THE INTRODUCTION OF AN UNRESTRICTED REIMBURSEMENT POLICY FOR ATYPICAL ANTIPSYCHOTIC MEDICATIONS IN NEWFOUNDLAND AND LABRADOR: THE IMPACT ON HOSPITAL UTILIZATION BY PATIENTS WITH SCHIZOPHRENIA

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DARIA JOAN O'REILLY

THE INTRODUCTION OF AN UNRESTRICTED REIMBURSEMENT POLICY FOR ATYPICAL ANTIPSYCHOTIC MEDICATIONS IN NEWFOUNDLAND AND LABRADOR: THE IMPACT ON HOSPITAL UTILIZATION BY PATIENTS WITH SCHIZOPHRENIA

By

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ABSTRACT

Objectives: To measure total days of hospitalization, length of stay (LOS) and readmission risk for patients with schizophrenia following the introduction of an unrestricted reimbursement policy for costly atypical antipsychotic medications.

Methods: A province-wide, observational, retrospective hospital chart review, using a before and after design, was used to identify all hospital admissions and quantify data on risk factors associated with LOS and readmission for acute episodes of schizophrenia. Three time periods were studied: 1) 1995/96 at the beginning of restricted access to atypical agents; 2) 1998 at the last year of restricted access; and 3) 2000 the second year of open access. Multivariable Cox proportional hazards and logistic regression models were used to identify risk factors influencing LOS and readmission within one year of discharge respectively. Retrospective administrative prescription claims provided data on the use of and expenditure for atypical agents before and after the policy change.

Results: Total days hospitalization for schizophrenia in 1995/96 was 15,089, 16,318 in 1998 and 15,691 in 2000. There were 57 (18.2%) fewer patients admitted to hospital and 98 (16.7%) fewer admissions during the period of open access (2000) when compared to baseline (1995/96). However, median LOS in 2000 was significantly longer than in 1995/96 (22.0 vs. 15.0 days, $P<0.001$). Being admitted in 2000 compared to baseline was a significant predictor of increased LOS (HR: 3.04, CI=1.57-5.86, $P=0.0009$); independent of requiring ECT (HR: 2.49, CI=1.69-3.66, $P<0.001$); seclusion (HR: 1.87, CI=1.41-2.50, $P<0.001$); thought disorder (HR: 1.41, CI=1.11-1.81, $P=0.006$); suicidal

ideation on admission (HR: 0.70, CI=0.57-0.86, P=0.0007) and discharging against medical advice (HR: 0.38; CI=0.27-0.54, P<0.001). No change in the number of readmissions was observed over the study period.

Expenditures for atypical agents were $217,273 in 1995/96, $1.3 million in 1998, and 3.8 million in 2000, a 17.5 fold increase.

Conclusions: The unrestricted reimbursement policy for atypical antipsychotic medications was associated with a large increase in government expenditure for these drugs, which was not associated with a decrease in hospital utilization in the province by schizophrenia sufferers. Although a decrease in hospital admissions occurred, this was negated by an increase in LOS.

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LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AHFS	American Hospital Formulary System
AIMS	Abnormal Involuntary Movement Scale
AMA	Against Medical Advice
ANOVA	Analysis of Variance
BAS	Barnes Akathisia Scale
BPRS	Brief Psychiatric Rating Scale
CA	Cost Analysis
CBA	Cost Benefit Analysis
CCA	Cost-consequence Analysis
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CEA	Cost-Effectiveness Analysis
CGI	Clinical Global Impression (scale)
CMA	Cost Minimization Analysis
CME	Continuing Medical Education
CPGs	Clinical Practice Guidelines
CUA	Cost Utility Analysis
DHCS	Department of Health and Community Services

DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
ECT	Electroconvulsive Therapy
EPS	Extrapyramidal Side Effects
ESRS	Extrapyramidal Symptom Rating Scale
GAF	Global Assessment Functions
GIS	Guaranteed Income Supplement
HAM-D	Hamilton Rating Scale for Depression
ICD-9	International Classification of Diseases, Ninth Revision
ICER	Incremental Cost Effectiveness Ratio
IPA	Independent Practitioner Association
LOCF	Last-Observation-Carried-Forward
LOS	Length of Stay
MADRS	Montgomery-Asberg Depression Rating Scale
MSE	Mental Status Exam
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NLMA	Newfoundland and Labrador Medical Association
NLPDP	Newfoundland and Labrador Prescription Drug Program
NOSIE	Nurses' Observation Scale for Inpatient Evaluation
NPA	Newfoundland Psychiatric Association

ODB	Ontario Drug Benefits
PANSS	Positive and Negative Syndrome Scale for Schizophrenia
PANSS-GPS	Positive and Negative Syndrome Scale for Schizophrenia-General Psychopathology
PANSS-P	Positive and Negative Syndrome Scale for Schizophrenia-Positive Symptoms
PANSS-N	Positive and Negative Syndrome Scale for Schizophrenia-Negative Symptoms
PAS	Psychotic Anxiety Scale
QALY	Quality Adjusted Life Year
QLS	Quality of Life Scale
RCT	Randomized Controlled Trial
SADS-C	Schedule for Affective Disorders and Schizophrenia-Change Version
SANS	Scale for the Assessment of Negative Symptoms
SARS	Simpson-Angus Rating Scale
SSNL	Schizophrenia Society of Newfoundland and Labrador

CHAPTER I – INTRODUCTION

1.1 Background of Study

Prescription drugs play an important role in Canada's health care system and are often used as a substitution for other treatments and medical interventions, including surgeries.[1] As their role in the health care system expands, so does their cost. In 1980, 5.8% ($1.3 billion) of total spending on health care in the country was spent on prescription drugs. By 2001, this percentage increased to 12% representing a total of $12.3 billion for prescription medications.[1]

Prescription drug costs will continue to rise in the future. To slow the growth in pharmaceutical expenditures, drug benefit programs have implemented a variety of utilization control mechanisms that are intended to have no impact on access to effective health care.[2] Examples include: restricted formularies (i.e., lists of pharmaceuticals approved for reimbursement that may include only the older, less expensive medications); limits on the numbers of prescriptions or units allowed; high deductibles and co-payments; reference drug pricing; and prior authorization requirements for newer medications. The main concerns about drug cost-containment is that patients may switch to less effective treatments, become non-adherent, or be hospitalized more frequently.[3 4]

Antipsychotic medication is the cornerstone of treatment for schizophrenia. These medications help manage the positive symptoms of the disease and delay or

prevent relapse. In the last decade, new "atypical" antipsychotics have been introduced. Compared to the older "conventional", "classical" or "traditional" antipsychotics these medications appear to be equally effective for helping reduce the positive symptoms like hallucinations and delusions—but may be better than the older medications at relieving the negative symptoms of the illness. The primary advantage of these new drugs is the decreased risk of developing extrapyramidal side effects (EPS) such as parkinsonism, akathisia, acute dystonia, and tardive dyskinesia.[5 6] Medications with fewer and/or milder adverse effects may improve patient adherence with therapy, which may lead to improved effectiveness when used in clinical practice. As a result, the value of reduced or absent side effects and/or enhanced efficacy may have economic implications by reducing the need for hospital admission that may justify the higher drug acquisition costs.

For example, the Canadian Coordinating Office of Health Technology Assessment (CCOHTA) commissioned the economic evaluations of risperidone and clozapine.[7] One analysis estimated an annual cost savings of approximately $389 million in direct health care expenditures when clozapine is compared to chlorpromazine or haloperidol in hospitalized patients with treatment-resistant schizophrenia with moderate symptomatology. The second analysis concluded that the use of risperidone compared to haloperidol, haloperidol decanoate or fluphenazine decanoate in the treatment of hospitalized patients with chronic schizophrenia who had experienced an exacerbation of

symptoms was associated with $662 million in annual cost savings. The potential 'savings' in both instances were mainly due to reduced hospitalization offsetting the associated incremental increase in drug expenditure for clozapine of $63 million and $113 million for risperidone.[7]

Prior to December 23, 1998, the Newfoundland and Labrador Prescription Drug Program (NLPDP), which provides prescription drug coverage for all residents of the province who are either on social assistance or are aged 65 and older in receipt of the Guaranteed Income Supplement (GIS), relied on a restricted access policy for these new, expensive atypical antipsychotic medications. In order for a pharmacist to get reimbursed for dispensing an atypical antipsychotic prescription by the NLPDP, a physician was required to submit a written request to prescribe them and approval was based on defined criteria: a diagnosis of schizophrenia and either failure to respond to two adequate trials of conventional agents, or intolerance of conventional agents. During 1998, there was mounting pressure from the schizophrenia community, psychiatrists, the pharmaceutical industry and the media to allow unrestricted access to these new medications, and the results of the CCOHTA economic analyses supported such a policy change. The response by the Department of Health and Community Services, Government of Newfoundland and Labrador, was the introduction of an unrestricted reimbursement policy for the atypical antipsychotic medications (risperidone

(Risperidal®), clozapine (Clozaril®), quetiapine (Seroquel®) and olanzapine (Zyprexa®)), provided the impact of open access on hospitalization for schizophrenia was studied.

In the province of Newfoundland and Labrador (provincial population = 541,000) hospital services are the responsibility of six Institutional Boards: 1) Health Care Corporation of St. John's; 2) Avalon Health care Institutions Board; 3) Peninsulas Health Care Corporation; 4) Central East Health Care Institutions Board; 5) Central West Health Corporation; and 6) Western Health Care Corporation. Additionally, there are two Integrated Boards: 1) Grenfell Regional Health Services; and 2) Health Labrador Corporation. These Institutional Boards are contained in six health care regions: St. John's, Eastern, Central, Western, Grenfell and Labrador (Appendix A). The St. John's region is served by three acute care divisions and a number of chronic care divisions within the Mental Health Program, is predominantly urban and has a population of approximately 195,000. Additionally, this region has the only psychiatric hospital in the province. The Eastern region is served by three secondary care hospitals, is predominantly rural and has a population of 109,682. The Central region is predominantly rural and has a population of 106,682. The Western region is served by one tertiary care hospital and 5 community hospitals, is predominantly rural and has a population of 87,736. Both the Grenfell and Labrador regions are rural and are served by one secondary hospital with a combined population of 42,453(Appendix A).[8]

1.2 Purpose of Study

The current study was undertaken at the request of the Department of Health and Community Services, Government of Newfoundland and Labrador to evaluate the impact of open access to atypical antipsychotic medications on hospital utilization for schizophrenia in the province. Government and various sectors of the pharmaceutical industry agreed to collaborate in this research endeavour. Other stakeholders such as the Schizophrenia Society of Newfoundland and Labrador, the Newfoundland and Labrador Psychiatric Association, the Newfoundland and Labrador Medical Association (NLMA) endorsed the study.

This study has been designed to determine whether the increased utilization of expensive atypical antipsychotic medications resulting from the implementation of the unrestricted reimbursement policy would be associated with a reduction in hospital utilization by patients with schizophrenia in Newfoundland and Labrador. The primary objective was to measure changes in hospitalization and time to readmission by schizophrenia sufferers as well as changes in drug utilization and expenditures before and after the advent of unrestricted access to atypical agents. As multiple factors influence hospitalization, length of stay and readmission, multivariable modelling permitted the examination of the impact of study year while taking account of other factors that influence these outcomes. The main hypothesis was that as the utilization of atypical antipsychotic medications increases, patients with a diagnosis of schizophrenia will

experience fewer episodes of relapse requiring admission to hospital and a reduced length of hospital stay. In addition, as the penetration of atypical antipsychotic medications in the marketplace increased so the number of admissions would decrease. Consequently all admissions to both acute and psychiatric hospitals for schizophrenia during three 12-month periods were studied: 1) at the beginning of restricted access to atypical antipsychotic drugs in 1995/96; 2) at the end of restricted access in 1998; and 3) during the second year of unrestricted access in 2000. A secondary objective was to measure the impact of the policy change on the NLPDP budget.

To our knowledge no comprehensive studies have assessed hospital utilization patterns and drug use following an unrestricted access policy for atypical antipsychotic medications within Canada.

CHAPTER II – LITERATURE REVIEW

2.1 Burden of Schizophrenia

Schizophrenia is an expensive disease. Although it occurs in only 1% of the general population, it has a much greater impact on the national budget than the numbers suggest.[9] Patients with schizophrenia are at significantly increased risk for suicide, violence, substance abuse/dependence, unemployment and homelessness. The disease has an early age of onset and causes long-term morbidity; necessitates maintenance drug therapy, and frequent admission to hospital occurs. In 1996, the direct and indirect cost associated with schizophrenia was estimated to be $1.12 billion in Canada.[9] The largest single category of direct costs was acute care hospitalizations (29%), followed by provincial psychiatric hospitalizations (21%). By 2002, the annual direct and indirect cost of schizophrenia in Canada has been estimated to have reached $4.35 billion.[10]

2.2 Treatment for Schizophrenia

At present, there is no cure for schizophrenia. As a result, the goals of treatment include the improvement of symptoms, patient rehabilitation, improved quality of life, and the prevention of relapse and re-hospitalization. In addition to clinical needs (e.g., symptom reduction), treatment for persons with schizophrenia must address a variety of needs related to the illness including housing, income support, psychological interventions, family interventions, vocational rehabilitation, assertive community treatment and case management. However, pharmacotherapy is the cornerstone of

treatment for schizophrenia and the most extensively evaluated type of intervention for the disease.

2.2.1 Pharmacotherapies

The modern era of pharmacotherapy for schizophrenia began in the early 1950s when the antipsychotic properties of chlorpromazine were discovered.[11] Following this discovery, numerous other antipsychotic drugs have been developed. In clinical trials, these agents have been shown to be more effective than placebo in controlling the positive symptoms of schizophrenia (e.g. auditory hallucinations and delusions) and in moderating acute episodes of the condition.[12 13] Despite being the mainstay of psychopharmacological treatment for patients with schizophrenia for more than four decades, these antipsychotics are only moderately effective in treating the positive symptoms of 70 to 80% of schizophrenia sufferers.[11] Treatment responders still have a high rate of nonadherence that is thought to be due in part to limited insight into their illness and to the increased risk of inducing acute and tardive extrapyramidal side effects (EPS).[11 14] In addition, these antipsychotic agents appear to have little effect on the negative symptoms (e.g. blunted affect and emotional withdrawal) of schizophrenia. Whilst representing a major step forward in the treatment of schizophrenia when introduced, the overall impact of conventional antipsychotics is still marred by the frequency and severity of side effects.

In response to the problems of conventional therapies outlined above, the pharmaceutical industry has put considerable effort into developing new, 'atypical', or second generation, antipsychotics. The term 'atypical' was originally used to describe drugs that in animal models predict antipsychotic effects but do not produce catalepsy (the behavioural equivalent of EPS). At present, an atypical agent is generally defined as one that has a low propensity to produce EPS or other movement disorders and elevated serum prolactin levels.[15] Additionally, they are promoted as reducing both the negative[16] [17] and positive symptoms of schizophrenia.[5 6]

Antipsychotic medications affect specific brain receptors in specific regions and block dopamine D_2 receptors. While this does not prove a causal relationship between D_2 blockade and antipsychotic response, it is believed that the association between the two is undeniable.[18] Prospective studies have largely confirmed that a "threshold" D_2 occupancy is required to induce antipsychotic response. However, it is unclear exactly what this threshold is and whether the threshold for inducing response is the same as the one for maintaining it.[19] Nonetheless, there is a mechanism of antipsychotic response that relies on D_2 occupancy alone. Additionally, it has been noted that as D_2 occupancy increases, especially as it rises above 80%, the incidence of extrapyramidal side effects increases. Elevation of prolactin levels may also show a threshold relationship with respect to D_2 occupancy. While D_2 occupancy may be necessary for response, it is not always sufficient, as there are patients who do not respond despite adequate D_2

occupancy.[20] However, Kapur et al.[18] claim that it is fair to say that D_2 occupancy provides a reliable pharmacological predictor of response to antipsychotic medications, extrapyramidal side effects, and elevation of prolactin levels.

Drugs that demonstrate clinical features associated with atypical antipsychotics (i.e., low extrapyramidal side effects and prolactin elevation) have higher ratios of serotonin 5-HT_2 (5-hydroxytryptamine) receptor to dopamine D_2 receptor blockade *in vitro,* in comparison with conventional antipsychotics such as haloperidol, due to their lower affinity at the D_2 receptor.[21] Compounds such as risperidone may share features of both typical and atypical agents with some differences, disappearing at higher doses.[22 23] Thus, criteria for an atypical agent are somewhat flexible.

2.2.1.1 Clinical Evidence for Atypical Antipsychotics in Schizophrenia

The introduction of novel antipsychotics has been heralded as a major advance in the treatment of schizophrenia and as a result has raised expectations of improved outcomes for individuals with schizophrenia. Initial evidence supporting the efficacy of atypical antipsychotic medications has been obtained, in large part, from studies of clozapine, which have demonstrated its increased efficacy in patients with treatment-resistant schizophrenia in which conventional antipsychotics were no longer efficacious.[24 25] Second generation antipsychotic medications introduced subsequently are also widely believed to have greater efficacy compared to conventional antipsychotic

drugs, although the evidence for this is variable. The following sections will provide review of this evidence for each drug affected by the policy change and will be divided into two sections: 1) evidence available to inform the initial policy decision; and 2) evidence published after the implementation of the unrestricted policy, as the latter influences atypical antipsychotic utilization for the treatment of schizophrenia. This review compares the efficacy of atypical antipsychotics with older antipsychotics as well as with other atypical agents. Many psychometric rating scales have been used in clinical trials to assess the impact of various treatment regimes on patients with schizophrenia and in order to compare the studies, a basic knowledge of the psychometric instruments used for measuring efficacy is necessary.

2.2.1.2 Psychometric Rating Scales

All efficacy measures are clinician-administered, but some measure global symptoms while others measure symptoms more specific to psychotic disorders. The Clinical Global Impression Scale (CGI) measures severity of illness, clinical improvement, and therapeutic efficacy of treatment by comparing conditions of the person standardized against other people with the same diagnosis.[26] A seven-point scoring system is usually used, with low scores showing decreased severity and/or overall improvement. Also global in nature, the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-C)[27] is a structured interview that measures change in symptoms and assesses anxiety, depression, manic features, and delusions or

disorganization. The Nurses' Observation Scale for Inpatient Evaluation (NOSIE) is a global observational tool that consists of 30 specific patient behaviors, each rated on a 5-point scale ranging from 0 = 'never' to 4 = 'always'.[28] The Brief Psychiatric Rating Scale (BPRS) [29] consists of 24 symptom constructs, each rated on a 7-point scale of severity ranging from 1 = 'not present' to 7 = 'extremely severe'. Scores can range from 0-168, with high scores indicating more severe symptoms. The Positive and Negative Symptom Scale for Schizophrenia (PANSS)[30] is a semi-structured patient interview based on the BPRS. This validated rating scale is a 30-item scale with 16 general psychopathology symptom items (PANSS-GPS), seven positive-symptom items (PANSS-P), and seven negative symptom items (PANSS-N). Each item is scored on the same seven-point severity scale varying from 1-absent to 7-extreme, resulting in a range of possible scores from 30 to 210. In contrast to the PANSS, the Scale for Assessment of Negative Symptoms (SANS) is a specific scale that measures negative symptoms only.[31] This six-point scale gives a global rating of the following negative symptoms: alogia, affect blunting, avolition-apathy, anhedonia-asociality, and impaired attention. Higher scores indicate more symptoms. The Montgomery-Asberg Depression Rating Scale (MADRS)[32], a depression instrument particularly sensitive to measuring drug-related changes, may be used to assess the depressive features of schizophrenia. Another scale used to assess depression is the Hamilton Rating Scale for Depression (HAM-D).[33] This scale rates the severity of depression in patients who are already diagnosed as depressed. The higher the score on the scale, the more severe the depression. The Bunney-Hamburg

rating scale for psychosis is based on a 15-point scale, and has a range such that 1-3 is normal, 4-6 is mildly psychotic, 7-9 moderately psychotic, 10-12 severely psychotic and 13-15 very severely psychotic.[34]

2.2.1.3 Literature Search and Study Selection

Randomized controlled trials were identified that compared the new generation antipsychotics listed on the Newfoundland and Labrador Prescription Drug Program formulary (clozapine, risperidone, olanzapine, and quetiapine) with conventional antipsychotics or alternative atypical antipsychotics in patients with schizophrenia. A combination of text and index terms of MEDLINE, EMBASE, PsycINFO, and the Cochrane Library were used to locate randomised trials comparing the efficacy of atypical and conventional antipsychotic drugs. The review was based only on data obtained from controlled trials and meta-analyses in English-speaking journals published between 1988 and 2002 inclusive.

The titles and abstracts were screened and articles were excluded if they included geriatric and childhood/adolescent schizophrenia patients or if they did not use an active comparator. Articles that compared the efficacy of atypical antipsychotics and placebo were not reviewed. If the primary focus of the paper could not be clearly identified by reviewing the title or abstract, the article was obtained for further review.

Descriptive information on the population, interventions evaluated, the study year, country of study, and results were extracted from each study and are summarized in appendices B, C, D, E and F.

2.2.1.4 Atypical versus Conventional Antipsychotics

Clozapine

Clozapine, a dibenzodiazepine derivative, is an atypical antipsychotic due to its preferential occupancy of 5-HT_2 receptors versus D_2 receptors and the ability to completely occupy 5-HT_2 receptors when compared with conventional antipsychotics. This antipsychotic was developed over 45 years ago and was the first atypical agent to become available in Canada. Early controlled trials indicated that clozapine is an effective antipsychotic agent for acutely and chronically ill inpatients with schizophrenia and the drug demonstrated a low incidence of extrapyramidal side effects.[35-38] Clozapine's use in the clinical setting was hampered in the 1970s when it was discovered that the drug was associated with an increased risk of agranulocytosis, a potentially life threatening side effect. Treatment with clozapine necessitated the introduction of regular blood monitoring for those taking the drug. All of the clozapine studies reviewed are summarized in appendix B.

Studies published prior to policy implementation

Interest in clozapine surfaced again in the 1980s following a pivotal multicentre study by Kane et al.[25], which compared clozapine (500-900 mg/day) with chlorpromazine (1000-1800 mg/day) in 268 hospitalized treatment-resistant schizophrenic patients. The study found that after six weeks, 38 percent of the patients taking clozapine showed clinically important improvement, as compared with only 5 percent of patients taking chlorpromazine. The study also showed that EPS were generally absent.

Two other double blind, randomized studies assessed the antipsychotic efficacy of clozapine versus chlorpromazine in hospitalized patients. Claghorn et al.[39] randomly assigned 151 schizophrenic patients to clozapine treatment (150-900 mg/day) or chlorpromazine (300-1800 mg/day). The authors found that clozapine-treated patients exhibited unequivocally superior efficacy to that of patients in the chlorpromazine group. Throughout and at the end of the study, clozapine patients were significantly better, using the Brief Psychiatric Rating Scale (BPRS) items and Clinical Global Impression (CGI) scores. A decade later, a second study, also conducted in treatment-resistant patients, randomly assigned forty patients to clozapine (100-900 mg/day) or chlorpromazine treatment (200-1800 mg/day).[40] Six clozapine-treated patients (28.6%) showed more than 20% improvement in BPRS score and were classified as responders. No chlorpromazine-treated patient showed improvements. There were significant

differences between clozapine and chlorpromazine as measured by changes in the BPRS, PANSS, positive and general symptoms.

In an open-label study by Essock et al.[41], the effectiveness of clozapine was examined in long stay hospitalized patients by comparing clozapine to an alternative antipsychotic chosen by the clinician at a mean dose of 1386 mg/day chlorpromazine equivalent. Participants (n=227) were followed for 2 years and the authors reported that compared with usual care, clozapine was associated with significantly greater reductions in side effects, disruptiveness, and hospitalization, but was not more effective in reducing symptoms or improving quality of life. The groups did not differ in likelihood of being discharged; however, once discharged, clozapine patients were less likely to be readmitted. The authors concluded that clozapine did not produce dramatic improvements in symptomatology or hospital utilization. Additionally, the study revealed that clozapine treatment resulted in an increase in symptom severity of about 2.7 points based on the BPRS.

There was one study which compared clozapine with fluphenazine.[42] In this crossover, placebo-controlled, double-blind comparison, twenty-one patients with treatment-resistant schizophrenia were treated with optimal doses of clozapine (mean, 542.9 mg/day), which resulted in significantly lower BPRS total scores than in the fluphenazine treatment group (mean, 28.9 mg/day).

Two double-blind, randomized controlled trials compared the efficacy of clozapine with haloperidol in treatment refractory schizophrenic patients.[43 44] Rosenheck et al.[43] randomly assigned 423 hospitalized patients to receive clozapine (100-900 mg/day) or haloperidol (5-30 mg/day) for 1 year. Symptom outcome was assessed using the Positive and Negative Syndrome Scale for Schizophrenia (PANSS), with a 20 percent reduction considered to represent clinically important improvement. After six weeks and six months of treatment, significantly more patients assigned to clozapine had a clinically important improvement in symptoms than those assigned to haloperidol. The differences between the groups were not significant at the end of the study. However, the study did show that clozapine was associated with markedly greater reductions in the tardive-dyskinesia (P=0.005), akathisia (P<0.001) and extrapyramidal symptoms (P<0.001) over time. Additionally, patients assigned to clozapine treatment had, on average, 24.3 fewer days in the hospital for psychiatric reasons in a year than those patients assigned to haloperidol (143.8 days vs. 168.1 days, P=0.03).[43]

The second, much smaller study (n=39) included treatment resistant community dwelling schizophrenia patients in a 10-week study.[44] Nineteen patients were given clozapine, and 20 patients were given haloperidol. Doses at the end of the trial were 410.5 mg/day and 24.8 mg/day for clozapine and haloperidol, respectively. This study found a minor difference between clozapine and haloperidol, using the Scale for the Assessment of Negative Symptoms (SANS). Response was defined *a priori* as a 20% or

greater decrease in BPRS positive symptom scores *and* a BPRS positive symptom score of less than 8. Response rates were 44.4% for clozapine compared with 5.6% for haloperidol, a difference of 39 percentage points (P=0.017). The authors concluded that clozapine was superior to haloperidol for treating positive symptoms in outpatients with chronic schizophrenia who are partially responsive to neuroleptics.

Overall, the studies of clozapine prior to the policy change demonstrated that clozapine has some advantages over conventional antipsychotic medications in mostly hospitalized, treatment-resistant patients with schizophrenia.

Studies published following policy implementation

The results from a study by Kane et al.[45] who, in 2001, examined the efficacy of clozapine with moderate-dose haloperidol in partially responsive schizophrenic patients, are consistent with those found in Rosenheck et al.[43] and Brier et al.[44] Thirty-seven subjects were randomized to receive a target dose 500 mg/day (200-800 mg/day) of clozapine and thirty-four subjects to receive 10 mg/day (4-16 mg/day) of haloperidol. This multicentre, double blind study discovered that subjects randomized to clozapine were significantly more likely to complete 29 weeks of receiving study medication than were subjects assigned to haloperidol (P=0.03). Additionally, the authors found that 56.6% of the clozapine group improved (defined as a BPRS score reduction by 20% from

baseline for at least 2 consecutive assessments), compared with 24.8% for the haloperidol group (P=0.02).

Risperidone

Risperidone, a benzisoxazole derivative initially marketed in 1993, represents the second atypical antipsychotic approved in Canada. Risperidone has been shown to have a higher D_2 occupancy than clozapine.[18] The potent antipsychotic effects of risperidone have been confirmed in patients with schizophrenia. Improvements have been seen not only in positive symptoms, but also in both negative and affective symptoms. The following section will provide an overview of 14 controlled studies that compared the efficacy of risperidone with that of other conventional antipsychotic agents. 86% of the studies used haloperidol as the comparator (Appendix C).

Studies published prior to policy implementation

Claus et al.[46] recruited 44 chronic, hospitalized schizophrenic patients in a 12-week double-blind trial of risperidone (12 mg/day) and haloperidol (10 mg/day). The risperidone group showed greater improvement on the Positive and Negative Symptom Scale for Schizophrenia (PANSS), the Schedule for Affective Disorders and Schizophrenia-change version (SADS-C), and the Nurses Observation Scale for Inpatient Evaluation (NOSIE) but these did not reach significance by the end of the study. The

authors concluded that risperidone is at least as effective as haloperidol, but has a safer EPS profile.

A large (n=1,362) 8-week, multinational, dose-finding trial of patients with chronic schizophrenia measured the efficacy advantages of risperidone over haloperidol.[23] Patients from 15 countries were recruited into the study if they met DSM-III-R criteria for schizophrenia and had a total PANSS score between 60 and 120. Eligible patients were then randomly assigned to risperidone 1, 4, 8, 12 or 16 mg/day or haloperidol 10 mg/day. Symptomatology and efficacy were assessed 6 times during the trial (days 0, 7, 14, 28, 42, and 56) using PANSS and the Clinical Global Impressions-Severity of Illness scale (CGI-S). The results demonstrated that the difference in response rates in haloperidol-treated patients and risperidone-treated patients did not reach statistical significance. However, a later sub-analysis of the patients from Germany, Austria, and Switzerland (n=169) reported some advantages for risperidone-treated patients over haloperidol-treated patients, according to PANSS and its subscales, and on total BPRS scores.[47] The authors concluded that the optimal dose of risperidone, in terms of efficacy, was 4 mg/day.

A smaller study (n=35), using similar types of chronic patients (PANSS scores >60 and <120) compared risperidone (5-10 mg/day) with haloperidol (5-10 mg/day) over 8 weeks and reported no significant differences in outcome.[48]

An 8-week, double-blind, placebo-controlled, dose-finding study of hospital inpatients (n=388) randomized patients to four different doses of risperidone (2, 6, 10, and 16 mg/day), and 20 mg/day of haloperidol.[22] The authors found that clinical improvement (defined as ≥20% reduction in total PANSS scores) at the study end point was demonstrated by 35% of the patients receiving 2 mg of risperidone, 57% receiving 6 mg, 40% receiving 10 mg, and by 30% receiving haloperidol. Statistically significant differences in responses were found between 6 mg/day and 16 mg/day of risperidone versus haloperidol, although no other efficacy differences between risperidone and haloperidol were identified. In addition, the incidence of extrapyramidal symptoms in patients receiving 6 mg of risperidone was no higher than placebo.

