PLATINUM ANTICANCER DRUG SHORTAGES

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I declare that this MPhil thesis on platinum anticancer drug shortages submission is my own work and to the best of my knowledge it contains no material previously written or published by other authors, and no material that has been accepted or used for the award of any degree or diploma at The University of Sydney, or any other institution, except where otherwise indicated, I also hereby declare that the intellectual content of this thesis is the produced by my own work.

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Abrar F. Arbaeen
July 2019

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Abbreviations

ASP	Average-Sales-Price
ASHP	American Society of Health-System Pharmacists
API	Active Pharmaceutical Ingredient
CRGH	Concord Repatriation General Hospital
GPO	Group Purchasing Organization
EML	Essential Medicines List
FDA	Food and Drug Administration
ISMP	Institute for Safe Medication Practices
WHO	World Health Organization
UUDIS	University of Utah Drug Information Service
EMA	European Medicines Agency
EU	European Union
US	United States/United States of America
CNS	Central Nervous System
RCT	Research Corporation Technology
UICC	Union for International Cancer Control
NDA	New Drug Application
DIS	Drug Information Service
TGA	Therapeutic Goods Administration (Australia)
ICR	Institute of Cancer Research
Crcl	Creatinine Clearances
AMH	Australian Medicines Handbook
PBS	Pharmaceutical Benefits Scheme
5-FU/LV	5-fluorouracil, leucovorin

Abstract

The platinum-based chemotherapy drugs cisplatin, carboplatin, and oxaliplatin remain, despite their long-term use, as integral components in the treatment of more than 25 different human cancers. As such, shortages in their supply can have serious health and societal impacts on both the outcome and welfare of patients and on the healthcare systems as a whole. As all three drugs are no longer under patent protection, they are supplied in Australia, the U.S. and the U.K. by between four and 17 different pharmaceutical companies, which reduces the risk of drug shortages. Determining the number and impact of platinum drug shortages in various regions of the world is difficult because legislation to monitor shortages has only been passed recently. All three drugs have suffered from shortages since 2017 with the most common shortage being due to discontinuation of the drug by the company. Other causes include production disruptions, changes in customer demand, problems in supply such as transport and storages, and other reasons. The median duration of drug shortage is 22 days (shortest and longest supply shortages are 3 and 79 days, respectively). Shortages appear to be rare in developed western countries and western European countries, but more common in eastern European countries where platinum drugs are never available or are available only half of the time. This project highlights the lack of information available on platinum drug shortages and the end to further examine platinum drug shortages in regions that are more likely to be impacted, such as Africa, south-east Asia, central and southern America, and the Middle East.

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I dedicate this thesis to my God, thank you for your guidance, strength, powerful, protection, skills and for giving me a good healthy life. All of these, we offer to you.

Thank you all, for always being with me.

Chapter One

Introduction

1.1. Drug shortages

Drug shortages remain a significant problem throughout the world with many health agencies and regulatory bodies, such as the U.S. Food and Drug Administration (FDA), the American Society of Health System Pharmacists (ASHP), Health Canada, the Therapeutic Goods Administration (TGA) in Australia, and the Institute for Safe Medication Practices (ISMP), stating that drug shortages are a chronic and critical problem.[1-3]

However, there is no consensus on the definition of the term *drug shortage*. The ASHP defines a drug shortage as "a supply problem affecting how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers use an alternative agent".[2,4] Alternatively, the U.S. FDA defines a drug shortage as when "demand, or projected demand, for a medically necessary drug in the United States exceeds it is supply".[1] In Australia, the TGA defines a medicine shortages as "when the supply of a medicine is not likely to meet the normal or projected consumer demand for the medicine within Australia for a period of time".

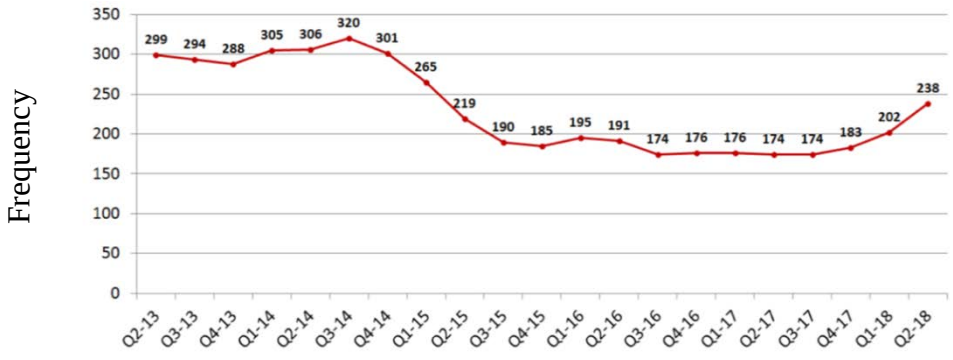

Figure 1. Total drug shortages in the USA between 2013 and 2018 as reported by the UUDIS.[5]

There is clear evidence that over the last decade the incidence of drug shortages has remained significantly high (Figure 1).[2,6,7] The number of drug shortages identified by the University of the Utah Health Information Service (UUDIS) over the last five years indicates that there has been between 174 and 320 shortages of medicines in any given quarter,[5,8] and for the most recent report period (mid-2018) there were 238 reported shortages.[5]

The situation in European Union (EU) countries is similar. Between 2010 and 2013, 671 drugs were listed as being in short supply in seven EU countries.[9] In November 2018, the European Association of Hospital Pharmacists reported that 38 EU countries experienced a drug shortage and that those shortages arose on a daily or weekly basis.[10]

1.2. Reasons for drug shortages

The root causes of drug shortages are complicated and can involve many factors at different points of the supply chain. These include: manufacturing issues, regulatory and legislative issues, business and market factors, distribution factors, supply and demand issues, natural disasters, inventory issues, and human factors.[9,11-13] Additionally, each of these factors can be influenced by a number of subfactors. An example of a subfactor in a manufacturing supply problem is the necessity of manufacturing multiple medicines on a single piece of equipment. In this case, there is only limited time available to manufacture and formulate each drug and the prioritisation of one drug other another can result in a shortage of the latter drug.

