A STUDY OF REFILL NON-COMPLIANCE AND PREDICTORS OF REFILL NON-COMPLIANCE TO TRICYCLIC AND SSRI ANTIDEPRESSANTS IN A POPULATION SETTING

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A Study of Refill Non-compliance and Predictors of Refill Non-compliance to Tricyclic and SSRI Antidepressants in a Population Setting

By

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A thesis submitted to the School of Graduate Studies in partial fulfilment of the requirements for the degree of Master of Science

Division of Community Health
Faculty of Medicine
Memorial University of Newfoundland

1997

St. John's

Newfoundland

DEDICATION

To my parents, Bronsten and Judy, and my grandparents, Llewelyn and Nellie who taught me the value of hard work and perseverance

And

To my brother, Mark who has always been a willing listener and strong support in times of turmoil

And Finally,

To my fiancee, Kristopher, who helped me gain the courage to pursue the goals I once thought were unreachable

ABSTRACT

The current study utilized the Atlantic Blue Cross Prescription Drug Database to examine patient refill compliance to antidepressants from the tricyclic and selective-serotonin re-uptake inhibitors (SSRI) classes. The primary goals of the study were to describe and compare non-compliance between the tricyclic and SSRI users, to ascertain whether patient age and gender, treatment cost, and regimen complexity were predictors of non-compliance, and to evaluate the problems involved with utilizing the Atlantic Blue Cross Database for compliance research.

Non-compliance was measured by using three outcome measures. First the percentage of non-compliant days (defined as the percentage of days during treatment without medication) was found. Second, the early medication 'stoppers' were compared to the medication 'continuers'. Finally, the time course of non-compliance was studied by finding the time till the first non-compliant gap for users.

Results showed that the mean percentage of non-compliant days was 8.4% (95% CI; 7.9-8.9) for the tricyclic and SSRI users who filled more than one prescription. In addition, between 8.1-11.4% of users stopped the antidepressant medication early. Survival analysis suggested

that the greatest drop in the cumulative probability of having a non-compliant gap occurred early in treatment for both classes. No differences were found in the comparisons of the tricyclics and the SSRI's in terms of non-compliance. The predictor variable age was weakly associated with non-compliance; as age increased, non-compliance decreased. In addition, regimen complexity as measured by the number of concurrent medications and the number of doses per day was also weakly associated with non-compliance. More specifically, as the number of concurrent medications increased, compliance increased and as the number of doses per day increased, compliance decreased.

A number of problems were identified with the Blue Cross Database. In a number of cases, data was missing. Data contamination problems were identified that were probably the result of data entry errors. Cleaning protocols were developed to deal with some of these problems. A number of other problems were also identified which were inherent to the database. For example, there was a lack of documentation concerning dates of entry and exit to the Blue Cross Program.

ACKNOWLEDGEMENTS

There are a number of special people who have provided countless moments of support throughout this project. First, my supervisor, Dr. Roy West who has guided me through this project. My committee, Dr. Mohamadtaki Kara and Dr. Doreen Neville who have offered insights. Dr. Vereesh Gadag who provided the statistical expertise for the project. Denise Beaton who has been there to offer her help. Aliesje MacInnis and Kristina Oje from Blue Cross of Atlantic Canada who worked closely with me during the initial stages of the project. Blue Cross of Atlantic Canada who provided the data for the study. The MUN Pharmacy Resource Centre headed by Ms. Audrey Fultz who provided their pharmacological expertise. Christine Hobeika who has been a wonderful support over the past year. The entire staff and faculty of the Division of Community Medicine who offered kind words, encouragement, and helpful insights throughout the project. Kristopher and Mark who provided countless hours of their time. Mom and Dad who drove me back and forth to St. John's during the final stages of the project. Finally, one of my greatest supports, Ms. Alison Edwards, without whom this project could not have been conquered. Her database and research expertise were invaluable resources. Many special thanks to each and every person.

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INTRODUCTION

Compliance to drug regimens by patients is a major determinant of the clinical and cost effectiveness of drug treatments. Studies have shown that regardless of the patient population, the disease state, or the compliance measurement used, compliance rates usually fall well below 100% and that long-term medication therapies tend to elicit less compliance than short term therapies (Rogers and Bullman, 1995).