The article described above reported the US arm of a US-Canadian collaborative investigation of risperidone in schizophrenia. Chouinard et al.[49] published the Canadian results for the 135 hospitalized patients with chronic schizophrenia (DSM-III-R). The authors also found that risperidone, 6 mg/day, was significantly superior to haloperidol on the total PANSS, PANSS-GPS, and BPRS scales. Of note, risperidone 6 mg/day was not shown to be significantly superior to haloperidol 20 mg/day on the primary efficacy outcome determined *a priori* of a 20% or greater reduction in the PANSS total score.

In another double-blind eight week study, hospitalized patients were treated with either risperidone 2-20 mg/day or haloperidol 2-20 mg/day.[50] A very good remission

(50-100% relative change in BPRS from baseline) and a partial remission (25-49% relative change in BPRS from baseline) were achieved in 45% and 32%, respectively of the risperidone group. The corresponding figures in the haloperidol group were 45% and 42% respectively, revealing no statistical difference in therapeutic efficacy. The authors thought that this was most likely due to the high doses of risperidone used in the study.

Borison and coworkers[51] randomized 36 schizophrenic patients in acute exacerbation to receive risperidone (2-10 mg/day, mean, 9.7 mg/day) or haloperidol (4-20 mg/day, mean, 18.0 mg/day). The authors found that risperidone-treated patients had a faster onset of antipsychotic activity than haloperidol-treated patients and showed a trend toward greater improvement. In addition, risperidone produced significantly fewer extrapyramidal side effects than did haloperidol.

In 1996, Blin et al.[52] randomized 62 patients hospitalized for acute exacerbations to receive risperidone (mean dose, 7.4 mg/day), haloperidol (mean dose, 7.6 mg/day), or methotrimeprazine (mean dose, 100 mg/day) for 4 weeks. Clinical improvement, defined as a 20% reduction in total PANSS scores at end point, was attained by 81% of the risperidone patients, 60% of the haloperidol patients, and 52% of the methotrimeprazine patients. The differences between risperidone and haloperidol and haloperidol and methotrimeprazine did not reach statistical significance. The reductions in total PANSS and Clinical Global Impression Scale severity scores from baseline to end point were

significantly greater in the risperidone patients than in the other two groups ($P<0.05$). Extrapyramidal symptoms were more severe in the haloperidol patients than in the other two groups, but few differences were apparent between risperidone and methotrimeprazine patients.

Two studies compared risperidone with conventional antipsychotics other than haloperidol.[53 54] The first was conducted in 1993 by Hoyberg et al.[53] The authors compared risperidone (5-15 mg/day, mean, 8.5 mg/day) with that of perphenazine (16-48 mg/day, mean, 28 mg/day), in an 8-week, double-blind, multicentre, parallel-group study in 107 chronic schizophrenics with acute exacerbation. The reduction in total PANSS score to endpoint did not differ significantly, although there was a tendency in favour of risperidone. The researchers noted that the overall prevalence of side effects was similar in the two groups.

The second study evaluated the respective efficacy of risperidone (mean, 8 mg/day) and zuclopenthixol (mean, 38 mg/day) in a double-blind, randomized, multicentre study in 98 patients with acute exacerbations of schizophrenia or schizophreniform disorder in Finland.[54] This 6-week study found that risperidone is at least as effective as zuclopenthixol for the treatment of acute schizophrenic episodes, with a trend towards greater improvement in the overall severity of symptoms and the rate of clinical improvement.

The studies comparing risperidone with conventional antipsychotic medications were, in general, of short duration dealing primarily with relatively few, hospitalized chronic schizophrenia patients. The results from the majority of these studies showed that there was no significant difference between the two therapies but some showed a trend toward improvement.

Studies published following policy implementation

In 2001, two post-hoc sub-analyses from Peuskens' study involving approximately 1,300 patients with chronic schizophrenia from 15 countries reported that patients receiving risperidone, 4 mg/day (n=227), improved more rapidly than patients receiving haloperidol (n=226) as measured by PANSS total and CGI-S scores [55], and patients hospitalized for more than 60 days (median, 351 days) who received risperidone, 4 mg/day (n=75), improved significantly more than patients treated with haloperidol (n=69).[56]

Olanzapine

Olanzapine, the third atypical antipsychotic medication, was approved in Canada for the treatment of schizophrenia and related psychotic disorders in 1996. Olanzapine displays high receptor affinity binding in vitro at serotonin 5-HT_2, dopamine D_1, D_2, D_3, D_4, muscarinic M_{1-5}, adrenergic α_1, and histamine H_1 receptors.[57] Appendix D outlines the studies reviewed in this section.

Studies published prior to policy implementation

The antipsychotic efficacy of olanzapine has been evaluated in three large, 6-week randomized controlled trials.[58-60] In these studies, olanzapine was compared with haloperidol. The first multicentre trial used data from a North American population (n=335) to compare three dosage ranges of olanzapine (5±2.5 mg/day, 10±2.5 mg/day, and 15±2.5 mg/day) to a dosage range of haloperidol (15±2.5 mg/day) and to placebo.[58] The authors concluded that olanzapine, 15±2.5 mg/day, was significantly better than haloperidol, 15±5 mg/day, in reducing negative symptoms in patients with schizophrenia after 6 weeks.

The second acute phase study used the same methodology as above to examine international data to determine whether olanzapine demonstrated a dose-related ability to decrease overall psychopathology in patients with schizophrenia.[59] The primary efficacy analysis showed that there were no statistically significant differences in mean improvement in BPRS total score, CGI severity, PANSS total, negative or general psychopathology scores between any of the treatment groups.

The third study, an international double-blind randomized trial (n=1,996), was the largest.[60] The authors found that olanzapine, 5 to 20 mg/day was significantly better than haloperidol, 5 to 20 mg/day, over the 6-week study period in reducing overall psychopathology, positive symptoms, negative symptoms, and depressive symptoms.

Based on the mean change from baseline to endpoint in Brief Psychiatric Rating Scale (BPRS) score, the analysis revealed that olanzapine-treated patients had significantly higher response rates (52%) than haloperidol-treated patients (34%) ($P<0.001$). EPS was lower in the olanzapine group compared with the haloperidol group. Additionally, the proportions of patients discontinuing the treatment, both for lack of efficacy and for adverse events, were significantly smaller in the olanzapine group.

Patients responding to treatment in Beasley et al.[58], the North American, 6-week acute phase trial, were eligible to enter a 46-week extension. Hamilton et al.[61] used the first 24 weeks of this extension data and designed a study to address efficacy of olanzapine in altering the long-term course of schizophrenia. Of the 335 patients enrolled in the initial acute phase study, 95 (28.4%) continued into the responder extension. The completion rate for the total population was 42.1% (53.2% in olanzapine group, and 22.2% in the haloperidol group). Data analyzed after 24 weeks of therapy showed that there was no significant difference in either the BPRS total scores or the CGI severity scores observed between the haloperidol treatment group and the three olanzapine treatment groups. The only significant difference was found on the Scale for the Assessment of Negative Symptoms (SANS) summary score among the patients randomized to the high dose olanzapine group (15±2.5 mg/day) and the haloperidol group.

Additionally, Tran et al.[62] examined the long-term efficacy of olanzapine based on pooled data obtained from the double-blind extensions of all three acute phase studies. The authors measured the time to relapse and found that fewer patients treated with olanzapine relapsed during the 1 year follow-up period (19.7%), compared with patents receiving haloperidol (28%)(P=0.034).

Only one study compared olanzapine to a conventional antipsychotic other than haloperidol. Conley et al.[63] designed a prospective, randomized, double-blind study to compare the efficacy of olanzapine versus chlorpromazine in treatment-resistant schizophrenia. This 8-week, fixed-dose trial of olanzapine, 25 mg/day, or chlorpromazine, 1200 mg/day, plus benztropine, 4 mg/day showed that there was no difference in efficacy (defined as at least a 20% reduction in the total BPRS score compared to the baseline score) between the two drugs. Of patients, 7% in the olanzapine group and none in the chlorpromazine group met *a priori* criteria for clinical response. There were also no differences in dropout rates.

Much of the literature on the efficacy of olanzapine at this time was based on data from the same study protocol. The studies were of short duration and enrolled a combination of hospitalized and community-dwelling patients as well as different types of schizophrenic patients (i.e. treatment-resistant). The results are often conflicting with

olanzapine being superior to the conventional agent on some outcome measures and in some cases, the drugs proved to be equally efficacious.

Studies published following policy implementation

Breier and Hamilton[64] compared the relative efficacy of olanzapine (dose range 5-20 mg/day, mean of 11.1 mg/day) and haloperidol (5-20 mg/day, mean of 10.0 mg/day) for symptomatology and parkinsonian side effects in a group of treatment-resistant schizophrenic and schizoaffective patients. The authors examined a subpopulation of patients (n=526) meeting treatment-resistant criteria selected from the Tollefson et al., prospective, double-blind, 6-week study.[60] Response was defined *a priori* as at least 20% improvement in BPRS total score from baseline and an endpoint BPRS total score less than or equal to 24. The results of the analysis demonstrated that olanzapine had a significantly greater mean improvement in PANSS negative symptoms and comorbid depressive symptoms. Significantly greater response rates were observed in olanzapine-treated (47%) than haloperidol-treated (35%) patients in the last observation carried forward (LOCF) analysis (P=0.008), but significance was not reached in the analysis of those who completed the study (P=0.093).

Quetiapine

Quetiapine is a dibenzothiazepine which, like clozapine and olanzapine, binds to a variety of neurotransmitter sites. Quetiapine exhibits a greater affinity for brain serotonin

5-HT_2 receptors than for dopamine D_2 receptors, together with considerable activity at histamine receptors and α-adrenoceptors.[65] Quetiapine was approved in Canada in 1997. The studies reviewed are summarized in appendix E.

Studies published prior to policy implementation

Arvanitis and Miller[66] conducted a multiple fixed dose study of quetiapine (75, 150, 300, 600, and 750 mg/day), haloperidol (12 mg/day), and placebo using 361 subjects over a 6-week period. Patients had their psychopathology and overall function rated weekly, using Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) and Schedule for the Assessment of Negative Symptoms (SANS). Patients in this trial were all acutely unwell, with a long history of illness, multiple hospitalizations and considerable previous exposure to antipsychotic medications. In all measures of efficacy, quetiapine was comparable to haloperidol.

The only complete published study that compared quetiapine with chlorpromazine, allowed flexible dosing (quetiapine mean dosage, 404 mg/day and chlorpromazine mean dosage, 384 mg/day) and had a follow-up of 6 weeks.[67] The analysis showed that quetiapine was at least as effective as chlorpromazine in improving the symptoms of acute schizophrenia, as indicated by changes in BPRS, PANSS negative symptoms subscale and CGI severity of illness scores in the 201 hospitalized patients. However, using a pre-defined response criterion of a 50% improvement from baseline at

any time point within the trial, quetiapine was associated with a statistically greater response rate than chlorpromazine. Using this criterion, quetiapine was associated with a response rate of 65%, compared with 53% in the chlorpromazine group, a statistically significant difference (P=0.04).

Studies published following policy implementation

Copolvo et al.[68] conducted a multinational, 6-week randomized controlled trial comparing quetiapine, at a mean daily dose of 455 mg/day, with haloperidol (8 mg/day) in the treatment of 448 hospitalized patients with acute exacerbations of schizophrenia. Both groups showed meaningful improvements in symptoms, as measured by the PANSS total score and by responder rates (score reduction of 30% or more). There were no statistically significant differences between the two treatments in these efficacy measures, suggesting that the two treatments were equivalent. Quetiapine was better tolerated than haloperidol in terms of EPS. At the same time, quetiapine-treated patients mainly experienced somnolence and weight gain.

An international, double-blind study compared the efficacy and tolerability of 8 weeks' treatment of quetiapine 600 mg/day with haloperidol 20 mg/day in 288 patients who had a history of partial response to conventional antipsychotics.[69] The difference in PANSS total score after 8 weeks was not statistically significant (P=0.234). For the secondary endpoint, defined as the proportion of patients experiencing a decrease in

PANSS total score ≥20% from baseline to endpoint, response rates were statistically higher in the quetiapine group than in the haloperidol group (P=0.043).

2.2.1.5 Head-to-Head Comparisons of Atypical Antipsychotics

Clozapine versus risperidone

Despite the fact that clozapine and risperidone were the first two atypical antipsychotic drugs approved for schizophrenia, there is relatively little information about the comparative efficacy of the two atypical antipsychotic medications from head-to-head clinical trials. The studies described below are summarized in appendix F.

Studies published prior to policy implementation

The short-term efficacy and safety of risperidone was compared to clozapine in treatment-resistant chronic schizophrenic patients.[70] This controlled double-blind, multi-centre study randomly assigned 86 inpatients with chronic schizophrenia (DSM-III-R), resistant to or intolerant of conventional neuroleptics, to receive risperidone or clozapine for 8 weeks after a 7-day washout period. The final mean doses were 6.4 mg/day of risperidone and 291.2 mg/day of clozapine. At endpoint, 67% of the risperidone group and 65% of the clozapine group were clinically improved (reduction of 20% or more in total PANSS) and in both groups, severity of schizophrenic symptoms was significantly ameliorated. Additionally, no significant differences between therapies were found at any time.

Studies published following policy implementation

Another short term study was designed to examine the comparative efficacy of clozapine and risperidone in chronically ill, partially responsive patients with schizophrenia.[71] After a baseline 2-week treatment period with fluphenazine, 29 patients participated in a 6-week, double-blind, parallel-group comparison of the effects of clozapine and risperidone using flexible dosing. Clozapine was superior to risperidone for treating positive symptoms, but there were no significant differences between the drugs on two measures of negative symptoms (SANS and BPRS withdrawal/retardation score), BPRS total score, and depression scores.

A more recent double-blind comparison of clozapine with risperidone in 273 chronically ill schizophrenic patients with poor previous treatment response[72] showed that at follow-up; patients in the clozapine group had significantly lower symptom levels than did those in the risperidone group (BPRS, P=0.006 and CGI total scores, P=0.008). The proportions of patients with decreases in mean BPRS total score of ≥20% and ≥30% at the end of the study (12 weeks) were significantly higher in the clozapine group than in the risperidone group (P<0.01).

Risperidone versus olanzapine

Studies published prior to policy implementation

Risperidone and olanzapine have been compared in two multicentre randomized clinical trials.[73 74] The first evaluated risperidone (4-12 mg/day) and olanzapine (10-20 mg/day) in a double-blind, 28-week study involving 339 treatment refractory inpatients.[73] Both antipsychotics were found to be effective in reducing the severity of overall psychotic symptoms, although olanzapine exhibited significantly greater efficacy on negative and depressive symptoms. More olanzapine than risperidone participants were rated as treatment responders, defined as >40% reduction in scores on the PANSS (olanzapine 36.8% vs. risperidone 26.7%, P=0.049). Moreover, fewer EPS were reported by the olanzapine-treated patients than by their risperidone-treated counterparts (P<0.05).

Studies published following policy implementation

The second randomized trial[74] investigated the relative efficacy of risperidone and olanzapine in schizophrenia sufferers. Participants' psychopathology was evaluated with the Positive and Negative Syndrome Scale with clinical improvement defined as a ≥ 20% reduction in total score. The 377 eligible participants were randomly assigned to receive risperidone (2-6 mg/day) (n=188) or olanzapine (5-20 mg/day) (n=189) for 8 weeks. Clinical improvement was seen in 50.7% of the risperidone group (n=69) and 47.6% of the olanzapine group (n=68) at week 8.

In an open-label study by Ho et al.[75], 42 people with DSM-IV schizophrenia who had been treated with risperidone (n=21) or olanzapine (n=21) under actual clinical practice conditions were examined over a 6-month period. After an average of 4 weeks, improvements in negative, psychotic, and disorganized symptoms were noted with both risperidone and olanzapine groups. The only between-treatment difference was an increased severity of akathisia in the risperidone group. Further improvements in symptoms and quality-of-life scores were noted in both groups at 6 months, with a substantial between-treatment difference: the improvement in psychotic symptoms was greater in the risperidone group.

Quetiapine versus risperidone

Studies published following policy implementation

A four month, multicentre, randomized, flexible dose, open-label trial enrolled 728 outpatients with DSM-IV diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, delusional disorder and Alzheimer's dementia to receive quetiapine or risperidone.[76] Patients with schizophrenia, schizoaffective disorder and schizophreniform disorder made up 65.0% of the population and the researchers found that quetiapine (mean, 253.9 mg/day) was at least as effective as risperidone (mean, 4.4 mg/day). Both treatments produced similar improvements in the PANSS score, and its negative and positive sub-scales.

Clozapine versus olanzapine versus risperidone

Studies published following policy implementation

Clozapine, olanzapine, risperidone and haloperidol were compared in a randomized controlled trial comprising a sample of 157 patients with chronic schizophrenia who had not responded adequately to other antipsychotic medications.[77] Patients were randomly assigned to one of the four treatment arms: clozapine (n=40), olanzapine (n=39), risperidone (n=41), or haloperidol (n=37). Trial duration was 14 weeks (8 weeks' fixed dose, followed by 6 weeks flexible dose) with only 58% (n=91) of the subjects completing the study. The mean dose levels achieved by the end of the study period were 30.4 mg/day for olanzapine, 11.6 mg/day for risperidone, 526.6 mg/day for clozapine, and 25.7 mg/day for haloperidol. Compared with haloperidol, there were significant advantages for clozapine and olanzapine regarding overall improvement (PANSS total) and general psychopathology, and for clozapine, risperidone, and olanzapine regarding negative symptoms. The overall pattern of results suggests that clozapine and olanzapine have similar general antipsychotic efficacy and that risperidone may be somewhat less effective.

Despite the rapid acceptance of these new medications, few studies have compared the efficacy of the atypical antipsychotic agents in head-to-head trials. These studies were performed in relatively homogeneous populations and because of the

methodological differences, it is difficult to interpret the results of these studies and draw conclusions across them in terms of the comparative efficacy.

2.2.1.6 Quality of Studies Reviewed

A review of the published literature shows that in several key areas, evidence for the efficacy of atypical antipsychotics compared to older drugs and to each other is, in general, of poor quality. The most obvious criticism is that the overwhelming majority of the randomized controlled trials enrolled small numbers of patients (underpowered) and were short-term studies (4 to 8 weeks long). The severe clozapine-related side effect of loss of white blood cells (agranulocytosis) as well as other side-effects such as tardive dyskinesia may occur later than the first 4-8 weeks of treatment, and may thus be under-reported in short-term studies. On the other hand, deficiencies of global and social functioning caused by schizophrenia may take much longer to improve, and the beneficial effect of the antipsychotic drugs under investigation may thus be underestimated in short RCTs. Thus, the conclusions that can be drawn from the majority of the studies are limited.

All of the trials enrolled patients based on stringent inclusion criteria such as diagnosis (DSM or ICD classification), and response to previous treatment (resistant and/or intolerant). Rigid inclusion criteria ensure internal consistency, but exclude a large number of patients who have co-existing substance abuse disorders or other

comorbid mental disorders, such as depression, for example and reduce the 'real world' external validity, or generalizability, of the trial results. Also, an important characteristic of nearly all of the treatment-resistant studies is that patients are defined as treatment-resistant based on trials with conventional antipsychotics. Patients are then randomly assigned to the newer agent or a conventional agent. This design clearly prejudices the results in favour of the newer agent.

The setting also compromises the generalizability of the trials. Most of the research was undertaken in hospital and therefore is generalizable to people with acute episodes of schizophrenia. However the majority of people have chronic schizophrenia and are treated with maintenance doses of antipsychotic drugs in the community.

The procedure by which concealment of allocation took place was seldom described. The trials usually declared only randomization and double-blind protocol but did not report how these procedures were performed.

There was a poor consideration of statistical power on the part of study authors. In small studies, just because an 'atypical' drug and its comparator have not been shown to be significantly different does not mean that they are equivalent in effect. Studies which demonstrate equivalence need to be more highly powered than those which are designed to show a difference. Therefore although many of the atypicals were not shown

to be significantly different from typical drugs or each other on measures of efficacy we cannot say with confidence that they are as efficacious as the typical drugs or each other.

Most clinical trials of medications for schizophrenia have used the classical rating scales, either the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS), in order to measure symptom reduction in schizophrenia patients. However, the definitions of improvement differ across trials. This warrants some caution in drawing conclusions, as it is difficult to decide whether the results concerning clinical improvement are comparable. Most trials did not address the effect of the new atypicals on negative symptoms, which is surprising given the claims made for efficacy with regard to these symptoms by many of the atypical antipsychotic manufacturers. In the small number of studies that do report on negative symptoms, they do not make it possible to establish whether the improvement on negative symptoms is due to the resolution of secondary symptomatology (due to EPS) or to a specific effect on primary negative symptoms of schizophrenia. Outcome reporting using the aforementioned scales means that improvement was mainly symptom and clinically oriented. Global and functional outcomes, such as being well enough to be discharged and working ability were seldom reported. Patient satisfaction was hardly ever reported and family burden was not reported at all.

Dosage of the drugs used in the trials is also very important. Comparator drugs may have been given in inappropriately high doses in some of the trials. This would most likely produce a high incidence of EPS in the haloperidol group and lead to bias in the result for 'movement' disorders/outcomes in favour of the new drug. A low dose of an atypical drug may give an overly negative view of its efficacy when compared to an appropriate dose of a comparator drug; however a high dose of the same drug may lead to overestimation of the incidence of side effects in comparison to an appropriate dose of a comparator drug. Moreover, it should be noted that in many trials the antipsychotic medication used as a comparator has been haloperidol, which may be associated with a higher incidence of EPS than other typical agents and therefore may not be considered the 'gold standard' in the evaluation of improvement of EPS and secondary negative symptoms.

With respect to the reporting of adverse effects, most of the studies showed that the new antipsychotics do indeed seem to cause fewer movement disorders than typical antipsychotics, although variability in definition and reporting of symptoms limit the confidence that can be placed in these results. Also, weight gain is a common side effect of the newer antipsychotics that has been poorly reported.

The high rates of attrition in most of the studies need to be kept in mind when interpreting the results of the studies, particularly as the majority of participants were

recruited and managed in an inpatient setting. Drop out may be the result of lack of efficacy or of adverse effects or neither. However, a number of trials reported tolerability differences between drugs using a drop out rate despite the fact that drop out is confounded by issues that relate to adverse effects.

One solution to the lack of power in many RCTs may lie in the pooling of data from several studies in a meta-analysis. Meta-analysis is a statistical approach to the aggregation of independent research studies. This method synthesizes data from existing studies thereby increasing the sample size and overcoming the power limitations of undersized studies, or small treatment effects, and is intended to provide (relatively) unbiased quantitative summary estimates. Pooling the data from many trials of the same drug on different patient groups permits researchers to study the effects of the medication across much broader populations.

There have been a number of meta-analyses published to evaluate the efficacy of atypical antipsychotic medications.[78-85] The results of these studies concluded that the atypical antipsychotic medications were as effective or only slightly more effective than conventional antipsychotic medications according to the study criteria for efficacy. Head-to-head comparisons of atypicals usually showed that clozapine was more efficacious than other atypical antipsychotics but only in treatment-resistant schizophrenia. However, the results are only as good as the data that go into them. As a

result, the criticisms of the published trials will undoubtedly impact the interpretation of the results of a meta-analysis, particularly those that relate to short follow up and restricted study groups.

One of the greatest limitations of a meta-analysis is that of publication bias, where trials with positive results are more likely to be published than those with neutral or negative results. Researchers commonly limit a meta-analysis to the inclusion of peer-reviewed, published studies on a given intervention, which runs the risk of discounting unpublished studies in which the data may show less or even no benefit from the intervention being tested. Another potential problem inherent in a meta-analysis of antipsychotics occurs because the trials are not identical: some compare the newer antipsychotic medications with placebo, while others compare the drugs to an active comparator, most commonly haloperidol or chlorpromazine. In addition, meta-analyses cannot balance qualitative differences.

In conclusion, more useful research is urgently needed: long-term trials involving large numbers of community-based people, with less rigid inclusion criteria, and outcomes that are relevant to patients with schizophrenia and their carers. Less rigid, more pragmatic trial protocols may help both to decrease attrition rates from the trial and to increase the generalizability of the results. The selection of an antipsychotic agent to treat people with schizophrenia is a complex decision for which the physician must weigh

individual patient factors and numerous drug factors, including efficacy, safety, tolerability, and cost in the context of long-term use.

2.2.1.7 Summary of Studies Reviewed

Despite the numerous limitations outlined above, the results from the available evidence allow the following tentative conclusions to be drawn. Atypical antipsychotics are at least as effective as conventional antipsychotics. Generally, analyses employing conservative criteria report few efficacy differences between atypical and conventional agents. However, there are now many well-controlled studies indicating modest advantages for the atypical antipsychotics in specific symptom domains. For the treatment of negative symptoms, olanzapine seems most promising. Risperidone, olanzapine, and quetiapine display advantages in improving cognitive and depressive symptoms. In head-to-head comparisons of atypical antipsychotics, none have shown consistent efficacy advantages. In severely refractory patients, no atypical antipsychotic has consistently been shown to be as effective as clozapine or superior to conventional agents. There are indications, however, that risperidone, olanzapine, and quetiapine have advantages over conventional agents in less severely refractory patients. Efficacy advantages for atypical antipsychotics in prospective randomized controlled trials in first-episode schizophrenia have not been reported.

2.2.1.8 Economic Evaluations of Atypical Antipsychotic Medications

The introduction of atypical antipsychotics has provided a new but expensive tool for managing schizophrenia. Depending on dosage, the cost of clozapine can range between CD$4,000 and CD$12,000 for a one-year supply, plus additional costs for laboratory tests, and the cost of other newer atypicals range from CD$1,000-$5,000 per person per year. The classical, or conventional, antipsychotic agents are relatively cheap, the annual cost of the oral preparations being in the order of CD$54-CD$230 while that of the depot preparations is approximately CD$700. Thus, the difference in acquisition costs between the traditional and second-generation antipsychotics can be quite profound. The potential impact of these new drugs on provincial drug budgets is substantial and their increased use will add millions of dollars to the annual drug expenditure. The high acquisition costs of atypical antipsychotics add to the problem of how best to allocate scarce resources to provide optimal care for patients with schizophrenia. As a result, a review of the economic literature for atypical antipsychotics is warranted.

2.2.1.9 Literature Search and Study Selection

An initial search strategy was developed to identify studies that conducted an economic evaluation of atypical antipsychotic medications for the treatment of schizophrenia. A combination of text and index terms of MEDLINE, EMBASE, PsycINFO, and the Cochrane Library were used to locate relevant articles. English language references published between 1990 and 2002 were selected for review.

The titles and abstracts were screened and articles were included if costs or cost analysis or cost evaluation were apparent in the title or abstract. Review articles were excluded if they did not discuss costing or economic analyses. If the primary focus of the paper could not be clearly identified by reviewing the title or abstract, the article was obtained for further review. All selected studies were reviewed and categorized into two groups based on the types of economic evaluation used in the analysis: i) full economic evaluation; and ii) partial economic evaluations. A full economic evaluation is the comparative analysis of alternative courses of action in terms of both costs and consequences. Therefore, the economic evaluations which identify, measure, value, and compare the costs and consequences of the alternative being considered were further classified into one of the five categories: 1) cost-minimization analysis (CMA); 2) cost-effectiveness analysis (CEA); 3) cost-utility analysis (CUA); 4) cost-benefit analysis (CBA); and 5) cost-consequence analysis (CCA).[86] The label partial economic evaluation indicates that the studies do not entirely fulfill both of the necessary conditions for economic evaluation (costs and consequences). However, cost analysis (CA), can provide useful information on 'upfront' costs compared to 'downstream' cost avoidance. For this reason, both full economic evaluations and cost analyses were included in this review.

Descriptive information on the populations, interventions evaluated, the study year, perspective, and country of study were extracted for each study. Data specific to

the costs and effectiveness of each cost comparison were also extracted and summarized in appendix G.

Full economic evaluations

The following section reports the findings of ten full economic evaluations dealing with the use of atypical antipsychotic medications for the treatment of schizophrenia.

A group of Canadian researchers[87] reported a cost-utility analysis of data collected during an 8-week, clinical dose finding trial comparing four fixed doses of risperidone (2, 6, 10 or 16 mg/day) with haloperidol 20 mg/day or placebo in the treatment of schizophrenia. Risperidone 6 mg/day was found to be the most efficacious dose, so data from these patients and the data from patients receiving haloperidol or placebo were used in the cost-utility analysis. The model estimated the cost of substituting risperidone for haloperidol. The value (utility) of changes in psychological, physical, and social functioning; current treatment; and drug-induced adverse effects with the switch were estimated by 100 psychiatric nurses assigning preference ratings. Utilities were assigned by using linear analog and standard gamble techniques to rate health status profiles designed to represent mild, moderate and severe symptoms of schizophrenia. Cost estimates were based on medication acquisition costs. Lifetime quality adjusted life years (QALYs) were calculated by subtracting the baseline utility

from the 8-week follow-up utility and then multiplying by the estimated number of remaining life years. The incremental QALY for risperidone over haloperidol was calculated to be 0.075/patient, about a threefold greater improvement in quality of life. The annual incremental treatment cost of risperidone over haloperidol was $1,600/patient, resulting in an incremental cost-utility figure of $24,259/QALY for risperidone compared to haloperidol.