Based on the information provided by the UUDIS in 2018, the cause of almost 50% of all drug shortages are unknown (Figure 2). The next most common cause of shortages is due to manufacturing problems and the discontinuation of drugs.[5]

An example of a drug that was discontinued is the modified release misoprosol pessary. The TGA reported in April 2019 that, Ferring Pharmaceuticals Pty Limited would be discontinuing the medication, and that their assessment on patient impact was that it would be "critical". The TGA defines a critical impact as "where a shortage of a reportable medicine is automatically considered to have a critical patient impact". Critical patient impacts can be life threating as is the case of unexpected heparin shortages for post-surgical patients.

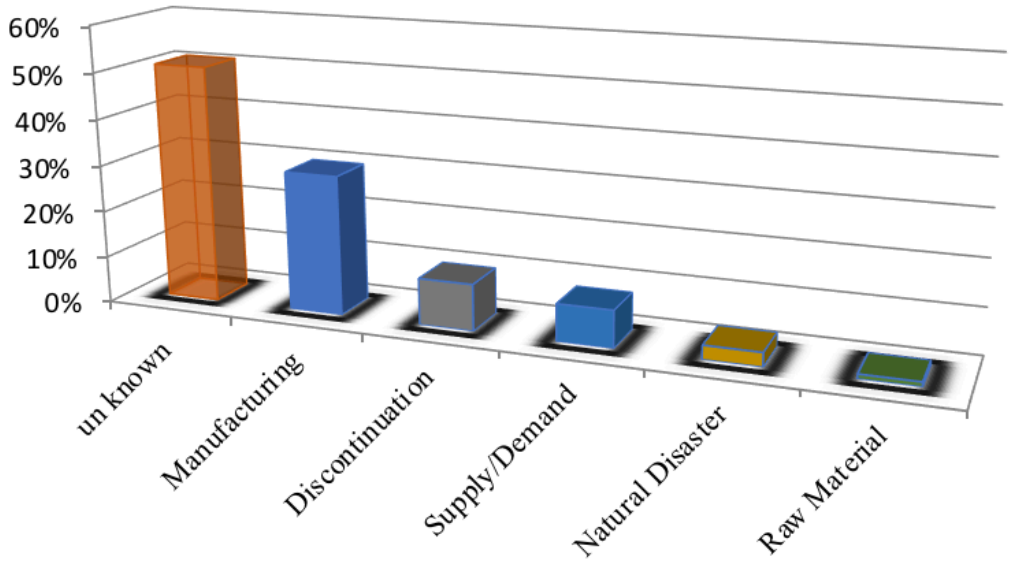

Figure 2. Sources of drug shortages in 2018 as reported by the UUDIS.[5]

It is important to also note that drug shortages tend to affect generic drugs more than they affect brand name medicines. The reason for this is that, generally, generics produce smaller profit margins for companies when compared to brand name medications, and so less effort is given to ensure their supply. According to a 2004 survey on the availability of drugs by the Jordanian FDA, the median availability of generic medications surveyed in the public sector for originator brands was only 27%.[14] In a similar survey conducted in 2018, it was found

that 77% of Europeans have experienced drug shortages caused by a lack of generic medication supply.[10] There are also differences in drug shortages when patients are treated in public versus private facilities. The availability of the same drugs in the private sector has been found to be higher when compared with public facilities, with median availabilities of 60% and 80%, for both generic drugs and brand drugs, respectively.[14]

1.3. Reporting of drug shortages

Although most countries have laws that make reporting of drug shortages mandatory, including Australia, how drug shortages are reported varies considerably between countries and regions; there are different rules for reporting shortages in the US, Europe, Canada, and Australia. Interestingly, Australian data contains more information about shortages when compared with the USA or Canada, whereas the lowest level of online data is available for Europe (Table 1).

Table 1. Drug shortage management systems in the EU, USA, Canada, and Australia.

Country	Institution	Type of reporting	Notes
EU	EMA	Searchable database List of nationally authorized medicinal products	Independent Management Board, network organization.
USA	FDA	Searchable database FDASIA.	
	ASHP		Information is available via mobile phones applications.
Canada	Health Canada	Shortage overview on Website, details for each drug.	address drug shortage for every 24-72 hours.
Australia	TGA	Searchable database including specific criteria.	Drug shortages report are not legally by Health Canada not maintain binding, and the reasons for shortages not always listed. Reasons for shortages are always listed.

While companies could voluntarily report drug shortages in Australia for many years, doing so only became mandatory at the beginning of 2019 with the passing of the Therapeutic Goods Amendment (2018 Measures No 1.) Bill. This legislation provides a nation-wide way to manage and communicate medicines shortages through the TGA in an effort to improve patient outcomes.

When appropriate, manufacturers are required to notify the US FDA or TGA 12 months in advance when they plan to discontinue a specific medicine. In all other instances, a minimum of six months is required, and if that is not possible, then a shortage must be reported as soon as practicable, but never later than five business days after a discontinuation or interruption in manufacturing. The laws require companies to report the expected duration of the shortage, the estimated time frame until supply returns to normal, and a reason for the shortage. For shortages of over the counter medications the sponsors must tell the TGA about the drug shortages within 2-10 business days.

1.4. Chemotherapy drugs

Chemotherapy is a term used to describe the treatment of cancer with drugs. As the number of cancer patients increases each year, the demand for chemotherapy drugs has also increased.[5] The World Health Organization (WHO) has reported that more than 9.6 million people around the world died from cancer in 2018.[15] In Australia, the Cancer Council expects that by 2040, the number of cancer patients living with, or surviving, the disease will increase to almost 1.9 million.[16]

There are many different classes of chemotherapy drugs and many drugs within each category. Examples include the antimetabolites (5-fluorouracil and methotrexate), the anthracyclines (doxorubicin and daunorubicin), the alkylating agents (carmustine), taxols (paclitaxel and docetaxel), the vinca alkaloids (vinblastine and vincristine), and the platinums (cisplatin, carboplatin, and oxaliplatin). Chemotherapy drugs are usually used in combination to produce higher efficacy compared with monotherapy. They can also be used either before (adjuvant) or after (neoadjuvant) surgery or radiation therapy.

