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Impact of type of drug insurance on adherence, persistence and costs of antidepressant drugs: A Quebec population-based study

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Impact of type of drug insurance on adherence, persistence and costs of antidepressant drugs: A Quebec population-based study

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Résumé

Contexte: À date, il existe peu de données sur l'adhésion, la persistance et les coûts associés aux antidépresseurs selon le type d'assurance médicament (privé ou public).

Objectif: Comparer selon le régime d'assurance médicament (privé ou public), l'adhésion, la persistance et les coûts des antidépresseurs.

Méthodes de recherche: Une étude de cohorte appariée a été réalisée en utilisant des bases de données du Québec.

Sujets: Nous avons sélectionné 194 patients assurés par un régime privé et 1923 patients assurés par le régime public de la Régie de l'assurance maladie du Québec (RAMQ) (18-64 ans) qui ont rempli au moins une ordonnance pour un antidépresseur entre décembre 2007 et septembre 2009.

Mesures: L'adhésion, mesurée sur une période d'un an, a été estimée en utilisant le *proportion of prescribed days covered* (PPDC). Un modèle de régression linéaire a été utilisé afin d'estimer la différence moyenne en PPDC entre les patients assurés par un régime privé et ceux assurés par le régime public de la RAMQ. La persistance a été comparé entre ces deux groupes avec un modèle de régression de survie Cox, et le coût mensuel d'antidépresseurs ($ CAN) a été comparé entre ces deux groupes en utilisant un modèle de régression linéaire.

Résultats: Le PPDC parmi les patients assurés par un régime privé était de 86,4% (intervalle de confiance (IC) 95%: 83,3%-89,5%) versus 81,3% (IC 95%: 80,1%-82,5%) pour les patients assurés par le régime public de la RAMQ, pour une différence moyenne ajustée de 6,7% (IC 95%: 3,0%-10,4%). La persistance après un an parmi les patients assurés par un régime privé était de 49,5% versus 18,9%

pour les patients assurés par le régime public de la RAMQ (p <0,001), et le rapport de risque ajusté était de 0,48 (IC 95%: 0,30-0,76). Comparativement aux patients assurés par le régime public de la RAMQ, les patients ayant une assurance privée ont payé 14,94 $ CAD (95% CI: $12,30-$17,58) de plus par mois en moyenne pour leurs antidépresseurs.

Conclusion: Les patients assurés par un régime privé avaient une meilleure adhésion, persistance, mais avaient aussi un plus haut coût pour leurs antidépresseurs que ceux assurés par le régime public de la RAMQ. Cette différence de coûts peut être due aux différentes exigences de paiement en pharmacie entre les deux régimes ainsi qu'aux limites des honoraires des pharmaciens imposés par le régime public.

Mots-clés : antidépresseurs, adhésion, coût, médicament, étude rétrospective, assurance santé PDC, PPDC

Abstract

Background: The influence of the type of drug insurance on adherence, persistence and cost of antidepressants is not well known.

Objective: To compare adherence, persistence and cost of antidepressants in patients with private and public drug insurance.

Research Design: A matched cohort study was conducted using prescription claims databases from Quebec, Canada.

Subjects: 194 privately and 1923 publicly insured patients (18-64 years) who filled at least one prescription for an antidepressant between December 2007 and September 2009.

Measures: Adherence over one year was estimated using the proportion of prescribed days covered (PPDC). The difference in mean PPDC between patients with private and public drug insurance was estimated with a linear regression model. Persistence was compared between the groups with a Cox regression model, and the monthly cost of antidepressants (CAD$) was compared between the two groups using linear regression.

Results: The PPDC was 86.4% (95% CI: 83.3-89.5) in patients with private and 81.3% (95%CI: 80.1-82.5) in patients with public drug insurance and the adjusted mean difference was 6.7% (95% CI: 3.0-10.4). Persistence was 49.5% in patients with private and 18.9% in patients with public drug insurance at one year ($p<0.001$), and the adjusted hazard ratio was 0.48 (95%CI: 0.30-0.76). Patients privately insured paid 14.94$ CAD (95% CI: 12.30; 17.58) more per month on average for their antidepressants.

Conclusion: Better adherence and persistence and higher costs were observed in privately insured patients. Cost difference might be due to different pharmacy payment requirements and pharmacists' honorary restrictions under the public plan.

Keywords: antidepressant agents, medication adherence, drug costs, retrospective studies, insurance health PDC, PPDC

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List of abbreviations

5-HT	Serotonin
CAI	Commission de l'accès à l'information
CI	Confidence interval
CLSC	Centre local de services communautaires
CPR	Cost persistent ratio
ECT	Electroconvulsive therapy
Ed	Emergency department
GIS	Guaranteed income supplements
HR	Hazard ratio
HSCM	Hôpital du Sacré Cœur de Montréal
Lot	Length of therapy
MDD	Major depressive disorder
Med-Écho	Maintenance et Exploitation des Données pour l'étude de la Clientèle Hospitalière
MOAI	Monoamine inhibitors
MPR	Medication possession ratio
NE	norepinephrine
NR	Not retained in the final model
PDC	Proportion of days covered
PPDC	Proportions of prescribed days covered
RAMQ	Régie assurance maladie du Québec
SNRI	Serotonin–norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic agents
TRD	Treatment resistant depression

Dedication

I would like to dedicate my master's thesis to my family who supported me all along my academic studies.

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I am eternally grateful to my director, Dr Lucie Blais and co-supervisor Dr Marie-France Beauchesne whose guidance and support allowed me to acquire the necessary skills to complete this degree.

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Preface

This thesis consists of nine chapters including an introduction, objectives, a review of the literature, a methodology and a results section, the manuscript submitted in a scientific journal and a discussion section. The chapters are then followed by a bibliography, supplementary tables and appendices.

The introduction provides the rationale and objectives of the study. It is then followed by the review of the literature which covers the main aspects of the study with an emphasis on adherence and persistence to antidepressants. The methodology and discussion chapters are a more detailed version on those found in the manuscript. The chapter on the results presents additional findings not reported in the manuscript. The discussion and conclusion summarizes the results and proposes future research interests. Lastly the bibliography covers all articles cited.

Chapter 1: Introduction

Health expenditures in Canada have increased considerably over the last two decades, reaching $192 billion in 2010.[1] Due to this increasing demand and cost for health services, the private sector in the universal Canadian health care system is receiving considerable attention. As such, assessing the effectiveness of private versus public health care services should be guided by scientific data which is currently lacking. In the province of Quebec, the public and private debate is drawing much attention. Surprisingly, in spite of the increasingly high cost, medications are rarely of concern. The Quebec universal drug insurance plan administered by the Régie de l'assurance maladie du Quebec (RAMQ) is the only universal plan in Canada that is based on a private and public partnership. Since January 1, 1997, it is mandatory for all residents of Quebec to have drug insurance coverage.[2] Those that do not have access to a collective drug insurance plan through their employer or their spouse's employer are automatically covered by the RAMQ's public drug insurance plan for their medications, which represents 43% of the Quebec population.[2]

The cost of the public portion of the Quebec universal drug insurance plan (i.e. the RAMQ's public drug plan) has been increasing steadily since its inception, escalating from 1.12 billion dollars in 1997 to more than 2.58 billion dollars in the RAMQ latest report in 2006.[2] While several causes might have contributed to this increase, non-optimal use of drugs due to physician non-adherence to treatment guidelines, or patient non-adherence to the prescribed therapy, is certainly one of the contributing factors. Indeed, several studies have demonstrated a large gap

between actual use of drugs and guidelines in the treatment of chronic and acute diseases.[3-19]

It is important to note that the vast majority of Canadian studies on the impact of non-optimal drug use have been conducted among patients covered by public drug insurance plans. Drug use research among publicly covered patients has been greatly facilitated by access to medication data recorded in several provincial computerized administrative databases, such as the RAMQ, and thus can be easily linked to other medical services databases (outpatient's visits, emergency department visits, hospitalizations) for the purposes of pharmacoepidemiologic research.

On the other hand, research on the usage of prescription drugs among patients covered by private drug insurance programs in Canada is almost nonexistent. This is mainly due to the absence of computerized drug databases that can be easily linked to other health databases. This leaves researchers in the dark with respect to the discrepancies between these two subpopulations as to the usage of drugs, the impact that their use on patient health and the associated costs on the health care system.

Due to the lack of computerized drug information on individuals covered by a private drug insurance program, we have recently developed a computerized registry called reMed. This registry stores data related to prescription drugs for residents in Quebec less than 65 years of age who are covered by a private drug insurance program. This registry is based upon the data that are purchased from the community pharmacies computer services provider (CSP), who manage the data transmission that is required for drug reimbursement by the private insurance

companies. One of the great advantages of reMed is that it contains the patient medical insurance number that allows the linkage of reMed to other Quebec computerized medical services databases.

To our knowledge, the Quebec public and private drug insurance programs have never been formally compared in terms of the usage of drugs, adherence, persistence, use of generics and the associated costs. We've decided to start within the context of antidepressants given the prevalent nature of depression as well as the heavy burden of this disease. Canadian public health authorities have reported that 5.8% of Canadians are taking antidepressants.[20] Furthermore, it is estimated that 14.4% of Quebec adults under a public drug insurance plan are taking an antidepressant.[21] The indications for antidepressants incur a heavy economic burden, moreover it is well documented that major depressive disorders alone is one of the most burdensome illnesses in Canada with a lifetime prevalence estimated at 10.8%.[22]

A number of studies conducted in the United States (US) have compared patients with private and public drug insurance.[23,24] Although not looking at antidepressants in particular, these studies have found that privately insured patients tend to use newer and more expensive medications, while using less generic medications than publicly insured patients. In addition, some US studies have found that patient's adherence to essential medications might differ according to the level of restriction of drug formularies and these restrictions might increase the need for health care services.[25-28]Furthermore, it is often difficult to generalize US or studies conducted in other countries to that of the Canadian context. This is

primarily due to the differences in socioeconomic status present in the US between publicly and privately insured people.

From what we have learned from the literature comparing private and public drug insurances and from the existing differences between the private and public drug programs, namely larger coverage of newer medications and less reimbursement restrictions from the private side, we hypothesized that patients covered by a private drug insurance program might more often use newer and more expensive drugs. In comparing the RAMQ and reMed, i.e. public vs. private, we planned a study examining if differences were present in adherence and persistence with antidepressants. Drug costs as well as the use of generics were also compared between these two drug insurance plans.

This study provides evidence on comparative patterns of behavior and expenditures between private and public drug coverage in a context where both plans coexist and are interdependent.

Chapter 2: Objectives & hypotheses

2.0 General Objective

To compare adherence, persistence and cost of antidepressants in patients with private and public drug insurance.

2.1 Specific objectives

1. To Compare adherence to antidepressants in patients with private and public drug insurance using the proportions days covered (PDC) and the proportion of prescribed days covered (PPDC) measures for all users and new users of antidepressants
2. To compare persistence to antidepressants for new users only in patients with private and public drug insurance.
3. To compare monthly cost of antidepressant subclasses in patients with private and public drug insurance.
4. To compare cost of 30 day prescriptions of antidepressant subclasses and individual drugs in patients with private and public drug insurance.
5. To compare generic and brand name use of antidepressants in patients with private and public drug insurance.

2.2 Hypothesis

Adherence, persistence, cost and brand name use of antidepressants will be higher in patients with private drug insurance.

Chapter 3: Literature review

This chapter will review the different drug insurance plans in Quebec as well as the prevalence, economic burden and pharmacology of antidepressants.

This chapter also encompasses a review of the guidelines of the treatment of major depression as well as a literature review of adherence, persistence and cost of antidepressants. These studies were identified with PubMed using the following keywords: antidepressants, adherence, persistence, cost, compliance, predictors, use, generic, medication, and depression. Only observational studies which assessed adherence, persistence or cost of antidepressants were included in the present review.

3.1 Prevalence and economic burden of antidepressants

Antidepressants are widely prescribed in the Canadian population. Estimates in Canada have shown that 5.8% of the population were on antidepressants in 2005.[20] Moreover 14.4% of the Quebec population under the RAMQ medication insurance plan have been reported to use an antidepressant according to 2009 estimates.[21]

Antidepressants are primarily prescribed for the treatment of mood disorders and anxiety; however their use has been extended too many other diseases which are not necessarily approved as an indication (see details below).[21] This has led to a wider and often non optimal use of this drug class which has also contributed to the economic burden of the diseases treated with antidepressants.[29,30]

The annual cost of antidepressant usage has been estimated at 128.8 million dollars (CAN) in 2009 for the adult population who are publicly insured in Quebec.[21]

3.2 Pharmacology and indications of antidepressants

Antidepressants are classified on the basis of their chemical structures and neuropharmacological effects. There are five main classes of antidepressants: First generation antidepressants are known as tricyclic and related cyclic compounds (TCA) and monoamineoxidase inhibitors (MAOI). Second generation antidepressants are known as selective serotonin re-uptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI) and atypical antidepressants (see Appendix). Although second generation antidepressants have similar efficacy to first generation antidepressants, TCA`s and MAOI`s are less commonly used due to their higher toxicity in overdose.[31]

The TCAs were the first group of antidepressants developed in 1950s. This category of antidepressants is known for its 3 ring structure with a side chain amine attached to the central ring. TCAs block the reuptake of norepinephrine (NE) and/or serotonin (5-HT) into noradrenergic and /or serotonergic nerve terminals, respectively by specific interactions with their plasma membrane transporters. The consequence of this inhibition is prolonged stimulation of NE and/or 5-HT receptors due to the NE and 5-HT released from these neurons not being rapidly terminated. In addition to inhibiting NE and 5HT reuptake the TCAs block muscarinic cholinergic receptors, alpha1 adrenergic receptors, and histamine H1 receptors as well which underlie many of their side effects.[32]

MAOI compound are inhibitors of MAO and are not selective therefore inhibit both MAO-a and MAO-b. These two enzyme are distinct gene products where MAO-a is responsible for catabolism of 5-HT, NE, and tyramine and MAO-b is responsible for the catabolism of dopamine and tyramine. These enzymes facilitate inward directed transporter activity thus inhibition of MAO causes increase in levels of monoamine concentration in the cytosol of the nerve terminal.[32]

SSRIs work by selectively preventing the reuptake of serotonin by the presynaptic neuron, thus maintaining higher levels of 5-HT in the synapse. SNRI`s however work by inhibiting the reuptake of the neurotransmitters serotonin and norepinephrine. This results in an increase in the extracellular concentrations of serotonin and norepinephrine and therefore an increase in neurotransmission. This is done without the nonspecific, side effect-inducing interactions of TCAs.[32,33]

Atypical antidepressants were introduced during the same period as the selective serotonin reuptake inhibitors (SSRIs). These include bupropion, which has primarily a dopaminergic effect, and trazodone, which is structurally similar to the tricyclic antidepressants (TCAs) but has a primary serotonergic mechanism.[32]

Although there are many indications for the use of antidepressants, they are primarily prescribed for depressive disorders such as major depressive disorder however anxiety disorders as well are often treated with antidepressants.[21] A recent report on antidepressant use in Quebec publically insured adults showed that antidepressants were primarily prescribed for major depressive disorder which represented 14.7% followed by anxiety disorders representing 14.1% of antidepressant prescriptions.[21] All the indications for antidepressants are listed in Table 1 below.