Another group of Canadian researchers conducted two separate economic evaluations: clozapine in treatment-resistant schizophrenia and risperidone in chronic schizophrenia.[7] Specifically, the report looked at two cost-utility analyses using meta-analysis techniques: 1) clozapine compared to chlorpromazine and haloperidol in hospitalized patients with treatment-resistant schizophrenia; and, 2) risperidone compared with haloperidol, haloperidol decanoate and fluphenazine decanoate in the treatment of hospitalized patients with chronic schizophrenia who had experienced an exacerbation in symptoms.

In the first evaluation, a cost utility analysis, using the results of 3 studies with a total of 157 patients, was performed to compare the costs and quality-adjusted outcomes treated with one of the agents. A decision analytic model was constructed to evaluate treatment sequences with the probabilities of each event derived from the literature and expert opinion. Health state utilities were obtained through interviews with 7 patients

with schizophrenia using standard gamble techniques and a rating scale. The direct health costs of treatment were included in the analysis and the authors found that compared to chlorpromazine, clozapine might save $38,879 per year while producing 0.04 more QALYs. Over a lifetime of 37 years, this could project to a savings of $682,204 and a gain of 0.07 QALYs per patient. This may be associated with $389 million in annual cost savings in direct health care expenditures and slightly higher utility compared with chlorpromazine or haloperidol.

The second economic evaluation by Oh and colleagues used the same methodology as above to compare risperidone with haloperidol, haloperidol decanoate, and fluphenazine decanoate.[7] The meta-analysis of 8, short term (4-12 weeks), studies of 645 patients revealed that risperidone had the highest efficacy rate (67%) compared to haloperidol (50%), haloperidol decanoate (46%) and fluphenazine decanoate (39%). The expected costs and utilities were calculated and it was determined that risperidone was the dominant therapy compared to haloperidol, haloperidol decanoate or fluphenazine decanoate since it was associated with the lowest overall cost and highest number of QALYs. The authors concluded that compared with haloperidol, the use of risperidone in schizophrenic patients with moderate symptomatology in a hospital setting will lead to lower management costs (savings of $6,510 per year) and higher utility (0.04 QALYs). This could translate into a savings of $114,230 over a lifetime.

Davies et al.[88] also developed a decision analytic model in Australia to estimate the comparative effectiveness and direct costs of risperidone and haloperidol for treatment of patients with chronic schizophrenia. The parameters in the model were based on the results of a meta-analysis of the efficacy and tolerability of risperidone and an expert panel.[89] A favorable outcome was defined as being in a clinical response phase at the end of the 2-year model period. The probability of a patient experiencing a favorable outcome at the end of 2 years was 78.9% for risperidone versus 58.9% for haloperidol. In this model, the total cost of treatment for 2 years was $15,549 for risperidone versus $18,332 for haloperidol. The expected cost per favorable outcome was $19,709 for risperidone versus $31,104 for haloperidol. The authors concluded that risperidone was more cost-effective than haloperidol for chronic schizophrenia and therefore was "dominant" because it produced a higher proportion of favorable outcomes at lower cost. However, sensitivity analysis showed that the difference in clinical response rate was a key determinant of cost-effectiveness.

Tunis et al.[90] utilized data from a multicentre double-blind randomized clinical trial of 1,996 schizophrenic patients[60] to compare the total cost of care between olanzapine and haloperidol over 1 year and combine cost and functional outcomes information to estimate the incremental cost-effectiveness ratio of the two therapies in this sample. Using the Medical Outcome Study Short Form (SF-36), the functional status of 812 patients from the United States was collected. The analysis included both

responders and non-responders and represented changes in SF-36 and hospital costs over a 1-year study period. Medical services were assigned an estimated cost in 1995 US dollars based on a standardized list of prices for services. The difference in hospital costs between olanzapine-treated and haloperidol-treated patients during the 52-week treatment period was $9,386.87. The authors suggest that large savings in hospital costs were experienced by olanzapine-treated patients, representing more than 15 days in hospital annually. Patients treated with olanzapine scored 5.75 units better on the physical heath and functioning composite score of the SF-36 and 1.66 units greater on the mental health and functioning composite than haloperidol-treated patients. This combination of greater effectiveness and lower cost produces an annual cost-effectiveness ratio, where improved effect is associated with extra savings rather than extra cost. Using these data, the incremental cost effectiveness ratios (ICER) were calculated as $1,632.50 for each point of change in the SF-36 physical health and functioning score and $5,654.74 per point of change on the mental health and functioning composite score. Statistical significance of these differences was not reported.

The cost-effectiveness of clozapine was compared with conventional antipsychotic medication alternatives typically used for patients with treatment-refractory schizophrenia in state hospitals.[91] 227 patients were randomly assigned to begin open-label clozapine treatment (n=138) or to continue receiving conventional antipsychotic medications (n=89). Measures of prescribed medications, service utilization, and other

costs were combined with a number of effectiveness measures (BPRS, quality of life, EPS, hours in special observation, occurrence of problematic behaviour) to estimate incremental cost-effectiveness ratios. The authors found that patients assigned to clozapine accrued, on average, $1,112 more cost in year 1 but $7,149 less cost in year 2 than did patients assigned to usual care. Clozapine was found to be more effective on some but not all effectiveness measures but fairly similar on cost, when the alternative was a range of conventional antipsychotic medications. The authors estimated incremental cost-effectiveness ratios for the 4 effectiveness measures where clozapine was more effective than usual care: EPS-free months, disruptiveness, psychiatric symptomatology, and weight gain. However, the actual ICER values were not reported in the paper but the probability of an ICER estimate for clozapine falling into the dominant strategy on the cost-effectiveness plane was provided. For example, the ICERs for number of EPS-free months indicated that there is 0.80 probability that clozapine was cost-effective.

Schiller et al.[92] utilized a pre-post design to retrospectively evaluate risperidone's effectiveness in reducing symptoms and its cost when compared with the effectiveness and cost of standard antipsychotic medication based on an intention-to-treat model. The authors identified 112 adults (56 were receiving risperidone, and 56 were receiving traditional antipsychotics) with schizophrenia or schizoaffective disorder receiving care in a public mental health system for which prescription and medical records data were

available for the 12 months before and after initiation of risperidone. Patients receiving conventional agents were matched to those in the risperidone group based on age, sex, ethnicity, marital status, medication clinic site, diagnosis and number of psychiatric emergency room visits in the previous year. Global Assessment Functions (GAF) scores were used to assess effectiveness while service utilization and medication data were extracted from subjects' outpatient charts to calculate the cost of treatment. The authors found the mean monthly total treatment costs were $370.18 higher in the risperidone group, however the difference was not statistically significant (P=0.08). Monthly GAF scores revealed no group differences in the effectiveness of the medications. The study showed that no significant change in health service utilization occurred. Controlling for differences in baseline GAF scores, the authors reported no significant differences in cost or effectiveness between the risperidone and comparison groups.

Guest et al.[93] used resource utilization data from a Swedish trial[94] in chronic schizophrenia to model the economic effect of treating patients with risperidone in the United Kingdom. Data on 31 patients originally enrolled in a short-term multicentre clinical trial comparing efficacy of risperidone and haloperidol were included. All patients received risperidone for 1 or 2 years regardless of the original study medications. Clinical data, based on scores from the PANSS, the CGI and the Extrapyramidal Symptom Rating Scale (ESRS), were reported for 31 subjects for 1 year, and 18 subjects for 2 years. Economic data were collected retrospectively and compared with data from

the year before risperidone was started. At the end of 1 year of treatment, the mean PANSS, CGI, and ESRS scores had fallen significantly ($P<0.0001$, $P<0.0005$ and $P<0.0002$, respectively). Clinical improvement was maintained during the second year of treatment for the 18 patients followed for 2 years. During year 1, inpatient days decreased significantly ($P<0.02$) while use of residential accommodations increased significantly ($P<0.03$) as did medication costs (not significant). During the second year, both inpatient days and use of residential accommodations declined slightly but remained fairly constant during year 2. Total costs of care decreased during both years compared to the year prior to risperidone. In this study, the decrease in total costs was due primarily to the decrease in days of inpatient care. The authors did a sensitivity analysis to look at changes in cost over a range of costs for inpatient bed days. For the patients followed for 2 years, a net cost reduction was demonstrated even if bed prices were reduced. The authors concluded that switching patients suffering from chronic schizophrenia to treatment with risperidone results in clinical improvements which potentially reduce costs. No statistical data for the cost analysis was reported in this study. The authors concluded that when a cohort of patients with chronic schizophrenia was treated with risperidone there were potential savings to the National Health Service (NHS) of £4200 per patient in the first year.

Another pre-post study by Galvin et al.[95] was conducted to compare both the clinical effectiveness and the treatment costs of atypical antipsychotic medications

(clozapine and risperidone) with those of older neuroleptic medications (chlorpromazine and haloperidol) for psychosis in a community mental health care setting. Participants received older medications for 1 year and newer medications for an additional year. The study used a retrospective, uncontrolled, open, nonrandomized, within-subject design and relied on medical records as a data source for 37 patients (23 on clozapine and 14 on risperidone). Effectiveness data were extracted from the medical record using a study specific scale. Use of either risperidone or clozapine was associated with a statistically significant reduction of clinical symptoms and tardive dyskinesia compared to traditional antipsychotic medications. Newer antipsychotics were associated with significantly higher medication costs ($P<0.0001$), but total cost of care was $3,000 less per patient per year with the newer medications. It was not clear whether drug costs were included in this calculation or not. Additionally, statistical tests were not reported for total costs.

Almond et al.[96] conducted a cost analysis using Markov modeling techniques to compare the costs of two atypical drug therapies (olanzapine and risperidone) with one another and with a conventional antipsychotic (haloperidol) in the treatment of schizophrenia. The analysis was based on a simulation model with BPRS scores, probabilities of suicide, relapse, rehospitalization, switching to another antipsychotic or dropping out of care. The data used to fill the model were based on results of a clinical trial[73], other published literature, and expert advice. The researchers found that the 3 therapies were approximately cost neutral over a 5-year period (olanzapine £35,701,

risperidone £36,590, haloperidol £36,653). This shows that the price advantage to haloperidol relative to the atypical therapies is lost because lower efficacy results in greater utilization of health services and a higher probability of switching to the more expensive drugs. There was evidence of greater efficacy with the atypical drugs (average percentage of 5 years with Brief Psychiatric Rating Scale (BPRS) scores < 18: olanzapine 63.6%, risperidone 63.0% and haloperidol 52.2%). The cost neutrality, together with the greater efficacy of olanzapine and risperidone compared with haloperidol in terms of reduced BPRS scores and relapse rates, suggests the former 2 drugs represent cost-effective treatment options.

Partial economic evaluations

Hamilton et al.[97] conducted a cost analysis of 817 subjects from the original 1,996 enrolled in the Tollefson's study[60] comparing olanzapine with haloperidol. Subjects who demonstrated symptom response and tolerated the study medication during the acute phase (first 6 weeks of the trial) were eligible for the second phase of the trial (46 additional weeks). Thus, cost comparisons for maintenance therapy were limited to the sub-sample of responders. Direct health care resource utilization (inpatient, outpatient, and medication use) by the study participants was quantified and assigned prices from a standard list. Costs were compared between treatment groups separately for the 6-week acute phase and the 46-week maintenance phase. In the acute phase, mean total medical costs were statistically significantly lower for patients receiving olanzapine ($6,114) than

for those receiving haloperidol ($6,502) even when the cost of medication was included in the analysis (P=0.033). This difference was mainly due to the decrease in hospital utilization in the olanzapine group. Analysis of costs during the 46-week extension phase revealed that mean total medical costs, including medication costs, were also lower for patients receiving olanzapine ($15,594) than for those receiving haloperidol ($16,230) but the difference was not statistically significant (P=0.128).

Albright et al.[98] linked five computerized databases to assess the change in healthcare resource utilisation and costs related to the initiation of risperidone therapy in 146 patients with chronic schizophrenia in Saskatchewan, Canada. This retrospective cohort study measured and compared resource utilization for the 10 months before and after initiation of risperidone. Resource utilization included hospital services, physician services, mental health services, and drug services. During the period of risperidone use, total hospital admissions declined from 180 to 73 (a decrease of 59%, P<0.001), their total hospital length of stay decreased from 3888 days to 1624 days (a decrease of 58%, P<0.001), and their total physician visits decreased from 3963 and 2881 (a decrease of 27%, P<0.001). Only small decreases in community health service use were observed. When services were assigned costs, the use of risperidone resulted in a net savings of approximately $8000 per patient per year, despite the statistically significant increase in the cost for medication (P<0.001). The incremental cost of risperidone therapy was offset almost 8-fold by these savings.

Glazer and Ereshefsky[99] developed a clinical decision analytic model for examining the medical costs of treating the "revolving door" schizophrenia patient with either haloperidol, haloperidol decanoate, or risperidone over 1 year. Under the baseline set of assumptions, the use of a depot neuroleptic in the year following hospital discharge was the least costly strategy. The cost of continuing a traditional oral neuroleptic was estimated to be $5,752, switching to a depot neuroleptic was estimated to be $4,595 and switching to an atypical oral antipsychotic was estimated to be $7,162 during the first post-discharge year. The authors varied the assumptions by increasing rates of adherence and by decreasing costs of medications and hospitalizations. Use of a novel antipsychotic was the least costly alternative only when the rate of adherence for the novel antipsychotic was considered to be equal to that of a depot antipsychotic. The authors concluded that for patients with a strong history of relapse and rehospitalization, use of traditional depot antipsychotic medications would result in the lowest direct treatment costs in the first year following hospital discharge. However, it was acknowledged that the application of this model in different clinical scenarios associated with different outcome probabilities and treatment costs may well provide different results.

Finley et al.[100] used a retrospective cohort, intention-to-treat analysis of all patients initiated on risperidone therapy at an inpatient veteran's psychiatric facility to analyze the financial impact of risperidone on the treatment of psychotic symptoms. This study included patients with treatment resistant and treatment intolerant schizophrenia

(n=49), bipolar affective disorder (n=5), and depression with psychotic features (n=3). Of the patients initiated on risperidone, 50 received a minimum trial of 14 days of continuous treatment and had complete medical record data permitting study inclusion and only 27 of these continued to receive risperidone for the entire 12-month post-treatment period and were therefore considered therapeutic responders. The total number of inpatient days decreased from 2,547 before risperidone to 2,021 days after, a decline of 526 inpatient days overall. Therefore the total decline in direct hospitalization costs yielded a savings of $203,036. Given that the total annual acquisition cost of risperidone in this analysis was $55,074, resulting in a net savings of $149,962 for the institution. Of note, the acquisition cost of other psychotropic medications received prior to the initiation of risperidone or for non-responders was not accounted for in the analysis.

Edgell et al.[101] used data from a multicentre, double-blind, prospective study of olanzapine (n=75) and risperidone (n=75)[73] to measure health service use of enrolled patients at baseline and prospectively, at 8-week intervals and at study completion (28 weeks). Median total, inpatient/outpatient service and medication acquisition costs were compared between treatment groups. The authors found that total per patient medical costs over the study interval were $2,843 (36%) lower in the olanzapine treatment group than in the risperidone treatment group (P=0.342). Medication costs were significantly higher for olanzapine-treated patients ($2,513 vs. $1,581; P<0.001), but this difference was offset by a reduction of $3,774 (52%) in inpatient/outpatient service costs for

olanzapine-treated patients in comparison with risperidone-treated patients ($3,516 vs. $7,291, P=0.083).

Health care utilization and health status for hospitalized patients with schizophrenia was measured following the commencement of clozapine treatment in a US study.[102] The mean total direct Medicaid costs for all subjects was $48,114 per person for the six months preceding clozapine treatment and $44,847 per person for the six months after for the 33 subjects recruited into the study. Of those who stayed on clozapine treatment (52%, n=17), the health care costs showed a savings of $11,464 per person. The main findings were that continued clozapine treatment was associated with reduced days of psychiatric hospital care, reduced costs even after including increased costs for outpatient care and residential costs for a period as brief as six months.

An Australian study on the long-term use of clozapine examined the clinical and economic outcomes 3 years after the prescription of clozapine to a cohort of 37 patients.[103] Experience during the 2 years before clozapine was compared with experience in the following 3 years on the basis of a retrospective review of health care records. Compared with the pre-clozapine period, there were significant reductions post-clozapine in hospital admissions (year 3) and hospital bed-days (year 2) by the total cohort and in hospital bed-days and hospital expenditure for those patients (n=25) who remain on clozapine (years 2 and 3). There was no significant increase or decrease post-

clozapine in the estimated combined cost of treatment attributable to bed use, clozapine tablets, and blood monitoring before and after the initiation of clozapine. For example, compared with 1 year pre-clozapine, the difference in cost for the cohort in year 3 post-clozapine was a reduction in $470 per patient per year.

2.2.2.1 Quality of the Studies Reviewed

It is important to note from the outset that most of the economic evaluations conducted to date in schizophrenia are not technically "cost-effectiveness" studies that measure cost per successful patient outcome over time, but cost-minimization analyses that measure total cost savings per patient over time. An ideal study would explicitly measure direct and indirect medical costs associated with the use of newer antipsychotic medications. Most published studies have used only a proxy for these costs (such as reduction in hospital days) to estimate cost-effectiveness. This proxy is useful because traditionally a majority of medical costs incurred in treating patients with schizophrenia are due to hospital costs. However, full enumeration of total costs is desirable.[104]

Many of the studies evaluated patients who were treatment-resistant or treatment intolerant and thus the generalizability of the results is decreased. The failure to include the costs of treatment dropouts may introduce bias since patients discontinuing treatment because of side effects or lack of efficacy are likely to be high users of heatlh care resources and therefore incur higher costs. Furthermore, many other aspects of care can

affect costs of care after a patient switches to an atypical agent. For example, hospital policies regarding decreasing length of inpatient stay for schizophrenia would affect this outcome. Given that this has been a growing trend in recent years, it is difficult to determine if decreases in hospitalization rates and costs are due to use of second-generation antipsychotics or to changes in healthcare policy. The question of whether the change in inpatient care is due to initiation of a new medication or a change in policy is very important since most cost savings with second-generation antipsychotics appear to be due primarily to decreased use of inpatient care. Additionally, any cost savings seen due to reductions in hospital utilization will be conditional upon the presence of adequate services to support the care of these patients in the community.

Schizophrenia is characterized by exacerbation and remission. However, the results of the studies were based on short-term follow-up and as a result there was insufficient data to confirm that any health status difference between patients treated with different classes of medications will remain stable over the patients' remaining lifetime. Studies without randomization or appropriate controls are likely to be biased in favour of the intervention, because the physician may provide better care, or there may be a placebo effect, or because something else changes in the health care system. Additionally, the evaluations did not take account of factors such as adherence rates that might modify the impact of these drugs in the "real world".

2.2.2.2 Summary of the Studies Reviewed

The majority of studies reviewed found that novel antipsychotics are at least cost-neutral and may offer cost advantages compared to traditional agents despite the increased acquisition costs of the former. Some studies also reported greater improvement in effectiveness and quality of life when novel antipsychotics were compared to traditional antipsychotic medications. However, given the uncertainty that surrounds the clinical data, and the uncertainty regarding the cost and outcomes data, small sample sizes and limited study designs available in the literature, it is difficult to reach any definitive conclusion as to whether the additional costs and benefits represent value for money.[105-107] It is necessary that sophisticated concurrent prospective economic evaluations be conducted in the real world to address whether novel antipsychotics are actually cost-effective.

2.3 Access to and Utilization of Pharmacotherapies

The increase in both pharmaceutical prices and drug benefit expenditures has prompted many payers to implement various policies as means to control costs and discourage inappropriate utilization. The two separate mechanisms that affect the extent to which people receive pharmacotherapies may be described as access and utilization. They work together to determine whether a particular drug is used widely in the health care system. Access is a complex concept and often refers to structural issues (e.g. coverage and benefit) within the health care benefit system that determine whether a health care service is available for use. Utilization is a more subjective concept and reflects the degree to which services that are available are actually used by the consumer or the extent to which a population 'gains access'. In turn, each of these components is influenced by several factors.[108]

2.3.1 Defining Access

Access to a particular health care service may be defined as the set of factors that affect the *potential* ability of an individual or a group to acquire timely and appropriate use of that service.[108] Health care payers have direct control over access via the design of their benefit programs. Among these, there are a number of factors that affect access to pharmaceuticals: patient-level restrictions on access, such as cost-sharing (co-payments) or drug prescription limits or caps (number), as well as efforts to improve patient adherence; and administrative restrictions that limit clinicians' ability to prescribe

particular medications, such as the imposition of a limited list of drugs eligible for reimbursement (formularies), category exclusions, or prior authorization requirements.[109-112] It is the sum of these interacting policies that defines drug policy and it is the global impact of these drug policies that is of importance to policy makers.

2.3.1.1 Patient-Level Restrictions: Cost-sharing and Prescription Limits

Benefit design is the primary mechanism that influences access to newer pharmaceuticals. Some health plans place restrictions on the number of prescriptions a given beneficiary may receive each month while others require program beneficiaries to pay a fixed amount toward the cost of each prescription in the form of co-payments or coinsurance. There are a number of objectives often cited for cost-sharing requirements, such as: deterring consumption of "unnecessary" drugs; making patients aware of the costs of medicines; helping to contain rising drug costs.[113] Contributions by patients, whether as a co-payment or a coinsurance, provide additional money to support the purchase of prescription drugs. Evidence from the literature consistently shows cost-sharing to be an effective source of additional funding for medicines. At the same time, patients reduce their consumption of prescription drugs as their out-of-pocket costs increase.[114-117] However, subtle changes in prescription drug consumption can have large health consequences. Ideally, changes in drug consumption would be limited only to "unnecessary" drug consumption. By definition, "unnecessary" implies there is little or no negative impact on health. On the other hand, to the extent that "essential"

medications are also affected, negative health impacts are expected.[113] Cost-sharing could actually inhibit the efficient use of scarce resources, e.g., reductions in the use of necessary medications thereby requiring treatments of increased frequency or intensity. Additionally, this approach places the burden on patients to identify which medications are necessary, and to select some drugs while rejecting others. However, it is unlikely that most chronically ill, elderly patients are adequately informed about the efficacy of their medications and, in many cases, may not be able to distinguish essential from less effective medications.[118] Thus, for poor and chronically ill individuals who have few financial resources and often multiple medical needs, there is a risk that high levels of cost-sharing will also reduce the use of effective and essential therapies.[109] From a policy perspective, the correct question to ask is whether the positive impact of imposing cost-sharing as a means to deter inappropriate use of prescriptions and providing additional funding is worth the health risks and costs observed when prescription drugs are used inappropriately. Adverse effects on people's health may lead to higher overall healthcare costs.[112 113 119]

Evidence of the deleterious effects of the introduction of a cost-sharing policy for drugs emerges from studies of changes to the Quebec public drug plan in the mid 1990s.[120] Quebec imposed user fees for the elderly and poor who had previously been exempt from these charges. The authors found that drug use decreased by 14.7% among welfare recipients and 7.7% among the elderly following the implementation of the

policy. Emergency room visits increased 71% and visits to doctors' offices increased by 17%. Emergency room visits by the mentally ill grew by 558%. The policy was estimated to have caused an extra 2,000 hospital admissions. The authors concluded that increased cost-sharing reduced the use of less essential drugs but also had the unintended effect of reducing the use of drugs that were essential for disease management and prevention. As a result, there was an increase in the rate of adverse events and emergency department visits in the post-policy period.

Cost-sharing arrangements influence the consumption of medications, the health of patients, and the cost of health care more broadly. Additionally, the injection of more private funding would take Canada further away from the model of largely public financing of pharmaceuticals that exists in most developed countries (generally less expensive and more equitable) and closer to the US model (more expensive and less equitable).

2.3.1.2 Administrative Restrictions on Prescribing

Administrative restrictions on specific drugs have been used increasingly as a cost-containment tool around the world. Most drug programs have adopted the use of formularies as a method for containing costs by limiting the availability of agents, namely by restricting access to expensive medications.

Special Authorization

Special authorization, a form of restriction on benefits, is used in many drug benefit programs under various designations (e.g., special authority, exception drug status). This policy requires pre-approval for reimbursement for particular drugs or drug categories and is intended to ensure optimal, cost-effective, evidence-based prescribing. In this situation, a physician is required to submit a specific request for each patient indicating why a non-benefit product is required and seeking approval for benefit coverage of the product. The process requires forms to be completed and reasons given for use of the drug. The health care payer organization approves or denies a particular prescription request based on a defined set of criteria. In theory, special authorization provides a method to target costly, newly introduced, and/or potentially toxic drugs only to recipients who truly need them, while eliminating their use in cases where less expensive or safer alternatives could be used. The rationale for using special authorization is based on several assumptions. These may include:

- No clinically important efficacy or effectiveness differences exist between two agents of a given class. Therefore, it is only necessary to reimburse one of these agents on a routine basis.
- The agents designated for special authorization have the potential for abuse by either providers or patients. Therefore it is necessary to restrict access to these agents and document clinical necessity prior to dispensing.
- The agents designated for special authorization are more expensive than other alternatives, while their increased benefit is less clear. Because lowering pharmaceutical expenditures is a valid endpoint in its own right or directly correlates with overall medical cost savings, dispensing of the more expensive agent should require special permission. [111 121]

Interchangeability

Some drug benefit programs have implemented interchangeability policies in their drug formularies. Interchangeability can be determined on the grounds of bio-equivalence or therapeutic equivalence. A bio-equivalent category is one in which all the products have the same chemical active ingredient which has been shown to be biologically equivalent in its absorption. Therapeutic equivalence is used for a therapeutic subclass of drugs. It is a broader concept and includes all listed drugs that are used to treat a specified diagnostic class of patients.[121] For example, all listed drugs which are used as antihistamines are considered to be in the same therapeutic class and identical for therapeutic purposes. From the point of view of drug benefit programs, interchangeability is a concept that allows drugs within a class to be identical for reimbursement purposes.

British Columbia introduced this type of policy within some therapeutic classes of drugs (H2 antagonists, vasodilating nitrates, non-steroidal anti-inflammatory drugs, and two classes of anti-hypertensives: ACE inhibitors and calcium channel blockers). This concept is also referred to as Reference Based Pricing, whereby only the cost of the lowest price drug in a therapeutic group is covered by drug benefit plans. The reimbursement price is set irrespective of the drug or brand prescribed. If patients wish to have a drug prescribed other than the reference product they must pay the difference out of their own pocket.[121 122] This policy functions like an ideal, fully informed market,

reducing the sale of products whose higher price is not matched by increased value.[123] It is a logical extension of policies to encourage the substitution of lower-cost generic drugs for high-priced branded equivalents, policies that will become less effective as Bill C-91 reduces the availability of generic substitutes.[119 121 124] This approach is designed to provide complete coverage for prescription drugs, reduce the amount paid out by drug-benefit plans and provide an incentive for pharmaceutical manufacturers to lower their prices.[125]

Restrictive formularies and other limitations may lower drug quantities and reduce expenditures.[126-129] But the direct effects are not necessarily a good indication of the total effects of these policies on overall health care costs and quality of care. Costs are often shifted to other areas, resulting in an increase in the use of other health services or a shift of the burden to patients or caregivers. There are numerous studies[109 130 127 121 129 131] that have found that while implementation of a restrictive formulary could reduce drug expenditures, these savings are more than offset by spending increases caused by service substitution elsewhere in the system. For example, Horn and co-workers[132 133] found that restrictive formularies tended to increase utilization of other health care resources for patients with diagnoses of arthritis, asthma, epigastric pain/ulcer, hypertension, and otitis media.

Administrative restrictions have become increasingly controversial for a number of reasons: they frequently deny beneficiaries access to newer, more expensive, and possibly more effective agents;[134] physicians are often concerned about the infringement of their ability to select whichever drug they feel is most appropriate; they create a physician "hassle factor," that is to say, the documentation required to get a prior authorization drug approved is too burdensome for most physicians to be willing to pursue;[111] and finally, the Pharmaceutical Industry argue that reduced manufacturer income might reduce their spending on research and development.

Global Budgets

In Germany, New Zealand, Northern Ireland and the United Kingdom, and other countries, drug and physician remuneration budgets have been integrated to make physician incomes or practice revenues partly dependent (negatively) on prescribing volume. Such integration, which recognizes the obvious fact that the prescribing physician is the critical actor in the chain of drug use, has had some success in cost reduction.[112 135 136 137 138] This type of system forces physicians to improve the management of pharmaceuticals as a component of their practice. They are encouraged to more closely monitor their patients' utilization of drugs and adherence with prescribed regimes.[139 119]

Fundholding

In the early 1990s, the National Health Service (NHS) in Britain introduced a general practice fundholding mechanism. Fundholding was an attempt to introduce a positive incentive for doctors to think carefully about their prescribing. In this arrangement, volunteer practices were responsible for managing their own prescribing budgets and purchasing a limited range of community health services and elective hospital procedures on behalf of their patients. Fundholders were able to make savings from their budgets, and invest these savings in additional services or improving facilities in their practices. It could not be used to increase the doctors' income or to benefit the practice generally. If fundholders made savings they could use these on other parts of the fund or they could use the fund to pay for any drug overspending.*[140] The desired effect of this funding arrangement was to decrease drug expenditure.

New Zealand has also implemented a similar system where independent practitioner associations (IPAs) were developed as a strategy for containing their expenditure growth on pharmaceutical and laboratory services through budget holding. One of these IPAs, Pegasus Medical Group, began a pharmaceutical budget holding in December 1994. The strategy focused on a broad range of activities: the development of guidelines by those involved; personalised feedback of prescribing costs; peer group

* fundholding has been replaced with a recognizable similar strategy of primary care groups (PCGs) when the New Labour government assumed power in the late 1990s.

discussions and sharing of information; providing information on the costs of pharmaceuticals; and professional incentives enabling the use of savings for alternative services.[136] Despite successfully reducing laboratory test behaviour, the arrangement was less successful in reducing prescribing costs. What is important to note here is the policy's success in establishing professional accountability for both cost and quality.