1.5. Shortage of chemotherapy drugs

Over 65% of hospitalised patients receive some form of chemotherapy as part of their cancer therapy;[17] therefore, any shortage in chemotherapy drugs can have an impact on cancer patients. From data provided by the UUDIS, the percentage of chemotherapy drug shortages almost doubled between 2013 and 2017,[5] which is an on-going concern in health care.[18,19] When compared to other classes of essential medicines, such as antibiotics, cardiovascular medications, antimicrobials, and central nervous system (CNS) drugs, the incidence of chemotherapy drug shortages is relatively low. For CNS drugs, there were 36 reported shortages in 2018 in the USA for both injectable and non-injectable drugs, but the rate for chemotherapy drugs was half that value (Figure 3).[5]

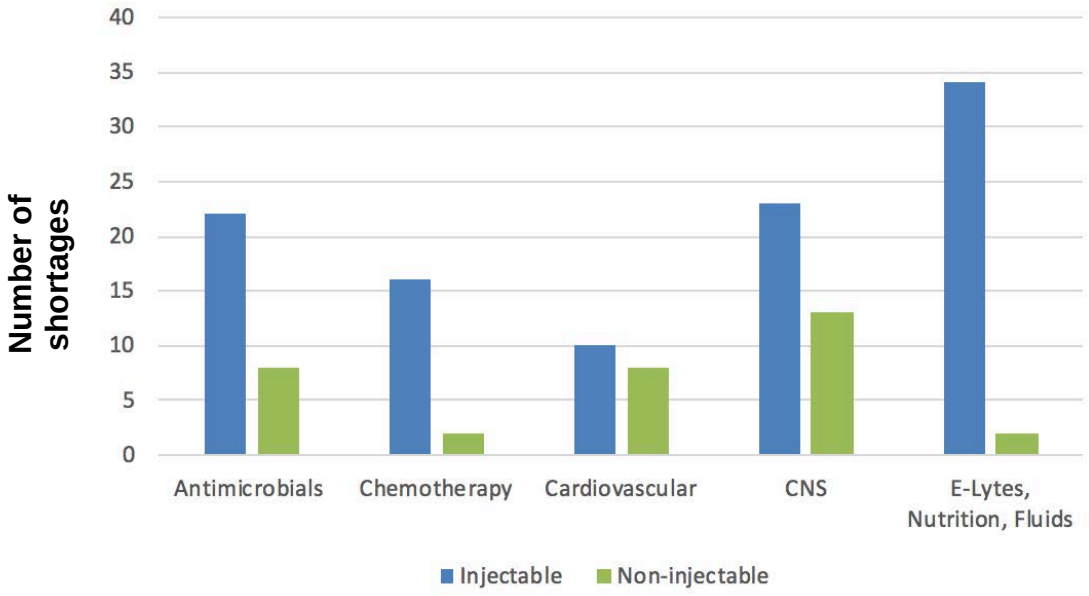

Figure 3. USA shortages by drug class in 2018 as reported by the UUDIS.[5]

Cancer drugs that have only a small number of manufacturing suppliers are at a higher risk of shortages than medications with more than five suppliers, although the relationship between the number of drug suppliers and shortages is not linear. The highest risk factor in the supply of chemotherapy drugs is the number of years since their approval, as medicines not under patent protection yield lower profits and are less likely to be of interest to manufacturers.[20,21] In the USA, the majority of the generic injectable products are supplied by only seven companies.[22] According to a joint study by the US National Library of Medicine and UUDIS, they found that with regard to first line chemotherapy drugs, there is a high possibility of shortages in the supply of the medications.[20]

1.6. Reasons for chemotherapy drugs shortages

Chemotherapy drug shortages have dramatically increased since 2006;[23] however, complexities in the chemotherapy supply chain make it difficult to determine the main causes for the shortages. One potential significant cause is economics. For instance, the two main causes for shortages in the supply of 71 chemotherapy drug as reported in seven European

countries were due to manufacturing and economic issues.[9] Furthermore, according to the TGA, 'price disclosure policy' plays a significant role in the shortage of drugs in Australia.

1.7. Clinical implications of drug shortage in oncology

1.7.1 Impact on patients

The impact of a drug shortage on a patient can be significant.[24] There have been a number of reported instances of chemotherapy drug shortages in the US and Europe which have resulted in patients experiencing interruptions or delays in their treatment.[25-29] According to a survey carried out in the American Medical Society, over 75% of oncologists believe that drug shortages lead to inferior patient care.[28] In another study, doctors were surveyed and reported when they were forced to use alternative treatment regimens. The findings showed that there was a 30% reduction in good outcomes for patient and higher rates of side effects (increase of 34%), when compared cases where the preferred medicines were available.[26]

1.7.2. Impact on health systems

Drug shortages can impact not just patients, but also the health care system itself.[30,31] According to information presented by the American Hospital Association dealing with drug shortages can be challenging in a number of ways. More than three-quarters of hospitals found that dealing with a drug shortage was a major challenge for them (Figure 4). Of the remaining respondents, they all considered dealing with drug shortages as a moderate challenge. None of the respondents indicate that drug shortages were only a small challenge or provided no challenge to their continued provision of health care.

