ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

The Ontario Drug Policy Research Network Drug Class Review on Low Molecular Weight Heparin Medications

FINAL QUALITATIVE REVIEW REPORT

April 2016

Prepared by the ODPRN Knowledge Translation Unit, Li Ka Shing Knowledge Institute Knowledge Translation Program, St. Michael's Hospital

Alekhya Mascarenhas, Radha Sayal, Sobia Khan, Julia E. Moore

Conflict of Interest Statement

No study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the drug class review for medications to treat overactive bladder.

Acknowledgments

The Ontario Drug Policy Research Network (ODPRN) is funded by grants from the Ontario Ministry of Health and Long-term Care (MOHLTC) Health System Research Fund. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources and supporting organizations.

Study Team

Qualitative Team: Julia E. Moore, Sobia Khan, Alekhya Mascarenhas, and Radha Sayal from the Knowledge Translation Program at the Li Ka Shing Knowledge Institute

Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Contents

Executive Summary

Background: The Ontario Drug Policy Research Network (ODPRN) conducted a drug class review on Low Molecular Weight Heparin (LMWH) medications, which was selected as part of an initiative by the Ontario Public Drug Programs to update the public drug formulary. This report highlights the findings of the qualitative study performed within the drug class review to determine the experiences of managing and treating adults with LMWH.

Methods: We conducted 18 semi-structured telephone interviews with stakeholders, including primary care physicians, internists, oncologists, hematologists, emergency physicians, and pharmacists. Interviews were recorded and analyzed using a framework for pharmaceutical policy analysis (i.e. the "Triple-A" framework: affordability, appropriateness, and accessibility of medications). Emergent findings were integrated into our framework, and the framework was adapted to convey specific experiences and perceptions relevant to LMWH medication funding policies.

Key Findings: Findings in this report are summarized to represent common experiences and perceptions described across patient, pharmacist and physician groups.

LMWH prescription may be linked to various factors, such as hospital formularies, physician familiarity with LMWH dose calculations, and the introduction of new oral anticoagulants: Physician participants from hospitals said that they are limited to prescribing the LMWH which is on their hospital's formulary. They did not feel that having a sole option results in sub-standard care; however, there may be some confusion amongst clinicians if a patient from the community is admitted to a hospital on a LMWH that is not on the formulary. Physician participants in the community described that their prescription choice is related to their familiarity with LMWH dose ranges and calculations. Other factors which may be influencing prescription were mentioned, such as the availability of LMWH in the community; patient weight and renal function; and patient ease of use. With the exception of cancer related VTE, the introduction of new oral anticoagulants was described as causing a decrease in LMWH prescription.

Participants described their impression that most patients are highly adherent to LMWH, despite the requirement for self-injection: The review of patient literature also described high adherence rates to LMWH. The literature revealed that patients across care settings viewed it as an acceptable treatment option. The factors which contributed to this feeling of acceptance included the following: the knowledge that LMWH would prolong their survival, the feeling of independence, the preference of LMWH over other alternatives (e.g., warfarin), and the integration of self-injecting into their routine. Barriers to adherence as described by participants included the lack of support with self-injection, the reduced availability of LMWH in the community and the high cost of LMWH.

Many physician participants may be inappropriately applying LU codes to obtain LMWH coverage for a variety of reasons. Physician participants admitted that they use code 188 for a wide range of indications, either because they find it easier to remember one code, they interpret the criteria for this code more broadly, or they believe applying the code in the best

interest of the health care system and of patients. Physician participants described using code 188 to get coverage for patients who do not have any alternative therapy options (e.g., cancer related VTE). Many participants believed that by falsifying an LU code and covering the cost of LMWH for a patient in hospital, they may be able to discharge the patient sooner and save on hospitalization costs. Similarly, they described that the system would save on the cost of physician remuneration and international normalized ratio (INR) testing if a patient is covered for a LMWH instead of warfarin.

Participants were split in terms of their perceived need for LU criteria revision: Some physician participants were satisfied with the criteria as they are and feel that having the LU program may trigger physicians to think twice before prescribing. These physicians tended to use more broad interpretations of the codes and did not perceive any barriers to access for patients. Other physician and pharmacist participants felt that the criteria could stand to be expanded to include indications for cancer VTE, and post-operative prophylaxis of VTE in patients undergoing orthopedic surgery for hip-fractures. With the current criteria, pharmacist participants described that they often feel caught in the awkward position of having to receive prescriptions with LU codes that may be falsified. These participants also suggested that LMWH could be moved to the general benefit program, since they do not perceive that there would be any difference in expenditure.

Physician participants said that their preference is to use the LU codes whenever possible and they do not have experience using the exceptional access program (EAP). Most have admitted to using it only once or twice and could not recall the details of their experience. One participant described having a staff person at their clinic responsible for processing EAP applications for patients. Pharmacist participants have observed that hospital in-patients who need EAP facilitated coverage usually remain in the hospital for longer which results in increased hospitalization costs.

Participants suggested some cost-saving measures for the LU Program: Participants explained that one way to reduce costs would be to reduce the amount of wasted prescription. They have noticed that if a patient switches dosages of LMWH or if they pass away (e.g., due to cancer) there is often prescription which has been paid for which goes to waste. In order to reduce wastage participants have suggested that there could be a limit on the amount of drug which is dispensed at certain time intervals and that the specific duration of treatment should be outlined in the code and on the prescription (e.g., one week). Other strategies included training pharmacists to administer injections to patients who need CCAC nursing support and negotiating with manufacturers to the have one LMWH adopted across the province.

