated with access to medical files, permitted a complete evaluation of each patient.

However, regarding the ethics committees, patient evaluations were only performed by local expert committees. This may result in a bias, with an overestimation or underestimation of DRP detection because of differences in clinical judgment. To limit this bias, the participating practitioners usually had similar backgrounds. The study also

has known common weaknesses of retrospective studies, such as incomplete files associated with an incomplete medical and medication history or wrong coding due to the different users of the patient files[222, 223]. We excluded patient files judged to be incomplete, leading to a potential underestimation of DRP readmissions.

5.2.2.2 *Drug-related problems readmission cost in two Belgian hospitals: Is it avoidable?*

The study was able to evaluate recent direct costs of DRP readmissions in two hospitals in Belgium. All cancers were included in the study, with a large share being lung, breast and haematological cancers. The largest costs concerned medical and paramedical care costs, followed by pharmaceutical costs, with different stratifications. The society perspective used highlighted the impact of health care costs for cancer patients in Belgium. The inclusion of two hospitals with different care practices might be a good representation of Belgian care. Considering the different area of specialization, they did not follow the same patient management processes and the costs related are different[237].

Nonetheless, the study was subject to a disadvantage of all retrospective studies. Some data was missing in the patient files. Moreover, the patient risk of neutropenia was missing, which would have been useful information for evaluating the potential savings. Finally, considering the specific health care reimbursement system in Belgium, the different costs cannot be generalized.

5.2.2.3 *Potential drug-drug interactions in cancer patients readmitted 30 days after discharge*

This study seems to be the first study to evaluate interactions between cancer treatments and all other prescribed or OTC drugs in cancer patients at their hospital readmission in Belgium. The participation of two large care facilities in Brussels allowed the analysis of a large number of patient files. Interactions were evaluated with well-known sources with good specificity and sensitivity. This evaluation highlighted an important proportion of interactions, such as CNS interactions, that can be considered

as potentially relevant to avoid patient harm. The statistical analysis revealed the potential indirect link between interactions and death onset.

Nevertheless, the retrospective study design had some limitations, such as missing drugs from patient files (all OTC and herbal drugs), which could be linked to an underestimation of interactions. Moreover, the time of taking the drugs was not always mentioned and could have led to an overestimation of some interactions. Furthermore, some drugs were missing during the analysis, which could lead to underestimation of the proportion of DDI.

5.3 General Discussion

This thesis work exposed the DRP problematic in two aspects of pharmacy practice: in community pharmacies and in hospital. These projects can lead to identify some limitations on which it will be beneficial to work on for practice and patient's follow up. DRP occurrence remains high, both in hospital and in community pharmacies, and affects particularly a more fragile population such as cancer patients. The evolution of science and the emergence of new treatments are pushing towards an improvement of pharmaceutical care in order to support patients in a more effective way.

In Belgium, studies and pharmaceutical care improvement in hospital context are very present and may lead to implement some cares in a national level. However, in community pharmacies more collaborations with Universities are necessary in order to improve pharmaceutical care and put on pharmacist's value such as in the study performed in the first part of this work. Considering current drug market, including pharmacies inside the supermarket (in France) or drug shopping on internet, community pharmacists should demonstrate their added value and their knowledge on drugs and on pharmaceutical care to remain closer to their patients as a primary care practitioner.

The first part of this thesis highlighted the added value of community pharmacists and their capability to detect, classify and resolve DRP after many interventions. The use of this tool helped pharmacists to detail DRP detected and to follow a clear pattern of resolution provided by the classification domains and subdomains. Moreover, this classification objectified the number of interventions performed by the pharmacists that were previously done unconsciously and without any type of record. These kind of

studies can provide an important database for research and can lead to identify some barriers in daily practice..

Hospital context offers some facilities to perform pharmaceutical care studies considering the number of patients and the accessibility of archived files. As exposed above, several studies in different Belgian hospital were conducted in order to improve clinical pharmacy and patient quality of life. However, only a few focused on cancer patients DRP and potential costs related to these DRP in Belgium.