In an American Pharmacist study which set out to examine awareness of drug shortages they found that 85% of medication errors occurred when pharmacists used alternative medicines.[32]

In a similar 2011 study, 22% of oncology pharmacists reported that an experience of a drug shortage resulted in a medication error at their institution, which included incorrect treatments being administered to patients.[33]

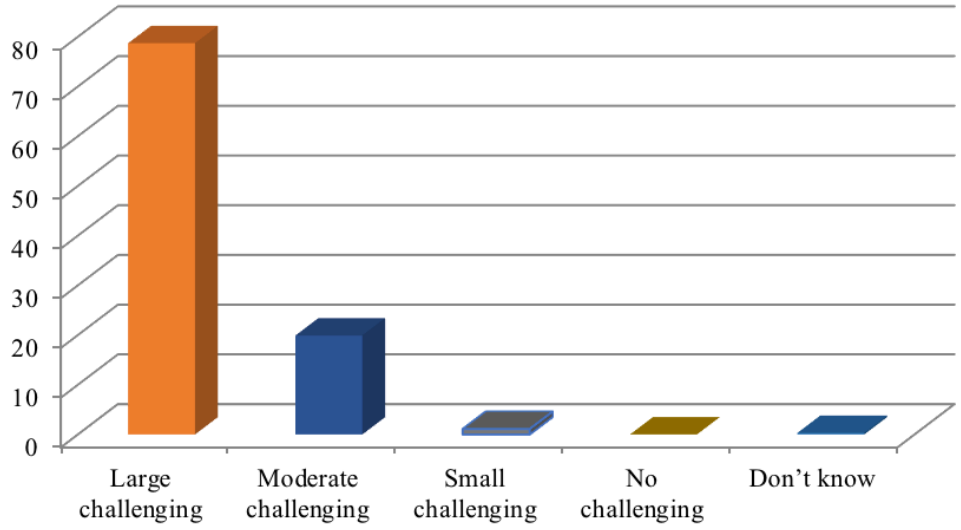

Figure 4. Percentage of the challenge experience of drug shortages at U.S. at community hospital between 2015 and 2017.[2]

Some of the challenges faced by the hospitals include having to purchase other, more costly, medications as substitutes for the required drugs **(**Figure 5);[2] shortages of cancer drugs increase the expenditure rate by up to 80%.[34] Drug shortages also cost significant staff time, can delay patient treatment, and can even pose significant ethical challenges.[10,25] A recent survey of pharmacists by the ASHP indicated that pharmacists were spending between eight and 12 hours each week and physicians were spending up to two hours each week, dealing with medicines shortages.[31]

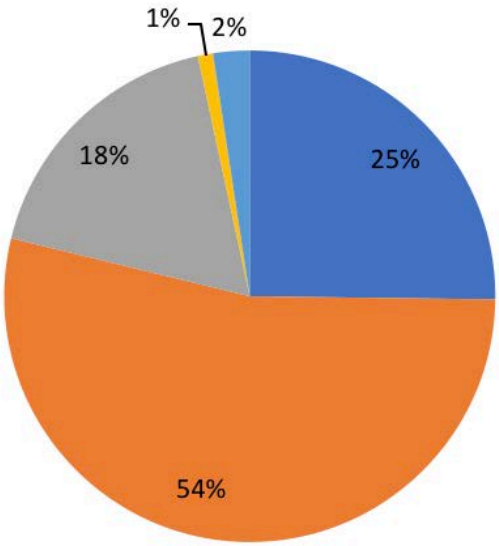

Figure 5. Impact of drug shortages on drug spending as reported in the U.S. between 2015 and 2017. Moderate impact (orange), extreme impact (dark blue), small impact (grey), have no idea about the impact (light blue), and no impact (yellow).[2]

1.7.3. Ethical implications of chemotherapy drug shortages

As the number of chemotherapy drug shortages has grown, several ethical frameworks for appropriately rationing these resources have been proposed.[35,36] In 2012, the Ontario Ministry of Health and Long-Term Care published an ethical framework to guide decision-making regarding the redistribution of drug supplies and how to improve health services when drugs are in shortage.[37]

One of the most challenging aspects of dealing with medications in limited supply is how to determine which patients warrant higher priority to receive the drugs in question. Cancer is a particularly aggressive disease, and a shortage of a drug can likely to result in the relapse of a patient. Likewise, a pharmacist or doctor may be faced with the dilemma of having two

cancer patients with similar disease progress and likelihood of treatment success but may only have enough to treat one patient. In this case, the health care worker is forced into a difficult decision on who is more worthy, or the option of potentially splitting the medicine and giving both patients a sub-optimal dose.

1.8. Platinum-based chemotherapy drugs

Platinum-based chemotherapy drugs have been in use for the treatment of human cancers since the 1970s. The first drug to be approved was cisplatin, followed by carboplatin in the 1980s and oxaliplatin in the 1990s (Figure 6).[38,39] All three drugs have world-wide approval, while there are some platinum drugs that have approval in just single nations, such as nedaplatin in Japan, lobaplatin in China, and heptaplatin in Korea.[38]

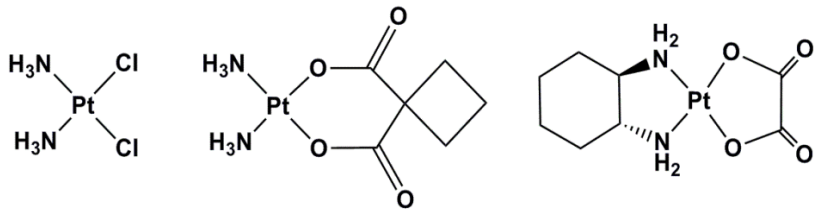

Figure 6. The chemical structures of the three platinum drugs which have worldwide clinical marketing approval: cisplatin, carboplatin, and oxaliplatin.

Platinum drugs are an essential component of many chemotherapy regimens. A recent study has shown that platinums are used to treat over 25 types of solid tumours, including colorectal, gastrointestinal, gynaecological, head and neck, multiple myeloma, lung and urogenital tumours (Table 2).[40,41] A recent hospital study has shown that nearly 50% of chemotherapy patients receive a platinum drug during their cancer treatment, and some patients receive two, and even three, different platinum drugs. Platinum drugs are also used in

combination with other antineoplastic drugs such as paclitaxel, fluorouracil, docetaxel, gemcitabine, irinotecan or pemetrexed.[42]

Table 2. The types of cancers that are typically treated with the platinum-based drugs cisplatin, carboplatin, and oxaliplatin, based on the chemotherapy protocols in the Australian EviQ database.

