ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

The Ontario Drug Policy Research Network Drug Class Review on Chronic Hepatitis B Medications

Final Report of Qualitative Study Results

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Executive Summary

Background: The Ontario Drug Policy Research Network (ODPRN) conducted a drug class review of chronic hepatitis B (CHB) therapies, which was selected as part of a formulary modernization initiative by the Ontario Public Drug Programs. This report highlights the findings of the qualitative study performed within the drug class review to determine the experiences of managing CHB.

Methods: We used qualitative methods in a framework approach. One-on-one telephone interviews were conducted with 2 infectious disease specialists, 4 hepatologists, and 5 patients. 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 to our framework, and the framework was adapted to convey specific experiences and perceptions relevant to appropriateness and accessibility of CHB.

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

Patient affordability was described as having a great influence on CHB therapy selection: Physician participants in our sample described that they frequently prescribe lamivudine and standard interferon to Ontario Drug Benefit (ODB) eligible patients over 40 years of age with a viral load >1,000IU/mL and stage 3 fibrosis or cirrhosis. Most of these participants noted that they would prefer to use tenofovir as a first-line therapy, but sometimes refrain from doing so because of the high cost of medications for those without coverage. Patient participants in our sample were reluctant to comment on affordability themes and all currently have third party coverage. Other influences on prescription included additional patient characteristics, such as disease severity, genetics, guidelines, research evidence, and physician specialty.

Physician participants desire revisions to Exceptional Access Program (EAP) criteria and cessation of annual renewal applications: Physician participants perceive that the EAP criteria for tenofovir and antecavir are not evidence based and should be revised to include patients with slightly less severe disease states. They believe it is more cost effective to cover these therapies for patients before they become cirrhotic. The turnaround time for an application for an average case was perceived to be reasonable, but not for emergencies. The requirement for renewal was described as unnecessary for cirrhotic patients who need to be on life-long therapy.

Challenges with CHB screening and diagnosis were perceived as barriers to cost-effective care: CHB was described an "invisible" disease and participants noted that patients may not perceive symptoms until it is well advanced. Those who discover their condition later in life may be more likely to be on life-long therapy. Stigma associated with CHB may be a barrier for patients to seek appropriate treatment or to request screening. Neonatal vaccination and screening of high risk patients was described as necessary to improve health outcomes and reduce long term costs to the health care system.

Conclusion: The findings from the qualitative study of the CHB drug class review informed the methods of other ODPRN research units conducting studies as part of the review, and helped to contextualize the review's results. Overall, our findings shed light on the experiences of prescribing CHB therapies, and unveil important information that has the potential to impact CHB care across Ontario.

Part 1: Introduction and Background

The Ontario Drug Policy Research Network (ODPRN) recently received funding to conduct 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) at the Ministry of Health and Long-Term Care (MOHLTC) to select key priority areas and topics for formulary modernization, conduct independent drug class reviews, and disseminate the results of the reviews to the OPDP to facilitate informed decision making on public drug funding policies. Chronic Hepatitis B (CHB) therapies were selected as a key priority area and topic for the ODPRN's seventh drug class review.

There are two types of CHB therapies: interferon therapies and nucleoside or nucleotide analogues. The goal for treatment is to prevent disease progression and induce disease regression. There are two interferon (pegylated, Interferon Alfa-2B) and five nucleoside/tide analogues (adefovir, entecavir, lamivudine, tenofovir, telbivudine) available in Canada. In the last couple of years, international guidelines have been updated to recommend tenofovir and entecavir as first line drugs for the treatment of CHB (Coffin, 2012). In Ontario, Interferon Alfa-2B, adefovir, entecavir, lamivudine, and tenofovir are available for access through the Ontario's Drug Benefit (ODB) Exceptional Access Program (EAP). Lamivudine is the first-line nucleoside/tide analogue which is available for patients with stage 3 fibrosis or HBV DNA > 1,000IU/mL. Adefovir, Entecavir, and Tenofovir are available for patients only if their viral load is high (> 1 x 106 IU/mL) or they have stage 4 fibrosis. There is limited information on how physicians decide to prescribe CHB for ODB eligible patients.