Table 1. Indications of use of antidepressants in mental and non-mental health conditions

Indications for mental health conditions
Depression[29]
Anxiety[29]
Schizophrenia and other psychotic disorders[29]
Personality disorders[29]
Adjustment disorders[29]
Eating disorders[34]
Insomnia[35]
Substance related disorders[29]
Attention deficit/conductive/disruptive behavior disorders[29]
Delirium/dementia/amnesia and cognitive disorders[29]
Migraines[30]
Impulse control disorders not elsewhere classified[29]
Indications for non- mental health conditions
Fibromyalgia[30]
Connective tissue diseases[30]
Nervous system disorders[29]
Female genital disorders[29]
Chronic pain disorders[29]
Intervertebral disc disorders and other back problems[29]
Premature ejaculation[30]
Tobacco cessation[36]

3.3 Main indications: Major depressive disorder and generalized anxiety disorder

Major depressive disorder is a mental health disorder characterized by one or more major depressive episodes. These episodes are characterized by a depressed mood or a lack of interest or pleasure for all or almost all regular activities for duration of at least two weeks and are accompanied with at least five other depressed symptoms (Appendix II).[33,37] Canadian estimates report a lifetime prevalence of 10.8% for major depressive episodes.[22] Furthermore according to the Global Burden Disease study major depressive disorder is one of leading causes of disability.[21]

Anxiety disorders are considers common disorders. Canadian estimates on one year prevalence of anxiety disorders are 12%.[38] Generalized anxiety disorder is characterized by excessive worry and anxiety that is difficult to control and causes significant distress and impairment for the majority of at least six months.[39] Generalized anxiety disorder is most often with onset during adulthood and a chronic course [40-43] and can lead to significant impairments in role functioning, diminished quality of life, and high health care costs.[42] [44] This disorder can be effectively treated with medication, psychotherapy, or a combination of the two modalities.

3.3.1 Guidelines for treatment of major depressive disorders

According to Canadian guidelines treatment of major depression can be viewed as consisting of two phases; the first is the acute phase which is the period from the start of treatment until an acceptable response has been obtained.[45] Depending on symptom improvement, acute phase treatment may extend anywhere from eight to twelve weeks.[45] The ultimate goal of this phase is to reach remission or 50% reduction in symptoms or on a validated depression scale. This is then followed by the maintenance phase which will ultimately have as a goal to minimize the risk of relapse and recurrence.[45] Guidelines recommend continuing maintenance phase treatment for six to 24 months and sometimes more at the required dose for achieving remission.[46] Clinicians thus focus on resolving any residual symptoms, treating comorbid conditions, returning to full pre-morbid functioning and preventing return of symptoms. In everyday practice, physicians examine whether patients no longer meet the criteria for major depressive

episodes.[47] Figure 1 outlines an algorithm for managing limited improvement with first line antidepressants.

Treatments for major depressive disorder include SSRI, SNRI, TCA's, MAOI's and certain atypical antidepressants.[45,48] First generation antidepressants, i.e. TCA and MAOI inhibitors are less commonly used due to their reduced risk benefit profile. In treatment resistant depression (TRD) commonly defined as lack of improvement or <20% reduction in depression scores following trials of two or more antidepressants, add-on treatments are often prescribed.[45,48-50] In severe depression, guidelines strongly recommend that the use of electroconvulsive therapy (ECT) should be included in the first line treatment together with antidepressants and psychotherapy. Often if the depression has psychotic features, antipsychotics will also be prescribed.[50]

Ultimately the choice of therapeutic strategies should be personalized to each patient's characteristics, previous response to antidepressants, side effect profile, comorbidities and cost.[37,45]

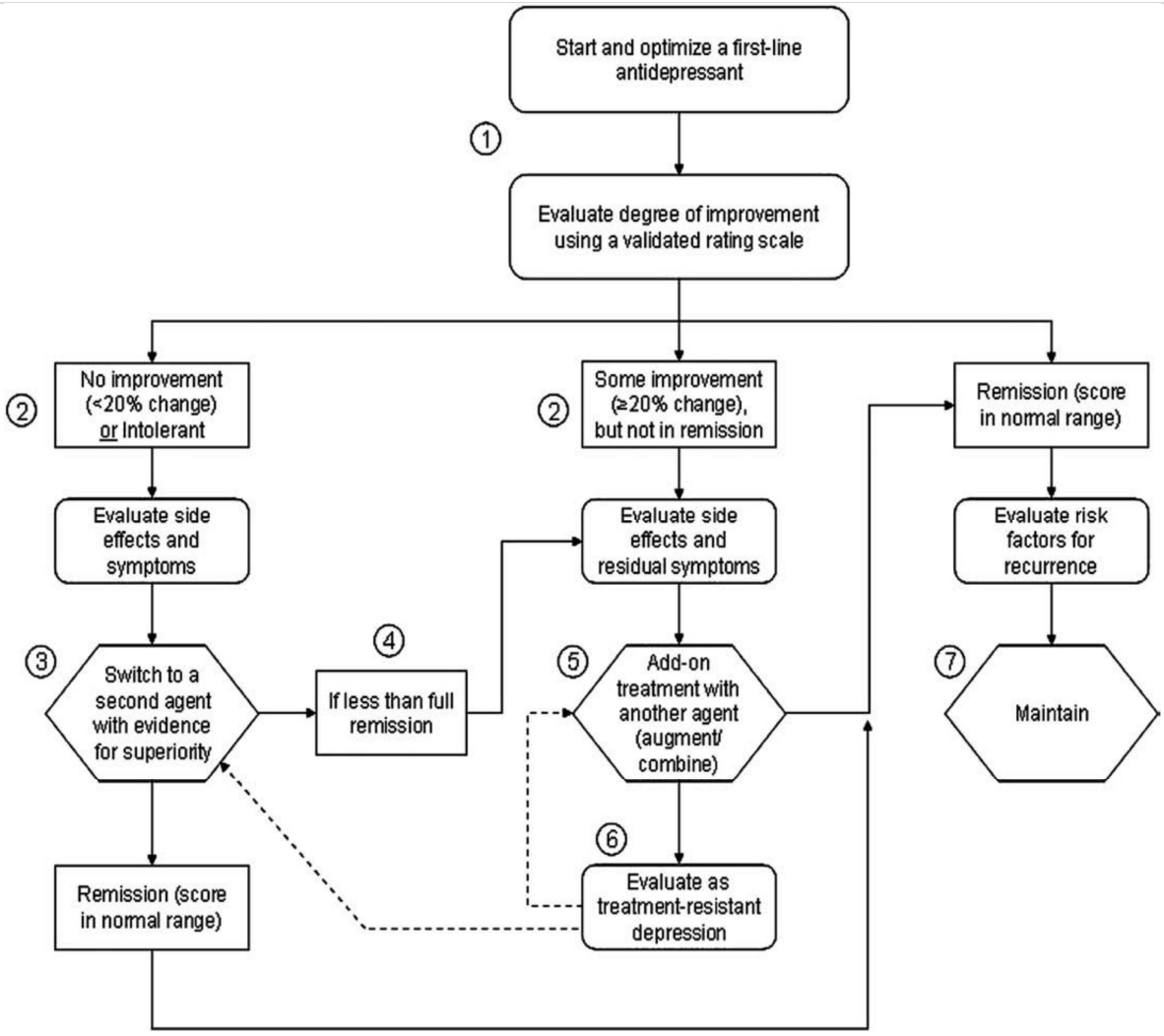

Figure 1. Algorithm for managing limited improvement with first line antidepressant. From Lam et al.[51]

3.3.2 Guidelines for the treatment of generalized anxiety disorder

First line treatments for generalized anxiety disorder are SSRI or SNRI antidepressants.[52] If effective, guidelines stress continuing SSRI or SNRI therapy for 12 months. The time necessary for a clinically meaningful response for an SSRI varies, however averages typically at four weeks. If the patient has not shown signs of improvement after six to eight weeks on an acceptable dose, the

medication should be tapered off and a different medication should be tried.[52] Non-response after adequate SSRI trials can be followed by a different SSRI, followed by a trial of a SNRI or tricyclic antidepressant. A partial response to the initial antidepressant can be followed with augmentation with buspirone, or (if insomnia) hydroxyzine.[52] Second-line medications for generalized anxiety disorder include tricyclic antidepressants, benzodiazepines, and certain anticonvulsants. Finally, non-response after adequate trials of second-line antidepressants can be followed by trials of other less well studied antidepressants.[52]

3.4 Medication insurance programs in Quebec

3.4.1 The RAMQ medication insurance

The Quebec Universal drug insurance plan administered by the Régie de l'assurance maladie du Québec (RAMQ) is the only universal plan in Canada that is based on a private and public partnership. Since January 1997, it is mandatory for all residents of Quebec to have a drug insurance coverage.[2] Those that do not have access to a collective drug insurance plan through their employer or their spouse's employer are automatically covered by the RAMQ's public drug insurance plan for their medications. Approximately 43% of the Quebec population is covered by the RAMQ drug insurance plan,[2] including the elderly (>65 years), beneficiaries of social assistance, and workers and their families (called adherents) without private drug insurance coverage and 57% by a private drug insurance plan. When considering individuals less than 65 years, the proportion of subjects covered by the RAMQ decreases to 30%, leaving 70% of this sub-population covered by a private plan.[2]

Coverage through the public drug plan for Quebec residents requires the payment of a premium, whether or not they purchase prescription drugs. The premium is paid through the Ministère du revenu du Quebec when income tax returns are filed. In 2011, the amount varied from 0$ to 563$ per adult which was dependent on their family income.[53]

Those exempted for payment of premiums are holders of a claim slip issued by the Ministère de l'emploi et de la solidaritié sociale to those on financial assistance which allows free access to prescription drugs and certain medical services. Also, persons age 65 or over receiving 94% to 100% of guaranteed income supplements (GIS) and children of parents covered by the RAMQ drug insurance plan are exempted. This includes all children under 18 year of age and full time students without a spouse and who live with their parents.[53]

The monthly deductible of 16$ is a fixed amount when making the first drug purchase during the month. The monthly co-insurance is the percentage of the cost of the prescription (32%) subtracting the deductible. The maximum monthly contribution is 80.25$ and the maximum annual contribution is 963$. The prices of drugs are indicated in the *Liste de médicaments* reimbursed by the RAMQ which are applicable only to those under public drug insurance. Under certain circumstances *les médicaments d'exceptions* which are drugs not included in the *Liste de médicaments* can be reimbursed if a request is made by the prescribing physician.[53]

The prices of drugs under the RAMQ are the same in every pharmacy since drug prices are negotiated with suppliers by the federal government. The

pharmacist then adds a standardized dispensing fee. A portion of the cost of a prescription is payable by the patient which is called the contribution while the other portion is paid by the RAMQ directly to the pharmacy.[53]

3.4.2 Private drug insurance plans in Quebec

Coverage through a private drug plan in Quebec also requires a premium, whether or not one goes to purchase prescription drugs. In most cases the premium is paid through payroll deductions throughout the year. The premium is negotiated between the policy holder and the insurer.

For the majority of private insurance plans only a portion of the cost of the drugs are paid by the insured known as the contribution and the balance is reimbursed by the insurer. There are three types of reimbursement methods. Certain private plans allow the persons they insure to pay the pharmacy only the amount of their contribution, while other plans require them to pay the pharmacy in full at the time of purchase and reimburse them afterwards for the difference.[54] The reimbursement can be done automatically or manually with the individuals having to file a claim. Private drug insurance plans are required to reimburse all drugs on the list de médicament and the maximum paid per year by an individual is the same as in the RAMQ.[53]

At last, although there are important differences in both plans, the vast majority of Canadian studies on the impact of non-optimal drug use have been conducted among patients covered by public drug insurance plans. On the other hand, research on the usage of prescription drugs among patients covered by private drug insurance programs in Canada is almost nonexistent. This is mainly

due to the absence of computerized drug databases that can be easily linked to other health databases. As described above these two drug plans have many differences and may therefore have discrepancies between these two subpopulations as to the usage of antidepressants particularly in adherence, persistence and the associated costs on the health care system.

3.5 Adherence to antidepressants

To date, there is no consensus on the exact definition of adherence to medications. As a result, the methods for defining adherence differed across the studies, as were cut off values in categorizing an adherent patient. However, adherence is generally understood as the extent to which an individual's behavior coincides with medical advice.[55,56] This section will provide a review of observational studies that have investigated adherence rates to antidepressants.

Several studies in the US studies and Canada examined adherence to antidepressants.[57,58] In a US study of privately insured patients with a diagnosis of depression or anxiety, adherence to incident use of selective serotonin reuptake inhibitors (SSRIs), one of the most used subclass of antidepressants,[45] was examined using three different measures of adherence [MPR, length of therapy (LOT) and a hybrid measure (MPR/LOT)]. Six month adherence rate was found to be approximately 43% (42.9-44.6) for all methods.[57] Adherence for new users of SSRI's indicated for depressive disorders were also examined in private employer insurance medical claims data. Three different SSRI drugs were compared; Fluoxetine, Sertraline and Paroxetine. Six month adherence was defined as

receiving at least four antidepressant prescriptions over the six months period was highest for Fluoxetine (57%) compared to 48% and 49% for Sertraline and Paroxetine respectively.[58]

Lastly, a study investigating non-adherence to psychotropic medications among Canadians of all insurance groups was assessed by the Canadian Community Health Survey.[59] Non-adherence was defined as a positive answer to an interview question asking "on a typical month were there any days where you either forgot to take the medicine or took less than you were supposed to?" Antidepressants had a 46% (95% CI 43-49) rate of non-adherence.[59] The authors were not able to exclude recall bias as a possible limitation because of the way the outcome was assessed. This survey was also used by Duhoux et al. in assessing adequacy of treatment for Canadians suffering from major depressive disorder and examining factors associated with this adequacy. Interestingly in this study, having medication insurance was not a significant predictor of adequate treatment for major depressive disorder.[37]

Several studies outside the U.S and Canada studied adherence to antidepressants. These studies were not presented in table 2 because of their lack of comparability with the Quebec population. In one study, a retrospective chart review was performed on 367 Japanese adult patients diagnosed with major depression.[60] Adherence to incident use of antidepressants as a class was estimated to be 77% using the medication possession ratio (MPR) with 55.6% of patients having a MPR>80% which was defined as adherent to therapy.[60] Another Japanese study conducted an internet based survey among 1151 Japanese individuals with major depressive disorders where adherence was measured by

asking on a scale from 0 to 5 how often they forget to take their antidepressants. The authors found that 33.1% of these patients were classified in the low adherence group defined as a score of ≤ 3.[61]

A retrospective study in Thailand using pharmacy data on newly diagnosed major depressive patients in a psychiatric hospital measured adherence using MPR (>80% defined as adherent). Only patients aged 15 years or older who received at least one prescription of an antidepressant were eligible. Results showed that 41% of patients were adherent for those attending the center twice.[62]

In a European study on patients diagnosed with recurrent depression, patients who previously took part in a clinical trial were studied to assess the effect of cognitive behavior on relapse prevention. These patients were recruited in psychiatric centers in the Netherlands and adherence to antidepressants was measured with a medication adherence questionnaire which defined non-adherence as missing 20% or more of their medication. Non-adherence rates ranged between 39.7% and 52.7% over 2 years.[63]

In a retrospective database study using the public health service prescription in the health region of Lleida, Spain, adherence to 7525 new users of antidepressant treatment for all indications with the exception of neuropathic pain was measured. Adherence was considered good if the medication was dispensed during 80% of the treatment period of 4 months. Twenty two percent of patients had good adherence. Also patients with high polypharmarcy were twice as likely to present good adherence (31% vs. 15.3%).[64]

In summary, in the eight observational studies summarized above, the reported adherence rates varied greatly, ranging from 15% to 77%. This wide range is likely the results of the different methods of measuring adherence, as well as the different patient populations being investigated. Furthermore, the follow-ups different greatly between the studies, and thus studies with relatively short follow-up were more likely to report higher adherence rates than those with longer follow-up. Table 2 below presents a summary of Canadian and US studies that have investigated adherence to antidepressants.