Non-compliance to drug therapies has been measured in a number of different ways. Several studies have looked at patterns of prescription fill and refill in a population by utilizing databases. An advantage of this method is that researchers do not contact the patients and thus, do not influence compliance. In population research using databases, non-compliance can be inferred from several indicators. First, gaps in treatment as evidenced by gaps between prescription refills are indicators of non-compliance. In many cases compliance is quantified by calculating the percentage of days during treatment that an individual is without any medication as indicated by the gaps in refill. A second method of measuring compliance looks at the individuals who discontinue taking the prescribed medication early. This method, unlike the

previously described one, looks at those people who completely stop the medication as indicated by a failure to return to the pharmacy for refills of the prescription. Both of these compliance outcomes were examined in the current study.

These outcome measures were compared between two classes of antidepressants, the tricyclic antidepressants (e.g. Imipramine) and the selective serotonin re-uptake inhibitors (SSRI's, e.g. fluoxetine, sertraline). It has been suggested that these two particular classes of antidepressants are nearly equivalent in clinical effectiveness but the tricyclics are tolerated less well due to more adverse side effects such as cardiotoxicity, psychomotor and anticholinergic effects (Montgomery, Henry, McDonald et al., 1995). Thus, research suggests that compliance to the tricyclic drugs is worse than compliance to the SSRI's (Anderson and Tomenson, 1994). A problem with much of this research is that the data has been taken from clinical trials. Many researchers feel that conclusions concerning compliance cannot be drawn from such controlled data. They have suggested that definitive conclusions can only be drawn from data taken from settings such as population-based studies.

Recent studies that have used population data to look

at medication compliance have found a number of variables that may have value in the prediction of non-compliant behaviours. More specifically, it has been suggested that the complexity of the medication regimen, the cost of the medication to the user, and certain demographic variables may aid the health care provider in predicting whether or not a patient will comply to a specified regimen of treatment. The value of identifying these potential predictors is great. Interventions designed to improve compliance can focus on the potential predictors and attempt to lower non-compliance based on changes in these predictors.

The demographic variables age and sex were examined in order to ascertain whether they influence the compliance measures. The effect of age on compliance is quite controversial. Research has shown positive, negative, and no effects of age on compliance to a variety of medication regimens. The effect of patient age on compliance to antidepressant medications was examined in this study because it has not been directly examined in a population (database) setting before. Patient gender has also been widely examined in regards to compliance. Most research does not show any association between an individual's sex and their drug compliance behaviours. However, it was valuable

to study this variable in relation to antidepressant medications because of the distinct demographic profile of these drugs. In particular, approximately 70% of antidepressants are prescribed to females (Wagner, Plekkenpol, Gray et al., 1992).

The literature suggests that the complexity of the medication regimen may impact on the level of patient compliance. Regimen complexity is thought to be influenced by such factors as the number of doses of medication per day and the number of concurrent medications that an individual is taking (Christenson, 1978). These factors have been studied in relation to other medications such as the lipid-lowering drugs and results have suggested that increasing the number of concurrent medications or the number of doses per day inversely impacts on compliance (Jones, Gorkin, Lian et al., 1995; Hamilton and Briceland, 1992). Again, research is deficit in terms of population studies which attempt to ascertain the impact of medication complexity on compliance to the tricyclic and SSRI antidepressants.

The notion that cost of treatment may influence compliance has been explored in a number of studies. For example, Thompson and McMillan (1995) examined the effect of a varying deductible (the base amount that an individual paid before insurance took over the drug cost) on refill

compliance to lipid-lowering medications in a Saskatchewan population. They found that the odds of stopping the medications increased marginally for each $10 increase in patient cost. Varying patient cost has not been studied in reference to compliance to antidepressant medications. The Atlantic Blue Cross Insurance plan which has a number of different insurance co-payment levels provided an excellent opportunity to compare subscribers who pay varying percentages of the total prescription cost for the same antidepressant medication. A second cost factor was examined in this study that has not been previously researched; the cost that a person was paying for other concurrent medications.