Type of cancer	Cisplatin	Carboplatin	Oxaliplatin
Head and neck	Yes	Yes	No
Gynecological	Yes	Yes	No
Respiratory	Yes	Yes	No
Upper gastrointestinal	Yes	Yes	Yes
Urogenital	Yes	Yes	No
Colorectal	Yes	Yes	No
Lymphoma	Yes	Yes	Yes
Sarcoma	Yes	No	No
Multiple myeloma	Yes	No	No
Bone and marrow transplants	No	Yes	No
Breast	No	Yes	No

1.9. Mechanism of actions and toxicity of platinum drugs

All platinum-based chemotherapy drugs are cell cycle non-specific. They act by cross-linking DNA via bonding at the N7 site of guanine and adenosine residues. This has the effect of inhibiting DNA syntheses and eventually leading to apoptotic cell death.[43]

Because they act on all rapidly dividing cells, not just cancerous cells, platinum-based chemotherapy drugs can induce more than 40 different side effect in patients. The most common side effects of platinum, include: anaphylaxis, cytopenia, hepatotoxicity, ototoxicity, cardiotoxicity, nausea and vomiting, diarrhea, stomatitis, mucositis, alopecia, anorexia, and asthma.

As well as the common side effect, each of the platinum drugs has a specific dose-limiting side effect. Cisplatin is known to cause severe nephrotoxicity (kidney damage),[43,44] whereas the major toxicity of carboplatin is myelosuppression (reduction in blood cells). Oxaliplatin's major side effect is peripheral neurotoxicity.

1.10. Knowledge gap

Cisplatin, carboplatin and oxaliplatin represent the most established and dominant members of the platinum drug family. Despite their extensive use for over four decades, little has been published on issues regarding their supply and whether shortages can impact patients.

Of the few studies that do exist, most analyse platinum shortages only in the context of larger research projects that examine shortages of chemotherapy drugs more broadly. These include a study by Salazar et al.[21] which examined the impact of cisplatin and other medication shortages via the Children's Oncology Group and in local clinical trials. Another study, published by McBride et al. used a national online survey to determine the effect of oncology drug shortages on cancer care,[33] and Hedlund et al. examined the impact of drug shortages on patients who were just starting their chemotherapy treatment.[45]

Understanding shortages of platinum drugs is important in determining the potential impact they can have on patients, determining the wider costs and impacts on the healthcare system, and drive the development of guidelines for medical staff on what to do in the event of shortages of platinum drugs.

1.11. Aims of the project

As it has been discussed, the factors behind drug shortages are multifactorial, and may change from region to region, company to company, and from drug to drug. As such, the first aim of this thesis was to examine common factors that may lead to shortages in platinum drug supply. These include the current state of intellectual property protecting the drugs and the number of suppliers of the medication. The second aim was to then examine reported drug shortages in different geographical regions, including which drugs have been in short supply, for how long they were in short supply, and the reasons behind the shortages.

Chapter Two

Methods

2.1 Study setting and design

This study sought to examine shortages of only those platinum drugs with world-wide approval: cisplatin, carboplatin, and oxaliplatin. Those drugs which only have approval in a single country: nedaplatin, heptaplatin, lobaplatin, and miriplatin, were not included in the study.

Data was collected through the analysis of the online drug shortage databases of the US FDA (including the center for drugs evaluation and research), Health Canada, ASHP, ISMP, UUDIS, TGA, and the European Medicines Agency (EMA). Information was also collected from pharmaceutical companies which supply platinum drugs. This included analysis of their annual reports and company announcements.

Further information was collected through grey literature searching of reports and publications on drug shortages available on the internet and data contained in published research articles. The journal search strategy utilized medicines and science databases, including PubMed and Scifinder Scholar, using word sensitive searches in order to retrieve the relevant articles. This included any record containing the words ‘cisplatin’, ‘carboplatin’ or ‘oxaliplatin’ in English and the key phrases of ‘platinum drugs’, or cisplatin or carboplatin or oxaliplatin ‘plus’ and ‘with’, ‘cancer shortage’ or ‘drug shortage’.

Chapter Three

Results

3.1. Potential of patent protection to limit supply

For companies to make a profit from medicines they need to have exclusive rights to manufacture and sell specific drugs and formulation. While they can use various intellectual property instruments to do this, such as trade secrets and copyrights, the most effective way to limit competition is through an international patent.

While each country or region have their own laws regarding the application, filing and approval of patents, commonly most patents are granted to inventors for a period of 20 years.[46] On expiry of a patent, other companies can then design and manufacture their own generic versions of the drug, usually at a much reduced sale price.

Because branded (patent protected) medicines make significantly more profits for companies compared with generic formulation, many companies will seek to find ways to extend their patient protection beyond 20 years. Some ways they do this can include changing or improving the formulation, changing the solid-state structure of the drug (different crystal form or amorphous compared with crystalline), or developing a new method for manufacturing the drug.[47]

Therefore, while the platinum drugs cisplatin, carboplatin and oxaliplatin have been around for a number of years, the approval of new patents for these drugs may be used to limit the introduction of generics, and through this reduce the number of suppliers, and result in drug shortages. It was therefore of interest in this study to examine the current state of patents that cover cisplatin, carboplatin and oxaliplatin. Table 3 provides examples of relevant

international patents that cover the three platinum drugs used world-wide. The table excludes those patents that are for derivatives of the drugs or those patents that relate to unique drug delivery formulations that include a platinum drug (i.e. nanoparticle or similar drug delivery formulations).

Table 3. Examples of international patents that cover the use of molecular carboplatin, and oxaliplatin for the treatment of cancers in humans.

Drug	**Original Filing Year**	**Country**	**Patent No**	**Notes**
Carboplatin	1972	USA	US 4140707	Original patent that included carboplatin
Oxaliplatin	1976	Japan	27818/1976	Original patent describing oxaliplatin as a potential anticancer drug
Oxaliplatin	1992	Japan	EP 617043	Better method of synthesizing oxaliplatin
Oxaliplatin	1998	France	WO 99/43355	Development of more stable formulations of oxaliplatin
Oxaliplatin	2005	USA	WO 2005/102312	Development of concentrated oxaliplatin solutions

It is not clear when cisplatin as a potential chemotherapy drug was first patented. While it was first synthesized in 1845 by chemist Michel Peyrone, the patent for its use in cancer treatment must predate Rosenberg's reporting of the drug in the journal nature in 1965. What it known is that cisplatin started its first clinical trial in 1971 and was given marketing approval in the USA in 1978. As such, patent protection of cisplatin is unlikely to have an effect on its availability to patients in our current era.