Table 2. Summary of Canadian and US observational studies of adherence to antidepressants

Authors	Study design	Setting	Study population	Drugs investigated	Definitions	Main results	Weaknesses
Dehoux et al.[37] n=1563	Cross sectional survey	Canadian community health survey and well being	Age 15 or older Male 46.3% MDD patients	Antidepressants	Prescription of antidepressant and 4 visits to MD or 12 visits to psychologists	Adherent 28%	Recall bias
Cantrell et al.[57] n=22,947	Retrospective cohort	U.S Database private	Mean age 43 years male 36.1%	SSRI fluoxetine, sertraline, citalopram, escitalopram, IR paroxetine, paroxetine CR	6month adherence Lot* MPR MPR/Lot	43% (42.9-44.6) Three Metrics not statistically different.	Generalizability
Crown et al.[58] n=2030	Retrospective cohort	U.S Electric pharmacy data Insurance claims	mean age 42 years male 31% Depressed population	fluoxetine, sertraline paroxetine	6 months adherence (at least 4 prescriptions in 6 months)	Fluoxetine 57% adherent Sertraline 48% adherent Paroxetine 49% adherent	Generalizability
Bulloch et al.[59] n=6201	Cross sectional survey	Canadian community health survey and well being	18-64 years old	Antipsychotics	Non adherence defined as yes to "forgetting or taking less medication than supposed to in the last 12 months:	45.4% non-adherent for antidepressants	Recall bias

*MPR: medication possession ratio
*Lot: Length of therapy

Researchers have studied factors associated with adherence to antidepressants. Low education has been shown to be a strong predictor of better adherence.[65] Studies have also shown than being treated by a psychiatrist when compared to a general practitioner is associated with better adherence.[65] One of the most common reasons for poor adherence is their lack of tolerability as side effects have been shown to be associated with poor adherence particularly in antidepressants.[66] Factors that were found to be associated with adherence are summarized in the table below in Table 3.

Table 3. Predictors of adherence to antidepressants

Factors associated with better adherence to antidepressants	**Odds ratio (95%CI)**
Low education[65]	3.89 (1.11; 13.69)
Prescription by a psychiatrist[65]	1.41 (1.25; 1.64)
Factors associated with lower adherence to antidepressants	
Lower age[61,65]	1.47 (1.05; 2.07)
side effects[66,67]	2.70 (1.21; 6.02)
Being a worker or student[61]	2.32 (1.53; 3.51)
Negative attitude towards antidepressants[66]	1.64 (1.08; 2.43)
Use of pain medication[65]	1.14 (1.04; 1.29)
Higher daily dosing frequency[61]	1.61 (1.15; 2.27)

3.7 Persistence to antidepressants

As with adherence, there is no consensus on a definition of persistence to treatment. However, it generally refers to how long a patient remains on therapy. It is often measured with use of prescription refill databases with the assumption that patients refill their prescription in order to adhere to treatment. Grace periods are usually defined in order to consider the patient persistent even if a given amount of time between refills has passed. A small grace period will yield results that

demonstrate less persistence while a longer period will yield to evidence of greater persistence.[68] Selected studies on persistence to antidepressants are summarized in table 4.

Several US and two Quebec studies have examined persistence to antidepressants at the population level. A cohort study on adult privately insured new users of antidepressants by Bambauer et al. found that 18% of patients did not refill their initial prescription in primary care. At six months, 53% of primary care patients discontinued their antidepressant prescription. These findings were compared to patients treated by a psychiatrist, 13% did not refill their prescription initially and 49% at six months.[65] Furthermore, Hansen et al studied discontinuation rates of antidepressants using medical and prescription claims from a national health plan in privately insured adult patients diagnosed with major depression. The authors found that 73% discontinued their treatment during the study period of 7 months.[69] In a retrospective cohort study, 71.4% of adult patients with depression, posttraumatic stress disorder, or social anxiety disorder who had a new prescriptions for brand-name SSRI discontinued their treatment within the first six months.[70]

Vanelli et al. showed using pharmacy records of 1157 pharmacies through the US that 38.8% of incident users and 18.8% of prevalent users of antidepressants discontinued treatment at 30 days. Discontinuation was defined with a 30day grace period. At six months, 74.9% of first time users discontinued their therapy. As for the prevalent users 48.3% discontinued their therapy within six months.[71]

In the study by Wu et al. on elderly patients with major depressive disorders, the rate of discontinuation defined as no refills within a period of 45 days was measured. Six-month discontinuation rates for new users of escitalopram compared to other SSRI or SNRI therapies were 60.8% and 65.9% respectively.[72] In another retrospective study using a US insurance claims database, the authors found similar results using a 60 day grace period demonstrating a better persistence with escitalopram than with other SSRI therapy at two months; (66.1% vs 61.9% $p<0.01$) and at six months (47% vs. 41% $p<0.01$).[73] Furthermore, another study using claims data from an administrative database on new adult users of antidepressants found that sertraline had a better rate of renewals compared to paroxetine (54.7% compared to 51.0%) respectively.[74] The use of paroxetine was also associated with a lower persistence rate compared to citalopram and sertraline.[70]

Bull et al. studied early discontinuation among 401 depressed patients who initiated an SSRI treatment through telephone interview. The authors found that 20% of patients discontinued their treatment after three months. Reasons given for ending treatment was side effects (36%) , feeling better (24%), insufficient results (20%) and others (20%).[75] Olfson et al. found using data from the Medical Expenditure Panel survey that 42.4% of depressed adults who initiated an antidepressant discontinued treatments 30 days after their initial prescription. Furthermore, only 27.6% continued their treatment for more than 90 days.[76] Interestingly, this survey did account for discontinuation of treatment rates between the private prescription insurance group and the non-prescription coverage group; however they were not significantly different. Moreover, private versus public

health insurance groups were also compared and only crude rates were significantly different however not after adjustment for baseline characteristics OR: (0.70 95% CI 0.47-1.04).

As for Quebec studies, Tournier et al studied an elderly population who initiated an antidepressant treatment in 2000 and were followed for 12 months. Using the RAMQ database, non-persistence was defined as treatment duration of less than 180 days and results showed that 55.6% of antidepressant treatments were non persistent.[77]

Lastly, in a publically insured Quebec population using the RAMQ prescription database, persistence to antidepressants was assessed for adults 18 years and older including patients over 65 years old using a treatment gap of 30 days. Persistence among incident users was found to be 38.5% at six months and 28.4% at one year.[21]

Several studies outside the United States and Canada also examined persistence to antidepressants. These studies were not presented in table 4 because of their lack of comparability with the Quebec population. The medical records of 367 outpatients' with a major depressive disorder in Japan who were on an antidepressant were examined. Persistence at 1 month, 3 month and 6 month was 72.8%, 54.0% and 44.3%, respectively. Interestingly 63.1% of these patients discontinued their treatment without consulting their physician.[60]

A Danish study using the National Health Insurance Registry found that 25.2% of patient discontinued their treatment in the second half-year following their initial prescription. Van Geffen et al found that 23.7% of adult first time users of antidepressants in the Netherlands refilled their prescription only one time.[78]

Another study done in Belgium found that 53% of patients remained on treatment when looking at persistence at six months. The median time on treatment was 22 weeks and 24% of patients did not inform the physician when ending their treatment.[79]

In summary, this section summarized thirteen observational studies that have investigated persistence rates to antidepressants. These rates ranged from 24%% to 75%, demonstrating great heterogeneity between studies. As indicated above, such differences are likely due to different methods of measuring persistence as well as different patient populations being studied. Furthermore, as with adherence, study follow-up is likely to have influenced the reported rates, with the longest follow-up periods associated with lower persistence rates. Table 4 below presents a summary of US and Canadian observational studies that have investigated persistence to antidepressants.

Table 4. Summary of Canadian and US observational studies of persistence to antidepressants

Authors	Study design	Setting	Study population	Drugs investigated	Definitions	Main results	Weaknesses
Wu et al.[72]	Retrospective cohort n=38,775	U.S Database MDD Diagnosis	Escitalopram (*n*=10,465) SSRI/SNRIs (*n*=28,310) Age > 65 years Male 34%	Escitalopram or other (SSRI/SNRI)	Non-persistence 45 days without refill	HR 0.96 (95% CI: 0.94, 0.99) HR 0.91 (95% CI: 0.87, 0.94)	Possible selection bias
Tournier et al.[77]	Retrospective cohort n= 12,825	Canada Quebec Database RAMQ	Age >66 Male/female	Trazodone Nefazodone Fluoxetine Fluvoxamine Sertraline Venlafaxine Citalopram Paroxetine	Treatment non-persistence (duration of less than 180 days) Cost persistent ratio (CPR)	Others: 64.6 (95% CI: 62.7–66.5) SNaRI: 53.3 (95% CI: 51.1–55.5) SSRI: 53.1 (95% CI: 52.1–54.2) CPR: newer drugs more favorable	Information on cost and indication needed
Hansen et al.[80]	Retrospective cohort n=4545	US prescription claims database	Privately-insured Male 35% Mean age 39 yrs	Any antidepressant prescription	30 day grace period 7-month follow up	73% discontinued	Not all drugs captured if cash purchases
Vanelli et al.[71]	Retrospective cohort n=211,565	US computerize pharmacy records	New and prevalent users of antidepressants Male 28%	Venlafaxine Paroxetine Sertraline Fluoxetine Escitalopram citalopram	30 day grace period 180-day follow up	38.8% discontinued in new-user group 18.8% discontinued in prevalent group	Missing diagnostic information, possible misclassification
Esposito et al.[73]	Retrospective cohort n=43921	US insurance claims database	New users of antidepressants	Escitalopram vs other SSRI generics	At least 2 prescriptions within 6months	Escitalopram 47.1% continued treatment at 6months vs 41.0% for SSRI	Generalizability, indication not validated

RAMQ Conseil du médicament[21]	Retrospective cohort n=364,921	Canada Quebec Database RAMQ	Quebec publicly-insured adults	Any antidepressant prescription	30-day grace period 1 year follow up	38.5% persistent at 6 months 24.8% at 1 year	Limited to publically insured

Researchers have studied factors associated with persistence to antidepressants. Studies have shown than being treated by a psychiatrist when compared to a general practitioner was associated with better persistence.[65] Moreover, being on psychotherapy as well was also associated with better persistence.[76] However, one of the most common reasons for early discontinuation is their lack of tolerability as side effects have been associated with early discontinuation particularly in antidepressants.[45,75] This has been shown to be more common in the TCA class.[45,69] Thus, discussing these side effects with patients is important as it has been associated with better persistence.[81] Factors that were found to be associated with persistence are summarized in the table below.

Table 5. Predictors of persistence to antidepressants

Factors associated with persistence to antidepressants	**Odds Ratio (95% CI)**
Having a psychiatrist as initial prescriber[65,82]	1.41 (1.25; 1.64)
Being treated with more than one professional[65,83]	1.20 (1.08; 1.33)
Old age[84,85]	1.35 (1.14; 1.61)
Being on psychotherapy[76]	1.82 (1.22; 2.71)
Discussing side effects before starting treatment with physicians[75]	2.04 (1.05; 4.00)
Being on high polypharmacy[64]	1.70 (1.60; 1.87)
Factors associated with non-persistence to antidepressants	
Taking a TCA[86]	2.94 (2.42; 3.58)
The experience of side effects[75]	3.20 (2.20; 4.97)
Low income[76]	1.56 (1.01; 2.43)
Level of education (less than 12 years) [76,86]	1.89 (1.27; 2.86)
Being told by the physician to take the treatment for less than six months[75]	3.12 (1.21; 8.07)

3.8 Drug insurance, costs and use of antidepressants

To our knowledge no study has compared antidepressant cost and generic use in private and public drug insurance settings. However, to date, only a few studies have examined antidepressant costs and how their use varies according to different medication insurance coverage's.

The three tier formulary in the US resulted in labeling certain brand medication non-preferred and required higher copayments for those medications. The authors suggest that this has impacted utilization of psychotropic medication particularly in antidepressant subclasses.[87]

In commercially insured patients in the US, higher cost sharing was associated with lower likelihood of adherence to second generation antipsychotics. Higher cost sharing was also associated with a shorter time to discontinuation as well (HR: 1.028 (1.006-1.051).[88]

Finally, a Canadian study on British Colombia seniors compared antidepressant initiation and discontinuation before and after the 2002 introduction of copayments and 2003 introduction of income based deductibles for prescription drugs.[70] Discontinuation was defined as failing to refill a prescription within 90 days of exhausting available supply. The authors found a considerable drop in antidepressant initiation following the new implementations; however discontinuation rates were not affected.

3.9 Conclusion

Antidepressants are widely prescribed in Canada and particularly in Quebec. Despite treatment guidelines stressing the importance of maintaining adequate adherence without early discontinuation to achieve clinical benefit, there are many studies reporting suboptimal usage of antidepressants in private and public health care settings. Comparisons of these health insurance settings on actual usage of antidepressants are limited to different population settings and survey data susceptible to recall bias. In Quebec, studies on the usage of antidepressants have been primarily examined in publically insured individuals who only represent 43% of the population.[21,77] Thus we do not know if this usage is in fact comparable to those in privately insured individuals. At last, no studies to date have examined the differences present in the usage, costs and generic versus brand name utilization of antidepressants within Quebec's unique public and private medication insurance programs. We have therefore studied whether the type of drug insurance impacted antidepressant adherence, persistence and costs within Quebec's public and private medication insurance programs.

Chapter 4: Methodology

4.1 Sources of data

This study used information from three sources: Régie de l'assurance maladie du Québec (RAMQ), Maintenance et Exploitation des Données pour l`Étude de la Clientèle Hospitalière (Med-Écho) and reMed. The RAMQ administrative database provides medical coverage to all Quebec residents and drug coverage to approximately 43% of the population.[89]This includes the elderly (>65 years), beneficiaries of social assistance, and workers and their families (called adherents) who do not have access to a private drug insurance plan from their workplace. The RAMQ database includes three types of files. The Beneficiary file gives information on patients' characteristics, such as age, sex, area of residence, social aid status and periods of coverage for the medication insurance. The Medical Services file contains all the information relative to medical services received e.g. the type, date, and location of medical service (outpatient clinic, emergency department (ED), hospitalization), diagnostic codes, as well as the specialty of the treating physician. The Prescription Drugs file contains data on prescribed medications dispensed in community pharmacies and includes notably the name of the medication, dosage, amount of medication given to the patient, the dispensing date, the type of prescription (new or refill), the number of refills allowed with a new prescription, the prescription duration, and the specialty of the prescribing physician. The Med-Echo database contains information on all acute care hospitalizations occurring in the province, the date of admission and length of

stay as well as primary and secondary diagnoses. These two administrative databases are routinely used[90,91] and validated for epidemiological research.[92,93]

reMed is a computerized on-going registry which stores data related to prescribed medications for residents in Quebec who are <65 years old and beneficiaries of a private or group insurance drug plan provided by an employer. Patients were recruited in hospitals, medical clinics and community pharmacies. Recruiting patients would be done by approaching potential candidates with a brief explanation of the use and contents of the reMed database and a signed consent form if eligible. In addition, reimbursement of medications had to be done automatically as a requirement to be included in reMed. This registry is based upon the data that are purchased from the community pharmacies' computer services providers, who manage the data transmission that is required for drug reimbursement by the private insurance companies. Drug data is be updated every two weeks. The registry contains information on patient characteristics such as age, sex, smoking status, body mass index and periods of coverage for medication insurance. It also gives information on prescribed drugs such as the name of the medication, dosage, dispensing date, duration of treatments, number of refills allowed as well as all associated costs.

The Med-Écho database provides information on acute care hospital admissions including data on the patient unique identifier (encrypted), the discharge diagnoses, and the duration of the hospitalization for all residents of Quebec.

4.2 Ethical considerations

The study was granted approval by the scientific and ethics committee of Hôpital du Sacré-Coeur de Montréal (HSCM) and la Commission de l'accès à l'information (CAI) which is responsible for administering the Act respecting access to documents held by public and private bodies and the protection of personal information.

4.3 Study design and study population

A retrospective matched cohort study was conducted through the linkage of the three databases previously described. To achieve the study objectives, we first selected reMed patients who received at least one prescription of an antidepressant agent in monotherapy from the following subclasses: selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA) and other second-generation drugs (Bubropion, Nefazodone, Mirtazapine, Trazodone, Moclobemide, Phenelzine and Tranylcypromine) from March 22nd 2008 until May 15th 2009. The index date was defined as the calendar date of the first prescription for an antidepressant filled after the date of recruitment in reMed. Patients had to be aged between 18-64 years at the index date. In the RAMQ cohort we selected patients who do not receive social assistance (the so called adherents), aged 18-64 years old that were prescribed at least one antidepressant agent in monotherapy between December 1st 2007 and September 30th 2009. Patients from reMed were matched to those of RAMQ (up to 10 RAMQ patients for each reMed patient) on age group (20-34, 35-

49 and 50-64), sex, CLSC territory (region of local community service center) and index date. Matching for index date was done by choosing for each reMed patient, the RAMQ patients with the closest prescriptions of an antidepressant dispensed in a period ranging between 2 months prior until 4 months after the index date of the reMed patient.