Supply-side initiatives such as fundholding affect prescription drug utilization and the cost of a drug benefit program. These initiatives aim to influence behaviour of prescribing physicians, encouraging them to consider costs as well as benefits in their prescribing decisions. These types of incentives can be successful in reducing costs by encouraging fundholders to search for more effective and cost-effective ways of delivering care.[141]

A concern with this arrangement is that many would over spend their budget and then be unable to treat patients at the end of the financial year. A second fear is related to the calculation of the budget. In Britain, the Department of Health decided to base the budgets on an historic cost basis. Practices would be given a budget based on last year's spending plus an 'uplift' factor. However, this way of setting the budgets created a perverse incentive. It was in the interest of practices to bid up their referrals and their drug spending in the year before they became fundholders and to sustain or increase it

thereafter. In response, the Department returned to the task of calculating a capitation formula. [140]

Outcomes Guarantee

A novel approach to ensuring maximum health benefits from a drug has been developed and piloted in the UK. This new method of risk sharing is referred to as an "outcomes guarantee," in which a pharmaceutical company and prescribing stakeholders agree on the outcomes that they would expect from a drug for a given indication.[142] If the drug fails to fulfil expectations, the pharmaceutical company refunds the cost of the drug. This encourages the pharmaceutical company to promote responsible prescribing for their drugs and ensures that healthcare resources are not wasted on ineffective treatments. The results of this pilot project have not yet been published but the researchers believe that the ultimate goal of refinement of clinical behaviour is achievable through the outcomes guarantee project.

2.3.1.3 Differential Access to Prescription Medicines in Canada

When Medicare was first introduced in Canada, prescription drugs played a limited role in the health care system and in the day-to-day lives of the vast majority of Canadians. Today, they are a fact of life for many Canadians. In fact, they have fundamentally changed the face of health care as is evident by the fact that 300 million

prescriptions are filled in Canada each year, amounting to about 10 prescriptions per person.[1]

The cost of medications in Canada while in hospital is covered but, like home care, there is no requirement under the Canada Health Act of 1984 for provinces to cover the costs of drugs prescribed outside of hospital. As a result, coverage across the country is variable with some provinces providing nominally universal programs (with high levels of co-payment), and others covering certain diseases (e.g. cancer). In all Canadian programs, eligibility for public drug insurance coverage tends to be based on age or socioeconomic circumstances while private drug insurance coverage largely depends upon employment status. There is considerable disparity among provincial plans in terms of who is covered, for what drugs, and what kinds of co-payments or deductibles are required. For example, British Columbia, Alberta, Quebec, Saskatchewan and Manitoba, have plans that offer coverage to all residents (universal). However none provide first dollar coverage, and the deductibles and co-payments are set sufficiently high to limit the number of residents receiving reimbursement and ultimately to limit the accessibility of prescription medicines. In Atlantic Canada, relatively fewer residents are eligible for plan coverage than other regions. As a result, Canadians with similar income and medical needs will receive widely varying levels of government plan benefits depending on the province they live in.[143]

There are few mechanisms in place to ensure continuity of coverage as changes in individuals' circumstances affect their plan eligibility, especially for those individuals who rely on employer-sponsored programs, or who move between provinces. While the size of the uninsured or underinsured population varies depending on what is considered adequate insurance, several groups appear less likely to have adequate coverage: 1) residents of the Atlantic provinces (other than those in targeted government programs [seniors, social assistance] and those in employer sponsored group programs) have no protection against catastrophic levels of drug expense; 2) in all provinces, other than Quebec, those working part time or in low wage occupations (less than $10,000 per year) are more likely to be uninsured or underinsured for routine drug expense compared to the general population under age 65, due to their lower coverage rates under employer sponsored group plans; and 3) in most provinces there is a clear reduction in coverage in the age 55 to 64 groups as adults start to withdraw from the labor force and are less likely to have an employer-sponsored group plan and do not yet qualify for seniors' programs.

Overall, approximately 90% of Canadians have some coverage for routine drug expenses. 11% can expect to obtain routine drug prescriptions without out-of-pocket costs. This full reimbursement coverage is normally provided either by social assistance or by employer sponsored group programs. An additional 69% of Canadians have drug plan coverage with relatively modest deductibles and co-payments. 10% are covered but

could be considered underinsured since their plan would pay less than 35% of a $1,000 annual expense.[143] Approximately 10%, or 3 million people, are considered uninsured for routine drug expenses having no plan coverage or having a plan that would only cover annual expenses higher than $1,000.[143]

2.3.2 Defining Utilization

Utilization is defined as the use of a health care service, procedure, device, or pharmaceutical. Utilization is influenced by access, although the actual utilization of a given pharmaceutical may not reach the maximum level expected given a specified level of access or availability. Utilization of health care services can be recorded in a number of ways (e.g. per capita, hospital admissions and length of stay, physician office visits, or number of prescriptions). With respect to pharmaceuticals, there are a number of factors that affect utilization such as physician prescribing behavior and patient adherence to prescribed medications.

2.3.2.1 Physician Prescribing Behaviour

Ultimately, a prescription drug can only be used as often as physicians prescribe it. It is therefore little wonder that patients, academics, policy makers, third-party insurers, and pharmaceutical manufacturers are interested in influencing physician

behaviour. Educational strategies have relied on passive strategies such as continuing medical education (CME), which generally includes lectures and other passive means of education. The ability of this method of affecting behaviour has been disappointing.[144] The dissemination of printed materials containing useful information such as practice guidelines by professional organizations has also been evaluated and the results have shown that this method may be insufficient to provoke a change in physician behaviour.[145-148] However, academic detailing (i.e., one-on-one education) has been shown to be an effective educational intervention in promoting optimal drug prescribing.[149-152]

Education alone may fail to change physician behaviour, and as a result various motivational interventions have been studied. Physicians may be motivated by their desire to be perceived as good doctors by their patients and colleagues. Feedback, also know as profiling, has been moderately successful in improving physician motivation. The goal is to show a physician how his or her practice patterns compares with that of his/her peers. The expectation is that people will try to fit their behaviour to the norm. For example, feedback on the use of antibiotic prescriptions has resulted in the use of less expensive agents in some settings.[153] A randomized trial with feedback to 97 physicians showed that diabetes care was improved with feedback.[154] However, feedback is not always successful and the success depends on things such as the timing of the feedback

and physician buy-in which can be assisted via enlistment of local opinion leaders.[155-157] Additionally, reminders and clinical decision support systems, which can also provide relevant and patient-specific information in a well-timed fashion, have the potential to facilitate improved clinical decisions.[158 159]

Despite the development of various methods of influencing prescribing practices, over-prescribing persists. A number of other factors within the health care system have been identified as contributing to this behaviour. The cost structure of the pharmaceutical industry creates very powerful economic incentives forcing manufacturers constantly to expand their sales. Massive resources are thus put into highly sophisticated marketing campaigns, and successful marketing means more drugs sold-more utilization.[119] Each year, more than $11 billion US is spent by pharmaceutical companies in promotion and marketing, $5 billion of which goes to sales representatives.[160] The time constraints imposed on physicians by the very nature of their occupation, make it difficult for physicians to keep up with clinical evidence on the appropriate use of new drugs. Doctors, therefore, may rely on pharmaceutical companies, whose primary interest is to sell their products, as sources of information. Thus, marketing-not science-could be playing a role in influencing prescribing patterns.[112] In addition, the industry sponsors numerous physician education symposia and programs that qualify for continuing medical education (CME) credit either at a local level or at national meetings. It can be

expected then, that there will be a steady rise in drug expenditures. The surging cost of prescription drugs is a concern, and the 20-year patent protection implemented by the introduction of Bill C-91 is a source of high prices.[119]

Over-prescribing may also result from the pressures of fee-for-service medical practice which make the prescription a critical stage in closing off a patient visit, symbolizing that the problem has been understood and the therapy chosen.[161] A study of Newfoundland GPs found that fee-for-service physicians gave antibiotic prescriptions to more patients than did salaried physicians.[162] Also, physician incomes are directly linked with a high throughput fee for service practice style.[163]

The basic structure and organization of our health care system potentially contributes to inappropriate prescribing by physicians. In our system, control over resource deployment is separated from accountability for efficient resource use. Clinicians are responsible for many resource allocation issues, but they do not have budgets for which they have to account. Clinicians do not deliberately go out of their way to be inefficient, but incentive mechanisms and constraints are not there to channel them into more efficient behaviour.[164] It may be argued that the central problem does not lie with clinicians as such but with the organizational system within which they operate.

2.3.2.2 Patient Adherence

An estimated 350 million prescriptions were dispensed in Canada in 2002.[165] Unfortunately, prescriptions filled does not indicate adherence with treatment. It has been consistently found that between one third and one half of patients fail to comply with medical advice and prescriptions.[166] As a result, the effectiveness of drug treatment in clinical practice is considerably lower than the efficacy shown in controlled studies. Discontinuing beneficial medication can cause preventable morbidity, and contribute to the burden of disease, at an estimated annual cost of $7 to $9 billion.[167] Included in this economic burden are the direct costs such as institutionalization and ambulatory care services (physician visits, laboratory tests, treatments), as well as the indirect costs associated with lost productivity and/or premature death. Likely consequences of medication non-adherence on health status include delayed recovery from acute illness, disease progression in chronic illness, and the subsequent need for more aggressive treatments.[168]

Medication adherence can be defined as the degree to which the patient follows a prescribed drug regimen. Three common forms of drug treatment non-adherence are: overuse and abuse, unintentional non-adherence (forgetting), and alteration of schedules and doses (intentional non-adherence).[169] Within these categories, non-adherence occurs to different degrees. For example, overuse can range from taking one extra tablet to taking many times the prescribed amount. Overuse of a prescribed medication may arise

from a belief that taking more of the drug will result in more health-related benefits, such as less pain or lower blood pressure. Conversely, patients may forget the occasional dose or they may forget many doses on a regular basis. Patients may intentionally lengthen the duration of time between doses, or they may take drug holidays of weeks or months during their treatment regimens.[169]

Some suggest that adherence is not an issue: patients do not perceive taking drugs entirely in terms of obeying the doctor's orders.[166] Instead, they weigh up the costs and benefits of taking particular medications as they perceive them within the contexts and constraints of their everyday lives and needs. For example, a common reason given for intentional discontinuation is that patients are often unconvinced of the need for treatment.[170] [171] Fear of side effects and fear of dependency are common reasons for altering drug dosages and frequency administration among the elderly.[169] [172] [173]

2.3.2.3 Summary

The various policies and interventions implemented to influence drug access and utilization should be assessed based on economic efficiency. Economic efficiency means that maximum benefits to society are derived from the available resources. That definition requires evaluating both the costs of providing the prescription drug coverage and the benefits derived. Importantly, because government funds the public provision of the majority of health care in Canada, the provincial prescription drug programs must be

evaluated within the context of that broader health care system. Unfortunately, policy decisions are often made in isolation from the broader context, resulting in a focus on the cost of the drug program and drug utilization, without considering the benefits or impact on other parts of the health care system. In turn, this makes it difficult, if not impossible, to assess, unambiguously, the economic efficiency of the various initiatives being evaluated. To do so correctly requires consideration of the cost of the drug program, equity, drug utilization, appropriateness of prescribing, patient health effects, and effects on the cost of health care more broadly.

CHAPTER III – DESIGN AND METHODS

3.1 Introduction

The decision to allow for unrestricted access to a class of prescription medications by a provincial drug formulary provided a unique opportunity to conduct an observational evaluation of some of the clinical and economic consequences of such a decision. This research project was designed to evaluate two separate but related issues surrounding the unrestricted access to atypical antipsychotic medications: 1) hospital utilization by persons suffering from schizophrenia; and 2) the utilization of and expenditure for these new agents by the Newfoundland and Labrador Prescription Drug Program (NLPDP). This study consisted of 3 phases of data collection: 1) 12 months (1995/96) near the beginning of restricted access; 2) the last year of restricted access (1998); and 3) the second year of unrestricted access (2000).

The hospital utilization portion of the study measured the total number of admissions, the length of stay, the total number of hospital days, and the time to readmission for those individuals who had a diagnosis of, were treated for, and discharged from acute care psychiatry with schizophrenia. Patient demographic, clinical and treatment information was collected for each of the study years so that account could be taken of differences in variables which could influence length of stay and readmission.

The ultimate goal was to determine whether hospital utilization decreased as the use of atypical agents increased over time.

The utilization and expenditures for atypical antipsychotic medications were identified using the NLPDP prescription claims database.

3.2 Ethical Considerations

This study was approved by the Human Investigation Committee of Memorial University of Newfoundland. Informed consent of patients was not required because their information was obtained through chart abstraction without patient participation. The hospital study can be viewed as an audit of patient care, which traditionally does not require patient consent. We did not interview individual patients nor did we use their identity in data analysis.

The measurement of the number of claims reimbursed and amount of money spent for antipsychotic medications by the Newfoundland and Labrador Prescription Drug Program over time did not require beneficiary consent.

Physicians identified as initiating atypical antipsychotic therapy for their patients during the study period were asked to participate in the study. A letter of intent describing the study and its purpose (appendix H) and a consent form (appendix I) were

mailed to each physician. Individual consent was obtained despite having received formal written support from both the Newfoundland Psychiatric Association and the Newfoundland and Labrador Medical Association. Participation was entirely voluntary and volunteers were to be reimbursed for their time. Participants were informed that all information collected was to be described in a manner that prevented identification of any individual. Confidentiality of information concerning physicians and patients was maintained by the investigator.

3.3 Hospital Utilization in Newfoundland

3.3.1 Data Source and Study Population

The study population comprised all patients, age greater than 18 years, discharged from all general and psychiatric hospitals in Newfoundland and Labrador with a diagnosis of schizophrenia during the three 12-month periods. The medical records departments of all hospitals in the province that admit psychiatric patients were contacted by letter to enlist their participation in the study. Each department was asked to provide the research team with a list of patients with both primary and secondary discharge International Classification of Diseases, 9th Revision (ICD-9)[174] diagnosis codes of 295.0-295.9 (schizophrenic psychoses) during 3 time periods: 1) at the beginning of restricted access (April 1, 1995 through March 31, 1996), 2) at the end of restricted access (January

1, 1998 through December 31, 1998), and 3) in the second year of open access (January 1, 2000 through December 31, 2000).

3.3.2 Data Collection

In order to collect relevant information from patient's charts, a team was assembled to create a data collection form. The team consisted of a psychiatrist, a clinical pharmacist who specializes in psychiatry, a clinical epidemiologist, a health policy analyst, and a member of the Mental Health Program with the Health Care Corporation of St. John's. The information to be included on the form was based on published clinical practice guidelines,[175 176] published psychopharmacological screening criteria,[177] quality of care indicators important to the Mental Health Program, and expert opinion. Data to be collected included demographic information, psychiatric status, management with pharmacotherapy and electroconvulsive therapy (ECT), utilization of various mental health programs, attempted suicide, use of seclusion, drug side effects, length of stay, previous admissions and readmission rates. This form was used to review ten hospital psychiatric charts and it was determined that the following data was not readily available in the chart: assessment and/or treatment by interdisciplinary care; referrals to services within the Mental Health Program; case management; ongoing counselling/therapy; drug side effects; and specific follow-up treatment plans. A revised version of the abstraction form was utilized to collect data.(Appendix J) Two research personnel reviewed the same five patients' charts independently to ensure consistency

between the abstracters. The researchers were satisfied that the same data was being collected, and independent abstraction was undertaken.

Each hospital medical records department in the province with patients admitted for the treatment of schizophrenia assigned staff to pull all of the patient charts. A member of the research team travelled to each site to conduct the chart abstraction process. While on site, each patient's hospital chart on the list was reviewed and all admissions to hospital during each study period were screened to determine whether they were related to the patient's psychiatric illness. This allowed the research team to capture all hospitalizations resulting from an exacerbation of schizophrenia (e.g. suicide attempts). Any admission not related to a patient's psychiatric diagnosis (e.g. patients admitted for the treatment pneumonia with a secondary diagnosis of schizophrenia) was excluded from the study. Lengths of stay that exceeded 365 days were also excluded.

Transfers between hospitals were treated as a single episode of care. The first episode of care identified in each study year was considered the index admission for that year and the first admission identified for the 3 study years was referred to as the study index admission. Patients were followed after each discharge in each 12 month interval and were censored at death or last follow-up.

All data collected were subsequently entered into Paradox® (version 7) for ease of data entry. After all data were checked and cleaned, the database was transferred to the Statistical Package for the Social Sciences (SPSS®) version 9.0 for Windows for analysis.

3.3.3 Outcome Measures

The primary outcome of interest was total days in hospital for schizophrenia per year. The number of admissions per year, length of stay in hospital, and the number of days from index discharge to re-hospitalization were secondary outcomes.

3.3.4 Demographic Characteristics

Demographic characteristics such as age, gender, region of domicile, education, income source, and occupation were obtained from the hospital chart. Region of domicile was categorized by placing the community where the patient lived from the home address provided in the chart and its location identified within one of the boundaries of the Regional Institutional Boards. Income source was defined as receiving social assistance, and other (employment, disability insurance, unemployment insurance, old age security, financial support from spouse, family, or children).

3.3.5 Psychiatric Symptoms and Clinical Presentation

Each study patient had their first psychiatric admission chart reviewed. This review enabled the researchers to determine the date of first psychiatric admission as well

as the calculation of duration of disease. The medical records departments of all of the institutions that admitted patients for the treatment of schizophrenia provided the researchers with a computerized printout of all previous admissions to that hospital, from which the total number of previous psychiatric hospitalizations were calculated.

In many cases, a brief examination of mental status is conducted on a psychiatric patient upon admission to hospital. These examinations identify patients as having any or all of the following characteristics: thought disorder (e.g. disorganized speech and delusions); perceptual disorder (e.g. auditory hallucinations); affect disorder (e.g., euphoric mood); and disordered behaviour (e.g. catatonic motor behaviour). Substance abuse (e.g. alcohol and/or drugs), non-adherence with prescribed pharmacotherapy prior to admission, discharged against medical advice, first psychotic admission and suicidal ideation on admission were all considered symptoms of disease. All of the aforementioned information was collected when the data was available in the chart.

The need for seclusion due to uncontrollable and/or violent behaviour and electroconvulsive therapy (ECT) while in hospital were also abstracted.

3.3.6 Pharmacotherapy

All of the medications ordered by the treating physicians and administered to patients while in hospital were documented in the clinical records. Dosage, route, date

started, and date discontinued for all antipsychotic medications were subsequently abstracted by the researchers for each patient. The antipsychotic medications were classified as being either an atypical antipsychotic (olanzapine, risperidone, quetiapine, clozapine) or a conventional antipsychotic agent (oral, injectable short acting and depot). The antipsychotic therapy prescribed on discharge was also abstracted from the chart.

3.3.7 Analytic Approach

Data was tabulated for each of the 3 phases of the study. Continuous variables were analyzed using one-way analysis of variance (ANOVA) or the Student's t-test, where appropriate. Approximately normal distributions of continuous variables were described with the mean and standard deviation; other distributions were transformed using logarithmic transformation and presented as medians. When continuous variables were found to be significantly different between the three years, post hoc analyses were conducted to determine which years were significantly different using Tukey's test of significance.

The length of stay in hospital was calculated by subtracting the admission date from the discharge date. All analyses of length of stay excluded patients who died in hospital since the length of stay was intended to be an indicator of improvement in psychiatric status. A Kaplan-Meier curve of the time to discharge was used to compare the length of stay for each study year. Lengths of stay were compared using the log rank

test statistic. Multivariable Cox proportional hazards regression analysis using a block entry of variables was used to determine significant independent predictors of both time to discharge (length of stay) and time to readmission. Block entry of variables is a procedure for variable selection in which the named variables are entered in a single step without checking any of the entry criteria. The analysis determined whether a hospital admission during one of the three phases of the study influenced time to discharge or time to readmission independent of demographic factors, psychiatric symptoms, and pharmacotherapy (switching from conventional to atypical agent). Given that the Cox proportional hazards model provides the risk of discharge from hospital, the hazard ratios and 95% confidence intervals were inverted so as to present the results as the risk of an increased length of stay.

When a patient was identified in more than one study year, only their first admission to hospital for the entire study period was included in the multivariable model in order to avoid multiple contributions and thus bias the results. These multiple admitters were separated and compared to those patients who did not appear in more than one study year using both Student's t-test and chi-square statistics where appropriate.

All categorical variables were recoded for computer analysis. Comparisons of categorical variables were done using cross-tabulations and chi-square statistics to evaluate significance. The results were presented as percentages.

The time to readmission was calculated by subtracting the date of discharge from the date of next admission. The variable, time to readmission, was recoded into a dichotomous outcome variable with two groups: those readmitted to hospital within 365 days of discharge and those who were not readmitted to hospital within 365 days of discharge. Bivariate statistical comparisons were made between the two groups using the two-tailed Student's t-test for continuous variables and chi-square statistics for categorical variables, with the level of significance set at 0.05.

Multivariable logistic regression was used to determine significant predictors of the probability of being readmitted within one year of discharge relative to not being readmitted within 1 year of discharge. Patients who either died or were confirmed to have left the province within 365 days of discharge were removed from the analysis, as they were not available for readmission. All independent variables were entered into the model using a standard method where all variables are entered at once. All variables were evaluated in relation to the dependent variable through use of partial correlation coefficients. This method was chosen based on theoretical relationship with the response variable. Again, demographic factors, psychiatric symptoms, and pharmacotherapy (atypical or conventional antipsychotic prescribed on discharge) were included in the multivariable analysis. The length of stay was included as an independent predictor in the multivariable analysis for readmission.

3.4 Patterns of Antipsychotic Medication Utilization and Expenditure in the Province of Newfoundland (NLPDP), 1995-2003

3.4.1 Utilization and Expenditure

Newfoundland and Labrador Prescription Drug Program (NLPDP) claims data were received biannually from the Department of Health and Community Services. The database includes all prescriptions (i.e., from all therapeutic categories) reimbursed by the program and uses the American Hospital Formulary System (AHFS), a therapeutic classification system, to group drugs. The AHFS groups drug products according to their therapeutic use. The therapeutic category corresponding to the relevant products (28:16.08) was used to extract the antipsychotics for the fiscal years 1994/1995 to 2002/2003, inclusive and was entered into an Excel database. These data allowed for the analysis of the utilization of individual pharmaceutical agents covered by the provincial drug plan as well as the amount paid by the program. Utilization was defined as the volume of prescriptions and type of antipsychotic medication reimbursed by the NLPDP. The database does not accurately record the number of pills dispensed per prescription and thus it was not possible to determine the duration of treatment. All antipsychotic agents were grouped into one of two categories: atypical and conventional. The atypical antipsychotic agents considered in this study include: clozapine, risperidone, olanzapine, and quetiapine.

3.4.2 Indication for Use of Atypical Antipsychotic Medications for Claims Reimbursed by the NLPDP

3.4.2.1 Identification of Prescribing Physicians

The implementation of an unrestricted reimbursement policy opens up the possibility that over-utilization of atypical antipsychotic medications could occur through prescription for disorders other than schizophrenia. The current study proposed to measure the appropriateness of initiating atypical antipsychotic medication therapy in patients covered by the NLPDP.

All patients prescribed an atypical antipsychotic medication for the first time were identified by manually reviewing all formal written requests for approval in the pre policy period. Each new patient started on an atypical antipsychotic was documented and assigned a date of first prescription. The information collected from this process was subsequently entered into an Excel spreadsheet so that the NLPDP claims databases received each year could be cross-referenced so that only new patients in each study year were included.

The information contained in the NLPDP database was deficient for our purposes because the database was created solely to reimburse claims submitted by the pharmacy where a prescription was filled. Therefore the only information a pharmacy was required to submit was for reimbursement: the beneficiaries' drug card number, name, prescribing

physician's name, drug description, cost of the prescription and date the prescription was filled. There was no patient specific information (e.g. age, gender, diagnosis) in the database and it was not possible to link the database with any other information to determine the indication for the use of atypical antipsychotic medications. It was decided to use information gathered from the prescribing physician to determine diagnosis and indication for atypical antipsychotic use.

All physicians in the province initiating therapy with an atypical antipsychotic medication were identified. Each physician was mailed a letter requesting their assistance in identifying the indication for use for each patient receiving an atypical antipsychotic through the NLPDP. The envelope contained a letter which outlined the intent of the study and its purpose (Appendix H) as well as a consent form (Appendix I). Prescribing physicians were to be interviewed to confirm diagnosis and indication for treatment. Participation was entirely voluntary.

The therapeutic decision to prescribe atypical antipsychotic agents was to be compared to practice guidelines applied by an expert panel. This panel of experts were to use the practice guidelines recommended by the American Psychiatric Association,[176] and the Canadian Psychiatric Association,[175] as well as other published literature on efficacy of antipsychotic medications, to complete its evaluation of appropriateness, inappropriateness, and uncertain appropriateness of pharmacotherapy. The academic

panel was to consist of a clinical epidemiologist, a professor of clinical psychiatric pharmacy, and a psychiatrist. Classification of the panel's decisions on the appropriate or inappropriate use of atypical antipsychotic medications was to be developed post-hoc.

3.4.2.2 Method of Data Collection

Visits to the participating physicians were arranged and interviews were conducted. Information collected during each visit included patient demographics, presenting complaints, symptoms, relevant past psychiatric history, diagnoses and types and quantities of antipsychotic medications prescribed, as well as factors influencing atypical antipsychotic prescription decision (Appendix K). The physician interviews took approximately 3-4 minutes per case and volunteers were paid $15.00 per interview. Participants were informed that all information collected was to be described in a manner that would prevent identification. Confidentiality of information concerning physicians and patients were maintained by the investigators.

The response from this request for participation was very poor and thus no useful data on the indication for use was obtained through this process. As a result, it was decided to assign each new prescription for an atypical antipsychotic in the years 1995/96, 1998 and 2000 to the prescribing physician and look at the specialty of the prescriber. This did not enable us to make any conclusions but would give an idea as to who was prescribing these medications (e.g. psychiatrists vs. other specialties). Using the

Newfoundland and Labrador Medical Association, Directory of Physicians, the speciality of each prescriber for each claim was assigned to each record in the database.

3.4.3 Atypical Antipsychotic Utilization in Canada

Data on estimated national totals of atypical antipsychotics prescriptions in the years 2000 to 2003 were obtained from Brogan Inc., a market research company that collects provincial and private drug program data from 8 of the 10 Canadian provinces and a number of major private insurers. This represents over 65% of all retail prescription drug sales in Canada. The National Brogan data used in this study is projected based on the Ontario Drug Benefits (ODB) Program and Private Payer data and was extrapolated to the entire country.

The ODB program covers approximately 2.2 million active claimants and pays for 68 million prescriptions annually. The ODB claimant population is approximately 66% seniors (over age 65). About 33% claimants receive benefits through social assistance, disability or catastrophic illness programs. All of these claims were adjudicated online and transmitted monthly to Brogan Inc, under a data services agreement with the Ontario government. The Brogan Inc. Private Payer database is comprised of drug benefits claims paid by a host of private insurers. The database in total collects information on over 10 million Canadians with 83 million prescriptions annually. Thirty-four percent of

records come from Ontario, 28% from Quebec, 29% from Western Canada and 9% from Atlantic Canada.

The database provided the number of prescriptions, as well as cost for each atypical antipsychotic (with the exception of clozapine), grouped according to diagnosis. Brogan uses various algorithms to determine the indication for use (Appendix L).

CHAPTER IV – RESULTS

4.1 Acute Care Hospital Utilization Over Time in Newfoundland

4.1.1 Summary of the Three Study Years

There were 314 patients admitted to hospital for the treatment of schizophrenia in Newfoundland and Labrador in 1995/96. The number decreased by 9.4% (n=287) and 22.2% (n=257) in 1998 and 2000 respectively. The total number of unique patients was 645 where 74.0% (n=477) appeared in one study year, 19.1% (n=123) were admitted to hospital in two of the years and a small proportion (7.0%, n=45) were admitted to hospital in all three years (Table 1). These 645 patients had 1,625 episodes of care resulting in a total of 47,098 hospital days. The mean number of episodes per patient per year was 1.9 in all study periods (Table 1).

There were 586 episodes of care evaluated in 1995/96, 551 (6.4% decrease) in 1998 and 488 (20.1% decrease) during the 12-month period of open access to atypical antipsychotic medications. However, the number of hospital days increased over the same time period (Table 1).

Table 1. Summary of the three study years

	1995/96	1998	2000	Total
Number of patients	314	287 (-8.6%)	257 (-18.2%)	645 unique patients 477 (74.0%) in 1 year 123 (19.1%) in 2 years 45 (7.0%) in 3 years
Episodes of care	586	551 (-6.0%)	488 (-16.7%)	1,625
Hospital bed days	15,089	16,318 (+8.2%)	15,691 (+4.0%)	47,098
Mean # episodes per patient per year (SD)	1.9 (1.4)	1.9 (1.5)	1.9 (1.4)	*P*=0.892

4.1.2 Sociodemographic Characteristics

Table 2 illustrates the sociodemographic characteristics of the patients admitted in each of the study years. Approximately two thirds of the study population in each study year were male. The patients admitted in 2000 were older than those admitted in 1995/96 (median=41.0 vs. 37.0). This may partly be explained by the fact that patients appearing in more than one study year were included and thus are increasing in age. Approximately 72 percent of each group were receiving social assistance and close to half of the populations had less than a grade 10 education.