The drug carboplatin was also developed by Rosenberg and colleagues at Michigan State University. It was first patented in 1972 and gained marketing approval in 1986. Similar to cisplatin, patent protection of carboplatin has long since lapsed and should not affect its availability to patients.

Only four years after the patent for carboplatin, oxaliplatin was patented in Japan in 1976. Interestingly, while the patent should have lapsed in the mid-1990s, the drug only came to market through Sanofi-Aventis in 1996.[38] The company however managed to maintain a monopoly in the market until 2012 through the filing on additional formulation patents. In the 2000s six generics manufacturers attempted to introduce their own formulations in the US. These companies manufactured oxaliplatin until 2010, at which time they were forced to discontinue supply. Generic formulations of oxaliplatin were then reintroduced in 2012. A search of the current literature has not revealed any current patents which restrict manufacturers from supplying generic products, and as such, this is not expected to impact on the supply of the drug to patients.

Overall, despite recent patent protection of oxaliplatin, all three drugs are available to be manufactured by generics companies, and drug shortages are not expected due a limitation in the number of potential suppliers.

3.2 Current suppliers

Given the lack of current patent protection of cisplatin, carboplatin and oxaliplatin, we next sought to determine the total number of companies that supply both generic and branded formulations of the drugs for the world-wide market. The results are presented in Table 4.

Table 4. Cisplatin, carboplatin, and oxaliplatin suppliers from 2003 to 2014.[20]

	Year											
Drug	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Cisplatin	5	5	5	4	3	3	3	3	3	2	3	4
Carboplatin	1	1	5	8	9	8	9	7	6	5	4	5
Oxaliplatin	1	1	1	1	1	1	1	4	5	5	7	7

Since the 2003-2014 study the number of suppliers approved to sell platinum-based chemotherapy drugs have increased significantly. A full list of companies that supply platinum drugs is provided at appendix 1.

In Australia there are four suppliers for cisplatin, six for carboplatin, and 12 for oxaliplatin (Table 5). For cisplatin the numbers of suppliers are 9 and 8 for the USA and UK respectively, for carboplatin they are 17 and 8, and for oxaliplatin the number of suppliers are 17 and 11, respectively, in the USA and UK (Tables 6 and 7).

A general trend can be seen where on average the fewest suppliers are for cisplatin, the oldest of the four drugs and potentially the drug in lowest demand. Oxaliplatin is manufactured by the highest number of suppliers which may reflect the growing importance of this drug in oncology as there appears to be little difference in the price (and hence profit) of the drugs.

Taking DPMA (dispensed price maximum amount) prices listed from the Australian Pharmaceutical Benefits scheme, the price per 100 mg of cisplatin is $58-77, which is higher than the price per 100 mg for carboplatin ($17-22) and per 100 mg of oxaliplatin ($47-61).

Overall, the number of platinum drug suppliers in each of the three countries appears to have significant in-built redundancy such that if one or two companies were unable to provide their formulation, then there are sufficient other suppliers to ensure accessibility to patients.

Table 5. Suppliers of platinum drugs in Australia as listed on the Australian Register of Therapeutic Goods in June 2019. (a) indicates those suppliers whose formulations are listed on the Pharmaceutical Benefits Scheme.

Cisplatin	**Carboplatin**	**Oxaliplatin**
Accord[a]	Accord[a]	Pfizer[a]
Hospira[a]	Hospira[a]	Accord[a]
Pfizer	Pfizer	Sun Pharma[a]
Sandoz	Teva	Sandoz[a]
	Fresenius Kabi	Wockhardt Bio
	Novotech	Hospira
		Apotex
		Alphapharm
		Juno Pharm
		Medis
		Link Medical Products
		Sanofi-Aventis

Table 6. Suppliers of platinum drugs in the U.S. as registered with the US FDA in June 2019.

Cisplatin	Carboplatin	Oxaliplatin
HQ SPCLT Pharma	West-Ward	Teva
PharmaChemie	Watson Labs	Sanofi-Aventis
Bedford	Fresenius Kabi	Actavis
Fresenius Kabi	Hospira	Fresenius Kabi
Teva	Pliva	Sandoz
West-Ward	Sandoz	Hospira
Mylan	Teva	Mustafa Nevsat
Accord	PharmaChemie	Sun Pharma
Gland Pharma	Cipla	Pliva
	Sun Pharma	Jiangsu Hengrui
	Actavis	Qilu Pharm
	Akorn	Luitpold
	Mylan	Eugia Pharma
	Eugia Pharma	Gland Pharma
	Gland Pharma	Accord
	Ingenus Pharms	Cipla
	Corden Pharma	Ingenus Pharms

Table 7. Suppliers of platinum drugs in the UK as registered with the Medicines and Healthcare Regulatory Agency in June 2019.

Cisplatin	Carboplatin	Oxaliplatin
Teva	Hikma Farmaceutica	Hospira
Accord	Fresenius Kabi	Sanofi
Ebewe Pharma	Accord	Aventis Pharma
Fresenius Kabi	Fannin	Teva
Caduceus Pharma	Cipla	Lek Pharmaceuticals
Sandoz	Teva	Fresenius Kabi
Cipla	Hospira	Sun Pharmaceutical Industries
Pharmacia	Ebewe Pharma	Torrent Pharma
		Aptil Pharma
		Sandoz
		Ebewe Pharma

3.3 Incidence, duration, and causes for platinum drug shortages in Australia, U.S. and U.K.

Next, we sought to examine the prevalence of drug shortages and disruptions to supply that have been reported in various countries. As was discussed in chapter 1, Australia, the U.S. and the UK recently introduced legislation making the reporting of drug shortages mandatory for pharmaceutical companies. Before, companies were able to voluntarily report shortages. Table 8 provides the details of all reported shortages for platinum drugs (including where the manufacturer has decided to cease production) in each of the three main countries of interest.