Conclusion: Overall, our findings shed light on the experiences of prescribing and using LMWH medications and unveil important information that can impact how patients in need can access these drugs across Ontario.

Background

The Ontario Drug Policy Research Network (ODPRN) is conducting a series of drug class reviews as part of an initiative to update the public drug formulary (i.e. formulary modernization). As such, the ODPRN works closely with the Ontario Public Drug Programs (OPDP) and the Ministry of Health and Long-Term Care (MOHLTC) to select key priority areas and topics for formulary modernization, then conduct independent drug class reviews and disseminate the results of each of these reviews directly to the OPDP to facilitate informed decision making on public drug funding policies. LMWH medications were selected as the topic for the twelfth drug class review.

Currently, there is limited information on how physicians prescribe LMWH medications to patients. Phase 1 of the ODPRN qualitative unit work will involve exploring the various factors that may be related to the prescription, dispensing, and use of LMWH medications for patients. This information is warranted to understand and contextualize prescribing and usage patterns in Ontario, as well as to highlight any health equity issues that may be prevalent but are currently unknown. Phase 2 of the ODPRN qualitative work will be to assess the social acceptability and feasibility of the final results and recommendations proposed by the ODPRN research team.

Methods: Phase 1

Design

This study was conducted using semi-structured interviews and a framework approach (Ritchie & Spencer, 1994). This approach helps researchers focus on specific areas of interest when exploring a topic, which can make the findings more applicable to policy contexts than alternative approaches. However, the approach also enables the incorporation of new ideas, emergent issues, or unanticipated results. The framework selected for this study was the “Triple-A” framework (see **Appendix A**) for pharmaceutical policy analysis developed by Morgan et al. (2009). This framework highlights the need to explore affordability, accessibility, and appropriateness of the selected drugs when determining policy-relevant issues.

Sampling

Stakeholders identified for the LMWH drug class review were: primary care physicians (PCPs), internists, oncologists, hematologists, emergency physicians, and pharmacists. Inclusion criteria are: clinicians (PCPs, internists, oncologists, hematologists, emergency physicians, and pharmacists) who have prescribed or dispensed LMWH medications to patients. All stakeholder groups were invited to participate in interviews. Patients were not interviewed as part of this project because targeted recruitment would be challenging given that there are a wide range of indications for LMWH treatment.

A purposive sampling approach using a convenience sample was used in order to elicit the

specific perceptions and opinions of those who will be involved in or affected by drug policy decisions related to LMWH medications. Given the rapid nature of study timelines, we aimed to recruit 6-8 participants from all stakeholder groups. We anticipated that this amount of participation may be sufficient to reach saturation amongst relatively homogenous groups of participants (Kuzel, 1999).

Recruitment methods were: a) cold calling; b) e-mailing and faxing; c) recruiting at primary care and specialist clinics; d) sending recruitment letters through e-mail distribution lists of professional organizations and advocacy groups; e) posting recruitment notices to the ODPRN website and social media (Twitter, Facebook) accounts; and g) snowball sampling (asking participants to connect with individuals they know who may be able to offer valuable insight to the issue for the purpose of recruitment to the study).

Data Collection and Analysis

Qualitative data were collected through one-on-one, semi-structured telephone interviews that were 30 to 45 minutes in length and conducted between August and October 2015. All interviews were conducted with a semi-structured interview guide developed using the “Triple-A” framework for pharmaceutical policy analysis (Morgan et. al., 2009) and collaboration from physicians and the drug class review team. Each interview was audio recorded. Interviews were transcribed, and transcripts comprised the primary source of data. The interviewer and/or a note taker took field notes during the interview to serve as a secondary source of data.

The framework approach was used to guide qualitative data analysis. Two independent analysts engaged in familiarization of the data by reading all primary and secondary data sources and generating initial codes that could be incorporated to the “Triple-A” framework (Morgan et. al., 2009). These codes comprised the coding framework. A modified coding consensus approach was used: the framework was reviewed by the qualitative research team and applied to 20% of transcripts by two analysts during in-depth analysis. Inter-rater reliability between the two analysts was > 80%. The remaining transcripts were coded by a single analyst. The analyst and the qualitative research team engaged in mapping and interpretation of the coded data to generate the final themes.

Since there were challenges with recruiting patients, a literature scan was performed to gather any relevant qualitative literature on patient preferences and experiences with LMWH. The search was performed in Medline and the search terms used were the following: low molecular weight heparin, qualitative research, interviews as topic, experiences, and views.

Phase II of the qualitative research study is described later on in the report.

Research Ethics

This qualitative study was approved by the St. Michael’s Hospital Research Ethics Board in Toronto, Ontario, Canada.

Part 3: Findings

A total of 18 participants took part in the study: 2 primary care physicians, 2 internists, 3 oncologists, 4 hematologists, 4 emergency physicians and 2 pharmacists. Detailed participant demographics can be found in **Appendix B**.

Key Themes Related to the Prescription and Use of LMWH Medications

PHYSICIANS AND PHARMACISTS

The following is summary of the key themes from physician and pharmacist interviews:

- **Influences on LMWH prescription**
- **Adherence to LMWH**
- **Perception of prescription trends**
    - **New oral agents**
- **Access to LMWH**
    - **Limited use program**
        - **Perceived effectiveness of program**
        - **Current use of codes**
        - **Suggested updates to criteria**
    - **Exceptional Access Program**
    - **Suggestions to reduce systemic costs**

Detailed findings on each of these themes are described below.

Influences on LMWH Prescription

Participants described various influences on their LMWH prescription choices, such as environmental factors (e.g., hospital formulary and availability of LMWH), personal factors (e.g., familiarity with dosage and perceptions of efficacy), and patient factors (e.g., weight, renal function, and ease of use).