This part of the thesis allowed to identify patients that can be at risk for DRP potentially leading to a readmission. This kind of study allowed to describe the epidemiology, the magnitude of cancer patients DRP and to identify the potential needs for patient's quality of life improvement.

Participating hospital healthcare practitioners expressed their wishes to include more regular inter-professional meetings and more pharmacists during patients' follow up.

Nevertheless, in community pharmacies as in hospitals, some barriers appeared in daily practice, leading to development and implementation of new strategies.

Some barriers were common in both settings interfering with an optimal daily practice.

The main barrier identified was the lack of communication between healthcare practitioners resulting on incomplete identification or resolution of DRP. Some patients' relevant information was missing, such as the medical history or the actual reason leading to the drug prescription, particularly in community pharmacies. Besides, "pharmacies shopping" and "doctor shopping" increase risk to a potential interaction, drug redundancy or contraindication not detectable by the principal pharmacist or the hospital healthcare practitioners.

Even if this kind of barriers is less important on hospital grounds thanks to patients' files and the medical electronic prescription, the need to implement a regular communication is needed.

Some strategies were implemented in Belgium to decrease the effect of these situations such as the reference pharmacist in community pharmacies who is aware about the patients' condition and treatment. However, some patients are reluctant to this process (limit of the privacy and freedom to choose any pharmacy). Another strategy is progressively implemented (Ehealth) in order to create communication between hospital

and community healthcare professionals. This platform includes health patients' information, drug prescribed and all medical exams.

Besides the strategies mentioned above, pharmacists' participation may help to find optimal tools as interaction checkers and/ or a DRP classification. The inclusion of these databases in hospital software or community pharmacist's software may improve drug monitoring and patient follow up. A specific interaction tool for patients at risk of DRP as cancer patients may be useful to manage potential DDI occurrence. Liverpool University associated to the Radboud UMC implemented a website for this kind of interactions[284].

The creation of a communication channel between all healthcare professionals can optimize drug monitoring during the different phases of the treatment (treatment tolerance, adherence, efficacy and ADE). This collaboration may lead to provide some complete patient's recommendations for OTC or herbs use during heavy treatments and avoid harm effects that decrease patient quality of life.

6. Conclusion and Perspectives

For many decades, DRP detection, intervention and resolution has become one of the main concerns in pharmaceutical care practice in hospital as well as in community pharmacies. Moreover, the large risk of DRP in cancer population remains an important issue that may lead to an unplanned readmission and includes a large healthcare team.
This thesis has studied DRP detection, its proportion and its impact in community pharmacies and in hospitals.
The first part of this work comprised the translation and the validation of the PCNE v6.2 DRP classification for Belgian daily use and the application of the Belgian adaptation of the PCNE v6.2 classification in a pilot study for Belgian pharmacies with a special focus on pain DRP.
The application of the PCNE classification in the daily use software could assist in documenting DRP to avoid unexpected outcomes that could compromise treatments[178]. Moreover, an evaluation linked to patient medical condition could give more information about the prevalence of DRP and could help to link a kind of DRP with a specific medical condition. Access by pharmacists to patient's medical data could improve the relation between all healthcare practitioners and put the patient at the centre of this collaboration.

This part allowed a tool to be validated and applied in Belgian community pharmacies, which highlighted the barriers in daily use practice and perspectives to improve pharmaceutical care in community pharmacies.
The second part studied DRP in oncologic patients. It evaluated the: proportion of (1) DRP readmissions within 30 days after discharge; (2) DRP readmission costs and preventability and (3) potential interactions in oncologic patients readmitted 30 days after discharge.
The results recognized the importance of paying more attention to cancer patient medication, especially for patients presenting certain risk factors such as the presence of "old" chemotherapies in the treatment, polypharmacy or a low Charlson score among Belgian cancer patients.
These results can provide information concerning reflection on the collaboration between different care practitioners (physicians from different fields, clinical pharmacists, community pharmacists, etc.) to improve cancer patient care and

pharmacovigilance around these “old” and “new” drugs. It could be interesting to include more pharmacists (community and clinical) during the follow-up to notify ADE more regularly or to detect some unknown ADE[224]. The establishment of interventions to improve health literacy, such as patient education, patient medication reconciliation and regular follow-up, could help to reduce DRP. The evaluation of the possible DRP readmission for patients treated by immunotherapy could be interesting and may highlight the potential ADE and/or readmission related to these treatments. Moreover, a prospective study would also be very interesting and would aim to have complete patient information such as the kind of self-medication, the proportion and the different variety of CAM (e.g. herbs, nutriments or vitamins).

