

Comprehensive Research Plan:
Treatment of Chronic Hepatitis B

Pharmacoepidemiology Unit

November 7, 2014

ODPRN Drug Class Review Proposal Pharmacoepidemiology Unit

Study Title: Epidemiologic Analyses of Chronic Hepatitis B Treatment

- Objectives:**
1. To examine national and provincial trends in use of treatments for chronic hepatitis B across Canada
 2. To perform cross provincial comparisons of the trends in drugs used for the treatment of chronic hepatitis B
 3. Describe the indications of use for the medications used for the treatment of chronic hepatitis B
 4. To describe characteristics of patients with hepatitis B treated in Ontario
 5. To investigate the treatment patterns of patients who newly initiate treatment for chronic hepatitis B in Ontario

Objective 1a: National and Provincial Trends in medications used to treat hepatitis B

- Study Design:**
- Design: Time series analysis with quarterly time intervals
- Study period:
- National and provincial trends (IMS Compuscript): January 2009 to September 2014
- Population: All provinces
- Data Sources:
- IMS Compuscript: aggregated data for all prescriptions dispensed at retail pharmacies across Canada

- Study Population:**
- Inclusion Criteria:**
- All privately and publically-funded treatment prescriptions dispensed in Canada;
 - Standard interferon
 - Pegylated interferon
 - Lamivudine
 - Adefovir
 - Entecavir
 - Telbivudine
 - Tenofovir

- Outcome(s) of Interest:**
- Measured over entire study period (quarterly):
- Number and rate of prescriptions dispensed
 - Total cost of prescriptions
 - Total number of units dispensed
- Stratify all analyses by:
- Province
 - Payer (Public, Private)

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- Limitations:**
- The IMS data is only available at the prescription and unit level. Therefore, national and provincial trends in prescribing cannot differentiate by indication.
 - These medications are used for many indications, thus the utilization is not specific to hepatitis B.

Objective 1b: Cross-Provincial Changes in Prescribing of Treatments Used for Chronic Hepatitis B in Public Drug Programs

- Study Design:**
- Design: Time series analysis with quarterly time intervals
Study period: January 2000 to December 2013
Data Source:
- National Prescription Drug Utilization Information System Database (NPDUIS): aggregated data for all publically funded prescriptions dispensed in Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, PEI and BC
 - Ontario Drug Benefit Database (ODB): individual level data for all publically funded prescriptions dispensed in Ontario. This dataset contains additional variables (long-term care residence, public drug plan coverage) that is not available through NPDUIS
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- Study Population:**
- Inclusion Criteria:**
- All publically-funded treatments of chronic hepatitis B prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI and BC
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- Outcome(s) of Interest:**
- Measured over entire study period (annually)
- Number and rate of users
 - Number of prescriptions dispensed
 - Total costs of treatment
 - Average cost of treatment per user
- Stratify all analyses by:
- Province
 - Age (18-65, 66+)
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- Limitations:**
- Publically-funded, patient-level prescription data is only available as of 2005 for PEI and 2006 for BC. We are therefore unable to determine use prior to that date.
 - There is no patient-level data available for publically paid prescriptions in Quebec, Newfoundland & Labrador or the Territories. Therefore, we will be unable to make comparisons between Ontario rates and rates of use in these provinces.
 - These medications are used for other indications and thus the utilization is not specific to hepatitis B.
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Objective 2a: Describe the Utilization of Treatments Used for Chronic Hepatitis B by indication

Study Design: Design: Cross-sectional analysis
Study period: January 2012 to December 2013
Data Sources:

- Ontario Drug Benefit Database (ODB)
- Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)
- National Ambulatory Care Reporting System Database (NACRS)
- Ontario Health Insurance Plan Claims Database (OHIP)
- Ontario HIV Database (HIV)

Study Population: **Inclusion Criteria:**

- All publically-funded beneficiaries with a prescription for a medication used for hepatitis B

Cohort Entry Date: defined as date of first prescription of any hepatitis B treatment over the study period

Index Drug: Defined as the product that was prescribed on cohort entry date

Variables of Interest:

For the established cohort, measure:

- Number of patients
- Number of prescriptions
- Prevalence of drugs used to treat hepatitis B among disease cohorts: (based on the year prior to index)
 - HIV
 - Hepatitis B
 - Hepatitis C
 - Hepatitis delta
 - Multiple Diagnosis
- Proportion of hepatitis B prescriptions by indication (i.e. diagnosis)

Stratify analyses by:

- Drug
- Age groups (18-65, 66+)

Limitations:

- No information on medication use when hospitalized.
- Individuals aged 65 are grouped in with those aged 18-64 because – although they have universal drug coverage, we have incomplete medical records for these patients in the prior year (e.g. when aged 64) since they were not eligible for public drug coverage at this time. Therefore, it is inappropriate to group these in with those aged 66+.

Objective 2b: Characteristics of Patients Treated for Chronic Hepatitis B in Ontario

Study Design:

Design: Cross-sectional analysis

Study period: January 2012 to December 2013

Data Sources:

- Ontario Drug Benefit Database (ODB)
 - Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)
 - National Ambulatory Care Reporting System Database (NACRS)
 - Ontario Health Insurance Plan Claims Database (OHIP)
 - ICES Physician Database (IPDB)
 - Citizenship and Immigration Canada (CIC)
 - Ontario HIV Database (HIV)
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Study Population:**Inclusion Criteria:**

- All publically-funded beneficiaries with a diagnosis hepatitis B in Ontario who are prescribed treatment for chronic hepatitis B. Defined by: 1-year look back for physician OHIP diagnosis codes or CIHI-DAD admission codes related to hepatitis B

Cohort Entry Date: defined as date of first prescription of any hepatitis B treatment over the study period-

Index Drug: Defined as the product that was prescribed on cohort entry date

Variables of Interest:

For the established cohort, measure:

- Number of patients
- Number and rate of new users
 - New users aged 66 and older defined as having no past chronic hepatitis B use in prior 365 days
 - New users <66 years of age defined as having a prescription for any drug in the past 181-365 days and who didn't have a prescription for hepatitis B treatments in the past 180 days
- Age at cohort entry date (mean, SD, and by category (18-40, 40-65, 66+))
- Proportion of patients who were male
- Proportion of patients residing in LTC at cohort entry
- Proportion of urban residents at cohort entry
- Socioeconomic status (measured using income quintiles at cohort entry)
- Proportion born outside of Canada
 - By geographic region of last permanent residence
- Average cost of treatment prescriptions per person
- Number of patients treated with multiple hepatitis b treatments concurrently
- Prescriber of initial prescription:
 - Specialist
 - Gastroenterology
 - Infectious Disease
 - General Practitioner
 - Other
- Specialist visit in past 3 months prior to index (yes/no):
 - Gastroenterology
 - Infectious Disease
- Number of past hospitalization or ED visit (past 1 year)
- Number of physician office visits within the last 1 year
- Comorbidities
 - Charlson comorbidity score (based on last 3 years of hospitalization data)
 - Individual Components
 - Number of different medications used in past year
 - Coinfections at cohort entry
 - HIV
 - Hepatitis C
 - Hepatitis delta

Stratify analyses by:

- Age groups (18-65, 66+)
 - Born outside of Canada (Yes, No)
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- Limitations:**
- No information on medication use when hospitalized.
 - Individuals aged 65 are grouped in with those aged 18-64 because – although they have universal drug coverage, we have incomplete medical records for these patients in the prior year (e.g. when aged 64) since they were not eligible for public drug coverage at this time. Therefore, it is inappropriate to group these in with those aged 66+.