Physician participants from hospitals described that they can prescribe only the LMWH that is included on the hospital formulary. Participants believed that the availability of only one LMWH is primarily based on negotiations with manufacturers to reduce drug acquisition costs. They did not feel that having a sole option results in substandard care because they believe that no one LMWH is superior to the rest. However, although LMWHs may be similar in effectiveness, they are available in different dosages (e.g., once a day or twice a day). Therefore, participants have noticed that when a patient transitions from the community into a hospital, there may be some confusion among clinicians if the patient is using a LMWH that is

not on the hospital formulary.

"if I write brand B to my out-patient and that patient is admitted to hospital and there's no brand B and there's a huge kerfuffle about what actual dosing the patient should get when they're admitted to hospital because the hospital only has brand A – not brand B – it makes it kind of difficult to actually choose brand B as an out-patient in someone who, despite the fact that brand B may be a better choice – maybe the syringe size is more fitting, maybe they're paying for it themselves and it's cheaper than brand A" –hematologist

In addition to the hospital formulary, participants also consider the availability of LMWH in their prescription decision making. The most commonly available LMWHs described were enoxaparin, tinzoparin, and dalteparin. Nadroparin was described as an older drug that is less readily available than the others. Participants did not elaborate on any hypotheses for why some LMWHs may be more available than others.

Aside from environmental factors, physician participants also described a couple of personal factors and patient factors that influence their prescription. First, they explained that their prescription choices are often related to their familiarity with LMWH dosages. LMWH dosages correspond to a patient's weight and there is some math involved in calculating the appropriate dose. Participants said they find the dose easier to calculate for some LWMHs compared with others, especially those that they have less experience prescribing. Second, though they mentioned that all LMWHs are similar in effectiveness, a couple of participants stated that enoxaparin, in particular, may not be optimally cleared from the kidneys. Therefore, in addition to weight, some physician participants also consider a patient's renal function when prescribing LMWH. Participants may not prescribe enoxaparin if a patient's creatinine clearance is not good. Lastly, most physician participants said that they prefer to prescribe prefilled syringes versus multidose vials because they have noticed that patients find it hard to draw up the correct dose from a multidose vial. They perceive that prefilled syringes result in more accurate dosing.

Perceptions of Prescription Trends

Participants described that they have noticed an increase in LMWH prescriptions for cancer-related thrombosis, and a decrease for indications where new oral anticoagulants (NOAC) (e.g., dabigatran, rivaroxaban, and apixaban) may be preferred.

"I'd be willing to guess that the proportion of cancer patients who are on low molecular weight heparin, versus an oral anticoagulant, is probably increasing as people realize that that appears to be a better option" –internist

"I know that when you go beyond Oncology there are the new medications like Rivaroxaban that are, I think, preferred in many situations and so I would guess there's probably overall less Low Molecular Heparin being used in there, than there was 10 years ago or something but within Oncology it's still I think the first thing that we use." –oncologist

With the introduction of the NOACs, some clinician participants described LMWHs as a "dying class" of medications in adult patients. Interview participants described three main reasons for

why the introduction of the NOACs may reduce the use of LMWHs. First, the NOACs and the LMWHs have similar levels of efficacy; however, they differ in the way they are administered. Physician participants indicated that they prefer prescribing the NOAC pill over the LMWH subcutaneous injection for two reasons: the NOAC pill is easier for patients to self-administer and less resource intensive since it does not require personnel to teach patients how to self-inject. Second, interview participants explained that their colleagues are becoming more comfortable and experienced with prescribing NOACs, which may lead to a decrease in the use of LMWHs. Third, although LMWH is often used as bridge to warfarin, physician participants stated that they prefer NOACs to warfarin because NOACs do not require laboratory monitoring (i.e., INR testing) or dose adjustment. This decreased reliance on warfarin may decrease the use of LMWH as a bridging agent.

Aside from the influence of NOACs, the only other LMWH trend noted by participants was that the hospital formularies may be impacting the prescription of LMWH in their surrounding communities. Physicians in the community may prescribe the same LMWH that a nearby hospital is using to minimize confusion when a patient is admitted to a hospital.

Adherence to LMWH

Participants described their impression that most patients are highly adherent to LMWH despite the requirement for self-injection. They believed that LMWHs are more convenient for patients who would have otherwise required treatment on warfarin because there is no need for regular international normalized ratio (INR) testing. In addition, participants said that because treatment with LMWH is short for those who are not taking the medication for cancer treatment, most patients may be willing to perform the injections even though they find them unpleasant. Lastly, they believed that injections are harder to forget in comparison with pills, which may facilitate patient adherence to LMWH.

Participants also described their impression that there may be some rare cases where patients may not be adherent to LMWH for a number of reasons, such as when there is a lack of support with self-injection, reduced availability of LMWH in their community, and challenges paying for LMWH. Most physician participants said they will require a clinic or hospital nurse to teach the patient how to perform the injection before the patient goes home. In some cases, patients are unable to inject on their own and will require nursing support at home through a community care access center (CCAC). Participants perceived that CCAC budgetary constraints may make it difficult to allocate nursing hours for the sole purpose of administering injections to patients, especially in rural areas. In these cases, adherence to LMWH is dependent on whether the patient gets help to inject LMWH. Similarly, participants have described that some pharmacies in the community, especially in rural areas, do not have stock of all LMWHs. There may be occasions when the patient has to wait a few days for the pharmacy to order the correct LMWH, and this impacts adherence. Lastly, the cost of LMWH was described as a barrier to adherence for patients who do not have any prescription drug coverage.