Phase I of the ODPRN qualitative unit work involved exploring the various factors that may be related to prescribing, dispensing, and using CHB therapies. This information was important for understanding and contextualizing prescription and usage patterns in Ontario, as well as to highlight any health equity issues that may be prevalent but are currently unknown. The findings from the qualitative study were also used to inform the research plans of the other drug class review research units to ensure that stakeholder issues and priorities were being considered in their analysis. Phase II of the ODPRN qualitative work involved assessing the social acceptability and feasibility of the final results and recommendations proposed by the ODPRN research team.

Part 2: Phase I Methods

Design

We used a framework approach (Ritchie & Spencer, 1994), which allows researchers to focus on specific areas of interest and obtain findings that may be more applicable and relevant to policy questions. However, the approach also enables researchers to incorporate new ideas, emergent issues, or unanticipated results. The framework selected for this study was the "Triple-A" framework for pharmaceutical policy analysis developed by Morgan et al. (2009; see Appendix A). This framework highlights the need to explore affordability, accessibility, and appropriateness of drugs when determining policy-relevant issues.

Sampling

Stakeholders identified for the CHB drug class review include primary care physicians (PCPs), gastroenterologists, infectious disease specialists, hepatologists, and patients. Inclusion criteria are clinicians (i.e., PCPs, gastroenterologists, infectious disease specialists, hepatologists) who have prescribed or dispensed CHB medications and patients who have current or prior experience using CHB medications.

A purposive sampling approach using a convenience sample was used to recruit participants who will be involved in or affected by drug policy decisions related to chronic hepatitis B. Given the rapid timelines for this study, we aimed to recruit 6-8 participants from each stakeholder group (i.e., clinicians and patients). We anticipate this amount of participation may be sufficient to reach saturation amongst relatively homogenous groups of participants (Kuzel, 1999).

Recruitment methods included 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 accounts (i.e., Twitter, Facebook), and g) snowball sampling (i.e., asking participants to connect with individuals they know for the purpose of recruitment to the study). Participants were recruited from across Ontario.

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 October 2014 and January 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 input from clinicians 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 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). This comprised the coding framework, which was reviewed by the qualitative research team and was

then applied to the data by two analysts during in-depth analysis. Inter-rater reliability between the two analysts was > 80%. The analysts 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 and PCPs, a literature scan was performed to gather any relevant qualitative literature on patient and physicians preferences and experiences. The search was performed in Medline and the search terms used were: Hepatitis B, access or barrier, Canada, factors affecting access, qualitative, prefer, and all the individual CHB therapy names.

Research Ethics

This study was approved by the St. Michael's Hospital Research Ethics Board in Toronto, Ontario, Canada in October 2014.

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

Part 3: Phase I Findings

Participant Demographics

Patients

A total of five patients with CHB were interviewed. The patient group was composed of 3 (60%) males and 2 (40%) females. Initial diagnosis and prescription of CHB medication was done by a liver specialist for all participants. In terms of current prescription, the sample was equally split between tenofovir and entecavir; however, one participant was not on any medication. Of participants on medication, the duration of medication use ranged from over 15 years (n=4, 50%) or 5-15 years (n=4, 50%).

Physicians

There were a total of 6 specialist physicians that participated in the study: 2 (40%) infectious disease specialists and 4 (60%) hepatologists. The specialists were highly experienced, with half the sample practicing for more than 15 years and the other half between 5-15 years. Of this sample, 5 specialists (80%) practice in urban settings and 1 specialist (20%) in suburban settings. All physician participants were passionate about access issues around CHB.

Detailed participant demographics can be found in **Appendix B**.

Key Themes Related to Chronic Hepatitis B Therapies

The following findings are based on the experiences and perceptions of interview participants, which have been summarized into three themes.

Factors that influence the prescription of Chronic Hepatitis B Therapies

- Patient Affordability
- Patient Physiology
- Guidelines & research evidence
- Physician specialty

Perceptions of Exceptional Access Program

- Criteria
- Application process

Challenges with Chronic Hepatitis B Management in Ontario

- Perception of symptoms
- Stigma
- Screening in primary care

Detailed findings on each of these themes are described below.