All patients were required to have at least 3 months of follow-up, and were followed until the first of the following events: 2 years of follow-up, 65th birthday, or termination of coverage by a private drug insurer for reMed patients or public drug insurer for RAMQ patients. Finally, in order to properly measure potential confounders we also obtained information on patients one year prior to index date.

4.4 Outcome variables

4.4.1 Physician adherence to antidepressants

We estimated physician adherence to the guidelines. The physician adherence was calculated by dividing the total days' supply prescribed by the total duration of the study.

Physicians adherence =

Total days' supply prescribed/ total days of study duration

Total days' supply prescribed was obtained by summing the duration of all prescriptions and the duration of all allowed refills of antidepressants recorded from all the physicians who prescribed antidepressant to a patient during the 12-month follow up period. The numerator was truncated to 365 days to exclude excess medication prescription.

4.4.2 Patient adherence to antidepressants

Adherence to a drug regimen is the extent to which a patient actual history of drug administration corresponds to the agreed upon prescribed regimen. [94]

Initially, a measure of refill adherence frequently used in studies was used. This adherence measure, referred as the proportion of days covered (PDC), is defined as the ratio of the total days' supply dispensed during the follow up over the number of days of follow up.[94]

PDC= total days' supply dispensed/ total days of study participation

Although the PDC adherence measure provides an accurate reflection of the use of medication throughout the duration of the study it may not accurately reflect patient adherence to their prescribed medication. In the presence of differing prescribing patterns, the PDC may fail to provide information about whether the patient is using the medication as prescribed.

The PPDC is an improved measure of adherence and is defined as total days' supply dispensed/ total days' supply prescribed. By using a denominator that corresponds to the number of days of follow up, the PDC assumes that the medication was prescribed for chronic daily use. The PDC reflects the behaviour of both the patient and the prescribing physician and consequently the usage of medications, while the PPDC tends to measure more specifically the behaviour of the patient as it measures patients adherence to the therapy that was actually prescribed, and not to the therapy that should have been prescribed according to clinical guidelines.

Both the numerator and denominator of the PPDC and PDC were truncated to 365 days to exclude excess medication possession and medication prescription, respectively.

4.4.3 Persistence to antidepressants

Persistence to treatment refers to how long a patient remains on therapy. Using our prescription refill databases with the assumption that patients refill their prescription in order to adhere to treatment, persistence with antidepressants was calculated at one year for patients being followed for at least 90 days. Patients were considered persistent if they continuously refilled their antidepressant prescription with gaps of 60 days or less (grace period) between the end of a prescription and the date of the next refill. Sensitivity analyses were conducted by varying the grace period using 45 and 90 days. Analysis of persistence for the subclasses was also calculated.

4.4.4 Cost

Cost of antidepressant medications was measured using the average cost per patient per month in CAN$. We took into consideration both the cost of medication and the honorarium of the pharmacist which might vary between public and private insurers. We also examined if there were cost differences between insurance groups amongst classes of antidepressants as well as the individual drugs. The product specific analysis was based on 30 days prescriptions and stratified by sub-class and brand name verse generic use.

4.4.5 Generic versus brand name antidepressants

Differences in generics versus branded medications prescribed were measured by comparing the proportion of generic antidepressants in publicly and privately insured patients.

4.5 Potential confounders

Demographic variables measured at index date were gender, age (20-34, 35-49 or 50-64), year at cohort entry (2007-2008 or 2009). Potential confounders measured in the year before the cohort entry included comorbidities (i.e. hypertension, dyslipidemia, other cardiovascular diseases, diabetes, gastrointestinal diseases, respiratory diseases and inflammation) – which were measured using filled prescriptions of medications indicated to treat the diseases (Appendix 3) -, all cause hospital visits, all cause emergency room visits, and all cause outpatient visits. We also assessed whether the patients were incident or prevalent users of antidepressants. Incident users were defined as not having a prescription of an antidepressant in the year prior to cohort entry. Prevalent users were defined as having filled a prescription of an antidepressant in the year prior to cohort entry. Finally, we considered the indication of the prescription (i.e. depression, anxiety, adjustment disorders and other diagnoses) as a potential confounder. Indication was evaluated based on the International Classification of Diseases 9 and 10 diagnoses codes in the Med Écho database. The antidepressants subclasses were not entered in the models for adherence, persistence and cost because this variable might be in the casual pathway

between type of drug insurance and the outcomes (adherence, persistence or cost).

4.6 Exposure

The exposure of interest was the type of drug insurance plan being either public or private. The RAMQ cohort represents the public drug insurance plan whereas the reMed cohort represents individuals enrolled in private drug insurance plan.

4.7 Statistical analyses

4.7.1 Descriptive analysis

The analysis started with a description of the cohort. We measured the proportions of individuals in each exposure group for various patient characteristics.

4.7.2 Adherence

Mean PPDC and PDC and 95% confidence intervals for antidepressant agents were calculated for both the entire class and subclasses among patients with private and public drug insurance. Linear regression analysis was used to compare PPDC as well as PDC between privately and publically insured patients for all users and new users of antidepressants. All relevant potential confounders were included in the initial full model. A backward selection strategy was used to select the final models.[94] Predictors were defined as a change of at least 10% in

the mean difference associated with the type of insurance when removed from the model. Those found to be a significant predictor of the outcome (p-value 0.05) were kept in the final model.[94]

4.7.2.1 Subgroup analyses

Linear regression analysis for adherence was performed in SSRI and SNRI subclasses of antidepressants separately. Furthermore, incident users of antidepressants were examined to see if differences were present in these SSRI and SNRI subclasses as well.

4.7.3 Persistence

The cumulative persistence rate was analyzed for incident users of antidepressants for the entire class using a Kaplan-Meier curve. Log rank test was used to evaluate differences between private and public groups. A Cox regression model was used to estimate the hazard ratio of non-persistence for all incident users of the entire class of antidepressants. The model was adjusted for the potential confounders outlined above using a backward selection strategy.

4.7.4 Costs

After testing for normality, linear regression analyses were used to compare the cost of antidepressant medications between patients with public and private

drug insurance. All relevant potential confounders were included in the initial full model. Backward selection strategy was used to select the final model.[94] T-tests were used to see if differences in costs were significant for prescriptions between the two insurance groups for the product specific analysis. This analysis was done for 30-day prescriptions only to ensure comparability among cost and duration of prescriptions.

4.7.5 Generics versus branded medications

Differences in generics versus branded medications prescriptions were measured by looking at the proportion of generic antidepressants in privately and publicly insured patients. Chi-squared tests were used to see if differences are significant. All analyses were performed using SAS software, version 9.2 (SAS Institute inc., Cary, NC USA).

4.7.6 Power calculations

We are planning a study with 194 privately insured patients and 1923 publically insured patients. With an alpha of 0.05 and a mean difference of adherence of 5% we will be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 100%.

Chapter 5: Manuscript

The results of this thesis are presented in the following manuscript:

The manuscript was submitted to the *Canadian Journal of Psychiatry*. The principal author confirms his original contribution to the cohort assemblies, statistical analyses and interpretation of the results, as well as in the writing of the research article.

The impact of the type of insurance plan on adherence, persistence, and costs of antidepressant drugs: A matched cohort study

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5.1 Abstract

Background: The impact of the type of drug insurance plan on adherence and persistence to antidepressants is not well known. The aim of the present study was to compare adherence, persistence and cost of antidepressants in Quebec patients who are covered by private and public drug insurance.

Methods: A matched cohort study was conducted using prescription claims databases: the reMed and RAMQ databases for Quebec residents with private and public drug insurance, respectively. Patients were aged 18 to 64 years and filled at least one prescription for an antidepressant in monotherapy between December 2007 and September 2009 (194 privately and 1923 publicly insured patients). Adherence over one year was estimated using the proportion of prescribed days covered (PPDC). The difference in mean PPDC between patients with private and public drug insurance was estimated with a linear regression model. Persistence was compared between the groups with a Cox regression model while the monthly cost of antidepressants (CAD$) was compared between the two groups using linear regression.

Results: The PPDC was 86.4% (95% CI: 83.3-89.5) in patients with private and 81.3% (95%CI: 80.1-82.5) in patients with public drug insurance and the adjusted mean difference was 6.7% (95% CI: 3.0-10.4). Persistence was 49.5% in patients with private and 18.9% in patients with public drug insurance at one year ($p<0.001$); the adjusted hazard ratio was 0.48 (95%CI: 0.30-0.76). Patients privately insured paid $14.94 CAD (95% CI: 12.30; 17.58) more per month on average for their antidepressants.

Conclusion: Better adherence and persistence and higher costs were observed in privately-insured patients. Cost difference might be due to different pharmacy payment requirements and the pharmacists' honorary restrictions under the public plan.

Keywords: antidepressant agents, medication adherence, drug costs, retrospective studies, insurance health PDC, PPDC

5.2 Background

According to national estimates, about 6 % of Canadians and 10% of Americans are treated with antidepressants.(1;2) Although these drugs are predominantly used for the treatment of depression, they are also prescribed for numerous other indications such as anxiety, fibromyalgia, and migraines.(3;4) These indications incur a heavy economic burden;(5) it is estimated that depression alone represents over 2.6 billion dollars in health care costs and loss of productivity in Canada and 83 billion in the US annually.(6;7) It is also well documented that increasing adherence and persistence to antidepressant medication leads to improved clinical outcomes and reduces the likelihood of relapse, thus reducing the associated economic burden.(8) However, despite consensus regarding the importance of maintaining adequate dose and adherence for all phases of antidepressant treatment, there is increasing evidence that patients do not adhere to their treatment regimen.(9-11)

Studies have investigated adherence and persistence rates with antidepressants (4;9-14), with adherence ranging between 42% and 51% at six months among privately-insured Americans and Canadians (9) (11;12), and persistence being 28.4% at one year among publicly-insured patients from Quebec, Canada(4) . Adherence is generally defined as the extent to which a patient takes medications as prescribed,(15) while persistence is defined as the act of continuing treatment for the prescribed duration.(16)

Even if factors known to have an impact on patient's adherence and persistence such as premiums, deductibles, co-payments, formulary restrictions, and reimbursement policies are likely to differ between private and public drug

insurance plans,(17) we found only one study performed among Latino Americans that compared the use of antidepressants between patients publicly and privately insured. This study reported higher discontinuation rates of antidepressants among publicly compared to privately-insured patients.(18)

Therefore, using prescription claims databases from Quebec (Canada), we conducted a matched cohort study to evaluate the differences in adherence and persistence to antidepressants between patients publicly and privately insured for their medications. We also compared the costs of antidepressants and use of generics versus branded antidepressants between these two sub-populations.

5.3 Methods

Under the Universal drug insurance plan administered by the Régie de l'assurance maladie du Québec (RAMQ), it is mandatory for all residents of Quebec to have drug insurance coverage.(19) Those that do not have access to a private drug insurance plan through their employer or their spouse's employer are automatically covered by the RAMQ's public drug insurance plan (the same plan for all publicly insured residents). Approximately 43% of the Quebec population is covered by the RAMQ's public drug insurance plan(19) including the elderly (≥ 65 years), beneficiaries of social assistance, and workers and their families not admissible to a private drug plan, and the remaining are covered by private plans that vary from one workplace to the other. When considering individuals less than 65 years of age, the proportion of subjects covered by the RAMQ's public drug insurance plan decreases to 30%.

5.3.1 Study design

A database matched cohort study was conducted to compare workers with private and public drug insurance. Patients publicly insured were restricted to workers not admissible to a private drug plan (excluding elderly and patients on social welfare) in order to minimize socio-economic differences between patients with public and private drug insurance. We first selected privately-insured patients aged 18-64 years who received at least one prescription of an antidepressant in monotherapy (selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA) and other second-generation antidepressants (Bubropion, Nefazodone, Mirtazapine, Trazodone, Moclobemide,

Phenelzine and Tranylcypromine) from March 15th 2008 to May 15th 2009 from the reMed database. Cohort entry was defined as the calendar date of the first prescription for an antidepressant filled on or after March 15th, 2008. reMed is a computerized registry which stores data related to prescribed medications (name, date of dispensing, quantity dispensed, duration of the prescription, dosage form, dose, number of allowed refills, etc.) for a sample of Québec residents who are <65 years old and covered by a private drug insurance plan with electronically processed reimbursement and recruited in community pharmacies, medical clinics, or blood sampling centers. Drug data are purchased from the community pharmacies' computer services providers, who manage the data transmission that is required for drug reimbursement by the private insurance companies, and stored prospectively in reMed. reMed contains also information on patient characteristics such as age, sex, smoking status, and body mass index, collected at recruitment.

For each privately insured patient, we selected up to 10 users of antidepressants among patients covered by the public drug insurance and recorded in the RAMQ database, restricting inclusion to the workers not admissible to a private drug plan. The RAMQ Prescription Drugs file contains data on prescribed medications dispensed in community pharmacies and includes the same drug information as the one included in reMed. Publicly insured patients were aged 18-64 years old and filled at least one prescription for an antidepressant in monotherapy between December 1st 2007 and September 30th 2009, and were matched to privately insured patients on age group, sex, region of local community service centre (in order to further minimize socio-economic differences), and date of cohort entry (within 4 months prior and 6 months after the date of cohort entry of the matched privately insured patient).

All patients were required to be registered in reMed or RAMQ database for at least one year prior and 3 months after cohort entry, and were followed until the first of the following events: 1 year of follow-up, 65th birthday, the start of a poly-therapy, a switch between public and private drug plans, or the end of the study period (April 31st 2010). For all selected patients, we also obtain data on medical services (date, location (outpatient clinic, emergency department (ED), hospitalization), diagnosis, specialty of the treating physician, etc.) from the RAMQ database, and on hospitalizations from the Maintenance et Exploitation des Données pour l`Étude de la Clientèle Hospitalière (Med-Echo) database (20) for the year preceding and the year following cohort entry. These administrative databases are often used for research(21;22) and the information related to medications has been proven valid.(23)

5.3.2 Drug plans

For the public drug insurance plan, which is the same for all insures, the premium is collected annually via income taxes and the amount varies between 0 and $563 per year according to family income. The deductible is fixed at $16 per month, the co-payment is fixed at 32% of the cost of the medications and the maximal monthly contribution is $80.25 ($963 per year).(24) Private plans vary from one workplace to the other with premiums negotiated with the insurer and usually taken in the form of payroll deductions throughout the year. The deductible is usually applicable to a one year period representing the first portion of a person's drug costs, while the co-payment varies between 0 and 32%, depending on the plan. The private plans should cover at least all medications covered by the public plan and the maximal contribution is set at $963 per year for all plans.

Reimbursement with private plans can be made at the time of purchase or differed, while patients on the public plan are always reimbursed at the time of purchase.

5.3.3 Outcome variables

Patient adherence to antidepressants was measured in the year following cohort entry using the Proportion of Prescribed Days Covered (PPDC) which is defined as the total days supply dispensed over the total days supply prescribed during the follow up period.(25;26) The total days supply dispensed was calculated by summing the duration of all prescriptions of antidepressants (new and refills) dispensed over the follow-up period. The total days supply prescribed is obtained by summing the duration of all new prescriptions and the duration of all allowed refills of antidepressants prescribed from any physician during the follow-up period. The duration of allowed refills is summed whether or not the patient went to the pharmacy to get the refills.