Table 2. Characteristics of patients admitted to hospital during each study year (percentages (numerator/denominator) of patients unless otherwise indicated)

Characteristic	1995/96 n=314	1998 n=287	2000 n=257
Sociodemographic			
Male	66.6 (209/314)	69.3 (199/287)	70.8 (182/257)
Median age in years (min, max)	37.0 (17, 85) n=314	39.0 (16, 88) n=287	41.0 (18, 83) n=257
St. John's Region	61.8 (194/314)	59.9 (172/287)	62.6 (161/257)
< grade 10 education	47.9 (146/305)	49.3 (135/274)	47.5 (115/242)
Social Assistance	73.6 (226/307)	71.6 (204/285)	72.7 (184/253)
Psychiatric status			
First psychotic episode	5.1 (16/314)	5.9 (17/287)	1.6 (4/257)
Substance abuse	32.3 (98/303)	29.6 (85/287)	30.0 (77/257)
Suicidal ideation on admission	30.9 (97/314)	36.9 (106/287)	30.4 (78/257)
Thought disorder	78.0 (245/314)	83.3 (239/287)	79.4 (204/257)
Perceptual disorder	62.7 (197/314)	55.1 (158/287)	68.9 (177/257)
Affect disorder	83.1 (261/314)	86.8 (249/287)	91.4 (235/257)
Disordered behavior	2.9 (9/314)	4.2 (12/287)	1.2 (3/257)
Discharged AMA	12.4 (39/314)	9.1 (26/287)	7.4 (19/257)
Non-adherent with medication	54.0 (157/291)	49.1 (141/287)	52.8 (131/248)
Median # of previous admissions (min, max)	7.0 (1, 85) n=314	8.0 (1, 91) n=287	10.0 (1, 94) n=257
Median # years of disease suffering (min, max)	12 (0, 52) n=307	13.5 (0, 53) n=284	14.5 (0, 59) n=251
Level of Care			
Recommended for ECT	5.7 (18/314)	7.7 (22/287)	9.0 (23/257)
Seclusion	12.7 (40/314)	13.2 (38/287)	9.3 (24/257)
Pharmacotherapy			
Atypical agent prescribed on	16.0	50.8	77.5

discharge	(47/293)	(136/268)	(183/236)

4.1.3 Psychiatric Status

The inpatient chart review revealed that about half of patients admitted to hospital were non-adherent with prescribed medications on admission in each year (Table 2). One third of the population expressed suicidal ideation and approximately 30% were substance abusers. The number of previous psychiatric admissions to hospital was shown to be higher in the final study year as compared to baseline (1995/96), but again the multiple contributions of readmitters would help explain this. Sixteen (5.1%) and seventeen (5.9%) patients experienced their first psychiatric admission to hospital during 1995/96 and 1998 study years. However, the number of first psychotic episodes in 2000 was significantly lower with only 4 patients (1.6%). This may partly explain the increase in average number of previous admissions in this same year. The number of patients admitted with perceptual disorder was higher in 2000 than in 1998 and there was a greater number of patients admitted with affect disorder in 2000 than in the baseline year. The percentage of patients discharging against medical advice (AMA) was 12.4, 9.1 and 7.4 in 1995/96, 1998, and 2000, respectively. This change may be clinically significant since it may indicate that patients are remaining in hospital longer to receive treatment.

4.1.4 Level of Care Required During Admission

Table 2 illustrates the level of care required while a patient was in hospital for the exacerbation of schizophrenia. The proportion of patients recommended for electroconvulsive therapy (ECT) during their hospital admission increased from 5.7% to 9.0% over the study period. At the same time, the percentage of patients requiring seclusion for uncontrollable behaviour was 12.7% (n=40), 13.2% (n=38) and 9.3% (n=24) in 1995/96, 1998 and 2000, respectively.

4.1.5 Pharmacotherapy Prescribed on Hospital Discharge

Forty-seven patients (16.0%) in the baseline population were discharged on an atypical antipsychotic medication following an index admission. The corresponding numbers were 136 (50.8%) and 183 (77.5%) in 1998 and 2000, respectively. This increase in atypical use corresponds to both the introduction of two more atypical agents (olanzapine in October, 1996 and quetiapine in December, 1997) and the introduction of the unrestricted access policy implemented in December 1998.

10.9% (n=31) of the patients receiving an atypical antipsychotic agent on admission in 1995/96 were also discharged on an atypical agent, compared with 38.3% (n=101) in 1998 and 65.2% (n=148) in 2000 (Table 3). 82.0% (n=233) of the baseline

study population were admitted and discharged on a conventional agent vs. 45.1% (n=119) and 18.9% (n=43) in the next 2 years. 14 (4.9%), 33 (12.5%) and 28 (12.3%) of hospitalized schizophrenia sufferers were switched from a conventional antipsychotic to an atypical antipsychotic during the index admission in the three study years (Table 3).

Table 3 Pharmacotherapy prescribed during annual index admission (number (percentages) of patients unless otherwise indicated)

Admission/discharge drugs	**1995/96 (n=284)**	**1998 (n=264)**	**2000 (n=227)**
Atypical to atypical	31 (10.9)	101 (38.3)	148 (65.2)
Conventional to conventional	233 (82.0)	119 (45.1)	43 (18.9)
Atypical to conventional	6 (2.1)	11 (4.2)	8 (3.5)
Conventional to atypical	14 (4.9)	33 (12.5)	28 (12.3)

4.1.6 Length of Stay in Hospital

The length of stay per episode of care in 2000 was longer than the length of stay per episode in 1995/96 and based on the log transformation of the length of stay, this difference was statistically significant ($P<0.001$)(Table 4). The post hoc analysis showed that both 1998 and 2000 were significantly longer than 1995/96. There was a significant difference between the numbers of hospital days per patient in each year as well. The post hoc analysis revealed that 2000 was significantly longer than 1995/96 (Table 4). There were instances where the maximum value of the total number of days per patient per year exceeds 365 days. This is explained by the fact that a few patients were

admitted to hospital prior to the study year but discharged in the year of interest and subsequently having hospital days outside of the 365 days of the study year.

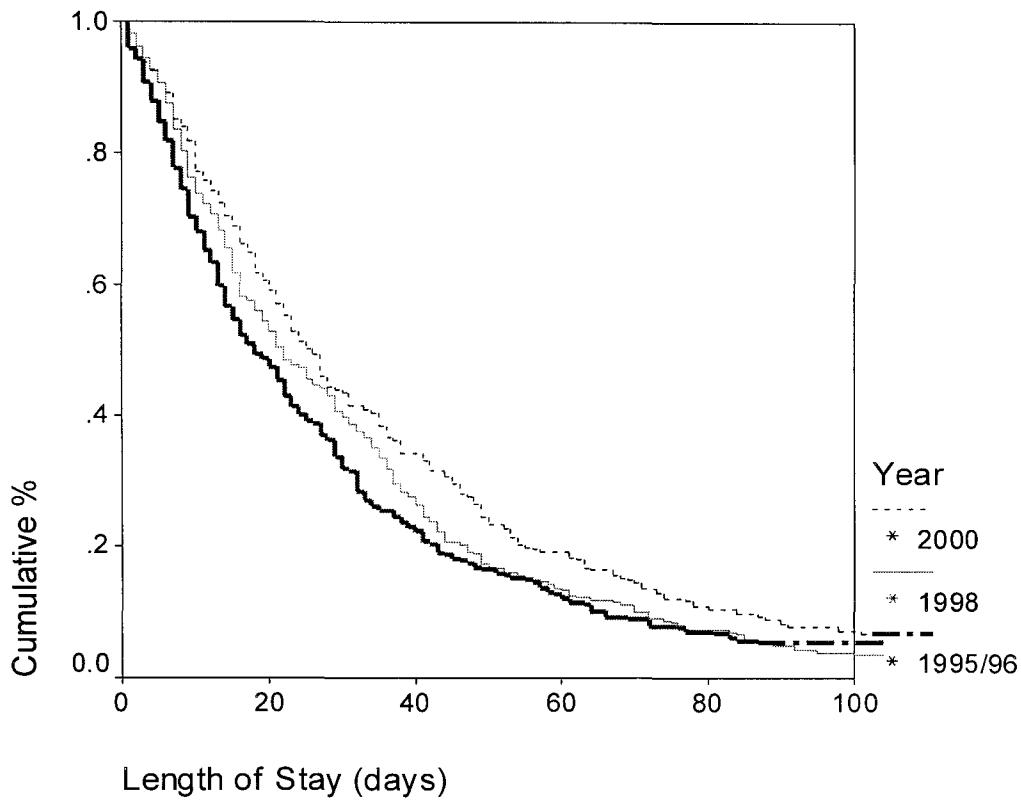
Table 4. Time spent in hospital in each study year

	1995/96	**1998**	**2000**	***P*-value**
Median LOS per episode (min, max)	15.0 (1, 319)	19.0 (1, 336)	22.0 (1, 296)	**<0.001*†**
Median days per patient per year (min, max)	32.0 (1, 369)	40.0 (1, 336)	40.5 (1, 372)	**0.006*†**

* = Significant at *P*-value < 0.05
† = based on log transformation

Kaplan Meier survival curves were created for each year of the study for the length of stay of the annual index admission (Figure 1). A comparison of these three curves using the log-rank test revealed a statistically significant difference between the curves (*P*=0.0192). The average length of stay during the annual index admission during 2000 was just over a week longer than the annual index admission during the baseline period of restricted access (39.2 days vs. 31.7 days). Pairwise comparisons using the log transformation of length of stay for the index admission revealed that this difference was significant (*P*=0.006).

Figure 1. Length of stay for the annual index admission for each study year



4.1.6.1 Comparison of Patients Admitted in Multiple Years vs. Patients Admitted in One Year

477 (74.0%) patients appeared in one study year and experienced 732 episodes of care over the course of the study and 22,660 hospital days while 168 (26.1%) schizophrenia sufferers appeared in at least 2 of the selected time periods and incurred 863 episodes of care and 24,438 hospital days (Table 5). The demographic information, psychiatric status, and level of care required in hospital for each population was

compared to see if they differed and thus bias the results of the multivariable analyses. The results revealed that the readmitters were younger (P=0.046) and were more likely to be on social assistance (P<0.001) than those patients who were admitted in only one study year (Table 6). Patients who were admitted to hospital in multiple study years were more likely to be non-adherent with prescribed medications on admission (P<0.001), more likely to discharge themselves from hospital against medical advice (P<0.001) and had significantly more previous psychiatric admissions (P=0.002) than those found in only one study period. In addition, multiple admitters were more likely to require seclusion for uncontrollable behaviour (P=0.008) (Table 6). Given these results the multivariable analyses included each patient once.

Table 5. Patients admitted in one study period compared to patients admitted in more than one study period

	1 Year	**>1 Year**	**Total**
# of patients (%)	477 (74.0)	168 (26.1)	645
Episodes of care	762	863	1,625
Hospital bed days	22,660	24,438	47,098

Table 6. Comparison of patients admitted in multiple years with patients admitted in one study year (percentages (numerator/denominator) of patients unless otherwise indicated)

Characteristic	1 Year (n=477)	>1 Year (n=168)	*P*-value
Sociodemographic			
Male	70.2 (335/477)	67.3 (113/168)	0.472
Median age in years (min, max)	39.0 (16, 88)	36.5 (17, 68)	**0.046*†**
< grade 10 education	46.4 (207/446)	50.3 (83/165)	0.393
Social Assistance	65.0 (305/469)	81.2 (134/165)	**<0.001***
Psychiatric status			
First psychotic episode	6.1 (29/477)	4.8 (8/168)	0.528
Substance abuse	31.6 (149/471)	39.3 (64/163)	0.076
Suicidal ideation on admission	30.4 (145/477)	37.5 (63/168)	0.090
Thought disorder	80.9 (386/477)	79.2 (133/168)	0.622
Perceptual disorder	62.9 (300/477)	61.3 (103/168)	0.715
Affect disorder	84.5 (403/477)	86.9 (146/168)	0.449
Disordered behaviour	2.9 (14/477)	2.4 (4/168)	0.708
Discharged AMA	6.5 (31/477)	16.7 (28/168)	**<0.001***
Non-adherent with medication	45.7 (208/455)	63.0 (102/162)	**<0.001***
Median # previous admissions (min, max)	6.0 (1, 71)	7.5 (1, 85)	**0.002*†**
Median # years of disease suffering (min, max)	12.0 (0, 59)	13.0 (0, 41)	0.306†
Level of care			
Recommended for ECT	6.7 (32/477)	3.0 (5/168)	0.074
Seclusion	9.2 (44/477)	16.7 (28/168)	**0.008***
Pharmacotherapy			
Atypical agent prescribed on discharge	45.4 (199/438)	23.0 (37/161)	**<0.001***

* = Significant at *P*-value < 0.05
† = based on log transformation

4.1.6.2 Significant Factors Influencing Length of Stay

The multivariable Cox proportional hazards model to determine the independent predictors of time spent in hospital included 78.9% (509/645) of the original population due to missing information for some variables for the 136 excluded patients. Of the 18 variables that were entered in the model, six were found to significantly influence the amount of time a patient admitted for the treatment of schizophrenia remained in hospital (Table 7).

Given the change in access to atypical antipsychotic agents over the course of the study, an interaction term was created to measure the effect of switching from a conventional antipsychotic to an atypical agent on length of stay in each year. The effect of switching in 1995/96 was shown to significantly increase length of stay when compared to the effect of switching in 2000 (hazard ratio 2.61, 95% CI = 1.12-6.11, P=0.027). Independent of age and gender, requiring ECT, seclusion and having thought disorder significantly increased a patient's time in hospital (hazard ratio 1.42, 95% CI = 1.11-1.82; P=0.006. Suicidal ideation on admission (hazard ratio 0.71, 95% CI = 0.58-0.87; P=0.0009) and discharging oneself against medical advice (hazard ratio 0.40, 95% CI = 0.28-0.56; P<0.001) were significant predictors of a reduced length of stay. Factors which failed to impact upon length of stay included years since first diagnosis, number of previous hospitalizations, the first psychotic episode, substance abuse, presence of

perceptual disorder, affect disorder, disordered behaviour, having low education, being non-adherent with prescribed medication on admission, and being in receipt of social assistance.

Table 7. Multivariable Cox Proportional Hazards Model of the independent variables predicting an increased length of stay by study index admission, for 1995/96, 1998 & 2000 (n=509/645, 78.9%)

Characteristic	**Hazard Ratio**	**95% CI**	***P*-value**
Sociodemographic			
Male	0.82	0.22-1.02	0.074
Age	1.01	0.99-1.02	0.400
< grade 10 education	0.90	0.74-1.08	0.258
Year of admission			
1995 vs. 2000	0.77	0.59-1.01	0.056
1998 vs. 2000	0.81	0.61-1.07	0.143
Social Assistance	1.01	0.81-1.25	0.949
Psychiatric status			
First psychotic episode	1.15	0.74-1.78	0.547
Substance abuse	0.99	0.80-1.22	0.918
Suicidal ideation	0.71	0.58-0.87	**0.0009***
Thought disorder	1.42	1.11-1.82	**0.006***
Perceptual disorder	1.00	0.82-1.22	0.995
Affect disorder	1.16	0.90-1.50	0.260
Disordered behaviour	1.35	0.78-2.34	0.286
Discharged AMA	0.40	0.28-0.56	**<0.001***
Non-adherent with medication	1.05	0.86-1.05	0.634
Mean # previous admissions	1.00	0.98-1.01	0.322
Mean # years of disease suffering	1.00	0.99-1.02	0.612
Level of care			
Recommended for ECT	2.58	1.75-3.80	**<0.001***
Seclusion	1.93	1.45-2.57	**<0.001***
Pharmacotherapy			
Drug switch (conventional to atypical)	1.26	0.74-2.14	0.401
Year of admission*drug switch			
1995 vs. 2000	2.61	1.12-6.11	**0.027***
1998 vs. 2000	1.62	0.81-3.25	0.170

* = Significant at *P*-value < 0.05

4.1.6.3 Length of Stay Associated with the Class of Antipsychotic Agent Prescribed on Admission and Discharge for Each of the Study Years

The number of patients admitted and discharged on an atypical antipsychotic medication increased by more than 475% from baseline to the final study year (Table 8). At the same time, the median length of stay for these patients increased from 13.0 days to 31.0 days, a difference of 18.0 days. The number of patients who were switched from a traditional antipsychotic to an atypical antipsychotic medication while in hospital remained relatively small in each study year, indicating that most patients were switched as outpatients. The median time spent in hospital for these patients was 72.5 days, 40.0 days, and 29.5 days in 1995/96, 1998, and 2000, respectively (Table 8).

Table 8. Length of stay associated with the class of antipsychotic agent prescribed on admission and discharge for each study year

	n (%)	Median LOS (min, max)
1995/96 (284/314, 90.4%)		
Atypical-atypical	31 (10.9)	13.0 days (3, 137)
Conventional-conventional	233 (82.0)	17.0 days (1, 314)
Atypical-conventional	6 (2.1)	41.5 days (3, 66)
Conventional-atypical	14 (4.9)	72.5 days (30, 319)
1998 (264/287, 92.0%)		
Atypical-atypical	101 (38.3)	28.0 days (1, 336)
Conventional-conventional	119 (45.1)	18.0 days (2, 216)
Atypical-conventional	11 (4.2)	43.0 days (14, 89)
Conventional-atypical	33 (12.5)	40.0 days (12, 180)
2000 (227/257, 88.3%)		
Atypical-atypical	148 (65.2)	31.0 days (1, 296)
Conventional-conventional	43 (18.9)	15.0 days (1, 203)
Atypical-conventional	8 (3.5)	59.0 days (9, 69)
Conventional-atypical	28 (12.3)	29.5 days (7, 198)

4.1.7 Readmission to Hospital

4.1.7.1 Rates of Readmission to Hospital

62.4% of the 314 patients admitted to hospital for the treatment of schizophrenia during the baseline study period were readmitted within 1 year of discharge. This rate of readmission was not significantly different from the other two study years, although the trend was lower (*P*=0.058) (Table 9). 50% of the study population were readmitted in 215 days in 1995/96, 221 days in 1998, and 223 days in 2000 (*P*=0.114) (Table 9).

Table 9. Index admission analysis for readmission to hospital

	1995/96	**1998**	**2000**	***P*-value**
Median time to readmission (days)	215	221	223	0.114†
Readmitted within 1 year of discharge (%)	62.4	59.2	58.6	0.058

† = based on log transformation

4.1.7.2 Factors Influencing Early Hospital Readmission for all Study Years

Before conducting the multivariable logistic regression analysis to identify predictors of early readmission to hospital, comparisons were made between patients readmitted within 1 year versus those who were not. Six patients were removed from this analysis because they had either died (n=5) or were confirmed to have left the province (n=1) within 365 days of discharge. The results of these analyses demonstrated that patients readmitted within 1 year were more likely to be receiving social assistance

(P=0.006), to have had significantly more previous psychiatric hospitalizations (P<0.001), and to have discharged themselves against medical advice (P=0.006) when compared to patients not readmitted within 1 year (Table 10). Additionally, it was found that patients admitted in 1995/96 were more likely to be readmitted within one year when compared to patients admitted in 1998 (P=0.021). However, this may be due to the fact that people readmitted from the 1995/96 cohort were removed from the 1998 and 2000 cohorts in the analyses. There were no significant differences with respect to gender, education, or patients who required a period of seclusion, between the two groups. Suicidal ideation, thought, perceptual, affect disorders, disordered behaviour, non-adherence with prescribed medications prior to admission, and the class of antipsychotic prescribed on discharge did not significantly affect the probability of readmission within one year. The median length of stay for patients readmitted within one year of discharge was shorter than that for patients who were not readmitted within one year (18.5 days vs. 23.0 days) and this was statistically significant (P=0.046).

Table 10. Comparison of patients readmitted within 1 year of hospital discharge with patients not readmitted within 1 year of hospital discharge (1995/96, 1998, and 2000) (n=639) (percentages (numerator/denominator) of patients unless otherwise indicated)

Characteristic	Readmitted within in 1 year (n=366)	Not readmitted within 1 year (n=273)	*P*-value
Male	67.8 (248/366)	71.1 (194/273)	0.371
Median age in years(min, max)	38.0 (16, 85)	39.0 (17, 88)	0.102†
< grade 10 education	50.0 (175/350)	43.8 (112/256)	0.128
Social assistance	73.3 (264/360)	63.1 (169/268)	**0.006***
Year of admission:			
1995/96 (reference)	53.6 (196/366)	43.2 (118/273)	
1998	27.3 (100/366)	34.1 (93/273)	**0.021***
2000	19.1 (70/366)	22.7 (62/273)	0.073
Substance abuse	36.0 (129/358)	30.0 (81/270)	0.113
First psychotic episode	6.0 (22/366)	5.5 (15/273)	0.782
Non-adherence (%)	51.7 (182/352)	47.9 (124/259)	0.350
Suicidal ideation (%)	34.4 (126/366)	29.7 (81/273)	0.204
Thought Disorder (%)	80.1 (293/366)	81.3 (222/273)	0.689
Perceptual Disorder (%)	63.9 (234/366)	61.5 (168/273)	0.535
Affect Disorder (%)	84.7 (310/366)	85.3 (233/273)	0.820
Disordered Behaviour (%)	2.2 (8/366)	3.3 (9/273)	0.388
Median # previous admissions (min, max)	7.0 (1, 85)	5.0 (1, 46)	**<0.001*†**
Median index LOS(min, max)	18.5 (1, 319)	23.0 (1, 336)	**0.046*†**
Discharged against medical advice (%)	11.7 (43/366)	5.5 (15/273)	**0.006***
Median years of disease suffering (min, max)	13.0 (0, 59)	12.0 (0, 52)	0.741†
Recommended for ECT (%)	4.4 (16/366)	7.7 (21/273)	0.075
Seclusion (%)	10.7 (39/366)	11.7 (32/273)	0.671
Atypical agent prescribed on discharge (%)	38.4 (127/331)	41.2 (108/262)	0.481

* = Significant at *P*-value < 0.05
† = based on log transformation

The multivariable logistic model included 81.5% (521/639) of the entire study population and revealed two significant, independent predictors for re-hospitalization within 12 months of discharge: leaving hospital against medical advice (OR = 2.57, 95% CI=1.12-5.92; *P*=0.027), and for every 1 more previous admission there was a 5% increase in likelihood that a patient would be readmitted (OR = 1.05, 95% CI=1.02-1.08; *P*=0.002) (Table 11). Contrary to expectation, neither being non-adherent with prescribed medications on the previous admission, nor receiving a prescription for an atypical antipsychotic medication on last discharge influenced the probability of being readmitted to hospital within one year of discharge.

Table 11. Multivariable Logistic Regression Model for predictors influencing hospitalization within 1 year of discharge from the index admission 1995/96, 1998 & 2000 (521/639, 81.5%)

Characteristic	**Odds Ratio**	**95% CI**	***P*-value**
Sociodemographic			
Male	0.67	0.43-1.03	0.070
Age in years	0.98	0.96-1.00	0.103
< grade 10 education	1.33	0.90-1.97	0.157
Year of admission			
1995 vs. 2000	1.08	0.38-3.04	0.892
1998 vs. 2000	0.61	0.20-1.81	0.370
Social assistance	1.09	0.71-1.66	0.670
Psychiatric status			
First psychotic episode	1.24	0.53-2.89	0.624
Substance abuse	1.54	1.00-2.37	0.052
Suicidal ideation on admission	1.24	0.81-1.90	0.318
Thought Disorder	1.02	0.61-1.68	0.955
Perceptual Disorder	1.02	0.68-1.51	0.943
Affect Disorder	0.80	0.47-1.38	0.427
Disordered Behaviour	0.92	0.31-2.73	0.884
Discharged AMA	**2.57**	**1.12-5.92**	**0.027***
Non-adherent with medication	1.10	0.73-1.65	0.648
# previous admissions	**1.05**	**1.02-1.08**	**0.002***
Index length of stay	1.00	0.99-1.00	0.502
Years of disease suffering	1.01	0.98-1.04	0.628
Level of Care			
Recommended for ECT	0.70	0.32-1.52	0.364
Seclusion	0.80	0.43-1.46	0.460
Pharmacotherapy			
Atypical on discharge	1.14	0.38-3.41	0.814
Year of admission*discharge drug class			
1995/96 vs. 2000	1.10	0.30-4.12	0.885
1998 vs. 2000	1.18	0.34-4.15	0.792

* = Significant at *P*-value < 0.05

4.2 Utilization of Newer Antipsychotic Medications by NLPDP 1995-2003

In 2000/01, the Newfoundland and Labrador Prescription Drug Program paid for 50,518 antipsychotic prescriptions. The atypical antipsychotic agents (clozapine, risperidone, olanzapine, and quetiapine) accounted for a large share of antipsychotic prescriptions, making up 49% of the total. In contrast, atypicals accounted for only 3.3% of Program antipsychotic prescriptions in 1995/96. Between 1995/96 and 2000/01, prescriptions for antipsychotics grew 24% while expenditures increased by more than 459%. Total NLPDP spending on antipsychotics was approximately $900 thousand in 1995/96, however this therapeutic category exceeded $4.1 million in 2000/01 with the atypical antipsychotic agents making up 90.4% of this amount (Figure 2). Olanzapine accounted for the largest share of spending for antipsychotics at $2.8 million (65.7%) and risperidone ranked second at $707 thousand (16.8%) (Figures 2 & 3). As of 2002/03, the use of atypical antipsychotic medications was still on the rise since the NLPDP paid for 59,904 prescriptions for antipsychotics and spent more than $6.5 million during that fiscal year with the atypical antipsychotic agents making up 94.5% of this amount (Figures 2 & 4). Despite this continued increase in the reimbursement for atypical antipsychotic medications, the number of persons eligible for the NLPDP was declining. In fact, by 2002/03, the number of claimants for the Program was at the lowest it had been in a decade (Figure 4). Figure 4 demonstrates that the number of cardholders in the social assistance program had decreased while the number of cardholders in the seniors program remained constant. Despite a decline in the number of beneficiaries for the

social assistance program the number of prescriptions for antipsychotic medications increased by 56.0% while the percentage of claims for the seniors program only increased by 4.0%.

Figure 2. NLPDP expenditures for atypical antipsychotic medications vs. conventional antipsychotic medications 1995-2003

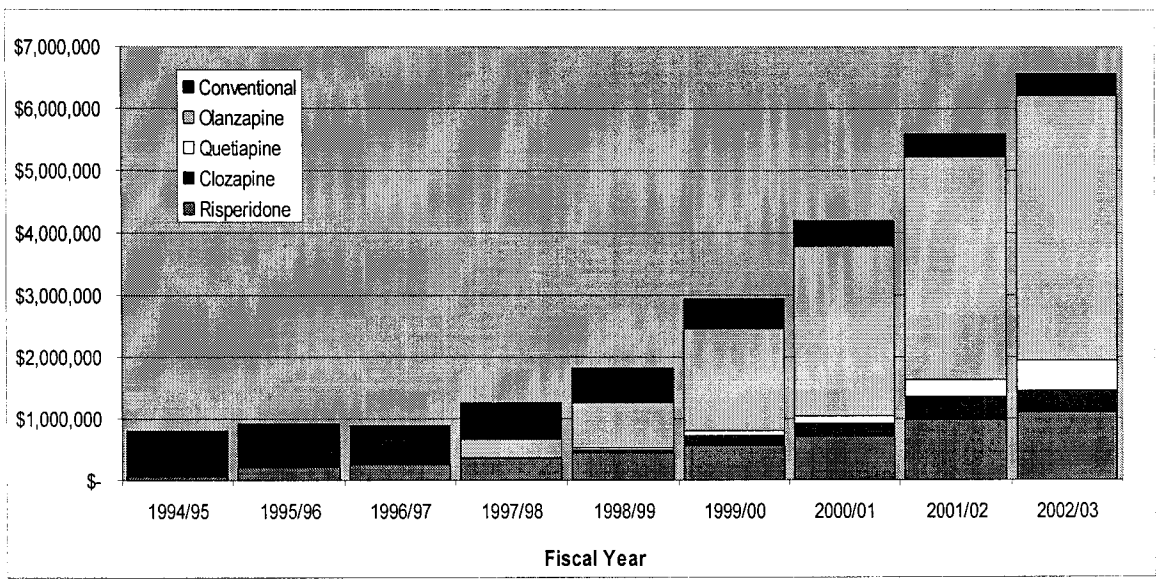


Figure 3. Share of the NLPDP expenditure by antipsychotic medication 2000/01

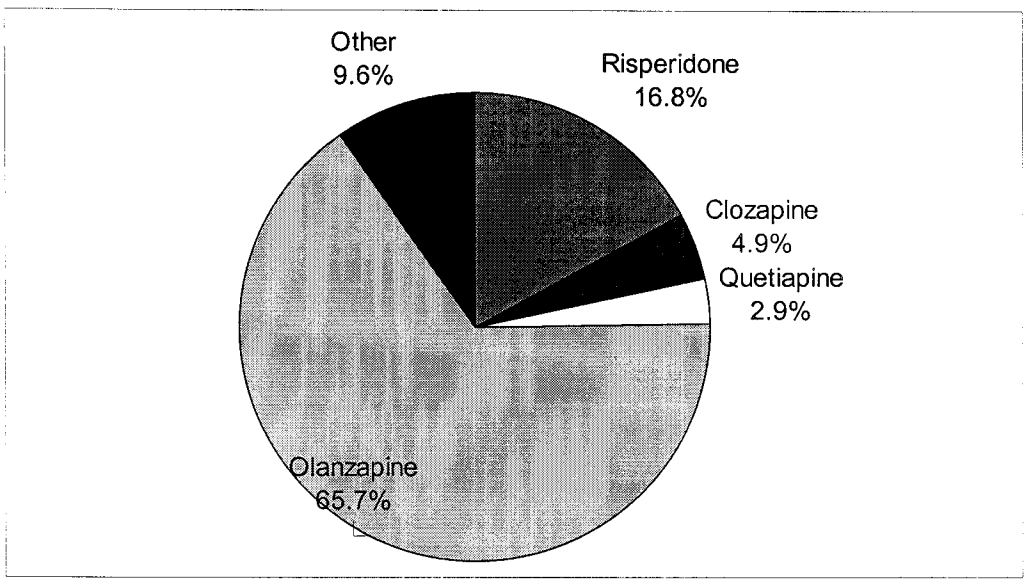
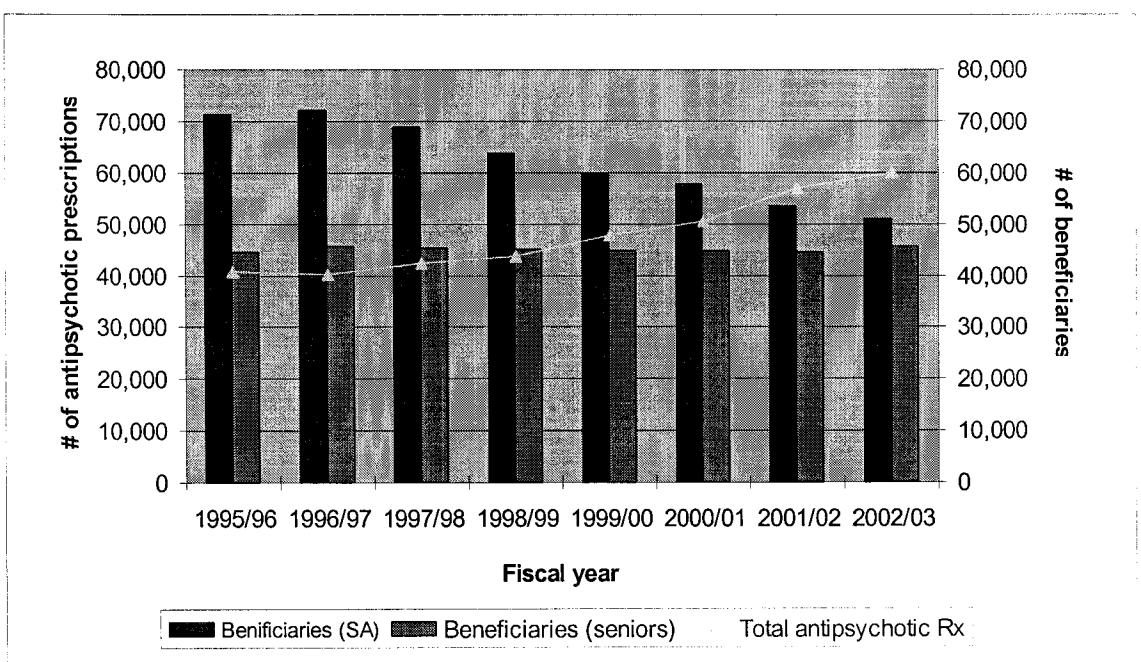


Figure 4. Number of beneficiaries and total antipsychotic prescriptions reimbursed by NLPDP 1992-2003



4.3 Indication for Atypical Antipsychotic Use in Newfoundland

The NLPDP database for the year 2000 revealed 2,140 NLPDP beneficiaries had received an atypical antipsychotic medication. A search of previous years revealed that 1,095 (51.3%) had had a prescription for an atypical antipsychotic medication prior to 2000. As a result, 1,045 patients were identified as first time atypical users during this 12-month period. Seven claims were removed due to missing information and ten drug card numbers were duplicated in the database and thus were removed. The remaining 1,028 patients formed the final database for 2000. The claims were sorted by the date the atypical antipsychotic prescription was filled and every third claim was selected for interview since this was a more manageable number (n=340) for this portion of the study. This database included 151 prescribing physicians with some having only 1 patient and one physician had as many as 22 patients. 3 physicians (2.1%) wrote 11.8% of the prescriptions. Of the 151 physicians, 43 (28.5%) agreed to participate. This participation rate only provided information on 33.8% (n=115) of the patients receiving an atypical antipsychotic medication. Given this poor response rate, this portion of the study was not analyzed as it was determined that we would not be able to identify how these new medications were being used in the community.