Factors that influence the prescription of Chronic Hepatitis B Therapies

Patient Affordability

Clinician participants described that patient affordability was one of the primary factors they considered when prescribing CHB therapies. Lamivudine was perceived as the most commonly prescribed because it is the most affordable out of the oral antiviral medications. Some physician participants would have preferred to prescribe tenofovir or entecavir as first line therapy, but described having to go against this preference for ODB eligible patients or those who do not have private coverage. For example, patients who are non-cirrhotic, have stage 3 fibrosis, and high levels of viral replication are not eligible to receive coverage for tenofovir or entecavir. Similarly, interferon alfa-2B, also known as standard interferon, was perceived to be more commonly prescribed than pegylated interferon for ODB patients because pegylated interferon is not listed for coverage. Pegylated interferon was preferred by clinician participants because it was perceived to have fewer side effects than standard interferon.

As an alternative to prescribing against their preferences, physician participants have described applying for "compassionate use" programs through pharmaceutical companies or trying to enroll their patients in clinical trials. This was especially true for pregnant patients with high viral loads. Non-cirrhotic pregnant patients with high viral loads, fewer than 40 years of age, who do not have private coverage, were described as particularly disadvantaged. Patient participants in our sample were reluctant to comment on affordability themes and all currently have third party coverage.

Patient Physiology

Physician participants described a number of additional patient characteristics which played a role in their decision-making for CHB therapies. These included disease severity, age, and genetics. Good candidates for interferon were described as those with hepatitis B genotype A, a high serum alanine aminotransferase and a low viral load. Physician participants also prescribe interferon to younger patients who desire a defined course of therapy, rather than a life-long therapy. Oral antivirals were described as more likely to be prescribed as a life-long therapy. Some participants preferred to treat patients with tenofovir if the patients have advanced liver disease, before they become cirrhotic, because they believed that the duration of therapy will be shorter. Others described reserving lamivudine for patients with very low or undetectable viral load and inactive disease, with the goal of preventing reactivation. Pregnant women with a viral load below 6 logs were described as not requiring therapy. Some clinician participants preferred to prescribe lamivudine less often because of their perception that the risk of resistance is higher than with other oral antivirals. Additionally, they also described a preference to prescribe tenofovir, not entecavir, to patients who have developed resistance to lamivudine (Table 1). Patients who have developed resistance to lamivudine were described as highly likely to develop resistance to entecavir as well.

Guidelines & research evidence

Many participants described that for patients without private coverage, there is a discrepancy between what is recommended in international guidelines and what is happening in practice. Most explained that their preference is to align with the guidelines whenever possible. Many also explained that they keep informed regarding published research studies on the different CHB therapies offered. The list of guidelines mentioned came from associations for the study of liver disease from Canada, Europe, and the United States. All these guidelines recommend more potent therapies, such as tenofovir and entecavir, as first line therapies.

Physician Specialty

Interviews with physicians revealed that there may be some differences between the prescription habits of infectious disease specialists and hepatologists. The four hepatologists we interviewed all believed that patients on lamivudine have a high risk of developing resistance. Whereas the two infectious disease specialists had differing opinions, with one believing that risk of resistance is just speculation. It was suggested that a specialist's knowledge of and beliefs about disease management may differ depending on the size of their CHB case load and their experience treating the disease. Some clinician participants expressed concern that data from research studies may be interpreted differently by different specialties and that may influence prescription habits.

Comments on specific formulations

The following table summarizes the comments from physicians regarding each of the different CHB therapies.