While companies are required to report the cause of drug shortages, they are not required to provide specific details on the nature of the shortage. As can be seen in the table 8, drug shortages can result from discontinued production, disruptions in production, a change (increase) in patient demand, and problems in supply (such as transport and storage).

For those drug shortages which do not include discontinuation, they are relatively short lived. The shortest and longest periods for a reported shortage were 3 and 79 days, respectively. The median length of shortage was 22 days, which is not expected to have a significant effect on patient outcomes.

When a company discontinues a platinum-drug the reasons behind the decision are usually not known. From an analysis of the annual reports for those companies that advised that they were discontinuing production, no reason behind the decision could be found. A similar result was obtained when each company' public announcements were searched.

Table 8. Reported drug shortages and disruptions to supply from 2017 onwards as reported to the TGA in Australia, Health Canada, the U.S. FDA, and the U.S. ASHP.

Drug	Size	Country	Company	Start	End	Reason
Cisplatin	50 mL	USA	Mylan	Jan 2018	N/A	Discontinued production
Cisplatin	100 mL	USA	Mylan	Jan 2018	N/A	Discontinued production
Carboplatin	20 mL	USA	Mylan	Jan 2018	N/A	Discontinued production
Carboplatin	40 mL	USA	Mylan	Jan 2018	N/A	Discontinued production
Carboplatin	50 mL	USA	Mylan	Jan 2018	N/A	Discontinued production
Carboplatin	100 mL	USA	Mylan	Jan 2018	N/A	Discontinued production
Carboplatin	15 mL	Canada	Pfizer	26 Oct 2017	09 Nov 2017	Disruption to manufacture
Carboplatin	60 mL	Canada	Pfizer	16 Apr 2018	19 Apr 2018	Disruption to manufacture
Cisplatin	100 mL	Canada	Accord Healthcare	06 Mar 2017	30 Mar 2017	Disruption to manufacture
Oxaliplatin	10 mL	Canada	Pfizer	13 Apr 2017	20 Jun 2017	Discontinued production
Oxaliplatin	40 mL	Canada	Pfizer	18 Aug 2017	20 Sep 2017	Demand increase for the drug
Oxaliplatin	10 mL	Canada	Teva	18 Jun 2019	Est 30 Jun 2019	Discontinued production
Oxaliplatin	20 mL	Canada	Teva	18 Jun 2019	Est 30 Jun 2019	Discontinued production
Oxaliplatin	10 mL	Canada	Sandoz	11 Jul 2017	28 Jul 2017	Delay in shipping
Oxaliplatin	20 mL	Canada	Sandoz	17 May 2017	28 July 2017	Other (limited inventory available to our customers)
Oxaliplatin	40 mL	Canada	Sandoz	20 Jan 2017	11 Apr 2017	Delay in shipping
Oxaliplatin	40 mL	Canada	Sandoz	17 May 2017	01 Sep 2017	Other (limited inventory available to our customers)
Oxaliplatin	10 mL	Australia	Sun Pharma	15 Dec 2018	N/A	Discontinued production

A potential reason for a company to discontinue the supply of platinum drugs may be due to the cost of raw materials and their ability to manufacture at a profit. For most organic-based drugs, the major costs of manufacture are facilities and staff, but for cisplatin, carboplatin, and oxaliplatin the cost of raw materials would be expected to affect profits to a larger extent.

Platinum is considered a precious metal with only 160,000 tonnes of the material being mined each year.[48] As such, the cost of platinum metal is very high. In June 2019 the spot price of platinum was US$814 per ounce, which is more than 50 times higher than the price of silver, but only 58% the cost of gold. However, based on the price of platinum, it appears that it is not contributing factor in company decision to cease cisplatin, carboplatin, or oxaliplatin production. The price of platinum reached a peak in September 2011 at a price of US$1,852 per ounce, and has since fallen by 44%. This does not include the effect of inflation which would have a further downward effect on the cost of platinum. As such, the raw material cost to produce platinum drugs has only gone down over the last decade, not up.

3.4 Incidence of platinum drug shortages in eastern European nations

In November 2018, while the study described by this thesis was underway, the European Society for Medical Oncology published their report titled Availability of medicines: Impact on public health.[10]

In this report, the committee analysed the availability of chemotherapy drugs that are listed by the WHO as essential medicines. Their list includes cisplatin as an essential medicine in the treatment of lung, ovarian, gastrointestinal tract cancers, and sarcomas. Carboplatin is listed as an essential medicine for breast, ovarian, and lung cancers, and oxaliplatin is listed as an essential medicine for colorectal cancer.[49]

Their report, which provides the availability of the platinum drugs in 48 individual nations, separates the countries based on geographical location by western and eastern Europe. With this grouping a significant and interesting observation on platinum shortages can be made.

For the 21 countries making up the western European group there were only two countries that did not report that all three platinum drugs were *always* available. Greece reported that cisplatin was only *usually* available for the treatment of sarcomas, and carboplatin was only available *half of the time* for breast cancer treatment. Australia reported that cisplatin was only *usually* available for the treatment of ovarian cancer. No western European country reported a problem with shortages for oxaliplatin.

In contrast, for those countries in eastern Europe, shortages were far more common. Of the 27 countries in this group, eight reported that cisplatin was only *usually* available, three reported that cisplatin was only available *half of the time*, and once country (Armenia) reported that it was *never* available.

For carboplatin, the statistics are worse. Eight countries reported that it was *usually* available, three reported it was available *half the time*, two reported that it was *occasionally* available, and three countries (Armenia, Serbia and Slovenia) reported it was *not available* (i.e. not approved for sale or no companies have made any available for sale). Only 13 of the 27 nations reported that carboplatin was *always* available for patients.