4.4 NLPDP Beneficiaries Started on an Atypical Antipsychotic Agent in 2000

Given that we could not ascertain the reasons why atypical antipsychotic medications were being prescribed in the community, it was decided to look at the

specialty of the prescribing physician. The NLPDP files were reviewed and patients who had received an atypical antipsychotic medication through the drug program for the first time in the year 2000 were identified. Of the 1,021 beneficiaries that were started on an atypical antipsychotic medication for the first time, 531 (52.0%) for olanzapine, 447 (43.8%) for risperidone, and 43 (4.2%) for quetiapine. There were a total 276 different physicians who prescribed these medications. 42 (15.2%) of the physicians were psychiatrists and they were responsible for 427 (41.8%) of the total prescriptions. The remaining 84.8% (n=234) of the 'other' physicians wrote 594 (58.2%) of the prescriptions. This may indicate that these medications are being prescribed for other indications besides schizophrenia in primary care

4.5 Atypical Antipsychotic Utilization in Canada, 2000

Using Brogan Inc. data based on the Ontario Drug Benefit Program and Private Payer data, the estimated number of prescriptions dispensed for risperidone, olanzapine and quetiapine increased 2.2 fold from 2.4 million prescriptions to 5.3 million prescriptions from 2000 to 2002. During this same time period, the amount of money spent by Canadian drug stores and hospital pharmacies increased by 56.9%, from $218 million to $342 million. In 2000, risperidone made up the largest portion of atypical prescriptions accounting for 49.7% (n=1,176,920) of the total number of claims. Olanzapine made up 42.5% of the claims (n=1,006,617) and quetiapine was last comprising the remaining 7.7% (n=183,023) (Figure 5). However, risperidone made up

only 27.5% of the total expenditure for these 3 drugs while olanzapine made up 67.5% of the expenditure at $147 million (Figure 6).

The greatest proportion of atypical antipsychotic medications was prescribed to treat dementia (35.3%). Second, atypical agents were used for patients suffering from bipolar disorder (29.4%), and the third largest indication was psychosis (27.8%) (Figures 5 & 7).

Figure 5. National atypical antipsychotic medication utilization in 2000 (source: Brogan Inc.)

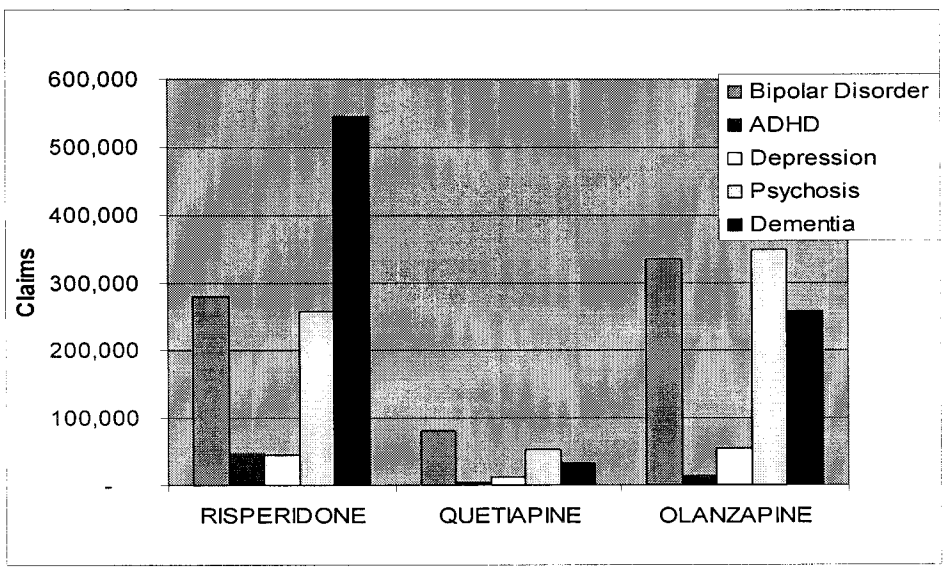


Figure 6. National atypical antipsychotic medication expenditure in 2000 (source: Brogan Inc.)

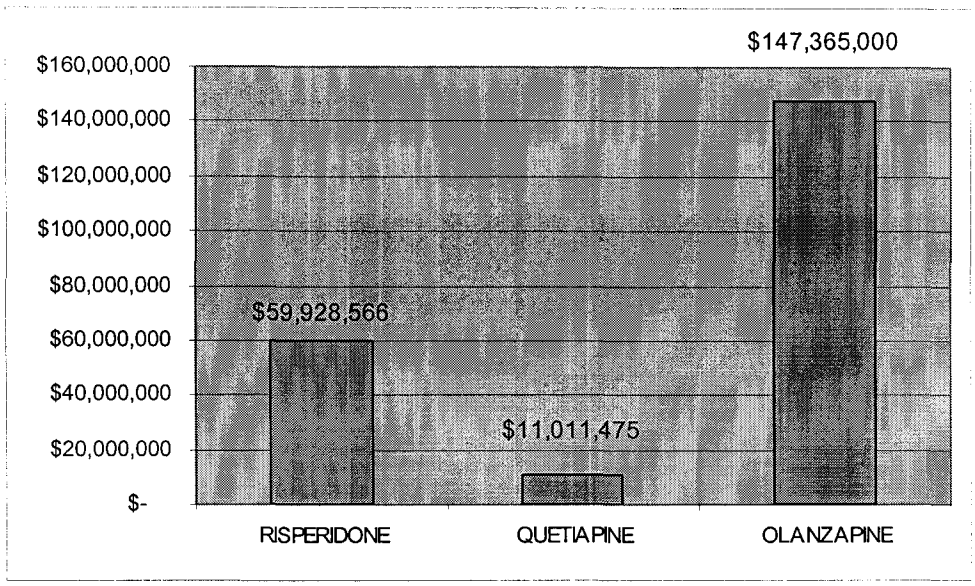
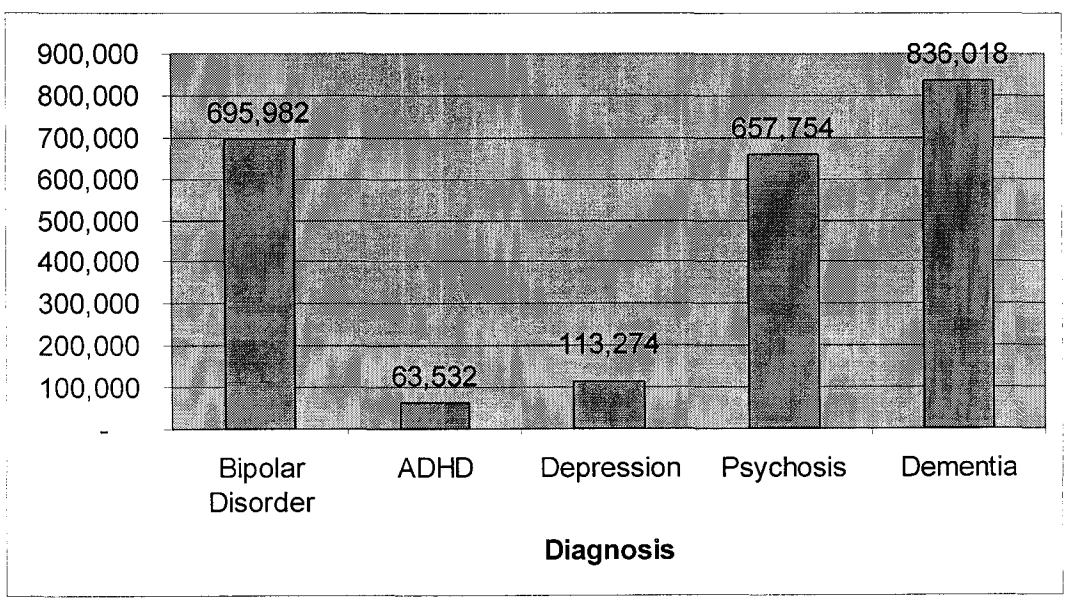


Figure 7. Total number of claims for atypical antipsychotic medications by diagnosis in Canada, 2000 (source: Brogan Inc.)



CHAPTER V –UNRESTRICTED ACCESS: A POLICY ANALYSIS AND ECONOMIC IMPLICATIONS

5.1 The Open Access to Atypical Antipsychotic Medications in Newfoundland: A Policy Analysis

Drug coverage policy, in its broadest sense, is intended to promote value in medical care by using reimbursement to favour the use of effective care and to avoid the use of ineffective care.[178] Restrictive reimbursement policies have become increasingly popular in recent years as a convenient way to contain costs and the NLPDP is no exception. This poses the question as to why the NLPDP decided to adopt an unrestricted reimbursement policy for new medications to treat schizophrenia especially given that the evidence in the literature regarding the effectiveness of these drugs did not support the introduction of such a policy. A description of the sequence of events accompanied by interviews with the key stakeholders at the time provides some insight into the factors that influenced the decision by the Minister of Health to allow for the unrestricted reimbursement of four atypical antipsychotic medications in Newfoundland.

The concern regarding lack of access to atypical antipsychotic medications came to the forefront in the fall of 1996. At that time, there were a number of groups that were lobbying for the special authorization policy to be abolished. Schizophrenia sufferers and their families believed that the newer drugs would help alleviate the suffering caused by the disorder and that these patients should not be denied access to therapy based on the

inability to pay for the newer agents.[179] Physicians felt that the restrictive policy was an encroachment upon their autonomy and presented an intrusion on their ability to prescribe when they felt it was appropriate for their patients' well-being. In addition, it was felt that it was a "hassle" to get coverage even when the patient met NLPDP defined criteria.[180]

The pressure to change the restrictive policy coincided with the time that Eli Lilly and Company released their atypical antipsychotic medication, olanzapine, onto the market.[181] This release was accompanied by a marketing campaign and information dissemination to physicians and drug plan managers. Restrictive policies limit manufacturer income.

Shortly after this time, a chapter of the Schizophrenia Society of Canada was formed in Newfoundland and Labrador, with financial support from Eli Lilly, and was legally incorporated in May 1997. The result was the formation of a sort of informal coalition consisting of the Newfoundland Psychiatric Association (NPA), the Schizophrenia Society of Newfoundland and Labrador (SSNL), and Eli Lilly to put pressure on the government to eliminate the restricted policy.

The goal of the NLPDP is to ensure that all residents of the province have equal access to quality health care in order to improve or maintain health status.[181] However,

due to the fiscal realities facing the province, namely fixed budgets and competing demands for the same funds, the Department must also attempt to ensure efficiency, and this reality was in conflict with the request for an unrestricted policy.

In October 1997, the NLPDP commissioned a local psychiatrist to review the scientific literature on the relative efficacy, safety, and incremental benefits of atypical antipsychotic medications and submit a report of his findings. The review concluded that no evidence existed for the use of these drugs as first-line treatment for schizophrenia and that these drugs should be used as a last resort.[182] The NPA opposed the recommendations of the report [180] and an Ad Hoc Committee was created to help come to some consensus.

On March 31, 1998 the Schizophrenia Society of Newfoundland and Labrador supplied the Department of Health and Community Services with a document entitled "Unrestricted Access to Atypical Antipsychotic Medications".[179] This document contained the Society's arguments for unrestricted access and was put together with the assistance/advice of psychiatrists, other health care professionals, pharmacists, persons with schizophrenia and their families, and the four drug companies who manufactured the atypical antipsychotic medications (Novartis, Eli Lilly, Janssen Ortho, and Astra Zeneca). The following month, a petition signed by all psychiatrists in the province (with the exception of one), recommended the de-restriction of the atypical neuroleptics.[183] [184]

Between August and September, 1998 there was media coverage of the suicide of a patient with paranoid schizophrenia at a hospital in St. John's which highlighted the pressure to improve access to atypical antipsychotic medications.[185] Various letters to the editor from the SSNL and NPA followed to appeal to the NLPDP to liberalize access to these expensive drugs for the treatment of schizophrenia.[186-188] A second suicide at the same hospital later that year only served to strengthen the argument.

In conclusion, the traditionally repressed interests of those affected by schizophrenia joined forces with the dominant interests of physicians and drug manufacturers to successfully eliminate a restricted reimbursement policy. Since the 'coalition' started its pressure in 1996, they used various tactics to define and portray their policy 'problems'. For example, the successful suicide at a local hospital highlighted the push for a policy change and a public plea to the government via the media ensued. Through the use of strategically crafted causal stories, the government's restricted access policy was noted to be responsible for unnecessary suffering, discrimination (inequity), decreased quality of life and even death. These pressures, plus CCOHTA's economic analyses suggesting that savings on hospital costs would offset the costs of the new medications, finally persuaded the government to change how they reimbursed for these agents.

5.2 The Open Access to Atypical Antipsychotic Medications in Newfoundland and Labrador: Potential Economic Implications of an Unrestricted Policy

Even before the results of the current study were available, there were some potential economic and efficiency implications that could have been foreseen following the introduction of an unrestricted access policy for atypical antipsychotic medications. The following section will begin with an explanation of efficiency in the allocation of health care resources followed by an examination of the potential implications of this type of policy.

5.2.1 Economic Efficiency

Economic efficiency can be described in at least two contexts: technical efficiency and allocative efficiency. Technical efficiency in the production of health implies that the maximum improvement in health status is obtained from a given set of inputs. Allocative efficiency describes the appropriateness of the mix of goods and services produced. This type of efficiency suggests that the best use of scarce resources occurs when they are used to produce the most valued commodities and, therefore, maximize health benefits of the community. Difficulty arises in choosing which health care services should be provided with limited resources. Consequently, the allocation of resources requires that value judgements must be made.[189-192]

The issue of technical efficiency appears to be more easily addressed than those of allocative efficiency with respect to government drug formulary decisions. Measuring technical efficiency with respect to providing coverage for various drugs involves determining the quantity and monetary value of resource inputs used to provide a medication. However, allocative efficiency considerations require additional information such as: the effects of pharmaceuticals on outcomes; equity of outcomes; and, equity of access.[193] Even with this information we are still not assured of appropriately addressing allocative issues. Donaldson and Gerard[194] assert that allocative efficiency can be sacrificed if cost savings are achieved at the expense of quality of care and the subsequent well-being of the patient. In order to achieve a desired health status in the most technical and allocative efficient manner, it is also necessary to measure the relationship between health status and the consumption of pharmaceuticals. Unfortunately, some outcomes are difficult and costly to measure on an ongoing basis.

Technical and allocative efficiency are especially difficult to achieve in the health care sector because resource allocation in many instances is undertaken on an incremental basis. Often programs are provided on a reactive basis to some crisis as opposed to being properly planned.[195]

5.2.2 Implications

When drug program managers make decisions whether and/or how to reimburse for a particular drug, other patient groups must also be considered, as money spent in one therapeutic area means that money is not available to fund drugs in other areas due to the existence of a fixed budget (opportunity costs). For example, the label recommendation at the time the policy change was made was that atypical antipsychotic drugs be limited to refractory or neuroleptic-intolerant schizophrenic patients. The de-restriction of atypicals by the NLPDP resulted in a decentralization of decision-making authority from the Program to all physicians. However, this transfer of decision-making authority from the NLPDP, who incurred the opportunity costs (benefits foregone), to physicians, was not accompanied by a decentralization of financial accountability. As a result, there was a high risk for over-utilization and thus an increase in costs to the drug budget. In essence, the new policy would not prevent the use of atypical antipsychotics for other schizophrenic patients and for those with non-schizophrenic psychosis, even though there was little evidence to support off-label uses at that time. The NLPDP allowed physicians to make all of the clinical decisions, which supports the doctor's freedom to use the medications according to clinical judgement and not be limited by labelled indications.

This highlights the potential danger of using data from cost-effectiveness analyses such as the CCOTHA report[7] for policy development since the total use of a medication or medications may not be limited to a specific disease in a specific population. If data

from these models are used for policy development, it is important that the clinical population, estimated costs, and treatment patterns in the model be similar to the conditions under which the policy is to be implemented.

CHAPTER VI – CONCLUSIONS AND DISCUSSION

6.1 Acute Care Hospital Utilization in Newfoundland

This study used a provincial, multi-centre, observational, retrospective hospital chart review to measure hospital utilization by patients with schizophrenia before and after a change in access to expensive atypical antipsychotic medications. The objective was to assess the relationship between antipsychotic treatment effectiveness and acute care service utilization. This study was unique in its detailed population-based perspective, examining multiple factors influencing outcomes that are important to the health care delivery sector, namely length of stay and re-hospitalization risk. Additionally, this study represents the first time the provincial drug program in Newfoundland and Labrador has evaluated a a policy decision and its impact on the acute care sector.

The results of this study revealed that there were fewer admissions to hospital by schizophrenia sufferers during a time of increased access to and utilization of atypical antipsychotic medications. However, the total number of days in hospital was unchanged because the length of stay per admission increased with no impact on readmission despite similar clinical and sociodemographic characteristics of the patients in each year.

Certain limitations of this study need to be considered. The first concerns the reliance upon existing records which suffer from missing, or less complete information

when compared to data collected prospectively. In many cases, it was assumed that if a particular characteristic was not noted in the chart then that finding was not present (e.g. suicidal on admission). The variable with the greatest proportion of missing data was whether a patient was non-adherent with prescribed antipsychotic medication prior to the current admission. However, we were still able to ascertain information for 92.7% of the patients in the study and thus should not bias the results.

The second limitation has to do with the factors included in this study. It is possible that the variables themselves were not sensitive enough to detect changes in length of stay or readmission risk. For example, the dichotomous variable indicating the presence or absence of thought disorder may not accurately represent the severity of the disorder. Even if all relevant clinical information was abstracted from the chart, there are numerous non-clinical factors that can influence the need for admission to hospital and the length of time spent in hospital. For example, this study did not address physician factors that affect treatment practices, nor did it control for a number of social factors that result in hospital admission and contribute to delays in discharge for persons suffering from schizophrenia. Placement problems, carer stress or an unsupportive living environment may result in the need for hospitalization and extend a person's length of stay. There is evidence in the literature demonstrating that a patient's living situation or lack of support are important predictors of length of stay and frequent hospitalizations.[196-201] Clinicians may be reluctant to discharge patients who live unsupported in the

community. However, after this study was completed, a policy was implemented to encourage physicians to discharge well psychiatric patients.

The newer atypical antipsychotic medications have been linked to increased levels of medications adherence.[82 202-204] However, the rate of adherence measured in this study was not altered with the increased utilization of atypical antipsychotic medications. At the same time, any implications of adherence in this study are difficult to conclude mainly due to the inadequacies in the reporting and measurement of adherence rates. We relied on written documentation of nonadherence in patients' charts and given that self-reporting is frequently inaccurate and biased by a reluctance to admit "improper" behaviour, coupled with the fact that patients suffering from schizophrenia often lack the insight required to adhere to their medication regime. Nonadherence measured in this study may be an underestimate of the actual rate and may partly explain why nonadherence was not found to be a significant predictor of recidivism in the current study.

Even if adherence rates could be accurately measured, the improved adverse effect profiles of atypical antipsychotic medications may only be part of the reason for continuing drug therapy. The literature suggests that there are other powerful predictors contributing to low adherence to schizophrenia treatment: patient-related factors (i.e. substance abuse); family-related factors (i.e. alienation from the patient); disease-related

factors (i.e. lack of insight into the disorder); and healthcare system and community support services (i.e. family therapy, community-based services, and general help with adherence strategies, may have a role in improving outcomes.[205-211] An in-depth review of the programs offered to persons with schizophrenia in Newfoundland and Labrador and the effectiveness of these programs on this population was not undertaken in this project but would have helped to interpret some of our findings and thus provided invaluable information for policymakers.

The current study used hospital readmission as the method of measuring patient outcome associated with antipsychotic therapy but it must be acknowledged that it was not possible to control or identify whether a patient changed drug therapy as an outpatient following hospital discharge. Additionally, while objective and not prone to error, readmission may not be the best measure of outcome for schizophrenia from a patient's or caregiver's perspective. Subtle differences in time to subjective improvements in violent and extreme psychotic behaviour or ability to gain employment may have been more relevant indicators of effectiveness. The perspective of the patient receiving the therapy is essential in determining its value however; this was beyond the scope of this study. If these outcomes had been assessed, differences associated with drug therapy may have been revealed.

The author acknowledges that there was insufficient evidence to support the assumption that all atypical antipsychotic agents could be categorized into one class which assumes that the drugs are equivalent in terms of pharmacological action or efficacy and side effect profile. However, given that the policy regarding reimbursement for these medications did not distinguish between individual drugs in this class, the analysis did not either.

In addition to these limitations, a number of mitigating factors could have potentially been operating in the background. For example, this study was particularly sensitive to changes in the social policy environment since it took place during a period of rapid change in the health care system, particularly in the St. John's region. Differences in hospital admission policies, length of stay for psychiatric patients, housing issues, bed availability, and availability of and demands on community resources influence hospital utilization. However, an examination of the total separations and total days' stay for schizophrenia in this region suggests that the results of this study cannot be explained by changes in the hospital infrastructure (e.g. bed closures). While total separations decreased, the length of stay increased during a time when the number of acute care beds in the mental health program in the St. John's Region decreased by about 7% from 1995/96 to 1999/2000.[212] Additionally, the services provided by the Community Care Program in the St. John's region and accessibility to them remained stable over the course of the study and thus cannot explain any change in hospital days or

readmission rates.[213] Perhaps inpatient savings may have been seen if an improvement in these outpatient programs coincided with improved drug therapies. Alternatively, physician practice may determine the time a patient remains in hospital regardless of patient symptom improvement.

6.2 Utilization of Newer Antipsychotic Medications in Newfoundland

The changes in the use of atypical antipsychotic medications resulting from a policy designed to increase access to these agents was evaluated using a retrospective analysis of administrative claims data between 1995/96 and 2000/01. This study measured only the number of claims reimbursed by the Newfoundland and Labrador Prescription Drug Program (NLPDP) for one of the four atypical antipsychotic medications (clozapine, risperidone, olanzapine, and quetiapine) listed as an open benefit.

The analysis of the NLPDP administrative database revealed that the second generation antipsychotics were accepted into common use and their use grew dramatically between 1995/96 and 2000/01. Concomitantly, the use of antipsychotics as a class grew by 24% while expenditures increased by more than 459%. Total government spending on antipsychotic agents exceeded $4.1 million in 2000/01 and the four atypical agents (clozapine, risperidone, olanzapine, and quetiapine) accounted for 90.4% of this amount. This implies that the introduction of atypical antipsychotic

medications did not merely replace older therapies, but instead expanded the market for use of these agents as a category.

The increase in antipsychotic prescriptions may be due to the fact that schizophrenia has long been neglected, by society and by pharmaceutical companies. For most patients partial remission of symptoms is the best that they can hope for. As a result, patients and their caregivers are always searching for something new. Any new medication, whether substantially better or not, is embraced with great enthusiasm, so it is not surprising that atypical antipsychotics have become synonymous with progress and hope for patients with schizophrenia.

This trend may also reflect an increased use of atypical agents for the treatment and management of other diseases, such as the behavioural disturbances associated with dementia. According to Glick et al.,[214] as of 1999 more than 70% of prescriptions for these drugs are being prescribed for conditions other than schizophrenia, such as major depression, bipolar disorder, posttraumatic stress disorder, obsessive-compulsive disorder, and geriatric agitation. Another study reported that of the 6.3 million antipsychotic prescriptions written by psychiatrists in 2001 in the United States, 43% were for schizophrenia, 22% for bipolar disorder, and 16% for depression. Primary care physicians wrote fewer prescriptions (2.3 million) for antipsychotics, of which 23% were for schizophrenia, 12% for bipolar disorder, and 18% for depression.[215]

At present, there are more small, short, open-label trials and case reports than large, double-blind, placebo-controlled studies of atypical antipsychotics establishing the efficacy of these drugs for the treatment of non-psychotic psychiatric illnesses.[216-221] Additionally, data are sparse on the efficacy of novel antipsychotics in children and adolescents with attention deficit hyperactivity disorder (ADHD), again the few reports in the literature consist mainly of case reports and open, non-controlled trials.[222 223] Atypical agents may be particularly helpful for children, the elderly, or adolescent patients who are especially susceptible to the side effects of medications and whose risk of tardive dyskinesia is high but further controlled studies are necessary.[214]

Unfortunately, the NLPDP database was created primarily for reimbursement purposes and as a result, there was no information regarding the patient, the patients' medical history, symptomology or quality of life. As well, the database was not set up to allow for linkages between the atypical antipsychotic prescription and any other patient-specific information to allow for inferences about how these drugs are being used in clinical practice. As a result, the original study protocol was designed to interview physicians prescribing these medications for their patients in order to collect information on diagnosis, indication for use, and factors influencing the decision to prescribe. However, lack of study participation by prescribing physicians resulted in the inability to measure the appropriateness of prescribing. This is a major limitation of this study. Escalating costs to provincial drug formularies strengthen the necessity of determining

the appropriateness of drug prescriptions. Inappropriate utilization may impose an economic burden on an already constrained health care budget.

Despite efforts to increase response rates: repeated follow-up letters and phone calls; researcher administered questionnaire resulting in very little effort required on behalf of the physician, and a monetary incentive, only 28.5% of the physician sample consented to participate in our study. There is no gold standard for an acceptable response rate and there is no agreed upon standard for a minimum acceptable response rate. Rates as low as 50% have been noted as acceptable for providing unbiased results[224] [225] however, most researchers suggest an 80% rate as being adequate.[226] [227] Given that the collection procedures produced returns from only a minority of the eligible population, the results would not be similar to the population as a whole, and thus would not provide any credible statistics.

6.3 Summary of Results

In conclusion, the implementation of the unrestricted access policy for atypical antipsychotic medications by the Newfoundland and Labrador Prescription Drug Program revealed that there was a significant increase in government expenditure for these drugs, which did not coincide with a decrease in acute care hospital utilization in the province by patients with schizophrenia. Although a decrease in hospital admissions occurred, this was negated by an increase in length of stay.