Table 1. Perceptions of specific formulations

Drug Name	Key points
Interferon Alfa-2B	• Administered 3 times a week • More commonly prescribed for ODB eligible patients because it is listed on the formulary
PEG	• Administered once a week • Less prescribed because it is not covered

	• Perceived to have less side effects than interferon alfa-2B
Adefovir	• Approved but not often used • Perception that tenofovir is a better option
Entecavir	• Once a patient has lamivudine resistance, risk of entecavir resistance is fairly high • Preferred over tenofovir if patient has pre-existing kidney disease or high strong risk factors for kidney disease • Mild side effects • Low frequency of resistance • Have to take it on an empty stomach-less convenient for patients
Lamivudine	• Most commonly prescribed because of affordability • Risk of developing resistance • Requires careful monitoring to avoid flares or viral breakthrough • Other nucleoside or nucleotide analogs are recommended over lamivudine in international guidelines • E-antigen negative patients with a relatively low hepatitis B viral load like a carrier, but going for immune suppression are good candidates
Tenofovir	• Most preferred option among hepatologists • No resistance mutations associated with it • In a small percentage of people causes renal kidney toxicity • If it went generic, would be used more frequently

Patient participants did not have specific comments on formulations. They found it difficult to perceive the effect of the medication but they believe the CHB therapies have positive effects because of the routine test results they get from their specialist.

Theme Summary:

The primary factor which was perceived to have the greatest impact on prescription of CHB therapies was affordability. For patients over 40 years of age without private coverage, and viral load >1,000IU/mL, lamivudine and standard interferon are more commonly prescribed. Most physician participants noted that they would prefer to use tenofovir as first-line therapy.
Other influences on prescription included patient physiological characteristics, such as disease severity and genetics, guidelines and research evidence, and physician specialty. Infectious disease physicians may have slightly different perceptions of drug resistance and preferences for therapy.

Perceptions of Exceptional Access Program

Criteria

Physician participants had the perception that the EAP criteria are not based on recent research evidence. They believed that the criteria may be loosely based on earlier studies of shorter duration that described uncertainty about the benefits of achieving virologic suppression. Specifically, the criteria for age were described as unnecessary because participants did not perceive that age is a predictor of health outcomes for CHB.

"*Patients die of this disease in their 20s and 30s as much as they die in their 60s and 70s so there is no reason that 40 was picked and as far as I can tell was picked out of a hat to justify why patients should or should not get therapy. I mean the fact that more, that older people die of this disease more than young people is true of any disease so that's just as people age they are more likely to die*"—physician

In addition, participants believed that the criteria should not be restricting tenofovir and entecavir to patients with cirrhosis or stage 4 fibrosis because it may be more cost effective to treat patients before they become cirrhotic. They explained that preventing complications from cirrhosis will result in long term savings to the health care system and may require fewer patients to be on life-long therapy. Patients in their practices who are on lamivudine also require more monitoring and follow-up than those on tenofovir and entecavir. Participants acknowledged that given resource constraints in the public payer system, it is not possible to treat everyone. However, they felt strongly that the criteria should be brought down from cirrhosis to a less severe disease state.

"*I would be quite happy if the criteria required some evidence of fibrosis and even if they wanted to say stage 2 fibrosis which is, I think a little late, but I would be, I think that would be reasonably in line with what they have done with Hepatitis C*." —physician

"*I'm not suggesting that the EAP should be so wide that we should say Hepatitis B infection equals treatment. I think it's fair to have, demonstrate some criteria of liver damage associated with the infection, but once that's been demonstrated we should be able to use the most effective therapies that are available.*" —physician

The criteria also do not include provision for pregnant women with viral loads greater than 6 logs. Participants expressed concerns that pregnant women who do not have private coverage and happen to have higher viral loads may be more likely to transmit CHB to their children.

Application Process

When physician participants were asked about the EAP application process, they mentioned that the turn-around time for new applications was reasonable. Specific cases where they noted barriers to the application process were: emergencies, complex cases, and CHB mono-infections. Specifically, participants wished to have an express application for patients who are pregnant or in crisis situations (e.g., liver failure). Liver disease was perceived as a mostly invisible disease during which symptoms may not manifest until it is very advanced and in need of immediate intervention. So, emergency situations are not uncommon. Participants also felt that any cases that are slightly unique are usually denied coverage. They held a belief that the reviewers of the EAP application

may not have experience with unique cases which may require exceptions beyond the stipulations in the criteria.