The PPDC is an improved version of an adherence measure commonly used with prescription claims data known as the Proportion of Days Covered (PDC), which we also measured in the present study for comparison purposes. The PDC is defined as the total days supply dispensed during the follow-up over the number of days of follow up. (27) By using a denominator that corresponds to the number of days of follow up, the PDC assumes that the medication was prescribed for daily use during the entire follow-up. The PDC reflects the behaviour of both the patient and the prescribing physician, while the PPDC tends to measure more specifically the behaviour of the patient as it measures patient adherence to the therapy that was actually prescribed.

Patients were considered persistent if they continuously refilled their antidepressant prescription with gaps of 60 days or less (grace period) between the end of a prescription and the date of the next refill. Sensitivity analyses were conducted by varying the grace period using 45 and 90 days.

Cost of antidepressants was retrieved from the RAMQ and reMed databases, expressed in CAD$, and took into consideration both the cost of the medication and the honorarium of the pharmacist.

5.3.4 Potential confounders

Demographic variables measured at cohort entry were gender, age (20-34, 35-49 or 50-64 years), and calendar year (2007-2008 or 2009). Variables measured in the year before cohort entry included co-morbidities (hypertension, dyslipidemia, other cardiovascular diseases, diabetes, gastrointestinal diseases, respiratory diseases and inflammation) – which were measured with filled prescriptions of medications indicated to treat the diseases –, all cause hospitalisations, all cause emergency room visits, and all cause ambulatory medical visits. We also assessed whether the patients were incident or prevalent users of antidepressants at cohort entry. Incident users were defined as not having a prescription of an antidepressant recorded in reMed or RAMQ databases in the year prior to cohort entry. Finally, we considered the indication for the antidepressant (i.e. depression, anxiety, adjustment disorders and other diagnoses) evaluated based on the International Classification of Diseases 9 and 10 diagnosis codes recorded in the RAMQ or Med-Echo databases in the year prior to cohort entry.

5.3.5 Statistical analyses

Descriptive statistics were used to summarize patient characteristics. PPDC and PDC for antidepressants as a class were calculated among patients with private and public drug insurance over a period of at least 3 months and up to one year. The proportion of patients with a PPDC> 80% and with a PDC >80% (considered as adherent)(28) were also calculated. Linear regression models were used to compare the mean PPDC and PDC between privately and publicly-insured patients. Final models were identified by using a backward selection procedure, starting with a model that included all of the aforementioned potential confounders.(25) The final model was obtained when no independent variable can be removed from the model without modifying the beta parameter associated with the type of insurance by 10% or more.(25) These analyses were performed among all patients and also among incident users only.

Kaplan-Meier curves were used to estimate treatment persistence to antidepressants as a class among incident users. A Log rank test was used to evaluate differences between private and public groups and a Cox proportional hazard model with a backward selection procedure was used to estimate the adjusted hazard ratio of non persistence associated with the type of drug insurance plan.

We estimated the average monthly cost of antidepressants as a class and for sub-classes among patients privately and publicly insured. These average costs were compared between the groups using t-tests. It is worth noting that we did not take into account adherence when calculating monthly cost. In addition, a linear regression model was used to estimate the adjusted mean difference in the

monthly cost of antidepressants between patients with public and private drug insurance. A backward selection strategy was used to select the final model.(25) We also compared the cost of a 30-day prescription for each antidepressant product between the two insurance groups using t-tests. This analysis was done for 30-day prescriptions only to ensure comparability among cost and duration of prescriptions. Finally, we compared the proportion of generic antidepressants between privately and publicly-insured patients using Chi-squared tests. All analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC USA).

Descriptive statistics were used to summarize patient characteristics. Crude PPDC and PDC for antidepressants as a class were calculated among patients with private and public drug insurance over a period of at least 3 months and up to one year. The proportion of patients with a PPDC> 80% and with a PDC >80% (considered as adherent)[28] were also calculated. Linear regression models were used to compare the mean PPDC and PDC between privately and publicly-insured patients. Final models were identified by using a backward selection procedure, starting with a model that included all of the aforementioned potential confounders.[25] The final model was obtained when no independent variable can be removed from the model without modifying the beta parameter associated with the type of insurance by 10% or more.[25] These analyses were performed among all patients and also among incident users only.

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adjusted hazard ratio of non persistence associated with the type of drug insurance plan.

We estimated the average monthly cost of antidepressants as a class and for sub-classes among patients privately and publicly insured. These average costs were compared between the groups using t-tests. It is worth noting that we did not take into account adherence when calculating monthly cost. In addition, a linear regression model was used to estimate the adjusted mean difference in the monthly cost of antidepressants between patients with public and private drug insurance. A backward selection strategy was used to select the final model.[25] We also compared the cost of a 30-day prescription for each antidepressant product between the two insurance groups using t-tests. This analysis was done for 30-day prescriptions only to ensure comparability among cost and duration of prescriptions. Finally, we compared the proportion of generic antidepressants between privately and publicly-insured patients using Chi-squared tests. All analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC USA).

5.3.6 Ethical considerations

The study was granted approval by the scientific and ethics committee of Hôpital du Sacré-Coeur de Montréal and la Commission de l'accès à l'information which is responsible for administering the Act respecting access to documents held by public and private bodies and the protection of personal information.

5.4 Results

A total of 194 patients met the study inclusion criteria for the privately-insured group and 1,923 patients for those publicly insured. As presented in Table 6, we observed that 46% of the patients were aged between 50 and 64 years old and about 23% were males. The groups were comparable for all variables, except for the proportion of patients who were incident users of antidepressants and the proportion of patients who filled a prescription for inflammation that were higher in the privately-insured group. However, the duration of follow-up was higher in the publicly-insured group ($p<0.001$).

Crude adherence rates are outlined in Table 7. Patients privately insured were significantly more likely to be adherent to antidepressants therapy for both PPDC and PDC measures than those covered by a public plan. The proportion of patients with a PPDC and PDC >80% (considered as adherent)(28) were 75.8% and 62.4% in the privately-insured group compared to 69.4% and 51.8% in the publicly-insured group, respectively. Linear regression analysis for the PPDC resulted in an adjusted mean difference of 6.7% (95% CI, 3.0 to 10.4) for all users and 19.4% (95% CI, 7.5 to 31.3) for incident users in favour of patients privately insured (Table 8). The final linear regression model for the PDC measure resulted in an adjusted mean difference of 11.4% (95% CI, 7.0 to 15.8) for all users and 34.4% (95% CI, 23.0 to 45.7) for incident users in favour of patients privately insured (data available upon request).

Persistence rate to antidepressants at one year among incident users was 49.5% for patients privately insured compared to 18.9% for patients publicly

insured; log rank test <0.001 (figure 2). Sensitivity analyses for 45 and 90 days grace periods produced similar differences (log rank test <0.001) (data available upon request). From the Cox proportional hazard reduced model, we estimated an adjusted hazard ratio of 0.48 (95% CI, 0.30 to 0.76) for non-persistence comparing patients privately and publicly insured.

As shown in Figure 3, we found that the average cost of antidepressants per patient per month was significantly higher among privately-insured patients [$48.17 (95% CI, 44.60 to 51.74) compared to $33.72 (95% CI, 32.93 to 34.50)]. This was noticeable for SSRI and SNRI subclasses, but not for TCA and other antidepressants. Linear regression analysis yielded an adjusted mean difference of $14.94 CAD (95% CI, 12.30 to 17.58), which represents a 31.0% increase in cost among privately-insured patients compared to publicly-insured patients. Average costs for 30-day prescriptions of specific antidepressants are presented in Figure 4. The cost of most individual drugs for both generic and brand names was significantly more expensive for privately-insured patients than publicly-insured patients, but the greater differences were observed in generic drugs. Finally, we found that at cohort entry, 69.4% of publicly-insured patients were prescribed a generic antidepressant compared to 53.1% for privately-insured patients (p value<0.001). During follow-up, the corresponding figures were 74.5% and 61.3%, respectively (p-value<0.001).

5.5 Discussion

Our study indicates that patients covered by a private drug insurance plan were more adherent to antidepressants than patients under a public drug insurance plan. This difference was even more pronounced among incident users of antidepressants. Persistence to antidepressants was also significantly higher at one year for patients privately insured. In addition, we found that generic use was higher in the public group, and patients with private drug insurance paid more for their antidepressants.

Our adherence results found among incident users of antidepressants are similar to estimates reported in the literature. Recent American studies on privately-insured patients have found rates of adherence to antidepressants ranging from 42% to 51%.(11;12) The overall persistence rate at one year was found to be 15.6% for the publicly-insured group in our study, which is lower than previous findings on persistence to antidepressants in a quite comparable publicly-insured population (28.4%).(4) This difference in persistence is possibly due to the latter study including elderly patients who have been shown to be more persistent than younger patients.(18)

The differences in adherence and persistence rates observed between patients privately and publicly insured may be due to differences in deductibles and co-payments between the two groups. Although overall drug cost was higher for the private group, the amount paid by the patient at the pharmacy when a medication is dispensed may be higher for patients publicly insured due to the fixed 32% co-payment and the monthly $16 deductible, factors that have been shown to impact adherence and persistence to antidepressants.(17) Furthermore,

workplaces that offer private insurances often have mechanisms in which they ensure that their employees seek appropriate medical and psychological treatment and comply with the treatment plans to ensure a faster return to work.(29)

As for costs, the RAMQ's public drug insurance plan has fixed prices set for pharmacist honoraries, which is not the case for private insurers and this might explain, at least in part, the higher cost of medications paid by patients privately insured. Moreover, the RAMQ's public drug insurance plan applies the method of the "lowest available price" in Canada, which means that the reimbursement is based on the lowest priced drug available.(30) This most likely explains the higher generic utilization in the publicly-insured group.

However, the results of this study should be interpreted in light of the following limitations. The exposure to antidepressants was based on dispensed prescriptions and it does not necessarily represent the actual intake of the medications. In addition, there is a possible volunteer bias for privately-insured individuals being that we actively recruited patients for the privately-insured group and not for the publicly-insured group. This can lead to overestimating adherence and persistence in the private group and thus overestimating the differences between these two groups. Even if present, the magnitude of this bias is likely to be limited due to the recruitment of patients at a high rate (77%) in reMed. Furthermore, the possibility of residual confounding cannot be dismissed due to unmeasured variables such as the specialty of prescribing physician, visits to psychologists, family income and level of education, which has been shown to be associated with adherence and persistence to antidepressants in several studies.(4;13;31) It is worth noting that only patients with low levels of income were found to be less persistent to antidepressants while those who were

considered to have a medium level income did not significantly differ in persistence from patients with high income levels.(31) In order to minimize the impact of socio-economic differences between patients privately and publicly insured, we restricted the study to workers and their families, and we matched on the area of residence. If socio-economic differences are still present between patients with private and public drug insurance they are likely to be small and should not have a major impact on treatment adherence and persistence. Finally, the study's external validity is limited to workers and their families and one should be careful in generalizing to other populations.

Despite these limitations, this study has several strengths. This is the first Canadian study to compare adherence, persistence and cost of antidepressants between patients privately and publicly insured for their medications. Furthermore, by comparing patients with private drug insurance to workers and their families covered by the public drug insurance and not including patients who received social assistance, we minimized socio-economic differences between the groups. Our multivariate analyses also took into account the presence of co-morbidities in the year prior to cohort entry, which helped minimize confounding bias. In addition, the RAMQ and reMed databases include data on prescribed medications that have been collected prospectively and that have been validated.21 Finally, the use of the PPDC measure provided us with a more precise measure of patient's adherence.

Adherence and persistence, particularly among incident users of antidepressants, remain suboptimal in the province of Quebec. Our study also showed that there were large differences between the compared groups, with patients privately insured starting an antidepressant therapy being close to 20%

more adherent than patients publicly insured, despite the fact that the cost of the medication was higher for patients privately insured. Difference in adherence might be explained by higher co-payment for patients with public drug insurance, while difference in cost is likely explained by dispensing fees that are fixed by the public insurer and not restricted by private insurers. Lastly, our study shows that it is important to include both patients with private and public drug insurance in drug use studies since they have different behaviours.

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Table 6. Comparison of characteristics between patients with private and public drug insurance

	Privately-insured patients	Publicly-insured patients	
	n (%)	n (%)	p-value
Number of patients	194 (100.0)	1923 (100.0)	
Measured at cohort entry			
Age group (years)			
20-34	29 (14.9)	289 (15.0)	0.995
35-49	76 (39.2)	759 (39.5)	
50-64	89 (45.9)	875 (45.5)	
Male	41 (21.3)	454 (23.6)	0.438
Antidepressant subclasses[1]			
SSRI	86 (44.3)	872 (45.4)	0.203
SNRI	61 (31.4)	485 (25.2)	
TCA	27 (13.9)	301 (15.7)	
Other	20 (10.3)	265 (13.8)	
Incident users of antidepressants	36 (18.6)	220 (11.4)	0.004
In the year before cohort entry			
≥ 1 hospitalization (all causes)	22 (11.3)	205 (10.7)	0.771
≥1 emergency department visit (all causes)	55 (28.4)	464 (24.1)	0.193
Ambulatory medical visits (all causes) (mean ± SD)	8.8 ± 10.4	7.3 ± 7.5	0.058
Mental health diagnoses			
Depression	50 (25.8)	469 (24.4)	0.669
Anxiety or adjustment disorders	65 (33.5)	618 (32.1)	0.698
Other diagnoses[2]	46 (24.9)	474 (24.6)	0.773
Filled prescription for the treatment of			
Hypertension	33 (17.0)	304 (15.8)	0.663
Dyslipidemia	35 (18.0)	372 (19.3)	0.661
Cardiovascular diseases	13(6.7)	133 (6.9)	0.910
Diabetes	14 (7.2)	132 (6.7)	0.854
Respiratory diseases	40 (20.6)	321 (16.7)	0.166
Gastrointestinal diseases	46 (23.7)	391 (20.3)	0.268
Inflammation	66 (34.0)	462 (24.0)	0.002
Measured during follow-up (up to 1 year)			
Follow-up duration (days: mean ± SD)	333.8 ± 73.8	357.2 ± 31.7	<0.001
Switch between sub-classes of antidepressants	24 (12.4)	168 (8.7)	0.093

[1] SSRI: selective serotonin reuptake inhibitors; SNRI: Selective norepinephrine reuptake inhibitors; TCA: Trycyclic antidepressants; Other: Bubropion, Nefazodone, Mirtazapine, Trazodone Moclobemide, Phenelzine and Tranylcypromine

[2]Schizophrenia, bipolar disorder, persistent delusional disorders, alcohol dependence syndrome, drug dependence, non-dependent abuse of drugs, sleep disorders, suicide and self inflicted injury and migraines.