For oxaliplatin the results are slightly better. Seventeen of the 27 nations stated that the drug was *always* available. Of the other ten, eight reported that is was *usually* available, one stated

it was available only *half of the time* (Armenia), and one stated that it was *never* available (Macedonia).

These results highlight a problem that is not observed in western countries and western European countries, and may hint at a larger problem in other regions. Other potential at risk regions, for which there is no data, are central and southern America, south-east Asia, Africa, and Middle Eastern countries.

Chapter Four

Conclusions and Future Work

The platinum-based chemotherapy drugs cisplatin, carboplatin, and oxaliplatin remain a crucial component in the treatment plan of many human cancer patients. As such, shortages of these drugs have the potential to impact patient outcomes and the provision of healthcare more broadly. In this thesis we examined the current state of platinum drug shortages in the world.

As all three drugs are off-patent they are widely available and in the three main regions of interest Australia, U.S., and the U.K., between 4 and 17 companies provide supply of the drugs. Where drug shortages are reported, these tend to be of short duration (median 22 days) and are caused by production disruptions, companies deciding to discontinue supply, changes in customer demand, problems in supply such as transport and storage, and other reasons.

While shortages are rare in western countries and western European countries, shortages of platinum drugs in eastern European countries is common. Some countries have reported never having available stocks of one or more platinum drugs.

The results of this thesis indicate that for those patients in Western countries the impact of platinum drug shortages is minor, but for patients in other regions (especially Eastern Europe) there is significant evidence that shortages will affect patient long term survival. What is now needed are government and health plans to what do in the instance of a platinum shortage, and supply chain solutions to minimise the number and length of platinum drug shortages.

In continuing this research a number of potential projects are recommended. The first is to examine whether there are any reported shortages for those drugs that are used in only single

nations. This would include nedaplatin, heptaplatin, lobaplatin, and miriplatin. The results for these drugs, given the presumably lower number of manufacturers, may be in contrast to the results found for cisplatin, carboplatin, oxaliplatin. This may especially be the case given the newest drug, miriplatin, is likely to still be under patent protection.

A second recommendation is that further work seeks to examine drug shortages in regions more likely to have trouble accessing platinum drugs. This could include central and south America, south-east Asia, Africa, and the Middle East.

If the second recommendation is adopted, then the final recommendation would be to also examine the impact on platinum drug shortages on patients in those identified regions. This would include looking at patient outcomes (overall five year survival rates), and how medical staff work around platinum drug shortages.

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Appendix One

Current manufactures of platinum chemotherapy drugs

Table S1. Current manufactures of cisplatin chemotherapy drugs.

Brand/Generic	Country	Company
Cisplatin	UK	Acoord
Cisplatin	United States	Pfizer
Cisplatin	United States	Mylan Pharmaceuticals
Platinol®-AQ	United States	Teva
Cisplatin	United States	WG Critical
Cisplatin	United States	Fresenius Kabi
Cisplatin	United States	Alvogen
Cisplatin	Australia	Hospira Pty Limited
Cisplatin	United States	Gland Pharma
Cisplatin	India	GLS Pharma Ltd
Cisplatin	Canada	Sandoz
Cisplatin	United States	Blue Point Laboratories
Platinol	United States	Athenex Pharmaceutical Division, Llc.
Cisplatin	United States	Spectrum Pharmaceuticals
Cisplatin	India	Taj Pharma
Cytoplatin	India	Cipla
Cisplat	India	Zydus Cadila
Platin	India	Cedila pharmacuticals Ltd
Platikem Nova	India	Alkem Laboratories Ltd

Table S2. Current manufactures of carboplatin chemotherapy drugs.

Brand/Generic	Country	Company
Carboplatin	UK	Acoord
Carboplatin	Australia	Hospira Pty Limited
Carpoplate	United States	Pfizer
Carboplatin	United States	Mylan Pharmaceuticals
Carboplatin	United States	Teva
Carboplatin	United States	Alvogen
Carboplatin	United States	Gland pharma
Carboplatin	United States	Sagent
Carboplatin	India	GLS Pharma Ltd
Carboplatin	India	Cipla
Womastin	India	Alkem Laboratories Ltd.
Biocarb	India	Zydus Cadila
Carboplatin	India	Dr.Reddy's Laboratories
Carbpa	India	Intas Pharmaceutical Ltd.
Carmuta	India	Emcure Pharmaceuticals Ltd.
Paraplatin	India	BMS
Stricarb	India	Strides Shasun Ltd.
Carbosin	South Africa	Pharmachemie Bv
Carboplatin	India	West-Ward Pharms
Carboplatin	India	Eugia Pharma
Carboplatin	United States	Akron
Carboplatin	China	Hong Kong
Carboplatin	United States	Sanja Pharmaceuticals
Carbosol	Austria	Sanova

Table S3. Current manufactures of oxaliplatin chemotherapy drugs.

Brand/Generic	Country	Company
Oxaliplatinum	UK	Acoord
Oxaliplatin	United States	Pfizer
Oxaliplatin	United States	Mylan Pharmaceuticals
Oxaliplatin	United States	Bedford Pharmaceuticals
Oxaliplatin	United States	Teva
Oxaliplatin	United States	Fresenius Kabi
Oxaliplatin	United States	Alvogen
Oxaliplatin	United States	Gland Pharma
Oxaliplatin	Germany	Sandoz
Eloxatin®	New Zealand	Sanofi Aventis
Elplat	Japan	Yakult Honsha
Oxaliplatin	India	GLS Pharma Ltd.
Oxaliplatin	India	Dr.Reddy's Laboratories
X-PLAT	United States	Cipla Limited
Oxaliplatin WKT	Australia	Wockhardt Bio Pty Ltd
Oxaliplatin	Australia	Hospira Pty Ltd
ELOXATIN®	Canada	Apotex Pty Ltd
Oxaliplatin	India	Cipla
ELOXATIN®	China	Qilu Pharmaceutical
PMS-Oxaliplatin	Canada	Pharmascience
Oxaliplatin	China	Jiangsu Hengrui Med
Oxaliplatin	United States	Actavis LLC
Oxaliplatin	Switzerland	Eugia pharma