6.4 Policy Options

1. There was a significant increase in expenditure for the four atypical antipsychotic medications by the NLPDP following the introduction of the unrestricted reimbursement policy which was not accompanied by a decrease in the use of hospital days. However, there was a decrease in the number of hospital admissions from baseline in both of the subsequent study years which may have been attributable to more atypical antipsychotic utilization. Therefore, open access for schizophrenia patients may have been appropriate but restricted access for other indications.

2. Alternative methods to contain pharmaceutical sector costs may be worthy of exploration, such as price management by actively negotiating or setting drug prices or profits, or contracting with industry so that the manufacturer shares the financial risk if higher-than-expected expenditures are incurred.

3. The number of days spent in the community decreased over the study period resulting in an increase in total hospital days. To complement drug therapy programs, those who suffer from a chronic, incurable illness and their families may require access to a full range of community-based services. These services include: housing, vocational rehabilitation programs, supportive employment programs and respite services for caregivers. Availability of these services should be assessed as

it may be necessary to consider improving and/or expanding the mental health programs for patients suffering from schizophrenia which may be contributing to a delay in the discharge of patients. This is particularly important given the current trend away from institutional- to community-based care. Additionally, the way in which physicians practice medicine may contribute to an increased length of stay and a policy which monitors physician practice would ensure the reduction or elimination of inappropriate hospital days in case this factor was contributing to this increase.

4. The rate of adherence with prescribed medication did not change over the course of the study. Models of community care such as assertive community treatment (ACT) and other interventions may be necessary and should be considered. This multidisciplinary team approach provides people with the support, treatment, and rehabilitation services they need to continue living in the community.

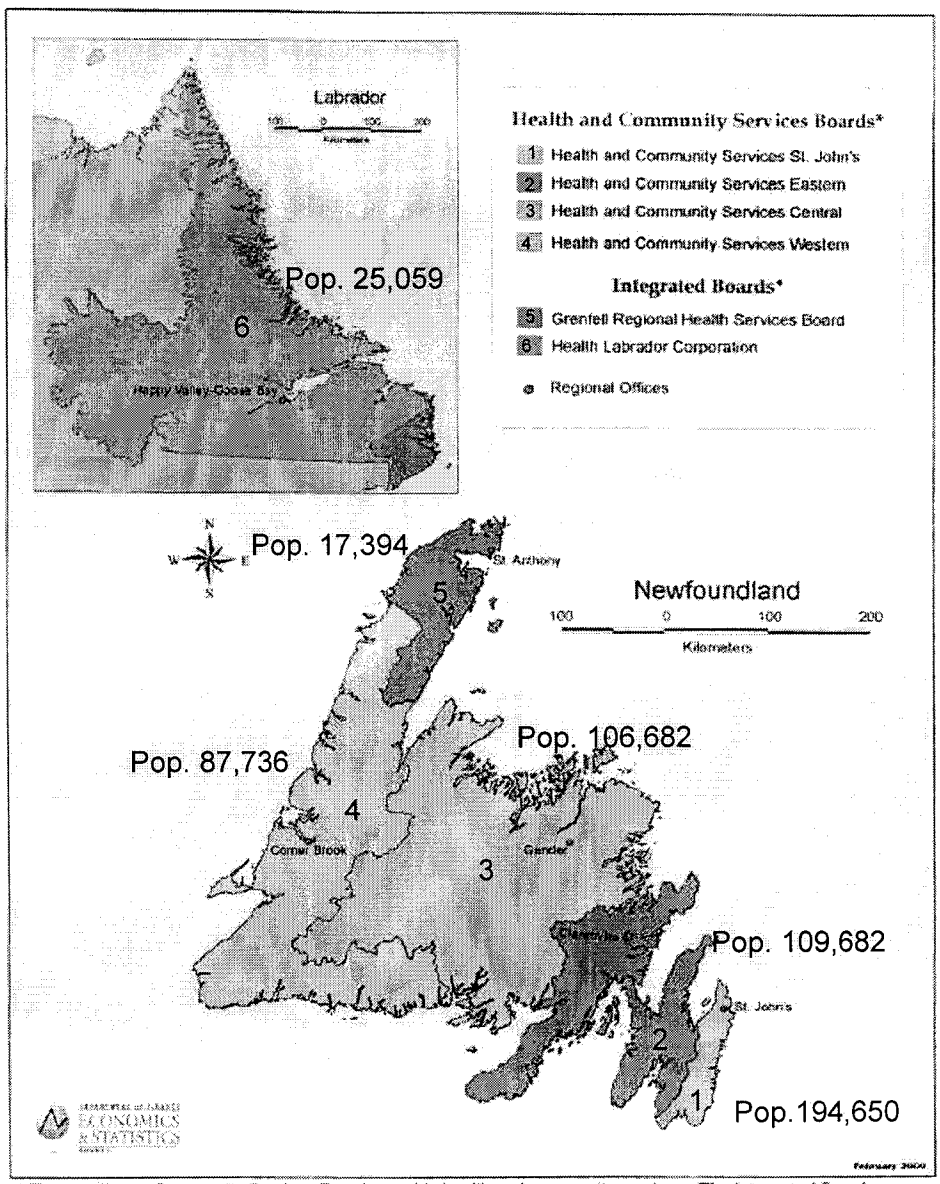
5 The decision to provide atypical antipsychotic medications as an open benefit on the NLPDP formulary was a difficult one. The development of an independent committee, which is at arm's length from government, the pharmaceutical industry and other vested interest groups, to systematically review and synthesize the clinical and economic literature to provide information to decision-makers may be warranted. For example, the National Institute for Clinical Excellence (NICE) in the

UK works on behalf of the National Health Service (NHS) and the people who use it. NICE is an independent organization responsible for providing national guidance on treatments and care using the best available evidence. NICE guidance is developed using the expertise of the NHS and wider healthcare community including NHS staff, healthcare professionals, patients and carers, industry and the academic community.

6. This study highlights the limitations and deficiencies of the current NLPDP claims database, e.g. no indication for use or demographic information, to determine whether there was a benefit associated with any off-label use. The original protocol for the study had planned to identify and interview physicians who prescribed atypical antipsychotic medications to their patients for the first time in 2000 to obtain patient specific information and determine the indication for use/appropriateness. Unfortunately, we were unable to get enough cooperation from the physicians after the study was initiated and this portion of the study was abandoned. The development of an electronic medical record with the ability to link with various other health and non-health care sectors would allow for the accurate recording of how drugs are being used and the impact of their use. This would strengthen the evidence with which policymakers can make rational decisions.

CHAPTER VII APPENDICES

Appendix. A. Health & Community Services Regions/Integrated Boards boundaries and corresponding demographic profiles



* The Health and Community Services Boards provide health and community services. The Integrated Boards provide institutional, and health and community services.

Appendix B.
Characteristics of comparative studies of clozapine with conventional antipsychotic medications

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Kane, J 1988[25]	Double blind, randomized	Treatment resistant schizophrenia (DSM-III) (268)	BPRS total score ≥ 45 & CGI ≥ 4 on 2 or 4 BPRS items of: conceptual disorganization; suspiciousness; hallucinating behaviour; unusual thought content	Inpatient	6	CLZ: mean 600 mg/day (500-900) vs. CHL: mean 1200 mg/day (1000-1800) + BENZ: 6 mg/day	BPRS; CGI; NOSIE	Statistically significant improvement in CGI; BPRS total score; improvement in ≥ 2 of 4 BPRS items; ≥ 20% reduction in BPRS total + CGI ≤ 3 or BPRS total ≤ 35	CLZ>CHL : BPRS, CGI, & NOSIE	US
Claghorn, 1987[39]	Double blind, randomized	Schizophrenia (DSM-II) (151)	Current hospitalization ≤ 6 months; score of 4 on ≥ 3 or the 6 BPRS items: emotional withdrawal; conceptual disorganization; hostility; suspiciousness; hallucinatory behaviour; unusual thought content	Inpatient	8	CLZ: mean 400 mg/day (150-900 mg/day) vs. CHL: mean 800 mg/day (300-1,800 mg/day)	BPRS; CGI; NOSIE	Changes in scores from baseline	CLZ>CHL: BPRS 5 items; total score; CGI and some NOSIE items	US

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Hong, C 1997[40]	Double blind, randomized	Treatment refractory schizophrenia (DSM-IV) (40)	Persistent severe psychotic symptoms (≥ 5 on the BPRS items: emotional withdrawal; conceptual disorganization; suspiciousness; hallucinatory behaviour; unusual thought content) for ≥ 6 months with adequate neuroleptics treatment with ≥ 2 classes	Inpatient	12	CLZ: mean 543 mg/day (100-900 mg/day) vs. CHL: mean 1,163 mg/day (200-1,800 mg/day)	BPRS; CGI; PANSS	≥ 20% reduction in BPRS total score	CLZ>CHL	China
Essock 1996[41]	Open label randomized	Chart diagnosis of schizophrenia or schizoaffective disorder (treatment refractory) (227)	Failure to respond to 2 adequate trials of ≥ alternative neuroleptics; 4 months hospitalization in current episode and 2 years in previous 5 years	Inpatient	104	CLZ: mean 496 mg/day vs. alternative antipsychotic: mean 1,386 mg/day CHL equivalent	BPRS	≥ 20% reduction in total BPRS and either a total BPRS ≤ 17 OR ≥ 20% reduction in BPRS psychotic items subscale (thought disturbance)	CLZ=conventional agents	US

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Pickar, D 1992[42]	Crossover, placebo-controlled, double-blind, randomized	Treatment resistant schizophrenia or schizoaffective illness (DSM-III-R) (21)	Drug intolerance (significant TD or EPS); history of being refractory to treatment (lack of satisfactory clinical response to ≥ 2 different antipsychotic drugs	Inpatient	FLU≥ 4 weeks; CLZ ≥ 3 weeks	CLZ: mean 542.9 mg/day vs. FLU 28.9 mg/day	BPRS; Bunney-Hamburg Global Psychosis Rating	≥20% reduction in BPRS; and either BPRS rating <36 or a Bunney-Hamburg Global Psychosis Rating ≤ 6	CLZ>FLU: BPRS total	US
Rosenheck R 1997[43]	Double blind, randomized	Schizophrenia (DSM-III-R); (423)	Refractoriness; severe symptoms; serious social dysfunction in the last 2 years	Inpatient	52	CLZ: 100-900 mg/day vs. HAL: 5-30 mg/day & 2-10 mg/day of BENZ	PANSS	≥ 20% reduction in PANSS	CLZ=HAL: ≥ 20% reduction in PANSS:	US
Breier, A 1994[44]	Double blind, randomized	Chronic schizophrenia (DSM-III-R) (39)	Partial response to neuroleptics; ≥ 8 on positive symptom score of BPRS on 4 items or ≥ 4 on any 1 of the items; ≥ 20 on SANS or ≥ 2 on at least 1 global item on SANS	Outpatient	10	CLZ: 200-600 mg/day vs. HAL: 10-30 mg/day	BPRS sum of the 4 positive items; SANS	≥ 20% reduction in BPRS positive symptom scores and BPRS positive symptoms score < 8 at week 10	CLZ>HAL: BPRS positive symptoms; SANS	US

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Post Policy Period										
Kane, J 2001[45]	Double blind, randomized	Schizophrenia or schizoaffective disorder (DSM-III-R) (71)	Treatment failure in ≥ 2 trials of conventionals for ≥ 6 weeks; moderate rating on ≥1 BPRS item	Inpatient & outpatient	29	CLZ: target dose 500 mg/day (range: 200-800 mg/day) vs. HAL: target dose 10 mg/day (range: 4-16 mg/day)	BPRS; SANS; CGI	Time to treatment discontinuation due to lack of efficacy; time to 20% improvement in 4 psychotic symptoms	CLZ>HAL: time to discontinuation & 20% improvement in 4 psychotic symptoms	US

Abbreviations: BENZ=benztropine mesylate, BPRS= Brief Psychiatric Rating Scale, CGI= Clinical Global Impression scale, CHL=chlorpromazine; CLZ=clozapine; DSM-II, III, IV-R=various editions of the diagnostic and statistical manual of diseases; EPS = extrapyramidal symptoms, FLU=fluphenazine; HAL=haloperidol; NOSIE= nurses observational scale of inpatient evaluation; PANSS= Positive and Negative Syndrome Scale, SANS=Scale for the Assessment of Negative Symptoms; TD = tardive dyskinesia;

Appendix C.
Characteristics of comparative studies of risperidone with conventional antipsychotic medications

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Claus 1992[46]	Double blind, randomized	Refractory schizophrenia (DSM-III-R) (44)	Chronic schizophrenia with residual symptoms despite optimized conventional antipsychotic therapy	Inpatient	12	RISP: 2-20 mg/day vs. HAL 2-10 mg/day	PANSS; SADS-C; CGI; NOSIE	≥ 20% reduction in total PANSS score from baseline	RISP 12>HAL 10: PANSS total; PANSS negative and SADS-C, NOSIE	Belgium
Peuskens 1995[23]	Double blind, randomized	Chronic schizophrenia (DSM-III-R) (1,362)	>60<120 on PANSS	inpatient	8	RISP: 1, 4, 8, 12, & 16 mg/day vs. HAL: 10 mg/day	PANSS; CGI	≥ 20% reduction in PANSS total score	RISP=HAL: PANSS Optimal RISP doses: 4 & 8 mg/day	15 countries
Moller 1997[47]	Double blind, randomized	Chronic schizophrenia (DSM-III-R) (169)	>60<120 on PANSS	Inpatient	8	RISP: 1, 4, 8, 12, & 16 mg/day vs. HAL: 10 mg/day	PANSS; CGI; BPRS	≥ 20% reduction in PANSS total score or BPRS score; ≥ 20% reduction in PANSS total score plus CGI ≤ 3	RISP=HAL: PANSS total; BPRS total; RISP 4 mg/day > HAL: CGI	Germany, Austria, Switzer-land

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Min 1993[48]	Double-blind, randomized	Chronic schizophrenia (DSM-III-R) (35)	>60<120 on PANSS	Inpatient and outpatient	8	RISP: 5-10 mg/day vs. HAL: 5-10 mg/day	PANSS; BPRS; CGI	≥ 20% reduction in PANSS	RISP=HAL	Korea
Marder 1994[22]	Double blind, randomized	Schizophrenia (DSM-III-R) (388)	>60<120 on PANSS	Inpatient	8	RISP: 2, 6, 10, 16 mg/day vs. HAL: 20 mg/day	PANSS; CGI; ESRS	≥ 20% reduction in total PANSS score from baseline	RISP 6 & 16 mg>HAL 20 mg: PANSS	US
Chouinard 1993[49]	Double blind, randomized	Chronic schizophrenia (DSM-III-R) (135)	>60<120 on PANSS	Inpatient	8	RISP: 2, 6, 10, & 16mg/day vs. HAL: 20mg/day vs. PL	PANSS; CGI; PANSS-GPS; BPRS; Global Evaluations	≥ 20% reduction in PANSS total score	RISP (6mg/day) > HAL on total PANSS; PANSS-GPS; BPRS; RISP=HAL: ≥ 20% reduction in PANSS total score	Canada

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Ceskova 1993[50]	Double-blind, randomized	Schizophrenia or schizoaffective disorder (ICD-9) (62)	None indicated	Inpatient	8	RISP: 2-20 mg/day vs. HAL: 2-10 mg/day	BPRS	BPRS total: very good remission (50-100% relative change from baseline) or partial remission (25-40% relative change)	RISP=HAL	Czech Republic
Borison 1992[51]	Double blind, randomized	Schizophrenia (DSM-III-R) (36)	≥ 30 on BPRS; ≥ 2 of BPRS 4 positive symptom items; CGI rating of moderate or greater illness	Not stated	6	RISP: 2-10 mg/day vs. HAL 4-20 mg/day vs. PL	BPRS; CGI	≥ 20% reduction in total BPRS score from baseline	RISP=HAL: BPRS	US
Blin 1996[52]	Double blind, randomized	Acute exacerbation of schizophrenia (DSM-III-R) (62)	Psychotic anxiety score (PAS) ≥ 34	Inpatient	4	RISP: mean 7.4 mg/day vs. HAL: mean 7.6 mg/day vs. METH: mean100 mg/day	PANSS; BPRS; CGI	≥ 20% reduction in PANSS total score	RISP=HAL: ≥ 20% reduction in PANSS total score; RISP>HAL & METH: total PANSS; CGI from baseline to end point	France

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Hoyberg 1993[53]	Double blind, randomized	Chronic schizophrenia with acute exacerbation (DSM-III-R) (107)	None other than diagnosis	Not stated	8	RISP 5-15 mg/day vs. PER 16-48 mg/day	PANSS; BPRS; CGI	Mean change PANSS from baseline	PANSS total from baseline: RISP=PER; CGI: RISP=PER; ≥ 20% reduction in BPRS: RIS>PER	Denmark and Norway
Huttunen 1995[54]	double blind, randomized	Chronic or subchronic schizophrenia or schizophreniform disorder (DSM-III-R) (98)	None other than diagnosis	Not stated	6	RISP 4-29 mg/day, mean, 8 mg vs. ZUC 20-100 mg/day, mean, 38 mg	PANSS; CGI	Mean change in PANSS total score from baseline and ≥ 20% reduction in PANSS total score	RISP=ZUC	Finland
Post Policy Period										
Rabinowitz 2001[55]	Post hoc subanalysis of double blind, randomized	Chronic schizophrenia (DSM-III-R) (453)	>60<120 on PANSS used data from Peuskens[23]	Not indicated	8	RISP: 4 mg/day; vs. HAL: 10 mg/day	PANSS total; CGI-S	Difference in initial change from baseline to first week on treatment with study medication and during the entire study	RISP>HAL at 1 week: PANSS total	15 countries

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Rabinowitz 2001[228]	Post hoc sub-analysis of double blind, randomized	Chronic schizophrenia (DSM-III-R) (144)	>60<120 on PANSS used data from Peuskens[23]	Not indicated	8	RISP: 4 mg/day; vs. HAL: 10 mg/day	PANSS total; CGI-S	Mean change in PANSS and CGI-S from baseline between the 2 groups	RISP>HAL: PANSS total; PANSS-GPS; BPRS activity and total BPRS	15 countries

Abbreviations: BPRS=brief psychiatric rating scale, CGI=clinical global impression, CGI-S=clinical global impression-severity of illness, DSM-III-R=third edition of the diagnostic and statistical manual of diseases, ESRS= extrapyramidal symptom rating scale, HAL=haloperidol, ICD-9=international classification of diseases 9th edition, METH=methotrimeprazine, NOSIE= nurses observational scale of inpatient evaluation, PANSS=positive and negative symptoms scale, PANSS-GPS=Positive and Negative Symptom Scale for Schizophrenia-General Psychopathology, PAS= Psychotic Anxiety Scale, PER=perphenazine, PL=placebo, RISP=risperidone, SADS-C=schedule for affective disorders and schizophrenia-change version, ZUC=zuclopenthixol.

Appendix D.
Characteristics of comparative studies of olanzapine with conventional antipsychotic medications

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Beasley 1996[58]	Double blind, randomized	Schizophrenia (DSM-III-R) (335)	Acute exacerbation BPRS ≥24; CGI ≥ 4	Inpatient	6	OLZ: 5±2.5 mg/day; 10±2.5 mg/day; 15±2.5 mg/day vs. HAL: 15±5 mg/day vs. PL	Mean change from baseline to endpoint in: BPRS; SANS; CGI-S	≥40% decrease in BPRS-total score OR an endpoint BPRS-total score ≤ 18	OLZ>HAL: SANS; BPRS neg. score	US and Canada
Beasley 1997[59]	Double blind, randomized	Schizophrenia (DSM-III-R) (431)	Acute exacerbation BPRS ≥24; CGI ≥ 4	Inpatient	6	OLZ: 5±2.5 mg/day; 10±2.5 mg/day; 15±2.5 mg/day vs. OLZ 1.0 mg/day vs. HAL:15±5 mg/day	BPRS; CGI; PANSS	≥40% decrease in BPRS-total score OR an endpoint BPRS-total score ≤ 18	OLZ=HAL: BPRS; PANSS	Europe, South Africa, Israel, and Australia
Tollefson 1997[60]	Double blind, randomized	Schizophrenia, schizophreniform, schizoaffective, disorder (DSM-III-R) (1,996)	BPRS ≥18 and/or intolerant of current antipsychotic mediations (excluding HAL)	Inpatient & outpatient	6	OLZ: 5-20 mg/day vs. HAL: 5-20 mg/day	Mean change from baseline to endpoint in total score in BPRS	≥40% decrease in BPRS-total score OR an endpoint BPRS-total score ≤ 18	OLZ>HAL: BPRS, PANSS-N, MADRS, CGI, QLS	Europe, US and Canada

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Hamilton 1998[61]	Double-blind, randomized	Schizophrenia (DSM-III-R) (95)	Treatment responders from acute phase (6-week) Beasley[58] and discharged from hospital by 4 weeks after acute phase was over	outpatient	24	OLZ: 5±2.5 mg/day; 10±2.5 mg/day; 15±2.5 mg/day vs. HAL: 15±5 mg/day vs. PL	BPRS; SANS; CGI; QLS	Change from baseline to week 24 for BPRS; SANS; CGI; & QLS scores	OLZ=HAL: BPRS and CGI; OLZ: 15±2.5 mg/day>HAL: SANS; OLZ=HAL: QLS	US and Canada
Tran 1998[62]	Pooled data from 3 RCTs[58-60]	Schizophrenia, schizophreniform, or schizoaffective;	Responded to acute therapy (BPRS total score decreased ≥40% from baseline or was ≤18) Beasley, Tollefson et al. 1996; Beasley, Hamilton et al. 1997)	Outpatient	46	Pooled data from 3 RCTs: Study 1[58] OLZ: 5±2.5 mg/day; 10±2.5 mg/day; 15±2.5 mg/day vs. HAL: 15±5 mg/day vs. PL; Study 2[59]: OLZ: 5±2.5 mg/day; 10±2.5 mg/day; 15±2.5 mg/day vs. OLZ: 1.0 mg/day vs. HAL: 15±5	Relapse	Hospital-ization for psycho-pathology	OLZ: less relapse (P=0.034)	US, Canada, Europe, South Africa, Israel, and Australia

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
						mg/day; Study 3[60]: OLZ: 5-20 mg/day vs. HAL: 5-20 mg/day				
Conley 1998[63]	Double-blind randomized	Schizophrenia (DSM-III-R) (84)	Treatment resistance: ≥2 periods of treatment in preceding 5 years with ≥1000 mg/day of CHL equivalent for 6 weeks (excluding HAL); no period of good functioning within 5 years; BPRS≥45; CGI≥4; ≥4 on BPRS psychosis items.	Inpatient	8	OLZ: 25mg/day vs. CHL: 1200 mg/day + BENZ: 4mg/day	BPRS; CGI; SANS	≥20% reduction in total BPRS compared to baseline; CGI score ≤ 3 or BPRS score ≤35; total BPRS score; score on 4 BPRS items; SANS	OLZ=CHL: BPRS total; BPRS 4 items; SANS; CGI; BPRS subscale score	US
Post Policy Period										
Breier 1999[64]	Double-blind randomized	Schizophrenia; schizophreniform; schizoaffective disorder (DSM-III-R) (526)	Subpopulation of non-responders from Tollefson[60]	Inpatient and outpatient	6	OLZ: 5-20 mg/day vs. HAL: 5-20 mg/day	BPRS:PANSS MADRS	≥ 20% increase in BPRS total score and an endpoint BPRS score ≤ 24.	OLZ>HAL: PANSS-N; MADRS total score (LOCF); OLZ> HAL: BPRS total; PANSS total; PANSS-P; PANSS-N; MADRS total	US and Europe

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
									(completers); OLZ>HAL: ≥ 20% increase in BPRS total score and an endpoint BPRS score ≤ 24. (LOCF); OLZ=HAL: ≥ 20% increase in BPRS total score and an endpoint BPRS score ≤ 24 (completers)	

Abbreviations: BENZ=benztropine, BPRS=brief psychiatric rating scale, CGI=clinical global impression, CGI-S=clinical global impression-severity of illness, CHL=chlorpromazine; DSM-III-R=third edition of the diagnostic and statistical manual of diseases, HAL=haloperidol; LOCF=last observation carried forward, MADRS=Montgomery-Asberg Depression Rating Scale, OLZ=olanzapine; PANSS= Positive and Negative Symptom Scale for Schizophrenia, PANSS-N=Positive and Negative Symptom Scale for Schizophrenia-Negative Symptoms; PANSS-P=Positive and Negative Symptom Scale for Schizophrenia-Positive; Symptoms; PL=placebo; QLS= quality of life scale; RCTs=randomized clinical trials, SANS=Scale for the Assessment of Negative Symptoms.

Appendix E.
Characteristics of comparative studies of quetiapine with conventional antipsychotic medications

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
Arvanitis, LA 1997[66]	Double blind, randomized	Acute exacerbation of chronic or sub chronic schizophrenia (DSM-III-R) (361)	≥ 27 on BPRS; score of 3 on ≥ 2 BPRS positive symptom items; ≥ 4 CGI	Inpatient	6	QTP: 75, 150, 300, 600, 750 mg/day vs. HAL: 12 mg/day vs. PL	BPRS total; CGI; SANS	≥ 30% reduction in BPRS total score at any time	QTP 75-750=HAL: BPRS, CGI, SANS	US and Canada
Peuskens 1997[67]	Double-blind randomized	Acute exacerbation of chronic or sub chronic schizophrenia, or schizophreniform disorder (DSM-III-R) (201)	≥ 27 on BPRS; ≥ 3 on 2 or more BPRS positive symptoms; ≥ 4 CGI	Inpatient	6	QTP: ≤ 750 mg/day vs. CHL: ≤ 750 mg/day	BPRS total score; CGI	BPRS total score: CGI; BPRS ≥ 50% reduction in BPRS total score from baseline	QTP=CHL: BPRS total; QTP>CHL: 50% reduction on BPRS from baseline	Belgium , UK, Spain, France and South Aftica
Post Policy Period										
Copolov 2000[68]	Double blind, randomized	Acute exacerbation of chronic or sub chronic schizophrenia (DSM-III-R) (448)	≥ 60 on PANSS; score of 4 on ≥2 PANSS items; ≥4 CGI	Inpatient	6	QTP: mean 455 mg/day vs. HAL: mean 8 mg/day	PANSS; CGI	PANSS total; ≥ 30% PANSS total	QTP=HAL: PANSS total; ≥ 30% PANSS total	14 countries
Emsley 2000[69]	Double blind, randomized	Schizophrenia (catatonic, disorganized, paranoid or	Persistent positive symptoms while on therapeutic doses of antipsychotics; ≥ 15	Outpatient	8	QTP: 600 mg/day vs. HAL: 20 mg/day	PANSS; CGI	Mean PANSS score after 4 weeks and 8	QTP=HAL: PANSS	UK and South Africa`

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
		undifferentiated type (DSM-IV) (288)	on PANSS; score of ≥ 4 on ≥ 1 BPRS positive symptom items; ≥ 3 on CGI					weeks; ≥ 20% reduction in PANSS total score from baseline; CGI ≤ 3 at week 8		

Abbreviations: BPRS=brief psychiatric rating scale, CGI=clinical global impression, CHL=chlorpromazine, DSM-III, IV-R=various editions of the diagnostic and statistical manual of diseases, HAL=haloperidol, PANSS=positive and negative symptoms scale, PL=placebo, QTP=quetiapine, SANS=Scale for the Assessment of Negative Symptoms.