Participants also did not feel it necessary to have an annual renewal application because most EAP patients are already in the cirrhosis stage and need to be on CHB therapies for the rest of their lives. The administrative work needed for submitting an application every year was described as a burden for physicians and potentially dangerous for patients who cannot live without their medication. Patients who are co-infected with HIV were perceived to have no barriers to coverage because they can get tenofovir under ODB's General Benefit Program, but those with CHB mono-infections are subject to the EAP renewal process. One participant's suggestion was to have a renewal of coverage every 5 years. Another was to have an electronic system where patients and doctors are alerted about impending renewals and where test results and other documentation can be uploaded directly, to avoid the use of forms. A third suggestion to improve the whole process was to have a linkage between Ontario Public Health Labs and EAP, so that test results can be shared and the administrative burden may be reduced.

"We don't have a warning system, an email warning system or a fax warning system that your timing is coming up. Think of a crisis situation where someone is running out of a drug, that could lead the emergence of resistance and failure if you have interruption"—physician

Theme Summary:

Physician feedback on EAP criteria:
- perceive that these are not based in evidence
- believe it is more cost effective to cover patients before they become cirrhotic

Physician feedback on EAP application:
- turnaround time for an average case is reasonable, but not for emergencies
- requirement for renewal is unnecessary for cirrhotic patients

Challenges with Chronic Hepatitis B Screening & Management in Ontario

Perception of Symptoms

One of the main challenges mentioned by patient and clinician participants is that CHB does not always manifest with symptoms in its early stages. Many patients in our sample were unaware of their diagnosis for many years until they either a) decided to donate blood or b) were admitted to the hospital after an unexplained "flare-up". After discovering their diagnosis, some of these patients agreed to participate in a 6month monitoring plan with a specialist. After this point, they were referred to a specialist who prescribed CHB therapy or changed therapy based on any changes in viral load every 6 months. Patient participants did not perceive any changes in their quality of life which they would attribute to these therapies. They described feeling fortunate that they were able to receive treatment early enough to prevent substantial liver damage. Physician participants described that those who discover their condition in its later stages are more likely to require life-long therapy.

P: "*For a long time, [my viral load] was two thousand something, then all these tests shot up to four hundred some million…*"

I: "*Okay, and so, aside from the, the change in the test result, did you experience any symptoms?*"

P: "*No. All I can say is I think his monitoring system, every six months, blood test, ultrasound; it's very, very good and very, very effective. Without that, I wouldn't have known anything.*"—patient

Stigma

Patient and clinician participants both mentioned that there is a stigma associated with CHB. Patient participants described that CHB is not talked about openly in their communities and only one participant mentioned speaking to immediate family about this condition. Those who have not spoken to their immediate family regarding CHB suspect that other family members may also be living with or may have died as a result of this chronic condition.

"*Hep B is a taboo for many people, certain, especially certain ethnic groups. Nobody wants to say, nobody wants to know, but that is one of the problems.*"—patient

Physician participants described that in their practices, stigma seems to stems from a misunderstanding about the routes of transmission for CHB. There may be a perception in certain ethnic groups that CHB can be transmitted through sharing cutlery, shaking hands, or hugging. So, those who have CHB may be isolated by their families, even if the rest of the family is vaccinated. Physician participants also hypothesized that the rates of diagnosis of CHB may be low because of a perceived "morality" associated with the disease. So, those who suspect they have CHB may not want to get tested or participate in certain types of transmission, such as injection drug use and unprotected sex. Participants also felt that stigma may also persist amongst certain physicians who may unintentionally screen for only certain types of patients.

"*They think well I would test my poor Chinese patient because he or she is from a low socioeconomic status and likely to have Hep B but I am not going to test my wealthy successful businessman because you know, those kind of people don't get Hep B which of course is nonsense*" —physician

Prevention & Early Detection

Patient and physician participants perceived a need for neonatal vaccination, improved screening, and early detection of CHB. It was mentioned that Ontario is one of the few places in the developed world where the Hepatitis B vaccine is administered at the pre-teen stage. Participants felt that those born in high risk ethnic groups must be protected right from infancy because of risk of transmission from parents, grandparents, and caregivers. It was mentioned that the Hepatitis B neonatal vaccines have been recommended by the World Health Organization as well as the Centre for Disease Control. The prevention of new infections was seen as a way to reduce long term costs to the health care system, such as reduced need for expensive prescriptions.