"there were delays in people starting for various reasons, like pharmacy was closed, like the pharmacy was going to charge them some huge amount of money that they couldn't afford, and they, you know, they couldn't pay for it that day" –internist

Access to LMWH

Limited Use Program: Perceived effectiveness

When asked about their perceptions of the LU program for LMWH, some physician participants were satisfied with the program the way it is; other participants felt it was inefficient because they did not perceive much difference between the way the LU program is used currently and the general benefit (GB) program. Those who held the latter perspective did not perceive that there would be any change in ODB program expenditure if LMWH coverage was moved to GB; they suggested that this move could actually save the health care system time and administrative costs. They also felt confident that these drugs would not be overprescribed or abused.

"To be honest, I don't see any reason why this type of medication should be under any limited access, because they're really not… there's no reason to abuse them…they also have a side effect profile that you don't want exposed patients that don't have a good indication for this type of treatment" –oncologist

"even though there are economic reasons for having the limited use codes there are costs associated with having pharmacists call or fax and having us take time and delay other Emergency Department patients, and so on, in order to look those up and sort those issue out; so, yeah, it's not just the limited use program or the funding of the drug that the limited use program has implications for – it has implications on other patients and Emergency Department wait times, and so on" –emergency physician

Those who said they were satisfied with the LU program felt that the codes are a good mechanism for encouraging physicians to think twice about what they are prescribing. Overall, the physician participants, including those who said they are satisfied with the LU program, admitted that they use the limited use codes for LMWH indications that are not included in the criteria. Participants described that most physicians will generally not hesitate to apply an LU code inappropriately if it is necessary to ensure an ODB-eligible patient gets the best available treatment.

Limited Use Program: Current use of codes

Physician participants described a variety of reasons for why they often use LU codes for LMWH coverage even if the indication does not directly apply. The most common LU code they use is code 188. First, they interpret the criteria for LU code 188 "*more broadly*" and use it for many indications, such as cancer thrombosis and perioperative medicine.

> "*At the present time I use the special access code saying that the patient doesn't tolerate [warfarin]. It's up to me to determine whether they tolerate [warfarin], or not. If it is frequent sampling, and poking them, giving the blood, they use antibiotics, or injections with drugs. Those are all good reasons for me to say they are not tolerating it, but of course I never even put the patient on [warfarin], but I will actually put that access code down, but I think that's kosher.*" –hematologist

Second, participants said they find it easier to remember one code rather than multiple codes, which is why code 188 has become a "*big grab bag*" for many indications covered by other codes. Third, they believed that it is in the best interest of overall costs to the health care system to sometimes use codes, particularly code 188, even if they don't apply. One relevant example that participants provided was that some ODB-eligible patients are sent home from

the hospital on warfarin because they cannot afford LMWH. While the ODB saves on the cost of covering LMWH for these patients, the health care system still incurs the costs of INR testing and physician remuneration that accompany the warfarin prescriptions.

> "*I use limited use codes for lots of reasons that aren't covered by the LU codes, because I think it's in the best interest of the healthcare system to do that.*" –internist

> "*By using limited use criteria even when it doesn't apply, we are able to discharge patients home sooner, and free up hospital bed for another patient. So, from a systems perspective, it makes sense*" –pharmacist

Fourth, physician participants described falsifying LU codes to ensure that patients who desperately need LMWH get access to it, especially in cases where there are no alternative therapies (e.g., pregnant women requiring LMWH and patients going for surgical procedures who have atrial fibrillation and a mechanical heart valve).

Limited Use Program: Suggested Updates to Criteria

Physician participants were split in terms of the perceived need for LU criteria revision. Some suggested that the criteria should be expanded to include coverage for patients who may be in an emergency and who do not have alternative therapies available to them. Those in favour of criteria expansion also pointed out that this would allow for more specific tracking of publically funded prescriptions. Currently, since code 188 is used for a variety of indications, many of the covered indications are not captured in utilization data. Other physician participants described that they are content to use the criteria as they are but interpret them more broadly so that they can ensure coverage for a wide range of indications.

Pharmacist participants described that they often feel caught in an awkward position since they sometimes have to call physicians either to request the correct LU code or to request the rationale for the use of the LU code. Physician participants said they are aware that pharmacists near academic hospitals or cancer centers are more amendable to using broad interpretations of the criteria whereas pharmacists located further away may be less familiar with LMWH prescription and may apply a more narrow interpretation. They feel that this may result in inequitable care for patients who live in more rural or suburban areas.

> *"We're torn between what's doing right according to the rules, and then what's doing right with the patient"* –pharmacist

Participants who offered suggestions for revision raised the following key points:

- The criteria should be expanded to include coverage for venous thrombosis embolism (VTE). Currently, the criteria vary for different drugs; some LMWHs are covered only for pulmonary embolism (PE) and some are covered only for deep vein thrombosis (DVT). Participants perceived that the treatment for PE and DVT are the same and should be under the umbrella term VTE.

  > *"We should be using the term Venous Thrombosis Embolism, because there's nothing that applies to DVT that doesn't also apply to pulmonary embolism. So, you know, somebody who would use an LU code for acute treatment of DVT wouldn't use it if the patient had PE? That doesn't make sense, right?"* –internist

- There should be coverage for cancer VTE either by adding to the criteria for code 188

or by creating a new code. Participants said that LMWHs are recommended as first line in current guidelines for the treatment of VTE in cancer. More specifically, participants felt that there should not be a limit on the length of coverage for cancer patients because some may need to be on LMWH for months or years. Participants also perceived that there should be some provision for the prevention of VTE in cancer patients post-surgery.