It could be interesting to evaluate prospectively the costs and the improvement that could be linked to an increase in G-CSF prescription. An inter-professional collaboration of healthcare practitioners composed of doctors, nurses and pharmacists (clinical and community) could create a closer follow-up with the patient to be aware of the possible ADE that could occur and save costs related to treat these ADE.

Analyses of potential DDI with a larger population of cancer patients in a prospective manner can be very informative. The prospective approach may lead to have a complete review of all drugs taken, including OTC medicines, herbal medicines and food supplements. The engagement of a multidisciplinary team in this kind of research may improve communication and help to detect drug associations that can result in patient harm.

Moreover, the high probability of finding a potential interaction required more caution from healthcare professionals. To be more careful about all medication prescribed and other medication such as CAM, an easier communication channel may be helpful. Indeed, the implementation of a patient-centred follow-up that includes healthcare practitioners, both on hospital grounds and outside (GPs, pharmacist, physiotherapist or home healthcare nurse), and patients may result in better communication. Besides, all practitioners would be aware of all medication or CAM taken by the patient, which would result in better prevention of or faster intervention in a DRP. Some studies showed the important place that community pharmacists can have concerning cancer patients. A

study evaluated the benefits of community pharmacist involvement for cancer patients by evaluating patient adherence to their oral chemotherapy. The results identified a significant lack of knowledge concerning when to take the treatment and potential ADE related to it[291].

The role of the pharmacist in the healthcare team for better patient follow-up is widely recognized in the literature and may lead to some savings[54, 78, 80, 149, 292]. Our results showed a high cost related to ADE, particularly to neutropenia. Even if conclusions on their preventability required more information, attention to patient characteristics and risk factors may result in fewer readmissions and greater cost savings.

This work demonstrated a large presence of DRP in both community pharmacies and hospital. Community pharmacists are willing to improve their practice. Nevertheless, a more specific tool for community pharmacies may be more effective and may lead to a better practice.

The second part of this work detailed some interesting risk factors and the large presence of interactions among cancer patients to consider in order to decrease potential DRP readmissions and the costs related to them. However, an improvement in communication between patients and healthcare professionals inside the hospital context and outside (including community pharmacists and physicians) may lead to better follow-up and a potential decrease in these readmissions. The main objective of this collaboration remains to improve the patient's quality of life and knowledge about his pathology and treatment.

Some additional training for community pharmacists in some clinical fields may be necessary for more complete care. This training can lead to better results that should result in the promotion of pharmacists' autonomy[293, 294]. The combination of these perspectives may lead to patient sensitization about pharmaceutical care but also greater confidence in and acceptance of their pharmacists.

However, it seems important to continue research on patient pharmaceutical care to improve and optimize it for the future. The research may include academic researcher team in collaboration with practitioners and maybe pharmaceutical companies in order to improve patient condition, quality of life and healthcare practitioner's collaboration.

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8. Supplementary Material :

Supplementary Material 1: Belgian Adaptation of the PCNE tool V6.2

Part	Section	Item(s)	Modifications	Other information
General information	/	/	Added	To collect patient descriptive information
"Problems"	Treatment efficacy	Wrong drug effect	Removed	
	Adverse event	Toxic adverse event	Removed	
	Other problem	Non-classifiable DRP	Added	
"Causes"	Drug choice	No available alternative	Added	
	Drug use	Drug abuse/addiction	Added	
	Logistic and administrative causes	Medical device not available	Added	
		Reimbursement criteria not met	Added	
		Illegible prescription	Added	
		Incomplete prescription	Added	
		Forged prescription	Added	
		Drug to the wrong patient	Added	
	Cause linked to patient	Doubt, fear about the medication	Added	
		Drug intake influenced by perception and religion	Added	
		Life style conflicting with drug intake	Added	
		Many physicians consulted	Added	
Intervention	Prescriber level	An intervention was proposed and refused by the prescriber	Divided into two items	1: with a justification 2: without a justification
Results	Not solved	Not solved because no intervention	Added	