"*We are seeing infections every year in Ontario that are completely avoidable*" –physician

Physicians described that those who develop a CHB early in life are at greater risk for developing liver cancer later in life. Screening and early detection were also seen as lacking in Ontario. It was suggested that PCPs practicing in Asian or south Asian communities may be more likely to screen for CHB. However, the perception was that the vast majority of PCPs do not routinely screen any patients for hepatitis B because they do not recognize the risk factors associated with the disease.

"*I don't think they do anything until you have problem, problem in your blood test*"—patient

"*We should try to catch it early so that people get taken care of. If you wait until it becomes cirrhosis and cancer, it's too late, it's too expensive*" –patient

Theme Summary:

Challenges in hepatitis B screening management in Ontario are:

- CHB is an "invisible" disease and patients may not perceive symptoms until it is well advanced
- Stigma associated with CHB may be a barrier for patients to seek appropriate treatment
- Neonatal vaccination and screening of high risk patients is needed to improve health outcomes and reduce long term costs

Qualitative Literature Scan

There were 21 relevant qualitative research articles published on CHB found in MEDLINE. Most of these were studies about the factors influencing CHB screening and management, and only one about specific treatment with CHB therapies. The study regarding CHB therapies was an American questionnaire about patient preferences completed by 421 patients. Lamivudine was the most well-known drug among study participants. Most preferred pill formulation with once-daily dosing and a defined duration of therapy. Drug efficacy was described as the most important factor when choosing therapies. When shown the risks, benefits, and efficacy of the different CHB therapies available, entecavir was the most preferred choice. The majority of patients were willing to spend no more than $8 USD daily for therapy (Lim, Aung et al. 2013).

The remaining studies on CHB management included a cross sectional study conducted in Toronto, Ontario (Li, Zhang et al. 2013) which revealed that CHB stigma is associated with reduced rates of screening for CHB. The rest of the studies were conducted in the United States and Australia. The essential components of successful CHB management were described as: a systematic approach to screening populations at risk; consensus on clinical guidelines; effective communication between patients and health providers; and improved knowledge and resources, on CHB infection and management, for general practitioners (Wallace, 2013, 2012). General practitioners described a lack of self-efficacy with managing CHB due to inadequate training and noted stigma and apathy in their patients (Yang, 2013).

Part 4: Discussion

Key Findings

This study suggests that many Ontario specialist physicians may be practicing in a way that is inconsistent with their preference to prescribe tenofovir for ODB-eligible patients who have an active disease but are not cirrhotic. Additional influences on prescription choices, such as disease severity, genetics, guidelines, and research evidence, are over shadowed by patient affordability. Physician participants desired revisions to EAP criteria and cessation of annual renewal applications for cirrhotic patients. The turnaround time for an application for an average case was perceived to be reasonable, but not for emergencies. Overall, they believe it is more cost effective to cover more potent therapies, such as tenofovir or entecavir, for patients before they become cirrhotic. The lack of routine CHB screening and detection were perceived as barriers to cost-effective care. For example, CHB was described an "invisible" disease and patients may not perceive symptoms until it is well advanced. Stigma associated CHB may also be a barrier for patients to seek timely treatment or to request screening. Neonatal vaccination and screening of high risk patients was described as necessary to stop the incidence of new infections. The summary of interview responses revealed that the public drug reimbursement system would see a reduction in long terms costs if more Hepatitis B infections were prevented and if CHB patients were diagnosed earlier and treated earlier.

Health Equity Considerations

The findings from this study highlight the disparity in access to appropriate CHB treatment between individuals who do and do not have private drug coverage. This inequity exists in part because of the high cost of clinically effective CHB, as well as the obstacles to accessing CHB drugs through the EAP. ODB eligible patients who are under 40 years of age, non-cirrhotic, have stage 3 fibrosis, and high levels of viral replication are not eligible to receive coverage for CHB therapy. Non-cirrhotic pregnant patients, who are under 40 years of age, have high viral loads greater than 6 logs, and who do not have private coverage may be particularly disadvantaged. They may also risk transmitting the virus to their children during birth. Physicians may refrain from prescribing CHB therapy to these patients, which may result in significant differences in long-term health outcomes, reduction in quality of life, and increased risk of disease transmission.