Table 7. Adherence to antidepressants up to one year

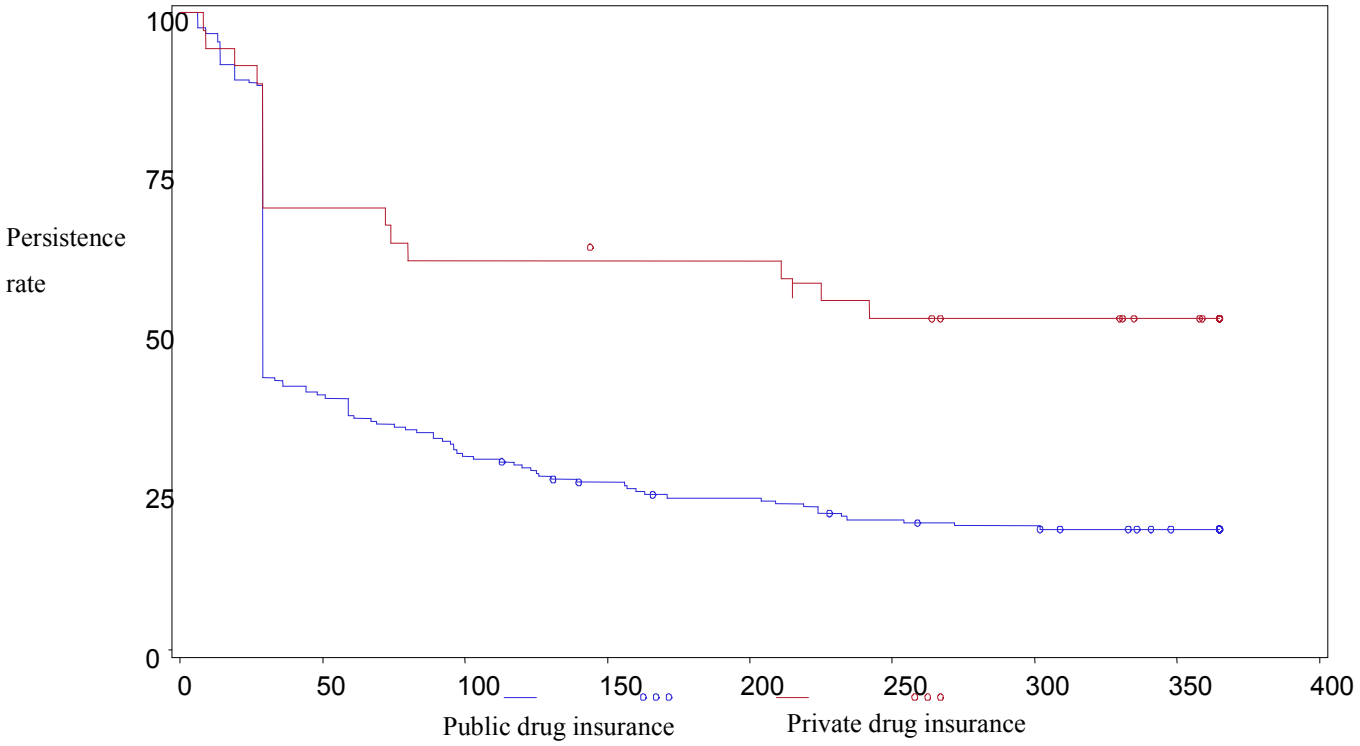
	Privately-insured patients	Publicly-insured patients		
	Mean ± SD[4]	Mean ± SD[4]	Mean difference	p-value
Number of users of anti-depressants	194	1923		
Proportion of days prescribed [1]	88.2 ± 22.7	81.5 ± 27.7	6.7	<0.001
PPDC[2]	86.4 ± 21.8	81.3 ± 26.6	5.1	0.003
PDC[3]	76.2 ± 28.1	67.5 ± 33.3	8.7	0.001
Number of incident users of antidepressants	36	220		
Proportion of days prescribed [1]	78.8 ± 31.4	55.1 ± 35.9	23.7	<0.001
PPDC[2]	78.4 ± 30.2	59.0 ± 34.2	19.4	0.002
PDC[3]	61.2 ± 36.6	30.3 ± 31.3	30.9	<0.001

[1] Proportion of days prescribed [1]=Total number of days prescribed by physicians divided by the number of days of follow-up
[2] PPDC= Proportion of prescribed days covered
[3] PDC=Proportion of days covered
[4]SD= Standard deviation

Table 8. Association between insurance status and adherence to antidepressants measured with the PPDC

Variables	Final model **All users of antidepressants**		Final model **Incident users of antidepressants**	
	Mean PPDC difference (%)	95% CI	Mean PPDC difference (%)	95% CI
Private versus public drug insurance	6.7	(3.0; 10.4)	19.4	(7.5; 31.3)
Age at cohort entry				
18-34	NR		NR	
34-49				
50-64				
Female versus male	2.6	(0.1; 5.2)	NR	
Cohort entry in 2009 versus 2007-2008	3.8	(0.9; 6.7)	NR	
Incident versus prevalent users of antidepressants	23.0	(19.7; 26.3)	Not included in the full model	
Filled prescription for the treatment of cardiovascular diseases	5.7	(1.5; 9.9)	NR	
Other indications	-2.7	(-5.1;-0.2)	NR	

Abbreviations: NR: Not retained in the final model; PPDC= Proportion of prescribed days covered SSRI: selective serotonin reuptake inhibitors; SNRI: Selective norepinephrine reuptake inhibitors; TCA: Trycyclic antidepressants; Other: Bubropion, Nefazodone, Mirtazapine, Trazodone Moclobemide, Phenelzine and Tranylcypromine



	Number of incident users persistent				
	90 days n (%)	**180 days n (%)**	**270 days n (%)**	**365 days n (%)**	**Log rank p-value**
Insurance status					
Private n=36 (reMed)	22 (61.1)	22 (61.1)	17 (49.5)	16 (45.4)	<0.001
Public n=220 (RAMQ)	73 (33.2)	52 (23.9)	42 (19.5)	34 (15.6)	

Figure 2. Persistence to antidepressants up to one year

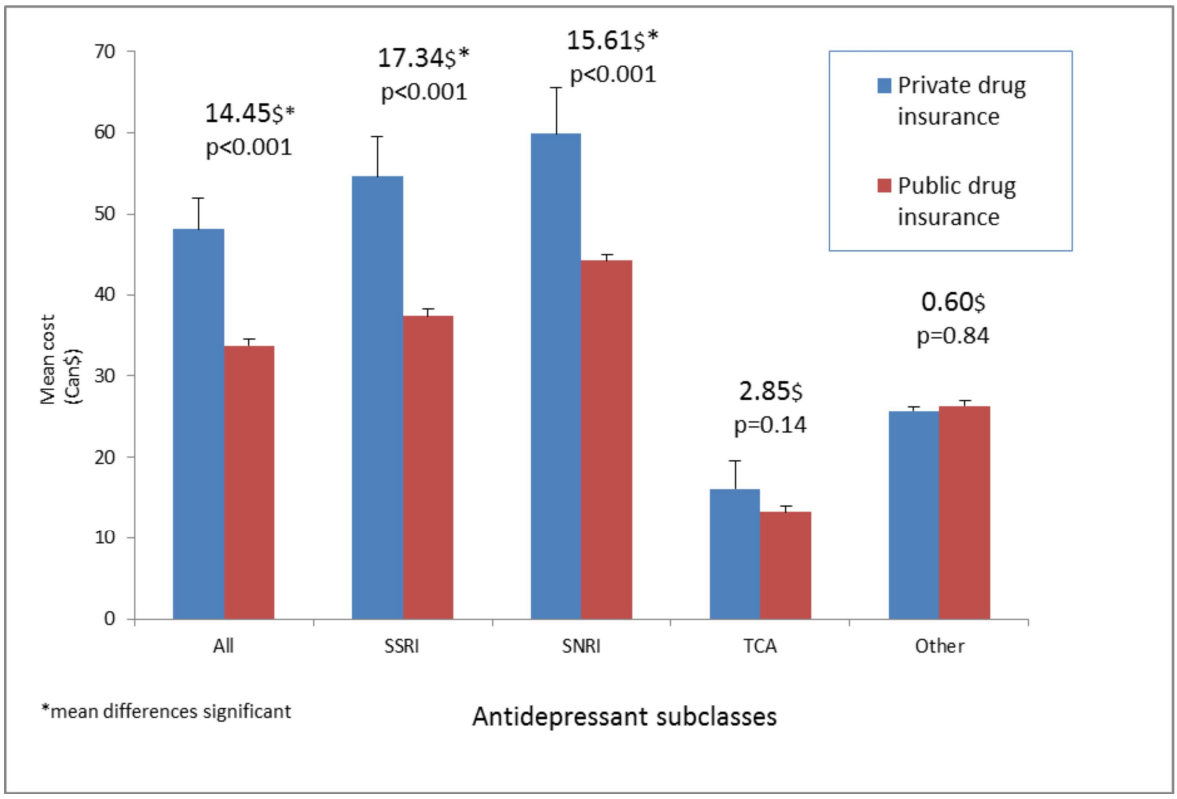


Figure 3. Average cost of antidepressants per patient per month up to one year of treatment

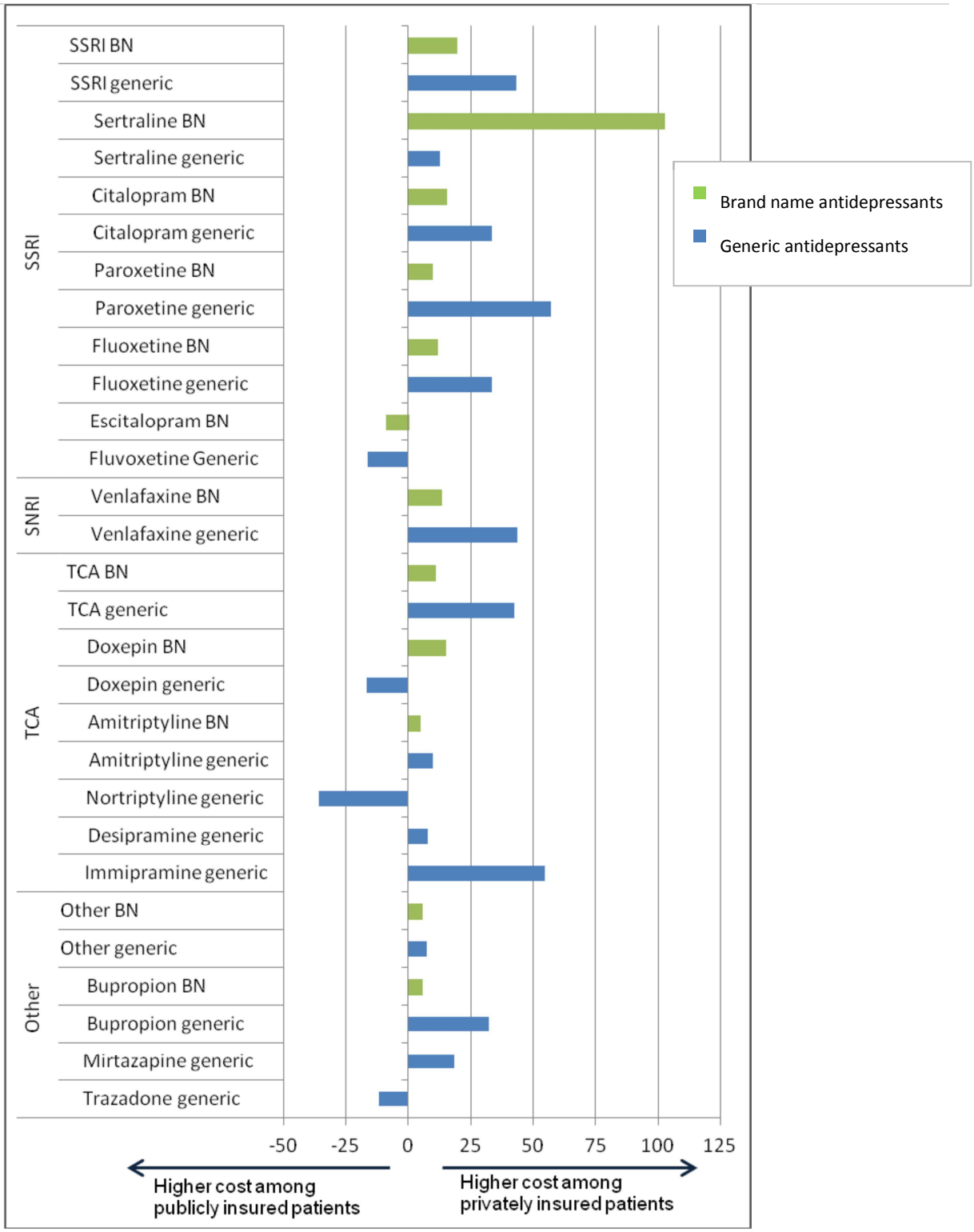


Figure 4. Percent cost difference for a 30-day prescription of antidepressants between patients with private and public drug insurance

Chapter 6: Supplemental results

This chapter is a supplement to the results presented in the manuscript. Results presented in the manuscript are not presented in this chapter.

6.1 Adherence and persistence

Table 9 presents the proportion of days prescribed, PPDC and PDC for individual antidepressant subclasses. The PDC for the SSRI and SNRI classes were significantly higher in the privately insured group, 80.3% vs. 71.5% and 84.0% vs. 74.6%, respectively. Only the PPDC for the SNRI classes was significantly different, 89.6% in the private group compared to 84.1% in the public group. The PDC and PPDC for the TCA and Other antidepressants were not statistically different between insurance groups.

Crude, adjusted and final models for incident users of antidepressants for the PDC measure of adherence is presented in table 10. After adjustment of all significant confounders, the linear regression produced a mean difference of 34.4% (95% CI 23.0-45.7) in favor of the privately insured group.

Persistence to antidepressants for up to 2 years is presented in table 11 and in figure 5. At 18 months 37.8% in the private group remained persistent versus 12.5% in the public group. At 24 months 9.3% remained persistent in the public group and none in the private group.

Regression analysis for crude adjusted and final models of average cost per patient month is presented in table 12. Mean difference was 14.45$ (95% CI 11.73; 17.16) for cost favoring the privately insured group, however after adjustment of all

variables the mean difference was 14.95$ (95% CI 12.28; 17.59). Lastly the final model contained yielded a mean differences of 14.94$ (95% CI 12.30; 17.58) being more expensive for those privately insured.

6.2 Subgroup analyses

Linear regression analysis for the PDC of the SSRI class produced a statistically significant mean difference of 9.0 (95% CI: 2.4; 15.6) favoring those privately insured, (Table 13) however the mean difference for the PPDC was not significant 3.4 (95% CI: -2.1; 8.9). (Table 14)

Linear regression analysis for the PDC of the SNRI class produced a statistically significant mean difference of 10.7 (95% CI: 2.1; 19.2) in favor of the private insured group as shown in Table 15. Lastly, the mean difference for the PPDC was not significant, 5.8 (95% CI: -1.1; 12.7). (Table 16)

Chapter 7: Discussion

This chapter presents additional discussion on the results presented in the manuscript, as well as the supplemental results presented in Chapter 6. This discussion is organized according to the three objectives covered in this thesis, namely, adherence, persistence, and cost of antidepressants between private and publicly insured individuals. The Chapter will then end with a discussion of the clinical impact of the results, and their relevance to healthcare policy and future research.

7.1 Adherence to antidepressants

Overall, our study indicates that patients covered by a private drug insurance plan are more adherent to antidepressant therapy than patients under a public drug insurance plan. Using the PDC and PPDC, we were able to measure adherence over a one year period, with rates of 76.2% and 86.4% for those privately insured compared to 67.5% and 81.3% for publicly insured with the RAMQ program, respectively. Interestingly, adherence was considerably lower in new users of antidepressants, regardless of insurance program. However, adherence was much higher in terms of PDC and PPDC in privately insured patients compared to the publicly insured patients for such patients (mean differences: 34.4% and 19.4%, respectively). While it is known that incident users are those less likely to be adherent to a given therapy, our study indicates that insurance status (i.e. private versus public) is also an important determinant of adherence. As such, treating

physicians should be aware of this fact, and perhaps be more vigilant with patients publicly insured for their medications. Furthermore, it is clear from this study, at least for the Quebec population, that adherence rates in privately and publicly insured patients are not interchangeable.

When comparing our adherence results to those published in other studies, it appears that our adherence rate is higher. Recent US studies on privately insured patients have indeed found lower rates of adherence to antidepressants ranging from 42%-51%.[57,95] However, it is important to note that there are varying levels of private medical coverage in the US. It is possible that in certain private US drug plans, patients minimize their claims as to not exceed their annual maximums. Furthermore, drugs are typically more expensive than in Canada, resulting in a higher co-payment, and thus potentially resulting in a lower adherence. Future research should focus on factors that can explain the discrepancies in adherence rates between Quebec and the US.

7.2 Persistence to antidepressants

In this study, one-year persistence rates to antidepressants were also significantly higher for patients privately insured compared to patients publicly insured, 49.5% versus 18.9%, respectively. Our low persistence rate of 18.9% for publicly insured patients was lower than what was reported in a recent study conducted within the RAMQ population, which was reported to be 28.4%.[21]

However, in contrast to our study, the previous RAMQ study included elderly patients, which have been shown to be more persistent than younger patients.[84]

While it is known that persistence to antidepressants in particular is low, the differences observed between publicly and privately insured patients is remarkable. As with adherence, our results highlight the importance of not interchanging these two subpopulations when investigating persistence to antidepressants. Thus, treating physicians should be aware of this fact, and perhaps be more vigilant with patients publicly insured for their medications. While this study focused on antidepressants, it is possible that such differences also exist with other pharmacotherapies. Given the large differences in persistence rates, future research should make a distinction between these two patient populations when investigating persistence.