Supplementary Material 2: Pharmacists' evaluation of the manual and the DRP classification tool (n=15)

	Criteria	Elements	Level 1	Level 2	Level 3	Level 4	Total %	ICV-I
MANUAL	Clarity	Aim of the classification	6.5 (1)	0	54 (8)	39.5 (6)	100 (15)	0.9
		DRP definition	0	0	39.5 (6)	60.5 (9)	100 (15)	1
		DRP registration formulary description	0	0	20 (3)	80 (12)	100 (15)	1
		Definition of "manifest problem"	0	20 (3)	33 (5)	46.7 (7)	100 (15)	0.8
		Definition of "potential problem"	0	6.5 (1)	46.7 (7)	46.7 (7)	100 (15)	0.9
		Elements in the chapter "DRP Classification"	0	0	85.7 (13)	14.3 (2)	100 (15)	1
		Elements in the section "DRP Cause(s)"	0	0	46.7 (7)	54 (8)	100 (15)	0.9
		Elements in the section "Intervention Classification"	0	0	39.5 (6)	60.5 (9)	100 (15)	1
		Examples in the section "DRP Classification"	0	0	39.5 (6)	60.5 (9)	100 (15)	1
		Examples in the section "DRP Cause(s)"	0	6.5 (1)	26.5 (4)	67 (10)	100 (15)	0.9
		Examples in the section "Intervention Classification"	0	0	39.5 (6)	60.5 (9)	100 (15)	1
	Helpfulness	Examples in the section "DRP Classification"	0	0	33 (5)	67 (10)	100 (15)	1
		Examples in the "DRP Cause(s)"	0	0	33 (5)	67 (10)	100 (15)	0.9
		Examples in the section "Intervention Classification"	0	6.5 (1)	33 (5)	60.5 (9)	100 (15)	0.9
		S-CVI						0.9
REGISTRATION FORM	Representativeness	Elements in the section "DRP Classification"	0	0	60.5 (9)	39.5 (6)	100 (15)	1
		Elements in the section "DRP Cause(s)"	0	0	26.5 (4)	73.5 (11)	100 (15)	1
		Elements in the section "Intervention Classification"	0	0	33 (5)	67 (10)	100 (15)	1
		Elements in the section "Intervention Result"	0	6.5 (1)	33 (5)	60.5 (9)	100 (15)	0.9
	Logical design	Elements in the section "DRP Classification"	0	0	67 (10)	33 (5)	100 (15)	1
		Elements in the section "DRP Cause(s)"	0	0	60.5 (9)	39.5 (6)	100 (15)	1
		Elements in the section "Intervention Classification"	0	0	60.5 (9)	39.5 (6)	100 (15)	1
		Elements in the section " Intervention Result"	0	0	60.5 (9)	39.5 (6)	100 (15)	1
	Completeness	Elements in the section "DRP Classification"	0	0	39.5 (6)	60.5 (9)	100 (15)	1
		Elements in the section "RP Cause(s)"	0	0	26.5 (4)	73.5 (11)	100 (15)	1
		Elements in the section "Intervention Classification"	0	0	26.5 (4)	73.5 (11)	100 (15)	1
		Elements in the section "Intervention Result"	0	0	39.5 (6)	60.5 (9)	100 (15)	1
	Uniqueness	Elements in the section "DRP Classification"	0	0	26.5 (4)	73.5 (11)	100 (15)	1
		Elements in the section "DRP Cause(s)"	0	0	39.5 (6)	60.5 (9)	100 (15)	1

	Elements in the section "Intervention Classification"	**0**	**0**	**20.5 (3)**	**79.5 (12)**	**100 (15)**	**1**
	Elements in the section "Intervention Result"	**0**	**0**	**26.5 (4)**	**73.5 (11)**	**100 (15)**	**1**
	S-CVI						**0.99**