Limitations

It should be noted that the majority of these themes were developed from findings in specialist physician interviews. Recruitment of patients and primary care physicians was particularly challenging and the five patient interviews which were conducted did not contain rich data. Interviewers noticed that some patient participants were hesitant to elaborate on questions about affordability and disease transmission. Interview data revealed that there is a stigma associated with CHB which may have hindered many from participating. Specialist physician participants also cautioned interviewers that most patients may not have knowledge about access issues surrounding CHB therapies unless their specialist has had a discussion with them.

Li, Tang et al. (2012) found that there is a stigma associated with CHB within East Asia communities, which deceases the likelihood of screening for this population. The associated stigma with the disease may influence patients' willingness to participate in research interviews. Study invitations were extended to primary care; of the participants who did respond, they indicated they did not see CHB patients or upon initial screening they were immediately referred to a specialist, thus did not believe they would be able to contribute.

It should also be noted that qualitative findings are not representative of the general population of individuals from which our study sample was drawn. There may be bias in sampling given that those who responded to interview requests may have been more likely than non-responders to be vocal about discussing CHB therapies and may be more highly involved in initiatives to improve access to CHB therapies. In an attempt to limit bias, we engaged in negative case sampling, which is to select interview participants who differ from the response trend observed in the recruited sample to date, so as to introduce different viewpoints.

Part 5: Conclusions

The findings from the qualitative study of the CHB drug class review aid in contextualizing the findings from other studies within the drug class review. On a broader scale, our study findings fill a gap in knowledge on CHB prescription and how prescription may be impacted by physician and patient factors. Overall, our findings shed light on the experiences of prescribing and using CHB for dementia, and unveil important information that can impact how patients in need can access these drugs across Ontario.

Part 6: Phase II Methods

Following the completion of this study and the accompanying CHB research studies, a consolidated report was drafted which included a set of potential reimbursement options for the funding of cognitive enhancers for dementia. 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 been developed, the participants from phase I 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 invites 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 then used by the team to make any necessary revisions to the reports.

Citizens' Panel

We have recruited a diverse set of 15 individuals from the general public to form a Citizen's Panel. The Citizens' Panel provides feedback on recommendations from all drug class reviews. Feedback from participants will be 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 key issues, findings, and policy implications were presented and members engaged in group discussion on the recommendations. Citizens' Panel members then 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 allows each person to express their idea(s); each person's opinion is taken into account (compared to traditional voting where only the largest group is considered). The findings from the citizens' panel surveys and discussion were then used by the team to make any necessary revisions to the reports and draft reimbursement options.

Part 7: Phase II 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 11 interview participants from phase I were invited to participate in a member checking and acceptability survey exercise. A total of four specialist physician participants completed the survey.

Participants were presented with the following policy options:

Option A: Lamivudine Limited Use and updated EAP criteria (entecavir first line option)
Option B: Lamivudine Limited Use and updated EAP criteria (entecavir and tenofovir first-line options)
Option C: Lamivudine and entecavir Limited Use and updated EAP criteria (tenofovir first line option)

Most of the specialist physician participants believed that policy option C was the most favourable of the three options because patients would have access to a therapy which they perceive is consistent with current international clinical guideline recommendations for CHB treatment (i.e., entecavir). Majority of participants were not in favour of option A because they believed that it did not align with guidelines. They stated that lamivudine may be cost effective, but it is not an effective therapy to treat CHB. Participants also felt that the EAP criteria for option B were too restrictive.

Citizens' Panel

The ODPRN Citizens' Panel meeting on cognitive enhancers for treatment of CHB took place on Monday June 22nd, 2015. There were six members in attendance during the meeting. Seven members completed the pre-meeting survey, and six members completed the post-meeting survey.

Prior to the meeting, the ODPRN research team, in consultation with clinician stakeholders, developed a fourth option:

Option D: Lamivudine, entecavir, and tenofovir all Limited Use

Citizens' Panel members were presented with all four options. The most preferred choice pre-meeting was Option D. This preference shifted slightly post-meeting as the preferred choice became option C (see table 2). While participants prefer option D because it encourages the greatest access, they also felt that it may place a large financial burden on the system. The least favorable choice, both pre and post meeting, was option A. Participants felt that option A was redundant in comparison with option B.