- There should be coverage for post-operative prophylaxis of VTE in patients undergoing orthopedic surgery for hip fractures. Participants perceive that many of these patients will be over the age of 65 and will need prophylaxis that extends beyond their post-operative stay at the hospital. Participants also highlighted that in the case of hip or knee replacement, there is a more effective and cheaper therapeutic alternative (e.g., oral anticoagulants – Rivaroxaban), so LMWH coverage is not needed.

  "The one drug that is covered post orthopedic surgery is Fondaparinux, which virtually no one would use, and I don't think you would want physicians who felt strongly about post-discharge prophylaxis to be using an even more costly drug" – internist

- Consider having "negative codes" when there are specific reasons why certain drugs or indications are not covered. For example, if there is good evidence for more effective and safer alternatives following hip and knee replacements, the criteria for LMWH could state, "Would not be supported to use low molecular weight heparin for prophylaxis after a hip and knee replacement."

- A specific duration for LMWH treatment should be outlined in the code and on the prescription (e.g., one week) to save on the cost of wasted prescriptions for noncancer patients.

  "if in fact from a provincial drug policy perspective we were worried about, you know, amount being dispensed, and therefore the cost, one could get specific in the limited use criteria, and say, you know, for bridging, to warfarin, the maximum duration of dispensed drug is like, I don't know, seven or ten days…Usually in 95 per cent of cases, you know, we really only use low molecular weight heparin for four or five days." –pharmacist

Exceptional Access Program

The majority of physician participants had very little experience using the exceptional access program (EAP) for LMWH and a vague understanding of the application process. Most have admitted to using it only once or twice and could not recall the details of their experience. One participant described having a staff member at the clinic who is dedicated to processing EAP applications for patients. Most physician participants said that their preference is to use the limited use codes instead of the EAP whenever possible.

"*It would be just way too much paperwork for no good reason…if this seems to be the*

standard of care, then no one should really go through that process in order to get the medications to the patients" –hematologist

The two pharmacist participants we interviewed described that they see very few EAP-facilitated prescriptions. They perceived that this may be because physicians find the application process onerous and inefficient. In addition, they have observed that hospital in-patients who need EAP-facilitated coverage usually remain in the hospital for longer, which results in increased costs to the health care system overall.

Suggestions to reduce systemic costs

Some participants described strategies that they felt may help maintain access to LMWH for patients but reduce costs to ODB and the health care system overall:

- Negotiate with the drug manufacturers to have one LMWH adopted across the province: The goal of the negotiation would be to reduce LMWH purchasing costs. This would also benefit patients because they would not have to switch to a different LMWH with a different dose when they transition from the community to a hospital.

- Limit the duration of LMWH coverage to reduce prescription wastage: Currently, if patients switch doses or their duration of treatment is not indicated on the prescription, they may end up with drug doses that have been paid for but will never be used. This could be remedied if physicians record the precise duration of LMWH treatment on the prescription. It could also be done by shortening the LU authorization period (e.g., coverage for VTE treatment drops from three weeks to two weeks).

- Limit the amount of LMWH that is dispensed for specified time intervals: Patients who are living with terminal cancer will likely require the drug until they die; however, when they do pass away, there may be LMWH prescription that is wasted.

  "So, you put a cancer patient on low molecular weight heparin at 30 dollars a day, and you give them six weeks supply, and they die in two weeks. So, there's a month of expensive low molecular weight heparin that's thrown away." –internist

  Similarly, pregnant women may be on LMWH only for the duration of their pregnancy and a month or two afterwards. In either of these cases, the LMWH could be dispensed one month at a time.

- Allow pharmacists to inject LMWH for those who are unable to self-inject: As described earlier, patients who are unable to self-inject and who do not have family need to use CCAC nursing help. Participants suggested this may not be the most cost-effective option; it may be more beneficial to train pharmacists to inject LMWH in the community.

  "I would say probably 75% of my colleagues are now injection certified, but we're not approved in Ontario to administer this medication – we're only approved for flu shot even though we've have been trained to administer both subcut and IM injections…I think that it would be far more cost effective for the Ministry of Health to pay a

pharmacist to administer it, instead of pay CCAC to come into the home." –pharmacist

PATIENTS

A qualitative literature search on patients' attitudes and perceptions about LMWHs was conducted in Medline. The initial search produced thirty citations and abstracts and sixteen articles were excluded because they were outside the scope of the study. The remaining eleven relevant full text articles were screened and 5 were excluded because no patient perspective was provided. The remaining 6 articles were included in the literature review. The journal articles included in the review were published from 1998-2015 primarily in Europe and were a combination of questionnaire and interview studies. The articles covered a range of indications and care settings such as palliative care, oncology, neo-natal, ambulatory and thromboembolism clinics. The journal articles primarily covered three main areas of inquiry: patients' comfort level with self-injection of LMWH, patients' adherence to LMWH, and patients' perception of the acceptability of LMWH as a treatment option.