7.3 Costs of antidepressants

As expected, average cost of antidepressants per patient per month was significantly higher for privately insured patients. Overall, those privately insured spent $14.45 more per month for their antidepressants than those insured under the RAMQ drug insurance plan. These price differences were comparable for the SSRI and SNRI classes as well.

Individual drug cost for 30-day prescriptions were more expensive for those under a private drug insurance plan. This was apparent for the SSRI and SNRI classes, but not so for the TCA and other classes. The latter drug classes are older

than the SSRI and SNRI classes, and are therefore no longer under a patent. As such, we expect the use of generics to be non-differential between publicly and privately insured patients, thus not affecting the amount spent. That being said, generic use was higher in publicly insured patients, both at cohort entry and during follow up.

7.4 Clinical significance

Adherence and persistence to antidepressants was found to be suboptimal in the province of Quebec, particularly among new users of antidepressants. This problem appears to be more pronounced among patients covered by the public insurance program. While such results raise concerns, clinicians and pharmacists should be aware of this issue, in order to better identify patients who are likely to become non-adherent and non-persistent to antidepressants, and thus stress the importance of maintaining optimal dose while continuously using the drug for the entire prescribed length.

7.5 Reasons for differences in the three measured outcomes between publicly and privately insured patients

The differences in adherence and persistence rates observed between patients privately and publicly insured may be due to differences in deductibles, co-payments, and reimbursement policies between the two groups. Although overall drug cost was more expensive for the private group, the amount paid by the patient

at the pharmacy when a medication is dispensed may be higher for patients publicly insured due to higher co-payments and deductibles, factors that have been shown to impact adherence and persistence to antidepressants.[88] Furthermore, companies which offer private insurances often have mechanisms in which they ensure that their employees seek appropriate medical and psychological treatment and comply with the treatment plans to ensure a faster return to work.[96]

As for reasons explain these differences in drug costs, the RAMQ has fixed the honoraria of pharmacists, whereas such honoraria fixing is not present with private drug plans. Therefore the cost of a particular drug may be significantly higher for a privately insured patient compared to a publicly insured patient. Moreover, the RAMQ applies the method of the “lowest available price” in Canada, which means that the reimbursement is based on the lowest priced drug available.[97] This most likely explains the higher generic use in the publicly insured patients. Furthermore, our findings on cost and generic utilization are in line with previous studies, demonstrating lower pharmacy costs when initiating treatment with a generic medication.[98]

7.6 Limitations

While our study produced some interesting findings, certain limitations need to be considered. There is a possible volunteer bias for privately-insured individuals being that we actively recruited patients for the privately-insured group and not for the publicly-insured group. The patients who accepted may have been

more health-conscious and adherent to therapy than those who did not accept to be included in the reMed project. This can lead to overestimate adherence and persistence in the private group and thus overestimate the differences between the two groups. Even if present, the magnitude of this bias is likely to be limited due to the recruitment of patients on all drug classes at a high rate (77%) in reMed.

Exposure to antidepressants was based on dispensed prescriptions, which may not necessarily reflect actual intake. As a result, it may have overestimated our adherence and persistence rates, by misclassifying non-exposure as exposure. However, continually refilling prescriptions on time is a reasonable indicator that patients were in fact adherent and persistent. Patients were deemed persistent if they refilled their antidepressant prescription within a 60-day grace period. This grace period may have overestimated persistence if the patient had in fact terminated the treatment, although sensitivity analyses using alternate grace periods of 45 days and 90 days did not significantly change the results. In addition, drug prescriptions were used as proxies of comorbidities, and it is therefore possible that this method may have missed individuals diagnosed with disease but not yet treated for it.

Furthermore, the reMed and RAMQ databases did not include the indication for which the antidepressants were prescribed. These drugs are now prescribed for a wide range of indications, ranging from anxiety to migraines.[21] As such, the duration and dose of therapy is not expected to be same across all these indications. In terms of adherence, this is more of a concern for PDC, since it does not take into account the duration intended by the prescribing physician. However,

this is less of a concern for PPDC which takes into account the intended duration of the prescription, which was one of the motivating reasons why we chose to use this measure as well. Furthermore, because antidepressants are prescribed for numerous indications which may differentially affect our study outcomes, we attempted to control for confounding by indication by adjusting the models with the major indications for antidepressant use, namely, depression, anxiety, or other conditions. While most patients fall into the depression/anxiety categories, residual confounding by indication is still possible.

As with any observational study, it is not possible to fully eliminate residual confounding from unmeasured variables. Such unmeasured potential confounders include the specialty of the prescribing physician for example, which was not available in the reMed database. This is a variable of interest, since patients treated by psychiatrists have been shown to have better adherence and persistence compared to patients treated by general practitioners.[21,65] Furthermore, other potential confounders which were not measured are those of psychosocial nature such as beliefs and attitudes towards pharmacotherapy in particular in depression and those related to the disease such as duration of treatment. Moreover, we did not have data on visits to psychologists which has been shown to affect treatment adherence.[21] It is possible that privately-insured patients had better access, through their insurance, to psychologists or other mental health professionals. While this may have occurred, this missing variable would have to be greatly differential between the insurance groups and strongly associated with adherence and persistence to substantially alter the results.

The precision and statistical power of our study was very strong. However, stratification by incident use and antidepressant subclass resulted in smaller number of exposed patients thereby affecting statistical power. Finally the study's external validity was limited to workers and their families in Quebec, and therefore these results should not be generalized to the general population.

7.6 Strengths

Despite these limitations, this study had several strengths. To our knowledge, this is the first study to compare adherence, persistence and cost of antidepressants between patients privately and publicly insured for their medications. The matching on age, sex, CLSC territory, and index date at the design stage led to limiting confounding bias. Furthermore, we tried to further minimize socio-economic differences by comparing patients with private drug insurance to the RAMQ ***"adherents"*** (i.e. workers and their families who do not receive social assistance). Our multivariate analyses adjusted for a number of potential confounders, in an effort to further reduce confounding. Moreover, the RAMQ and reMed databases include data on prescribed medications that have been collected prospectively and that have been validated.

7.7 Conclusion

Antidepressants are widely prescribed in Canada and particularly in Quebec. While guidelines stress the importance of maintaining antidepressant use at optimal levels and duration to achieve clinical benefit,[50] we found low adherence and persistence rates, representing a significant problem in management of

depressive disorders further contributing to the economic burden of these diseases.

The findings on adherence and persistence are consistent with many studies which have shown inadequate rates of adherence and persistence for new users of antidepressants across different population settings.[21,57,95] The PPDC adherence measure used in this study corrected for the prescribing patterns without having to consult patient medical records. This was a major strength and gave us greater insight on patient behavior towards antidepressants.

This study provides insight into Quebec's public and private medication insurance plans, an area of research that remained understudied. With respect to antidepressants, while it was not a surprise to observe cost differences, future research is needed to better understand patient adherence and persistence rates between public and private drug insurance programs. Furthermore, it would be interesting to examine if these differences are present in other chronic drug classes. This can be done using reMed since the database includes patients exposed to diverse drug classes. Finally, the next step will be to associate adherence and persistence rates to clinically relevant outcomes, such as relapse and disease progression in both publicly and privately insured patients.

In summary, adherence and persistence to antidepressants was suboptimal in the province of Quebec particularly for new users of antidepressants. This problem appears to be exacerbated by being covered by public insurance program. While such results raise concerns, they should also raise awareness of the potential differences that may exist between patients belonging to different

insurance programs. Additional research is needed to understand these differences, which can then be translated into clinical practice. This can be through patient education of the benefits of antidepressant therapy, and providing treating physicians with better tools to identify patients at risk of being non-adherent and non-persistent. Ultimately, this study can be the stepping stone for a broader research program focused on the use of different types of drugs in other indications between publicly and privately insured patients. Improving adherence and persistence to medications in susceptible populations is likely to highly impact clinical effectiveness.

Chapter 8: References

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Chapter 9: Supplemental tables & figures

This section presents the additional results discussed in the thesis which were not presented in the manuscript.

Table 9. Adherence to antidepressants by subclass

	Privately-insured patients mean ± SD	Publicly-insured patients mean ± SD	Mean difference	p-value
SSRI				
Number of patients	86	872		
Proportion of days prescribed (%)[1]	92.1 ± 17.2	84.4 ± 24.9	7.7	<0.001
PPDC[2]	87.4 ± 20.2	83.7 ± 24.1	3.7	0.120
PDC[3]	80.3 ± 24.3	71.5 ± 30.5	8.8	0.002
SNRI				
Number of patients	61	484		
Proportion of days prescribed (%)[1]	94.1 ± 11.7	84.8 ± 25.6	9.3	<0.001
PPDC[2]	89.6 ± 17.4	84.1 ± 25.9	5.5	0.031
PDC[3]	84.0 ± 18.8	72.6 ± 32.5	11.4	<0.001
TCA				
Number of patients	27	301		
Proportion of days prescribed (%)[1]	78.6 ± 34.4	77.0 ± 31.7	1.6	0.806
PPDC[2]	77.8 ± 31.5	73.3 ± 31.8	4.5	0.483
PDC[3]	59.6 ± 39.0	57.1 ± 36.6	2.5	0.733
Other				
Number of patients	20	265		
Proportion of days prescribed (%)[1]	79.3 ± 30.2	73.2 ± 33.0	6.1	0.425
PPDC[2]	76.4 ± 28.9	77.7 ± 28.6	-1.3	0.843
PDC[3]	62.3 ± 35.7	59.1 ± 36.9	3.2	0.708

[1] Proportion of days prescribed (%) [1]=number of days prescribed by physician divided by follow up
[2] PPDC= Proportion of prescribed days covered
[3] PDC=Proportion of days covered

Table 10. Association between insurance group status and adherence to antidepressant agents measured with the PDC among incident users

Variables	Crude		Adjusted		Final model	
	Mean difference (%)	95% CI	Mean difference (%)	95% CI	Mean difference (%)	95% CI
Insurance status						
Private	30.8	(19.5, 42.2)	32.5	(20.2, 44.8)	34.4	(23.0, 45.7)
Public	reference		reference		reference	
Age group at index date						
18-34	reference					
34-49	2.7	(-8.6, 14.0)	0.8	(-10.2, 11.8)	NR	
50-64	3.1	(-8.7, 14.9)	-0.5	(-12.4, 11.4)	NR	
Sex						
Male	reference					
Female	-1.8	(-11.7, 8.0)	-5.2	(-15.0, 4.5)	NR	
Year of cohort entry						
2007-2008	reference		reference			
2009	10.9	0.6, 21.3)	5.9	(-4.4, 16.3)	NR	
Indication						
Depression	3.6	(-7.1, 14.4)	0.4	(-10.1, 10.9)	NR	
Anxiety	5.1	(-3.8, 14.0)	3.9	(-4.8, 12.5)	NR	
Others	3.3	(-5.6, 12.1)	1.2	(-7.7, 10.1)	NR	
Comorbidities in the year prior to index date						
Hypertension	-2.9	(-18.1, 12.3)	-17.4	(-34.3, -0.5)	-17.5	(-32.9, -2.1)
Dyslipidemia	7.1	(-5.0, 19.2)	2.2	(-11.6, 15.9)	NR	
Other cardiovascular diseases	18.5	(-0.3, 36.7)	24.9	(4.1, 45.7)	29.1	(10.6, 47.6)
Diabetes	7.8	(-14.8, 30.4)	3.9	(-20.0, 27.9)	NR	
Respiratory diseases	-7.3	(-19.4, 4.8)	-14.7	(-26.4, -3.0)	-12.6	(-24.0, -1.1)
Gastro intestinal diseases	9.5	(-1.6, 20.6)	8.5	(-2.8, 19.8)	NR	
Inflammation	4.2	(-4.8, 13.1)	-1.1	(-10.3, 8.0)	NR	
Use of any healthcare services in the year prior to index date						
≥1 hospitalization	9.1	(-3.6, 21.9)	7.3	(-6.0, 20.5)	NR	
≥1 emergency department visits	-3.7	(-12.8, 5.5)	-8.1	(-17.4, 1.2)	NR	
Outpatients medical visits	0.5	(-0.1, 1.2)	0.3	(-0.5, 1.1)	NR	

NR: Variable not retained in the final model.

Table 11. Persistence rate for all antidepressants according to duration of follow-up n (%)

Insurance status	3 months	6 months	9 months	12 months	18 months	24 months	Log rank p-value
Private (reMed) (n=36)	22 (61.1)	22 (61.1)	17 (49.5)	16 (45.4)	13 (37.8)	-	<0.001
Public (RAMQ) (n=220)	73 (33.2)	52 (23.9)	42 (19.5)	41 (18.9)	27 (12.5)	20 (9.3)	

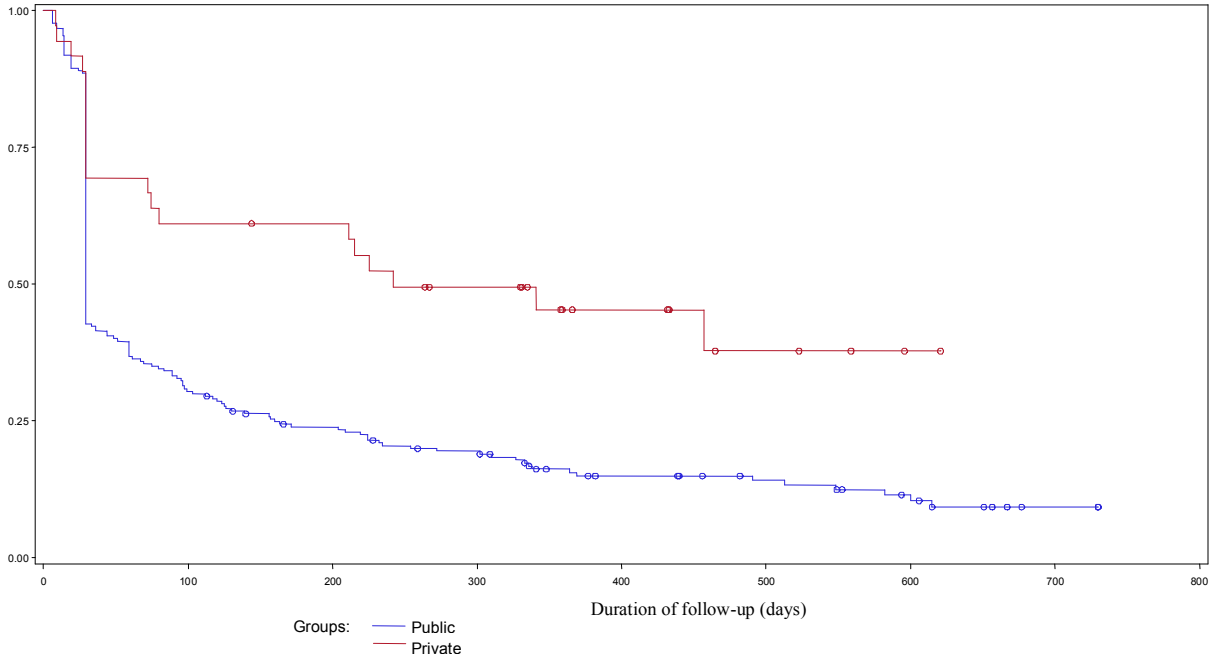

Figure 5. Kaplan-Meier curve displaying persistance to antidepressants according to drug insurance status after 2 years of follow-up