Table 2. Citizens' Panel final outcome rankings.

	Mean Ranking (1 = Most Acceptable 4 = Least Acceptable)
Option A	3.7
Option B	2.0
Option C	**1.7**
Option D	2.7

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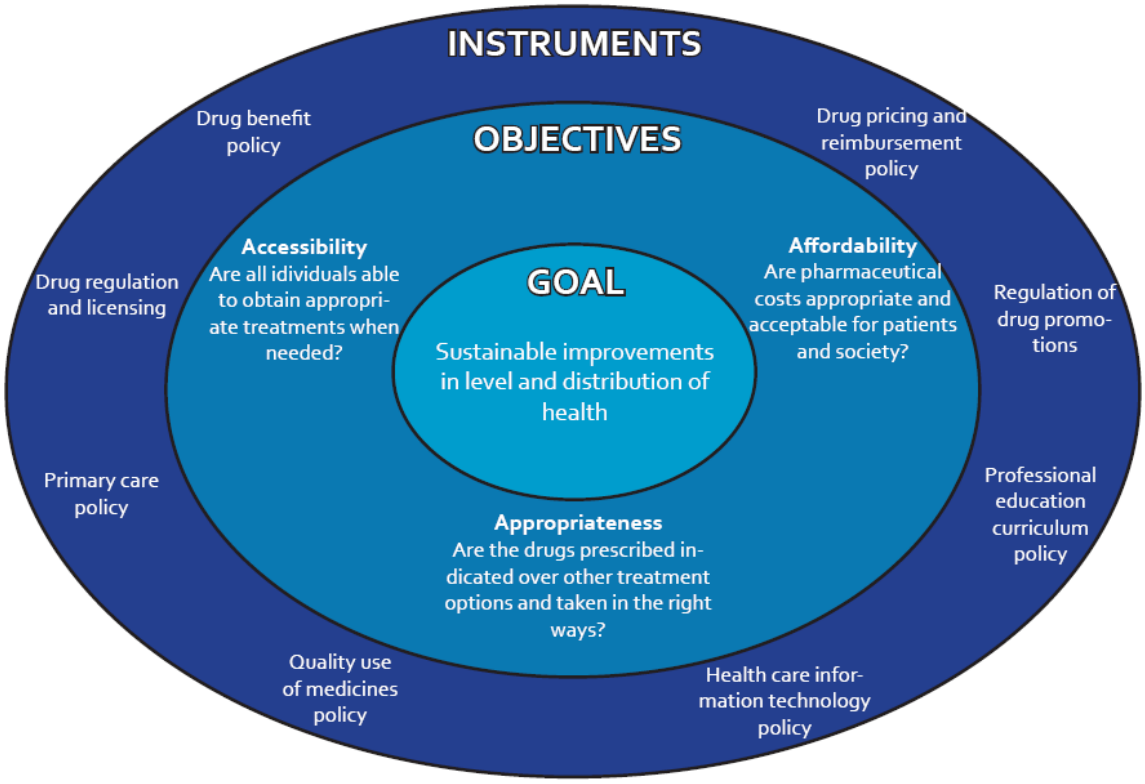
Appendix A: "Triple-A" Framework for Pharmaceutical Policy Analysis



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

Patient Demographic Characteristic (n=8)	n	%
Patient Gender		
Male	3	60%
Female	2	40%
Time on CHB Medications		
< 15 year	2	40%
5-15 years	3	60%
First Prescribed By:		
Specialists (infectious disease, hepatologists)	4	100%
CHB Patient is Currently On:		
Tenofovir	2	40%
Entecavir	2	40%
No medication	1	20%

Physician Demographic Characteristic (n=6)	n	%
Physician by Specialty		
Infection disease	2	40%
Hepatology	4	60%
Years of practice		
5-15	3	50%
>15	3	50%

Geographic Location		
Urban	5	80%
Suburban	1	20%