Majority of patients reported being satisfied with the training they received in regards to self-injecting LMWH (Harrison, 1998; Le Gall, 2006; Nobel, 2015), however, there was variability in patients' comfort level with the self-injections across the studies. There was a higher level of comfort with self-injection in the thromboembolism clinic setting (Harrison, 1998) versus the ambulatory setting (Le Gall, 2006). Fear around self-injection was primarily associated with fear of pain/needles and fear of incorrectly self-injecting (Le Gall, 2006).Patients described how the process of self-injecting LMWH transferred a sense of responsibility to them , which in turn helped them adhere to the treatment course (Le Gall, 2006). All reviewed studies that covered patient adherence stated that there was a high adherence rate to LMWH (Harrison; 1998, Le Gall, 2006; Patel, 2012; Nobel, 2005; Nobel, 2015). Overall patients across the reviewed studies and different care settings reported feeling favourable towards self-injecting LMWH and viewed it as an acceptable treatment option (Harrison, 1998; Le Gall, 2006; McLean, 2010; Patel, 2012; Noble, 2005; Noble, 2015). The following factors were described as having contributed to this feeling of acceptance: the feeling of mobility/freedom (i.e. not having to go to the hospital/clinic for injection) (Le Gall, 2006; Nobel, 2005); the knowledge that it would prevent further complications (i.e. prolong survival) (McLean, 2010); the preference of LMWH over other alternatives such as anti-embolic stockings (McLean, 2010) or INF testing associated with warfarin (Noble, 2005); and the integration of self-injecting as part of the patient's routine (Nobel, 2015).

> *"Every day my blood was checked and every day the dose of warfarin was changed ... Eventually they started me on heparin ... I wish they'd done it sooner ... a quick injection and then you're done ... no blood tests no hassle"* (SCA) (Nobel, 2005)

> *"The heparin is more than acceptable.... so much of my treatment has been sitting back and having things done to you ... I prefer this ... I feel that I have got control back in my life."* (1 ICS) (Nobel, 2005)

> *"I'll stick the needles in until doomsday… it doesn't make any odds to me as long as*

they're keeping me going" (PT2) (Nobel, 2015)

Some patients did mention that they would prefer an oral alternative if it was as efficacious and safe as LMWH (Nobel, 2015). For those patients that decided to discontinue LMWH treatment it was usually attributed to bruising and discomfort during injections (Le Gall, 2006; McLean, 2010; Noble, 2005). Some post-natal women did not feel as strongly about taking LMWH if the baby was delivered successfully or the women would forget to take the LMWH because their normal routine was disrupted due to the challenges of motherhood (Patel, 2012).

Part 4: Discussion

Key Findings

The experiences and perceptions from our interview participants have pointed to some main findings related to the prescription and use of LMWH medications. LMWH prescription may be influenced by various factors, such as environmental factors (e.g., hospital formulary and availability of LMWH), physician factors (e.g., familiarity with dosage and perceptions of efficacy), and patient factors (e.g., weight, renal function, and ease of use). The introduction of NOACs may be causing a decrease in LMWH prescriptions in many indications except for cancer related VTE, for which LMWH prescription is considered the standard of care. Participants described their impression that most patients are highly adherent to LMWH, despite the requirement for self-injection. The review of patient literature also described high adherence rates to LMWH. The literature also described that patients across care settings reported feeling favourable towards self-injecting LMWH and viewed it as an acceptable treatment option.

Physician participants admitted that they use code 188 for a wide range of indications, either because they find it easier to remember one code, they interpret the criteria for this code more broadly, or they believe applying the code in the best interest of the health care system and of patients. Many participants believed that by falsifying an LU code they may be able save on hospitalization costs, physician remuneration and the cost international normalized ratio (INR) testing for warfarin. Physician participants said that their preference is to use the LU codes whenever possible, and that they do not have experience using the exceptional access program (EAP). Participants were split in terms of their perceived need for LU criteria revision. Physician participants who tend to use more broad interpretations of the codes and did not perceive any need for revision. Other physician and pharmacists felt that the criteria could stand to be expanded to include indications for cancer VTE, and post-operative prophylaxis of VTE in patients undergoing orthopedic surgery for hip-fractures. Participants also suggested some cost-saving measures for the LU Program, which are aimed at reducing the amount of wasted prescription. These included placing a limit on the amount of drug which is dispensed at certain time intervals and that the specific duration of treatment should be outlined in the code and on the prescription (e.g., one week).

Healthy Equity Considerations

The findings from this study highlight a few key access issues for patients using LMWH. Those who are not eligible for ODB coverage (e.g., those under 65 years of age or those who do not qualify for Trillium) and those who do not have private insurance will have barriers to accessing LMWH; this is a common finding across the drug class reviews. Pregnant women and cancer patients who are not ODB-eligible and who do not have any alternative therapy options are particularly disadvantaged. In addition, if physicians did not interpret LU codes broadly to include cancer related VTE, ODB eligible patients who are living with cancer would also have inequitable access to LMWH. Lastly, patients in rural areas may be disadvantaged if their local pharmacists either do not have stock of LMWH or do not have extensive experience with LMWH prescription and interpret the LU codes differently in comparison with pharmacists in urban, academic centers.

Limitations

It should be noted that these interview findings are not representative of the general population of individuals from which our study sample was drawn because the sample size is small and because there may be bias in sampling. The potential bias in sampling may exist because those who responded to interview requests may have been more likely than non-responders to be vocal about discussing the impact of LMWH and may be more highly involved in advocacy initiatives related to LMWH treatment.

Part 5: Conclusions

The findings from the qualitative study of this review on LMWH informed the methods of other ODPRN research units conducting studies as part of the review. Moreover, our qualitative study helped to contextualize the results of the systematic review, pharmacoepidemiological analysis and environmental scan performed within the separate research units of this review. On a broader scale, our study findings fill a gap in knowledge on access to LMWH medications for patients and how this may be impacted by physician interpretation and use of the ODB LU codes. Overall, our findings shed light on the experiences of prescribing LMWH medications and unveil important information that can impact how patients in need can access these drugs across Ontario.