Objective 3: Investigate the Patterns of Use for Newly initiated chronic Hepatitis B treatments in Ontario

- Study Design:**
- Design: Cohort Study
- Study period: January 2003-December 2013
- Accrual period: January 2009-December 2012
 - Maximum follow-up date: December 2013 (1 year minimum follow-up)
- Data Sources:
- Ontario Drug Benefit Database (ODB)
 - Canadian Institute for Health Information-Discharge Abstract Database (CIHI-DAD)
 - National Ambulatory Care Reporting System Database (NACRS)
 - Ontario Health Insurance Plan Claims Database (OHIP)
 - ICES Physician Database (IPDB)
 - Continuing Care Reporting Systems (for Chronic Care) (CCRS)
 - Citizenship and Immigration Canada (CIC)
 - Ontario HIV Database (HIV)
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- Study Population:**
- Inclusion Criteria:**
- All publically-funded beneficiaries of Ontario with hepatitis B who newly initiate hepatitis B treatment over the study period
 - New users aged 66 and older, defined as having no past hepatitis B treatment prescriptions in prior 365 days
 - New users <66 years of age, defined as having a prescription for any drug in the past 181-365 days and who did not have a prescription for hepatitis B treatment in the past 180 days
 - Past diagnosis of hepatitis B (within 1 year prior to cohort entry date)
 - Cohort 1: Individuals aged less than 66 at time of hepatitis B therapy dispensing
 - Cohort 2: Individuals aged 66 and older at time of hepatitis B therapy dispensing
- Cohort Entry Date:** defined as date of first prescription of any hepatitis B treatment over the study period-
- Index Drug:** Defined as the product that was prescribed on cohort entry date
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Outcomes of interest:
Duration of Hepatitis B Therapy (defined in 2 ways):

- RELAXED DEFINITION OF CONTINUED USE
 - Define ongoing use of therapy according to receipt of a subsequent prescription within 180 days of the prior prescription. Set date of discontinuation as date of last prescription + days supply of final prescription
- STRICT CLINICAL CONTINUATION OF USE
 - Subsequent prescription within 1.5 times the days supply of the prior prescription. If no subsequent prescription, then person discontinued use. Set discontinuation date as date of last prescription plus days supply of final prescription.

For the established cohorts, measure:

- Number and rate of new users
 - New users aged 66 and older defined as having no prescriptions for hepatitis B treatment in prior 365 days
 - New users <66 years of age defined as having a prescription for any drug in the past 181-365 days and who didn't have a prescription for hepatitis B treatment in the past 180 days
- Number of new users with only 1 prescription dispensed over period of continuous use

Among users with more than 1 prescription dispensed over period of continuous use:

- Age at cohort entry date (mean, SD, and by category (18-40, 40-65, 66+))
 - Proportion of patients who were male
 - Proportion of patients residing in LTC at cohort entry
 - Proportion of urban residents at cohort entry
 - Socioeconomic status (measured using income quintiles at cohort entry)
 - Proportion born outside of Canada
 - By geographic region of last permanent residence
 - Average cost of treatment prescriptions per person
 - Number of patients treated with multiple treatments concurrently
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- Outcomes of interest (continued):**
- Prescriber of initial prescription:
 - Specialist
 - Gastroenterology
 - Infectious Disease
 - General Practitioner
 - Other
 - Specialist visit in past 3 months prior to index (yes/no):
 - Gastroenterology
 - Infectious Disease
 - Number of past hospitalization or ED visit (past 1 year)
 - Number of physician office visits within the last 1 year
 - Comorbidities
 - Charlson comorbidity score (based on last 3 years of hospitalization data)
 - Individual Components
 - Number of medications used in past year
 - Coinfections at cohort entry
 - HIV
 - Hepatitis C
 - Hepatitis delta
- Over period of ongoing use:
- Number of different hepatitis B drugs used within 1 year of cohort entry
 - 1
 - 2
 - 3+
 - Clinical outcomes within 1 year of cohort entry
 - All-cause hospitalization
 - Cirrhosis
 - Hepatocellular carcinoma
 - Death
 - Percent adherent after 1 year
 - Analysis: Kaplan Meier curves constructed and Cox proportional hazard model used to test for differences
- Stratify above analysis by:
- Age (18-65, 66+)
 - Born outside of Canada (Yes, No)

Limitations

- No information on medication use when hospitalized.
 - Individuals aged 65 are grouped in with those aged 18-64 because – although they have universal drug coverage, we have incomplete medical records for these patients in the prior year (e.g. when aged 64) since they were not eligible for public drug coverage at this time. Therefore, it is inappropriate to group these in with those aged 66+.
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