Table 12. Average cost in Canadian dollars of antidepressants per patient per month						
	Crude		Adjusted		Final model	
Variables	**Mean difference ($)**	**95% CI**	**Mean difference ($)**	**95% CI**	**Mean difference ($)**	**95% CI**
Insurance status						
Private	14.45	(11.73, 17.16)	14.93	(12.28, 17.59)	14.94	(12.30, 17.58)
Public	reference		reference		reference	
Age group at index date						
18-34	reference		reference			
34-49	-0.20	(-2.64, 2.24)	-0.17	(-2.51, 2.17)	NR	
50-64	-1.12	(-3.51, 1.27)	-1.10	(-3.50, 1.31)	NR	
Sex						
Male	reference		reference			
Female	-1.20	(-3.10, 0.70)	-1.65	(-3.40, 0.20)	NR	
Year of cohort entry						
2007-2008	reference		reference			
2009	-1.19	(-3.37, 0.99)	-0.49	(-2.56, 1.58)	NR	
Incident use of antidepressants	9.02	(6.59, 11.46)	9.39	(7.02, 11.26)	9.22	(6.87, 11.56)
Indication						
Depression	6.68	(4.83, 8.53)	6.03	(4.21, 7.84)	6.04	(4.27, 7.81))
Anxiety	4.23	(2.52, 5.94)	3.86	(2.21, 5.52)	4.06	(2.44, 5.69)
Others	-3.14	(-5.00, 1.27)	-2.42	(-4.26, -0.59)	-2.29	(-4.06, -0.52
Comorbidities in the year prior to index date						
Hypertension	-0.27	(-2.47, 1.93)	-0.08	(-2.48, 2.32)	NR	
Dyslipidemia	0.20	(-1.84, 2.24)	1.58	(-0.72, 3.87)	NR	
Other cardiovascular diseases	-2.06	(-5.24, 1.11)	-1.69	(-4.85, 1.46)	NR	
Diabetes	-0.91	(-4.08, 2.27)	-1.74	(-5.16, 1.68)	NR	
Respiratory diseases	0.94	(-1.20, 3.08)	0.52	(-1.56, 2.60)	NR	
Gastro intestinal diseases	0.59	(-2.57, 1.40)	0.48	(-2.50, 1.53)	NR	
Inflammation	-0.46	(-2.31, 1.40)	0.11	(-1.72, 1.95)	NR	
Use of any healthcare services in the year prior to index date						
≥1 hospitalization	0.29	(-2.31, 2.89)	-0.59	(-3.24, 2.05)	NR	
≥1 emergency department visits	1.58	(-0.29, 3.45)	1.48	(0.43, 3.39)	NR	
Outpatient medical visits	0.07	(-0.03, 0.18)	0.00	(-0.11, 0.11)	NR	

NR: Variable not retained in the final model

Table 13. Association between insurance group status and adherence to antidepressant agents measured with the PDC among SSRI users (n=958)

	Crude		Adjusted		Final model	
Variables	**Mean difference (%)**	**95% CI**	**Mean difference (%)**	**95% CI**	**Mean difference (%)**	**95% CI**
Insurance status						
Private	7.7	(0.8; 14.6)	9.5	(2.9; 16.0)	9.0	(2.4; 15.6)
Public	reference		reference		reference	
Age group at index date						
18-34	reference		reference			
34-49	3.5	(-2.3; 9.3)	1.0	(-4.6; 6.6)	NR	
50-64	10.7	(5.0; 16.4)	5.3	(-0.5; 11.0)	NR	
Sex					NR	
Male	reference		reference			
Female	0.7	(-4.1; 5.5)	1.7	(-2.9; 6.4)		
Year of cohort entry						
2007 or 2008	reference		reference			
2009	1.7	(-3.8; 7.2)	3.1	(-2.1; 8.3)	NR	
Incident use of Antidepressants	34.8	(27.4; 42.2)	32.6	(25.2; 40.0)	35.2	(27.8; 42.6)
Indication						
Depression	-6.9	(-11.4; -2.4)	-6.5	(-10.9; 2.2)	NR	
Anxiety	-6.4	(-10.6; -2.2)	-4.2	(-8.3; 0.2)	NR	
Others	-3.9	(-8.9; 1.1)	-2.8	(-7.7; 2.1)	NR	
Comorbidities						
Hypertension	8.7	(3.3; 14.1)	0.1	(-5.9; 6.1)	NR	
Dyslipidemia	10.7	(5.8; 15.6)	4.5	(-1.2; 10.2)	NR	
Cardiovascular diseases (other)	14.6	(6.9; 22.3)	9.5	(9.5; 17.3)	NR	
Diabetes	8.7	(1.4; 16.0)	1.2	(-7.0; 9.3)	NR	
Respiratory diseases	1.7	(-3.6; 6.9)	-1.7	(-6.8; 3.4)	NR	
Gastro intestinal diseases	3.7	(-1.3; 8.7)	-0.5	(-5.6; 4.7)	NR	
Inflammation	-0.2	(-4.9; 4.6)	-0.8	(-5.6; 3.9)	NR	
Use of any healthcare services in the year prior to index date						
≥1hospitalization	-0.1	(-6.4; 6.1)	-0.1	(-6.6; 6.3)	NR	
≥1 emergency department visits	-3.5	(-8.2; 1.2)	-1.1	(-5.9; 3.8)	NR	
outpatient medical visits	-0.1	(-0.3; 0.2)	0.0	(-0.3; 0.2)	NR	

NR: Variable not retained in the final model

Table 14. Association between insurance group status and adherence to antidepressant agents measured with the PPDC among SSRI users (n=958)

	Crude		Adjusted		Final model	
Variables	**Mean difference (%)**	**95% CI**	**Mean difference (%)**	**95% CI**	**Mean difference (%)**	**95% CI**
Insurance status						
Private	2.5	(-3.2; 8.2)	3.9	(-1.5; 9.5)	3.4	(-2.1; 8.9)
Public	reference		reference		reference	
Age group at index date						
18-34	reference		reference		reference	
34-49	4.6	(-0.1; 9.4)	3.0	(-1.7; 7.8)	NR	
50-64	7.0	(2.3; 11.7)	4.1	(-0.8; 9.0)	NR	
Sex						
Male	reference		reference		NR	
Female	-1.3	(-5.2; 2.6)	-0.8	(-4.7; 3.1)		
Year of cohort entry						
2007 or 2008	reference		reference			
2009	1.7	(-2.7; 6.2)	2.8	(-1.6; 7.2)	NR	
Incident use of Antidepressants	25.4	(19.3; 31.5)	23.7	(17.5; 29.9)	25.5	(19.4; 31.6)
Indication						
Depression	-2.5	(-6.1; 1.2)	-2.5	(-6.2; 1.2)	NR	
Anxiety	-3.9	(-7.3; -0.4)	-2.4	(-5.8; 0.9)	NR	
Others	-4.6	(-8.7; 0.5)	-3.5	(-7.6; 0.6)	NR	
Comorbidities						
Hypertension	4.1	(-0.3; 8.6)	-1.2	(-6.2; 3.9)	NR	
Dyslipidemia	5.2	(1.2; 9.2)	1.0	(-3.9; 5.8)	NR	
Cardiovascular diseases (other)	8.2	(1.9; 14.5)	5.5	(1.1; 12.0)	NR	
Diabetes	6.3	(0.3; 12.3)	2.5	(-5.7; 10.7)	NR	
Respiratory diseases	4.2	(-0.1; 8.5)	2.3	(-2.0; 6.6)	NR	
Gastro intestinal diseases	1.7	(-2.3; 5.9)	-0.6	(-4.9; 3.7)	NR	
Inflammation	-2.0	(-5.9; 1.9)	-2.1	(-6.0; 1.9)	NR	
Use of any healthcare services in the year prior to index date						
≥1hospitalization	-1.0	(-6.1; 4.2)	-0.6	(-6.0; 4.9)	NR	
≥1 emergency department visits	-2.2	(-6.0; 1.7)	-0.6	(-4.6; 3.5)	NR	
Outpatient medical visits	0.0	(-0.2; 0.2)	0.0	(-0.2; 0.2)	NR	

NR: Variable not retained in the final model

Table 15. Association between insurance group status and adherence to antidepressant agents measured with the PDC among SNRI users (n=545)

	Crude		Adjusted		Final model	
Variables	**Mean difference (%)**	**95% CI**	**Mean difference (%)**	**95% CI**	**Mean difference (%)**	**95% CI**
Insurance status						
Private	6.4	(-2.3; 15.2)	12.9	(4.3; 21.5)	10.7	(2.1; 19.2)
Public	reference		reference		reference	
Age group at index date						
18-34	reference		reference		reference	
34-49	5.1	(-2.9; 13.1)	4.3	(-3.6; 12.1)	NR	
50-64	10.7	(2.6; 18.8)	8.5	(0.3; 16.7)	NR	
Sex						
Male	reference		reference			
Female	1.5	(-5.0; 8.1)	5.3	(-1.0; 11.6)	NR	
Year of cohort entry						
2007-2008	reference		reference			
2009	9.0	(1.8; 16.2)	10.3	(3.4; 17.1)	NR	
Incident use of Antidepressants	33.1	(22.8; 43.4)	35.9	(25.5; 46.3)	35.0	(24.6; 45.3)
Indication						
Depression	-9.1	(-15.2; -3.1)	-8.5	(-14.4; -2.5)	NR	
Anxiety	-0.4	(-6.2; 5.4)	-0.2	(-5.9; 5.4)	NR	
Others	-4.9	(-11.7; 2.0)	-2.0	(-8.7; 4.8)	NR	
Comorbidities						
Hypertension	-3.3	(-11.1; 4.4)	-10.8	(-18.7; 2.5)	NR	
Dyslipidemia	9.5	(2.1; 16.9)	10.0	(-4.0; 12.5)	NR	
Cardiovascular diseases (other)	2.8	(-9.0; 14.6)	3.0	(-6.5; 17.4)	NR	
Diabetes	3.8	(-9.3; 16.8)	0.7	(-6.4; 21.0)	NR	
Respiratory diseases	0.1	(-7.5; 7.8)	-1.8	(-5.4; 9.5)	NR	
Gastro intestinal diseases	3.0	(-4.4; 10.3)	3.0	(-3.8; 11.2)	NR	
Inflammation	-2.0	(-8.4; 4.4)	-1.0	(-6.7; 6.1)	NR	
Use of any healthcare services in the year prior to index date						
≥1hospitalization	-0.6	(-9.9; 8.8)	4.4	(-5.3; 14.1)	NR	
≥1 emergency department visits	-4.2	(-10.7; 2.3)	-3.8	(-10.6; 3.0)	NR	
Outpatients medical visits	-0.2	(-0.6; 0.2)	-0.1	(-0.5; 0.4)	NR	

NR: Variable not retained in the final model

Table 16. Association between insurance group status and adherence to antidepressant agents measured with the PPDC among SNRI users (n=545)

	Crude		Adjusted		Final model	
Variables	**Mean difference (%)**	**95% CI**	**Mean difference (%)**	**95% CI**	**Mean difference (%)**	**95% CI**
Insurance status						
Private	3.0	(-3.9; 10.0)	5.8	(-1.3; 12.9)	5.8	(-1.1; 12.7)
Public	reference		reference		reference	
Age at index date						
18-34						
34-49	reference		reference		reference	
50-64	5.6	(-0.7; 12.0)	5.5	(-0.9; 12.0)	NR	
	6.2	(-0.2; 12.6)	5.4	(-1.4; 12.1)	NR	
Sex						
Male	reference		reference			
Female	-0.5	(-5.6; 4.7)	1.4	(-3.8; 6.6)	NR	
Year of cohort entry						
2007-2008	reference		reference			
2009	8.1	(2.4; 13.7)	8.6	(2.9; 14.3)	9.0	(3.4; 15.6)
Incident use of Antidepressants	14.5	(6.2; 22.8)	16.9	(8.4; 25.5)	16.2	(7.8; 24.5)
Indication						
Depression	-4.7	(-9.3; 0.3)	-3.9	(-8.8; 1.0)	NR	
Anxiety	-1.0	(-5.6; 3.5)	-0.7	(-5.4; 4.0)	NR	
Others	-2.8	(-8.2; 2.6)	1.7	(-7.3; 3.8)	NR	
Comorbidities						
Hypertension	-2.0	(-8.1; 4.2)	-4.9	(-11.6; 1.8)	NR	
Dyslipidemia	2.2	(-3.6; 8.1)	2.1	(-4.7; 9.0)	NR	
Cardiovascular diseases (other)	2.2	(-7.2; 11.5)	2.1	(-7.6; 11.9)	NR	
Diabetes	1.9	(-8.4; 12.2)	1.4	(-9.8; 12.5)	NR	
Respiratory diseases	0.1	(-6.0; 6.1)	-0.6	(-6.6; 5.5)	NR	
Gastro intestinal diseases	1.7	(-4.0; 7.5)	1.3	(-4.8; 7.5)	NR	
Inflammation	0.8	(-4.2; 5.9)	1.2	(-4.0; 6.5)	NR	
Use of any healthcare services in the year prior to index date						
≥1hospitalization	4.7	(-2.7; 12.2)	7.0	(-0.9; 15.0)	NR	
≥1 emergency department visits	0.3	(-5.4; 4.8)	-0.4	(-6.0; 5.2)	NR	
Outpatients medical visits	-0.1	(-0.4; 0.2)	-0.1	(-0.4; 0.3)	NR	

NR: Variable not retained in the final model

Appendix I

List of Antidepressants	
Classes	**Chemical name**
Selective serotonine reuptake inhibitors (SSRIs)	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxatine sertraline
Serotonine and norepinephrine reuptake inhibitors (SNRIs)	Desvenlafaxine Venlafaxine Duloxetine *Tryptophan*
Atypical antidepressants	Bubropion Nefazodone Mirtazapine Trazodone
Tricyclics (TCAs) and others cyclic antidepressants	Amitriptaline Clomipramine Desipramine Doxepin Imipramine Maprotiline Nortriptyline Trimipramine
Monoamide oxidase inhibitors (MAOIs)	Moclobemide Phenelzine Tranylcypromine

Appendix II

List of symptoms for the classification of depression
1. Depressed mood most of the day nearly every day
2. Markedly diminished interest or pleasure in most activities most of the day
3. Significant weight loss or gain or appetite disturbance
4. Psychomotor agitation or retardation
5. Iinappropriate guilt; diminished ability to think or concentrate or indecisiveness
6. Recurring thoughts of death, including suicidal ideation
7. Insomnia or hypersomnia

Appendix III. Classes ATC used for different comorbidities			
Comorbidity	**Classes**		**Exceptions**
Hypertension	Renin angiotensin inhibitors	C09****	
	Calcium channel blockers	C08****	CO8CA05
	Beta blockers	C07****	C07AA05,06,07 C07AB07,09 C07AG**
	Diuretics	C03****	C03BA08,C03AA01,C03CA02, C03DA**,CO3CC**
	Hypotensive	C02****	C02AA**,C02CC**, C02DD**C02KK**
	Urology	G04AA01	
	Others	V03AA01	
Other cardiovascular diseases	Cardiovascular therapy	C01****	
	Beta blockers	C07AA05,06,07 C07AB07,09 C07AG**	
	Diuretics	C03BA08 C03AA01 C03CA02 C03DA** C03CC**	
Diabetes	Anti-diabetics; Insulin, analogues and blood lowering drugs	A10****	

Anxiety	Anxiolytics	N05BA** N05BE** N05CD** N05CD**	N05BA05
	benzodiazepine	N03AE01	
Dyslipidemia	Statins	C10AA** C10AB** C10AC** C10AD** C10AX** C10BA** C10BX**	
	Bile acid sequestering	C10AC**	
	Fibrates	C10AB	
	nicotinic acid	A11HA**	
Respiratory diseases	Drugs for obstructive respiratoiry diseases; Andrenergics, Glucocorticoids, Anticholinergics, Antiallergic agents	R03****	
	Anti-histamines	H02****	H02AB01,H02AB08,H02AA02
Gastrointestinal diseases	Anti-acid H2 receptor antagonist Prostaglandins Proton pump	A02****	A02AA01

	inhibitors		
Chronic inflammation	Anti-inflammatory; Butylpyrazolidines Acetic acid derivatives Oxicams Propionic acid derivatives Fenamates Coxibs	MO1A**	M01AE12,M01AG01