Part 6: Phase 2

Following the completion of this study and the accompanying ODPRN LMWH research studies, a consolidated report was drafted that included a set of potential reimbursement options for the funding of LMWH. Phase 2 of the qualitative work included assessing the social acceptability and feasibility of the options proposed through the two steps outlined

below.

Soliciting Participant Feedback

Once the draft reimbursement options were developed, the qualitative interview participants from this study were invited to review all ODPRN reports from this drug class review. They were also invited to complete a brief survey about their impressions of the reimbursement options and the interpretation of the study results. This process allowed participants to provide feedback on the authenticity of the study results, which is an important component of qualitative research. The survey also measured aspects of social acceptability including affordability, accessibility and appropriateness of policy recommendations. The survey was developed online in FluidSurvey. The study coordinator sent the survey link and report through e-mail to participants. The findings from this survey were used by the team to make any necessary revisions to the consolidated report.

Citizens' Panel

We have recruited a diverse set of 15 individuals from the general public to form a Citizens' Panel. The Citizens' Panel provides feedback on recommendations from all drug class reviews. Feedback from panel members was obtained in two surveys and a webinar using the RAND Appropriateness Method (Fitch, 2001). First, an online survey was distributed to Citizens' Panel members, asking them to read the final report and recommendations, to provide their input and to rank the policy options. Next, Citizens' Panel members attended a webinar meeting, at which we presented key issues, findings and policy implications, and engaged in group discussion on the recommendations. Citizens' Panel members completed a second survey after the meeting, enabling them to provide additional feedback and giving them the opportunity to re-rank the policy options. This approach allowed each person to express their idea(s); each person's opinion was taken into account (compared to traditional voting where only the largest group is considered). The findings from the Citizens' Panel surveys and discussion were used by the team to make any necessary revisions to the reports and draft reimbursement options.

Part 7: Phase 2 Results

Detailed results are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Participant Feedback

All 18 interview participants from the LMWH drug class review consented to being contacted to participate in a member checking and acceptability survey exercise. Seven participants (i.e., one primary care physician, three hematologists, one internal medicine physician, and two emergency physicians) completed the survey. The exercise required participants to provide their thoughts and rank their level of agreement with each policy recommendation in terms of the burden of cost to the healthcare system, the benefits for those who require LMWH medications, and overall agreement and acceptability for accessing LMWH medications through the public drug programs. Participants ranked the following seven policy options:

Option 1a (status quo): Limited Use for LMWH and fondaparinux; Exceptional Access Program (EAP)

Option 1b: Addition of indications to Exceptional Access Program (EAP)

Option 1c: Addition of indications to both the Limited Use for LMWH and fondaparinux and Exceptional Access Program (EAP)

Option 2a: Only Limited Use for LMWH and fondaparinux

Option 2b: Simplified Limited Use codes (four simplified LU codes) for LMWH and fondaparinux

Option 3: General Benefit for all LMWH and fondaparinux

Option 4: Preferential listing for enoxaparin (as General Benefit) and EAP for dalteparin, nadroparin, tinzaparin, and fondaparinux (in patients in whom enoxaparin is contraindicated/not tolerated or for dalteparin for treatment of VTE in cancer patients)

Participants found policy option 3 and 2b to be the most acceptable policy options (Table1).

Table 1. Ranking of policy options in terms of acceptability (1 = most acceptable and 7 = least acceptable)

Policy Option	Overall Acceptability		
	Mean (*SD*)	Median	Mode
Policy Option 1a	4.14 (2.04)	4	3
Policy Option 1b	4.14 (1.68)	4	2
Policy Option 1c	4.57 (1.4)	5	5
Policy Option 2a	4 (1.91)	4	2
Policy Option 2b	3.14 (1.95)	3	1
Policy Option 3	2.86 (2.27)	2	1
Policy Option 4	5.14 (2.61)	7	7

Participants found option 3 to be a good option but some questioned whether this option may allow potential for inappropriate use. Option 2b was perceived by some to be the best option. Participants found policy option 4 to be the least acceptable policy option. In particular, participants felt that option 4 would result in medication errors that could be harmful to patients. Participants also mentioned that a preferential listing could destroy economic competition among the LMWH companies.

Citizens' Panel

The ODPRN Citizens' Panel meeting LMWH took place on Wednesday March 23, 2016. Two members attended the meeting and six members completed the pre-meeting survey. The post meeting survey results are not included however, due to a low number of respondents. The findings from the meeting should be interpreted with caution since they include the perceptions of only two participants. Overall, panel members had similar thoughts to interview participants; option 2b was chosen as the most acceptable option. One person elaborated:

"condensing the options will help solve the problems with the prescribers and in the long run [it] would be helpful from a policy perspective and there are no inequities related to patient access, so as long as the cost factor was also manageable than this would be most desirable"
–panel member

Option 1a was perceived to be the least acceptable option (Table 2). Panel members felt that the status quo with EAP is burdensome to the ODB and that not all prescribers may be aware of the telephone EAP process.

Table 2. Overall pre-survey aspect rankings for policy options

	Mean Ranking (*SD*) (1 = Most Acceptable 7 = Least Acceptable)
Option 1a (status quo)	5.8 (1.8)
Option 1b	5.2 (0.8)
Option 1c	4.4 (1.8)
Option 2a	3.6 (1.8)
Option 2b	2.2 (0.8)
Option 3	3.6 (2.3)
Option 4	3.2 (2.7)

References

Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P. (2001). “The RAND/UCLA Appropriateness Method user's manual.” RAND. Santa Monica

Harrison L, McGinnis J, Crowther M, Ginsberg J, Hirsh J. Assessment of outpatient treatment of deep-vein thrombosis with low-molecular-weight heparin. Archives of internal medicine. 1998; 158:2001-3.