Appendix F.
Characteristics of head-to-head comparisons of atypical antipsychotic medications

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
CLOZAPINE VS. RISPERIDONE										
Bondolfi 1998[70]	Double blind, randomized	Chronic schizophrenia (DSM-III-R) (86)	Resistant to or intolerant to ≥ 2 different classes of antipsychotics; >60<120 on PANSS	Inpatient	8	RISP : mean 6.4 mg/day (3-10 mg/day) vs. CLZ: mean 291.2 mg/day (150-400 mg/day)	PANSS; CGI	≥ 20% reduction in PANSS total	RISP=CLZ: PANSS total; CGI; ≥ reduction in PANSS total	Switzer-land and France
Post Policy Period										
Breier 1999[71]	Double-blind, randomized	Chronic schizophrenia (DSM-IV) (29)	Partial response to traditional antipsychotics: ≥ 8 for 4 BPRS positive symptom items; ≥ 20 on SANS	Not indicated	6	RISP: mean 5.9 mg/day (2-9 mg/day) vs. CLZ: mean 403.6 mg/day (200-600 mg/day)	4 positive symptom items on BPRS; BPRS withdrawal/retardation and anxiety/depression factor scores; BPRS total score; SANS total score; HAM-D	Efficacy compared at end of study with baseline; ≥ 20% reduction in BPRS total	CLZ>RISP: BPRS positive symptoms; RISP=CLZ: SANS score; BPRS withdrawal/ retardation score; BPRS anxiety/depression score; HAM-D; ≥ 20% reduction in BPRS total	US
Azorin 2001[72]	Double blind, randomized	Schizophrenia (DSM-IV)	≥ 4 on CGI; ≥ 45 on BPRS total score;	Inpatient and	12	RISP: 2-15 mg/day	BPRS; CGI; PANSS, PAS;	Magnitude of improve-	CLZ>RISP: BPRS; CGI	France and

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
		(273)	and ≥ 4 on 2 or more of the 4 core symptoms (unusual thought, hallucinations, conceptual disorganization, suspiciousness) Poor previous treatment response: continuous treatment in preceding 6 months without significant improvement; at least 1 unsuccessful trial of antipsychotic for at least 6 weeks; no period of good functioning for at least 2 years with use of 2 antipsychotics in 2 chemical classes (or 5 years despite 3 antipsychotic trials)	outpatient		vs. CLZ: 200-900 mg/day	Psychotic Depression Scale; Calgary Depression Scale	ment in BPRS and CGI scores; improve-ment in BPRS total score of 20%, 30%, 40%, or 50%; ≥ 20% reduction in BPRS total score and either post-treatment CGI ≤ 3 or post-treatment BPRS total score ≤ 35	scores ; PANSS ; Calgary Depression Scale; PAS	Canada
RISPERIDONE VS. OLANZAPINE										
Tran 1997[73]	Double-blind randomized	Schizophrenia, schizophreniform disorder or schizoaffective	BPRS ≥ 42; at least minimally responsive to 3 antipsychotics	Inpatient & outpatient	28	OLZ: 10-20 mg/day vs. RISP: 4-12 mg/day	PANSS total; PANSS subscales; PANSS	Mean change in PANSS total score; ≥ 40%	OLZ>RISP on SANS; ≥ 40% decrease in	Belgium France; Ger-many;

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
		disorder (DSM-IV) (339)					depression; BPRS; CGI; SANS	decrease in PANSS total score	PANSS total score	The Nether-lands; Spain; UK; South Africa, and US
Post Policy Period										
Conley 2001[74]	Double-blind randomized	Schizophrenia or schizoaffective disorder (DSM-IV) (377)	>60<120: PANSS	Inpatient (hospital-ized ≤ 4 weeks) & outpatient	8	OLZ: 5-20 mg/day vs. RISP: 2-6 mg/day	PANSS total; PANSS 5 factors; CGI	≥ 20% reduction PANSS total	OLZ=RISP: PANSS total; ≥ 20% reduction PANSS total; RISP>OLZ: PANSS scale positive and anxiety/depr ession factors	US
Ho 1999[75]	Open label, non-randomized	Schizophrenia (DSM-IV) (42)	Not receiving neuroleptic treatment	Inpatient	24	OLZ (5-20 mg/day, mean=12.4 mg/day) vs. RISP (2-6 mg/daymg/da y, mean=4.8 mg/day)	SANS; SAPS; BPRS; quality of life measures	None stated	RISP>OLZ: reduction of psychotic symptoms	US

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
QUETIAPINE VS. RISPERIDONE										
Post Policy Period										
Mullen 2001[76]	Open-label, randomized	Schizophrenia; schizophreniform disorder; schizoaffective disorder; delusional disorder, major depressive disorder with psychotic features, dementia of the Alzheimer's type with psychotic symptoms, vascular dementia, or dementia due to substance abuse (DSM-IV) (728)	Suboptimal efficacy of previous antipsychotic agents or patient intolerance of other medications	Outpatient	16	QTP: mean 253.9 mg/day vs. RISP: mean 4.4 mg/day	CGI; PANSS total; HAM-D	CGI; PANSS total; HAM-D differences from baseline	QTP=RISP: PANSS; CGI QTP>RISP: HAM-D	US

Reference	Design	Diagnosis (# subjects)	Eligibility criteria	Setting	Duration (weeks)	Interventions	Assessment of efficacy	Response criteria	Results	Country
CLOZAPINE VS. OLANZAPINE VS. RISPERIDONE										
Post Policy Period										
Volavka 2002[77]	Double-blind, randomized	Chronic schizophrenia or schizoaffective disorder (DSM-IV) (157)	Suboptimal response to previous treatment; >60 on PANSS	Inpatient	14	CLZ: mean 526.6 mg/day vs. OLZ: mean 30.4 mg/day vs. RISP: mean 11.6 mg/day vs. HAL: mean 25.7 mg/day	PANSS	Change in PANSS at endpoint	CLZ & OLZ>HAL: PANSS total score	US

Abbreviations: BPRS=brief psychiatric rating scale, CGI=clinical global impression, CLZ=clozapine; DSM-III, IV-R=various editions of the diagnostic and statistical manual of diseases, HAL=haloperidol, HAM-D=Hamilton Rating Scale for Depression, OLZ=olanzapine, PANSS=positive and negative symptoms scale, PAS=Psychotic Anxiety Scale, QTP=quetiapine, RISP=risperidone, SANS=Scale for the Assessment of Negative Symptoms; SAPS=Scale for the Assessment of Positive Symptoms;

Appendix G.
Cost comparisons of full economic evaluations of atypical antipsychotic medications

Reference	Population (n)	Country (currency & year)	Perspective	Study Design	Alternatives considered	Cost elements	Effectiveness measure	Nature of study[i]	Time horizon	Discount rate	Results
Chouinard 1997[87]	Chronic schizophrenia (135)	Canada using CAD ($) (year of values used not stated)	Drug payer	8 week, double blind, placebo-control-led	RISP (6 mg/day) vs. HAL (20 mg/day)	Cost of medicat-ions	QALY	CUA	lifetime	None stated	CAD$24,259/ QALY for RISP vs. HAL
Oh 1997[7]	Hospitalized, treatment-resistant schizophrenia (157)	Canada year of medicatio ns using 1995 CAD ($) values; doctor visits and lab test using 1992 CAD ($) values; communi-ty care using 1996 CAD ($) values; hospital-ization using	Government payer	Meta analysis results from 3 studies	CLZ vs. CHL and HAL	Costs of medica-tions; physician visits and lab tests; commun-ity care (nursing, social work, case manager, residential care); hospital-ization	QALY	CUA	1 year and lifetime	5%	Cost savings of CAD$52,561/ QALY

Reference	Population (n)	Country (currency & year)	Perspective	Study Design	Alternatives considered	Cost elements	Effectiveness measure	Nature of study[i]	Time horizon	Discount rate	Results
		1995 CAD ($) values									
Oh 1997[7]	Hospitalized, chronic schizophrenia (645)	Canada Year of medicat-ions using 1995 CAD ($) values; doctor visits and lab test in 1992 CAD ($) values; commun-ity care in 1996 CAD ($) values; hospital-ization in 1995 CAD ($)	Government payer	Meta analysis results from 8 studies	RISP vs. HAL, HAL deconate, FLU deconate	Costs of medicat-ions; physician visits and lab tests; commun-ity care (nursing, social work, case manager, residential care); hospital-ization	QALY	CUA	1 year and lifetime	5%	Cost savings of CAD$11,713/ QALY
Tunis 1999[90]	Inpatient and outpatient Schizo-phrenia; schizo-phreniform disorder; schizo-affective disorder	US, UK, Canada using 1995 USD ($) values	Health system payer	Double-blind Random-ized clinical trial	OLZ vs. HAL	Hospital-ization costs	Functional status (SF-36)	CEA	1 year	N/A	Savings of $US1,632.50/ unit improve-ment in SF-36 physical & functioning score ; savings of $US5,654.74/ unit improve-ment in mental

Reference	Population (n)	Country (currency & year)	Perspective	Study Design	Alternatives considered	Cost elements	Effectiveness measure	Nature of study[i]	Time horizon	Discount rate	Results
	(DSM-III-R) (812)										& functioning composite
Davies 1998[88]	Chronic schizophrenia (DSM-III-R)	Australia AU ($) (year of values used not stated)	Payer	Clinical decision analytic model	RISP vs. HAL	Hospital-ization ; outpatient ; drugs ; health care pro-fessionals ; govern-ment subsidized hostel accomm-odation	Response ; partial response ; increased dose response	CEA	2 years	N/A	Cost savings of AU$11,395/ favorable outcome for RISP than HAL over the 2-year period
Essock 2000[91]	Chart diagnosis of schizophrenia or schizo-affective disorder and failure to respond to adequate trials of ≥ 2 different anti-psychotics; hospital-ization of ≥ 4 months; total hospital-	US using 1993 US ($) values	Department of mental health; society; state of Connecticut	Open-label, random-ized, con-trolled study	CLZ vs. Conventional agent	Drugs ; hospital-ization ; lab ; nursing home ; outpatient and residential care ; ER ; product-ivity	Change in BPRS total ; quality of life ; EPS ; hours in special observation ; occurrence of problematic behaviour	CEA	2 years	N/A	CLZ increased cost $1,112 in year 1 but $7,149 less cost in year 2 than patients in usual care

Reference	Population (n)	Country (currency & year)	Perspective	Study Design	Alternatives considered	Cost elements	Effectiveness measure	Nature of study[i]	Time horizon	Discount rate	Results
	ization time of ≥ 2/5 preceding yrs; no medical contra-indication to CLZ (227)										
Schiller 1999[92]	Outpatient schizophrenia or schizo-affective disorder (DSM-III-R) (112)	US Mental heatlh services using 1994 USD ($) values ; lab in 1995 USD ($) values; medicatio ns using 1995 USD ($) values	Payer	Before/ after, retro-spective, quasi-experime ntal, matched-comp-arison	RISP vs. Standard therapy	Medi-cations ; outpatient services ; acute hospital services ; lab	GAF	CEA	1 year	N/A	RISP=standard therapy with cost increasing of US$370/month in RISP over standard therapy ; No difference in GAF between the two groups
Guest 1996[93]	Chronic schizophrenia (DSM-III-R) PANSS>60< 120 (31)	UK using 1993/94 GBP (£) values	Payer (NHS)	Before/ after design	RISP vs. HAL	Hospital-ization, residential accommo dation ; medi-cation costs ;	PANSS ; CGI	CEA	1 year (n=31) and 2 year (n=18)	N/A	Total mean cost savings of £1,188/pt in year 1 ; Total mean cost savings of £7,426 in year 2

Reference	Population (n)	Country (currency & year)	Perspective	Study Design	Alternatives considered	Cost elements	Effectiveness measure	Nature of study[i]	Time horizon	Discount rate	Results
						outpatient					
Galvin 1999[95]	Outpatient psychotic disorder (n=37, 34/37 with schizo-phrenia)	US using 1997 USD ($) values	Payer	Retro-spective, uncon-trolled, open, non-random-ized, within subjects	CLZ & RISP vs. Conventional	Medi-cations ; lab ; hospital services ; mental health clinic ; transit-ional living placement	Severity of general symptoms & side effects	CEA	1 year	N/A	Cost savings $3,000/pt/yr with atypicals
Almond 2000[96]	Simulated population	UK using 1996/97 GBP (£) values	Payer	Markov model	OLZ & RISP vs. HAL	Medi-cations ; hospital-izaitons ; supported accommo-dation	BPRS & relapse	CEA	5 years	6%	3 therapies were cost neutral
Hamilton 1999[97]	Inpatient and outpatient schizophrenia ; schizo-phreniform disorder; schizo-affective disorder (DSM-III-R) (817)	US using 1995 USD ($) values	Health system payer	Double-blind Random-ized clinical trial	OLZ vs. HAL	Hospital-izations; ER visits; day hospital; outpatient visits; home visits; medi-cations	N/A	CA	6 weeks (acute phase) & 46 weeks (main-tenance phase)	N/A	Cost savings of $US388 for OLZ vs. HAL in acute phase; Cost savings of $US636 for OLZ vs. HAL in maintenance phase

Reference	Population (n)	Country (currency & year)	Perspective	Study Design	Alternatives considered	Cost elements	Effectiveness measure	Nature of study[i]	Time horizon	Discount rate	Results
Albright 1996[98]	Schizophrenia (ICD-9) (146)	Canada using CAD ($) (year of values used not stated)	Payer	Retro-spective cohort data from 5 sources to see change in resource use before and after risperi-done use	RISP	Medi-cations ; physician ; mental health ; hospital-ization	N/A	CA	10 months	N/A	Cost savings of $7,925/pt.yr after initiation of RISP
Glazer 1996[99]	Hypothetical schizophrenia patient requiring repeat hospital-izations	US using USD ($) (year of values used not stated)	Payer	Clinical decision analytic model	Traditional oral agents vs. Traditional depot agents vs oral atypical agents	Medi-cations ; clinic visits ; hospital-izaiton ; case manage-ment ; manage-ment of moderate/ severe side effects	Not included	CA	1 year	N/A	Total cost of traditional oral agent was $US11,157 & oral atypical agent was $US2,567 more than depot in first year

Reference	Population (n)	Country (currency & year)	Perspective	Study Design	Alternatives considered	Cost elements	Effectiveness measure	Nature of study[i]	Time horizon	Discount rate	Results
Finley 1998[100]	Veterans with treatment resistance or treatent intolerant psychiatric disorders (schizo-phrenia, bipolar, depression with psychotic features)	US using 1994/95 USD ($) values	Veteran's inpatient psychiatric treatment facility	Retro-spective cohort, intention -to-treat analysis Before and after the initiation of RISP	RISP	Hospital-ization, RISP acqui-sition costs	N/A	CA	1 year	N/A	Decrease in hospitalization days after initiation of RISP resulted in a net saving of US$149,962 for the institution
Edgell 2000[101]	Schizophrenia , schizo-phreniform disorder, schizo-affective disorder (DSM-IV) (150)	US using 1997 USD ($) values	Payer	Data from RCT used to measure health care service utili-zation	OLZ (10-20 mg/day) vs. RISP (4-12 mg/day)	Drugs ; hospital-ization ; ER visits ; day hospital ; psych-iatrist visit ; health care pro-fessionals ; home visits	N/A	CA	28 weeks	N/A	Health service costs were US$3,774 less in the OLZ-treated group compared with the RISP-treated group
Blieden 1998[102]	Schizophrenia (DSM-III-R); hospitalizaed	US using 1993 US ($) values	Public payer	Before & after	CLZ vs.other treatment	Hospital-ization ; outpatient	N/A	CA	6 months	N/A	Cost savings of $3,267/person after 6 months

Reference	Population (n)	Country (currency & year)	Perspective	Study Design	Alternatives considered	Cost elements	Effectiveness measure	Nature of study[i]	Time horizon	Discount rate	Results
	with no previous CLZ treatment within 6 months; ability to be interviewed; refractory to at ≥2 different antipsychotics					and residential care					
Drew 1999[103]	Schizophrenia or schizo-affective disorder and started on clozapine	Australia using 1996/97 AU ($) values	Payer	Open-label retro-spective study of com-munity-based clinical practice	2 years before vs. 3 years after the start of CLZ treatment	Hospital ; hostel bed ; CLZ ; lab and CLZ Co-ordinator	N/A	CA	3 years	N/A	No significant increase or decrease following CLZ treatment

Abbreviations : AU=Australian dollars, BPRS=brief psychiatric rating scale, CAD=Canadian dollars CGI=clinical global impression, CHL=chlorpromazine, CLZ=clozapine, DSM-III, IV-R=various editions of the diagnostic and statistical manual of diseases, EPS=extrapyramidal side effects, FLU=fluphenazine, GAF=Global Assessment of Functioning, GBP=pound sterling, HAL=haloperidol, NHS=National Health Serive, OLZ=olanzapine, PANSS=positive and negative symptoms scale, QALY=Quality Adjusted Life Year, RISP=risperidone, RCT=randomized clinical trial, SF-36=Short Form-36 , USD=US dollars.

[i] **Nature of the study:**

Full economic evaluation:

CBA Cost Benefit Analysis

CEA Cost Effectiveness Analysis

CUA Cost Utility Analysis

Partial Evaluation:

CA Cost Analysis

APPENDIX H Letter of intent to prescribing physicians

GOVERNMENT OF
NEWFOUNDLAND AND LABRADOR

Department of
Health and Community Services
Drug Programs and Services Division

Dear Dr.<>,

I am writing to enlist your participation in an important research project that will attempt to define the current patterns of practice in the treatment of schizophrenia in Newfoundland and Labrador. The Department of Health and Community Services has commissioned the Patient Research Centre, Health Sciences Centre, to conduct this project. The Pharmaceutical Manufacturer's Association of Canada (PMAC) has agreed to fund the study. There is great interest in this research endeavour from all stakeholders: those who fund our health care system, GPs and psychiatrists who are entrusted with the care of schizophrenic patients, the Schizophrenia Society of Newfoundland (including patients and their families), objective researchers within the Faculty of Medicine, and industry representatives.

In the proposed study, appropriateness of atypical anti-psychotic medication utilization and prescribing practices will be determined by a third party academic panel of experts, blinded to physician specialty and patient and physician name, using practice guidelines derived from published evidence concerning efficacy. We are hoping to have a high percentage of participation of the GPs and psychiatrists in the province in order to describe past and current patterns of practice in the treatment of schizophrenia.

Governments and third party insurers are all seeking ways to limit their expenditures and one popular means is by not listing new agents or removing existing expensive agents from formularies. This serves to limit physician choice and increase the amount of paper work needed for justification of exception. Nonetheless, it can be argued that escalating costs to provincial drug formularies strengthen the necessity of conducting drug utilization reviews to determine the appropriateness of drug prescriptions. In this particular situation it is possible that over-utilization of atypical agents could occur

through prescription for disorders other than schizophrenia, even though there is little evidence to support these alternative uses. It is also possible that underutilization could occur if patients who benefit from these drugs don't get them. Inappropriate utilization may impose an economic burden on an already constrained health care budget.

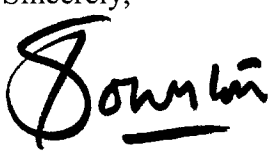
New patients started on atypical antipsychotics will be identified in 2000/1 and an interview with the physician will be completed to determine diagnosis and indication for use. You will be paid for your time and inconvenience at a rate of $15.00 per case. A case is defined as an instance identified by the Newfoundland and Labrador Prescription Drug Program database in which a client of the Drug Program was prescribed an atypical antipsychotic medication. We anticipate physician interviews will average 3 minutes per case. There is no maximum number of cases to be reviewed by each individual physician. In other words the number of cases to be reviewed per physician will depend on the number of patients prescribed atypical anti-psychotic medications by each individual physician.

All analysis of data will be identified in a completely anonymous fashion and no physician or patient will be identified to any outside agency. The intent of this study is not to identify individual physician's practices but to describe in a global sense, the prescribing patterns of psychiatrists and GPs.

A protocol synopsis is included for your perusal.

We look forward to working with you and having Newfoundland and Labrador general practitioners and psychiatrists lead the way to identifying patterns of practice based on published practice guidelines. If you have any queries please call either Dr. Patrick Parfrey directly at (709) 737-7261 or Pager 553-6218, his research associate Daria O'Reilly at (709) 737-6738, or Ann Rideout research nurse, study coordinator for the project at (709) 737-5031.

Sincerely,



Mr. John Downton
Department of Health and Community Services
Government of Newfoundland and Labrador

APPENDIX I Physician consent form

Faculty of Medicine, Memorial University of Newfoundland,
St. John's, Newfoundland A1B 3V6

CONSENT TO PARTICIPATE IN HEALTH CARE RESEARCH

RESEARCH STUDY TITLE: The Impact of Open Access to "Atypical' Anti-psychotic Medications in Newfoundland and Labrador on Physicians Prescribing Practices

INVESTIGATOR: Dr. Patrick Parfrey
Telephone: 737-7261

Please read this information carefully. It will tell you about the project we are undertaking, and help you decide if you want to participate.
Please ask the study staff to explain information that you do not clearly understand. You have been asked to participate in a research study. Participation in this study is entirely voluntary. You may decide not to participate or may withdraw from the study at any time.
A copy of the study protocol is available upon request.

Confidentiality of information concerning participants will be maintained by the investigator. The investigator will be available during the study at all times should you have any problems or questions about the study.

Purpose of the Study: The current study is being undertaken at the request of the Deaprtment of Health and Community Services, Government of Newfoundland and Labrador. The department requires accurately collected data, interpreted by objective health scientists, as a method of evaluating the impact of open access to atypical anti-psychotic medications in Newfoundland and Labrador, subsequent to the infusion of additional funding. The present study proposes:
(1) to evaluate the impact of an open access policy to atypical anti-psychotic medications
(2) to measure resource use (i.e., hospital admissions, drug utilization) due to schizophrenia, in Newfoundland and Labrador
(3) to measure the current patterns of care, and
(4) to determine the appropriateness of atypical antipsychotic prescribing.

Description of Study: The proposed study will address the following research questions:
Phase I: What has been the trend regarding the number of hospital admissions, length of hospital stay, quantity of antipsychotics used in the treatment of patients with

schizophrenia during the 1995/6 fiscal year and the 1998 calendar year in the province of Newfoundland and Labrador?
Phase II: What is the impact of an 'open access' policy to atypical antipsychotic therapy in Newfoundland and Labrador commencing in January, 1999?

Description of Procedures and Tests: The study will be conducted from January 1999 to April 2002. The study will consist of two phases. Patients with a diagnosis of schizophrenia will be identified through hospital admissions; patients prescribed atypical antipsychotic agents will be identified through the Newfoundland and Labrador Prescription Drug Program. Interviews with the individual's general practitioner/psychiatrist will be conducted to obtain information such as demographics (e.g., sex, age, employment status), history of present illness, relevant past history, (e.g., previous psychiatric hospitalizations, case management, previous medications) symptoms, drug allergies/intolerance. Subsequent to the data abstraction and at a time deemed convenient by the participating physician an interview will be conducted to determine diagnosis and indication for prescribing the atypical anti-psychotic agent. There will be no assessment of individual physician accuracy of diagnosis; a panel of experts will determine appropriateness of prescription based on conformation to the Canadian Clinical Practice Guidelines and the American Psychiatric Association Guidelines for the treatment of schizophrenia.

Duration of Participation: The study will take place from January 1999 to April 2002. You will be asked to designate a period of time from your practice to review identified cases of patients in your practice prescribed atypical antipsychotics in 2000. It will take approximately 3-4 minutes to review each case. There is no maximum number of cases to be reviewed by each individual physician. In other words the number of cases to be reviewed per physician will depend on the number of patients prescribed atypical anti-psychotic medications by each individual physician.

New patients started on atypical antipsychotics will be identified in 2000 and an interview with the physician will be completed to determine diagnosis and indication for use. The only time you will need to be directly involved with the study is during the interview process. You will be paid for your time and inconvenience at a rate of $15.00 per case. A case is defined as an instance identified by the Newfoundland and Labrador Prescription Drug Program database in which a client of the Drug Program was prescribed an atypical anti-psychotic medication.

Inconveniences: The inconvenience is associated with the giving of your time for the interviews. You will be paid a stipend of $15.00 to review each identified case in your practice.

Other Information: Findings of this study will be available to you upon request. Findings may be published but you and patients under your care will not be identified. The investigator will be available during the study at all times should you have any questions or concerns about your continued participation. All information that you provide will be kept strictly confidential, secured in a locked file, and accessible only to the investigators and research nurses.

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities.

I,_____, the undersigned, agree to my participation in the research study described.

Any questions have been answered and I understand what is involved in the study. I realize that participation is voluntary and that there is no guarantee that I will benefit from my involvement. I acknowledge that a copy of this form has been given to me.

_____ _____
Signature of Participant Date

_____ _____
Signature of Witness Date

To the best of my ability, I have fully explained the nature of this study to the participant. I have invited questions and provided answers. I believe that the participant fully understands the implications and voluntary nature of the study.

_____ _____
Signature of Interviewer Date

_____
Phone Number

APPENDIX J **Health record review for hospitalized patients**

Study #: _____ **Year of Present Admission:** _____

Patient Demographics:

Age in Years: Education Level attained:

Attending Psychiatrist:

Admitting Psychiatrist:

Institution:

Region of Domicile when first diagnosed:

Region of Domicile for current admission:

Income source: Occupation:

Date &/or age of first diagnosis: (d/m/yr) Date of 1st admission: (d/m/yr)

Presenting Complaints (researcher's narrative): _____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

ICD-9 code & description: _____

Reason for admission:		Y	N
1.	Potential danger to self, others or property	☐	☐
2.	Acute disturbance of affect, behavior or thinking	☐	☐
3.	Impaired social, familial or occupation functioning	☐	☐
4.	Elective admission for observation, investigation or treatment changes	☐	☐
5.	Legally mandated admission	☐	☐
6.	Inappropriate admission (Reason: _____)	☐	☐

Admission Number to this institution: Index admission? Y/N
If index, date of last d/c:_____
Total # of admissions since first admission to first of this study period:
Date admitted to Hospital: Date Discharged from hospital:
Reason for d/c this admission: If transferred, dates of episode:
Reason for d/c of episode:
outcome following d/c:_____ date of outcome:_____
Actual Length of stay (in days): Did patient expire? Y/N Suicide? Y/N

Genetics
Family history (genetics): Y N not indicated
Relationship? _____

Referred by:

		Yes	No
1.	Self	☐	☐
2.	Family member	☐	☐
3.	Friend	☐	☐
4.	RNC Lockup	☐	☐
5.	Physician	☐	☐
6.	Other medical facility	☐	☐
7.	Other _____	☐	☐
8.	Court ordered assessment	☐	☐

Validation of Diagnosis (MSE documents):

		Yes	**No**
1.	Thought disorder	☐	☐
2.	Perceptual Disorder	☐	☐
3.	Affect Disorder	☐	☐
4.	Disordered behaviour	☐	☐

	Yes	No	Comments
First Break (D/M/Y) / /			
Substance abuse			
Admission preceded by non-adherence			

Non-specific Indicators	Yes	No
Suicide ideology	☐	☐
Suicide Attempt (Prior to admission)	☐	☐
Suicide Attempt (In Hospital)	☐	☐
Left prior to discharge	☐	☐
Discharged against medical advice (AMA)	☐	☐
Time spent in TQ		
< 8 hours	☐	☐
> 8 hours	☐	☐
None	☐	☐

Drugs on Admission	Drugs on Discharge

Drugs on admission:

New _____

Old

Not indicated

Non-adherent

Adherence not indicated

No antipsychotic

N/A first break

No meds at all

Drugs on discharge:

New _____

Old

Not indicated

left prior d/c-none, new, old, no antipsychotic

left AMA-none, new, old, no antipsychotic

none given

suicide completed

patient expired

no antipsychotic

transferred-no drugs

Complications

	Yes	No	N/A
Regression	☐	☐	
Complications of medication Specify: _____	☐	☐	☐
Drug History completed by pharmacy?	☐		☐
Did patient receive ECT during admission?	☐	☐	
Complications of ECT Specify: _____	☐	☐	☐
Improvement in admitting symptoms by the 7th day	☐	☐	☐
Improvement in symptomology at 4 weeks	☐	☐	☐
Improvement in symptomology at 6 weeks	☐	☐	☐

Reason for change to atypical if stated:_____

Negative Symptoms Present? 1. Yes 2. No

All drugs during hospital stay:

Drug	Dosage	Route	Date started (d/m/y)	Date stopped (d/m/y)	N days Treated	Comments

Inpatient drugs:

New

Old

None- 1) already on long acting

2) short stay (<24 hours)

3) patient refused meds

4) none-overdose prior to admission

5) NPO surgery

Not indicated

No antipsychotic

	Yes	**No**
Hypnotic medication after 7th day	☐	☐
IM Neuroleptic >10 days (excluding depot medications)	☐	☐
Patient started on an atypical antipsychotic during this hospital stay?	☐	☐

Treatment strategy on admission:	Yes	No	Comments
1. ECT prior to out-patient/in-patient trial of anti-psychotic? (this admission)			
2. ECT following out-patient/in-patient trial of anti-psychotic? (this admission)			

APPENDIX K **Outpatient interview with prescribing physician**

Interview with Physician

Date of Physician Interview _____ Doctor # _____

Case # _____ Place of Residence (Pt) _____

Age in Years: _____

New Patient 1. Yes 2. No

History of presenting illness (as per psychiatrist's chart)

_____

_____

_____

_____

_____

_____

_____

Relevant past history (e.g., previous psychiatric hospitalizations, case management, previous medications, etc.)

_____

_____

_____

_____

_____

Symptoms: _____

_____

Diagnosis (interview): _____

Atypical Antipsychotics & Dosage Prescribed: _____

Indications for use: _____

Concomitant medications (e.g., psychotropics, mood stabilizers, sedatives, anti-epileptics, benzodiazepines, other anti-psychotics):

_____

_____

_____

Anti-psychotic Allergy/Intolerance: 1. Yes 2. No 3. Unknown
Specify: _____

Factors influencing anti-psychotic prescription decision: Please circle appropriate factor(s).

1. Clinical Judgment

2. Patient/Family Request

3. Allergy

4. Intolerance to Medications

5. Reason Not Provided

6. Patient non-compliance

7. Worsening of symptoms

8. No improvement in symptoms

APPENDIX L Algorithms to determine indication for use by Brogan Inc.

Bipolar Indication: Claimants must have a previous claim (within 2 years) for one of the selection of drugs: lithium, valproic acid (and related chemicals), carbamazepine, phenytoin, gabapentin, topiramate, and lamotrigine. These patients will always remain bipolar.

ADHD Indication: Patients who are not bipolar and who have recent claims (within 2 years) for methylphenidate, dextroamphetamine are classified under ADHD. New psycho-stimulants indicated for ADHD will be added to this list as they enter the market. These patients remain in ADHD, unless they claim a drug indicating bipolar.

In addition, patients under 13 not in the bipolar group are automatically categorized ADHD. These patients are re-assessed when they turn 13 and if a more likely indication is know, they will be mobbed to the other category for subsequent claims.

Depression Indication: Refractory depression is counted where a patient is not classified as bipolar or ADHD, and is known to have received antidepressants at least 30 days prior to ever starting any antipsychotic. In the event the patient subsequently drops the antidepressant, they are kept in this group. Once the patient turns 65, they are moved to dementia. No patient over 64 is included in this group.

Other Psychoses Indication: Claimants under 65 and WITHOUT previous bipolar, ADHD, cognitive enhancers or refractory depression indication. These patients will remain as Schizophrenia throughout their years in the database. If these patients ever receive a mood stabilizer, they will be moved to bipolar. Patients who initiate their first ever antipsychotic at age 60+ will be classified as dementia rather than schizophrenia.

Dementia Indication: The fifth criterion is for dementia. Anything not bipolar, ADHD, refractory depression or schizophrenia AND greater than and equal to the age of 65.

Brogan have taken refractory depression out of the limiting criteria. Prior refractory depression patients move to dementia once they reach 65. In addition, any patient with a record of taking cognitive enhancers (Aricept, Reminyl, Exelon) will be classified as dementia, regardless of age or other drug use.

Patients who initiate their first ever antipsychotic (minimum 2 years is searched) at age 60 or above, will be classified as dementia rather than other psychoses.

CHAPTER VIII REFERENCES

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