Kuzel, AJ. (1999). "Sampling in qualitative inquiry." In BF Crabtree and WL Miller (Eds.) Doing Qualitative Research (second edition). Thousand Oaks, CA: Sage Publications: 33-45.

Le Gall C, Jacques E, Medjebeur C, Darques L, Briand F, Haddad J, et al. Low molecular weight heparin self-injection training: assessment of feasibility, tolerance and economic analysis in emergency departments. European journal of emergency medicine : official journal of the European Society for Emergency Medicine. 2006;13:264-9.

McLean S, Ryan K, O'Donnell JS. Primary thromboprophylaxis in the palliative care setting: a qualitative systematic review. Palliative medicine. 2010;24:386-95.

Morgan S, Kennedy J, Boothe K, McMahon M, Watson D and Roughead E. (2009) *Toward an Understanding of High Performance Pharmaceutical Policy Systems: A “Triple-A” Framework and Example Analysis.* Open Health Services and Policy Journal: 2;1-9

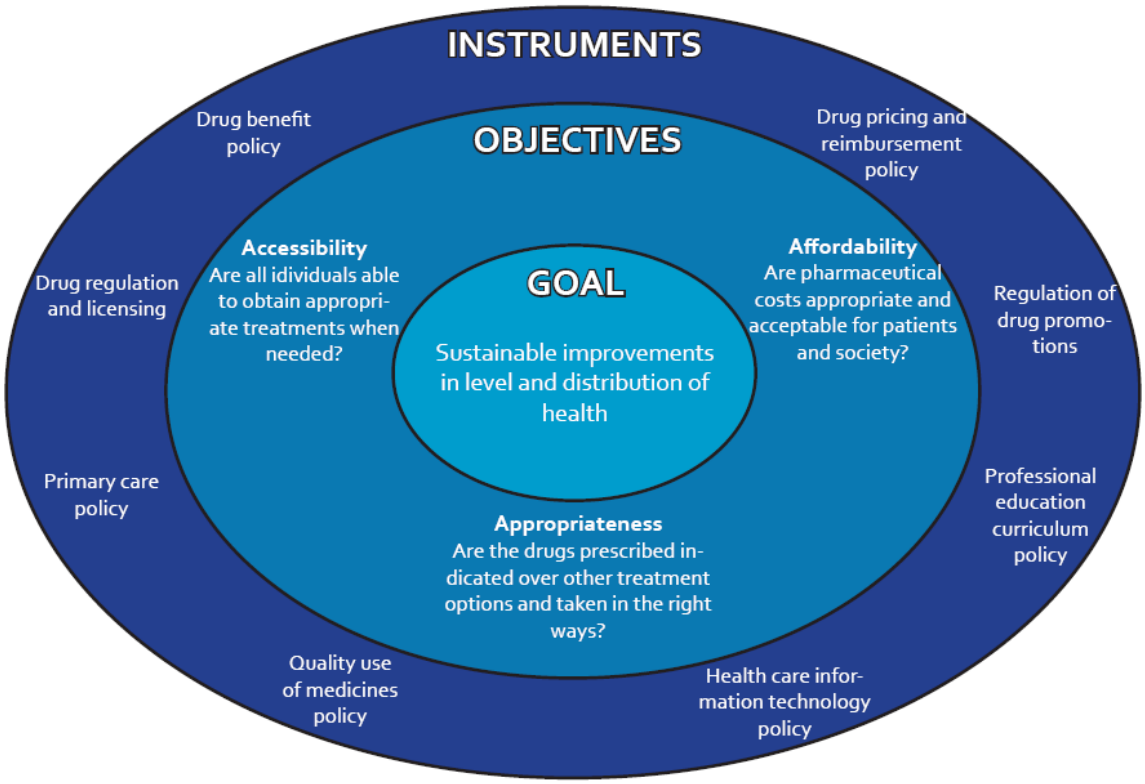
Patel JP, Auyeung V, Patel RK, Marsh MS, Green B, Arya R, et al. Women's views on and adherence to low-molecular-weight heparin therapy during pregnancy and the puerperium. Journal of thrombosis and haemostasis : JTH. 2012;10:2526-34.

Noble S, Finlay I. Is long-term low-molecular-weight heparin acceptable to palliative care patients in the treatment of cancer related venous thromboembolism? A qualitative study. Palliative Medicine 2005; 19: 197-201

Noble S, Prout H, Nelson A. Patients’ Experiences of LIving with CANcer associated thrombosis: the PELICAN study. Patient Preference and Adherence. 2015;9:337-345.

Ritchie J, Spencer L. (1994). “Qualitative data analysis for applied policy research.” In Bryman A, Burgess R, eds. Analysing Qualitative Data. London: Routledge: 173-194.

Appendix A: "Triple-A" Framework for Pharmaceutical Policy Analysis



Adapted from: Morgan S, Kennedy J, Boothe K, McMahon M, Watson D and Roughead E. (2009) Toward an Understanding of High Performance Pharmaceutical Policy Systems: A "Triple-A" Framework and Example Analysis. *Open Health Services and Policy Journal:2;* 1-9

Appendix B: Participant Characteristics and Demographics

Clinician Demographics Characteristics (n = 18)	N	%
Type of Clinician		
Primary Care Physician	2	11%
Internist	2	11%
Oncologist	3	17%
Hematologist	4	22%
Emergency Physician	4	22%
Pharmacist	3	17%
Years of Practice		
<5 years	3	17%
years	5	28%
>15 years	10	55%
Work setting		
Urban	14	78%
Suburban	2	11%
Rural	2	11%