A large population database, The Atlantic Blue Cross Prescription Database, was used as a source of data. The use of a private administrative database allowed for the study of problems inherent in the database such as contamination and incompleteness of the data, and for the development of data cleaning strategies.

A number of specific study objectives have been identified. The first five objectives relate to the actual study of patient compliance to antidepressant medication and the potential predictor variables of compliance. Objective number six relates to the use of an administrative database

for the study of compliance.

The study objectives are;

1. To describe the sample of antidepressant users in the Blue Cross database in terms of extent of non-compliance.
2. To determine whether differences in level of compliance exist between individuals using antidepressants from the tricyclic and SSRI classes.
3. To ascertain whether medication complexity as demonstrated by the number of concurrent medications per day and the number of doses per day effect compliance to the tricyclic and SSRI antidepressants.
4. To determine whether the demographic variables, age and sex, are predictors of compliance to antidepressants from the tricyclic and SSRI classes.
5. To establish whether the average cost paid per prescription for the antidepressant medication and for other medications impact on patient compliance.
6. To evaluate some of the problems and complications involved with utilizing the Atlantic Blue Cross Database for compliance research.

2 LITERATURE REVIEW

2.1 General Compliance

Patient compliance is a concept that is deeply rooted in the history of medicine. From the time of Hippocrates, physicians were able to learn about the therapeutic effectiveness of medicinal remedies by observing whether or not the patient took all of the portions of the medication. In recent years prescription drugs have become more widely accessible and drug regimens increasingly complex, especially for many chronic ailments where long term treatment is necessary.

This literature review focuses on patient compliance, in particular compliance to antidepressant medications. General compliance will first be discussed. More specifically, the significance of non-compliance in predicting medication outcomes will be discussed. In addition, past methods of studying compliance along with their associated problems will be explored. Following this, a brief description of the antidepressant classes being studied in the current project will be done. Next, compliance to antidepressant medications will be discussed. Finally, in the context of the current study, potential predictors of compliance as well as outcome measures drawn from previous database studies will be described.

2.1.1 What is Compliance?

Compliance, in a medical context, refers to a patient following the treatment orders of the physician or health care provider. Some of the literature distinguishes between biological and behavioural compliance. Biological compliance is used to describe the characteristics of a patients metabolism that allow therapeutic blood levels to be reached. Behavioural compliance refers to the extent to which a patient complies behaviourally to a medication (Frank, Perel, Mallinger, et al., 1992). It has been suggested that these two types of compliance will interact to determine the results of a specific medication for an individual. In this study, the term compliance will be used to denote behavioural compliance.

2.1.2 Forms of Non-compliance

How do people demonstrate non-compliance to their medication regimens? Research suggests that non-compliance can take several forms. Gerbino(1993) states that although the origins and motivations for non-compliance are complex, the manifestation of non-compliance is quite distinct. He lists five different forms of non-compliance; (1) not having the prescription filled, (2) taking an incorrect or wrong dose (this may involve taking too much or to little), (3) taking the medication at the incorrect time, (4) forgetting

to take one or more doses, and (5) stopping the medication too soon. In the first form of non-compliance, the patient rejects the treatment plan as recommended by the health care provider and does not have the prescription filled. In the second, third, and fourth forms of non-compliance, the patient accepts the treatment plan but does not comply to it by taking the wrong dose, taking it at an incorrect time, forgetting doses, or taking too many doses. In the final form of non-compliance, the patient may stop taking or refilling the prescription sooner than was recommended by the health care provider.

2.1.3 Significance of Non-compliance

Does non-compliance result in an increased risk to patient health? A considerable number of studies have looked at the effects of non-compliance to different medications on patient outcomes. Results from these studies suggest that patients who do not take medications as recommended will not receive benefits from the medication. This could adversely affect the patient's health (assuming the medication is effective). Rovelli, Palmeri, Vossler, et al. (1989) looked at compliance to immunosuppressive medications and outcomes from organ transplants. In the prospective portion of their study, 30 of 182 patients were considered non-compliant. 37% of the non-compliant group experienced organ rejection or

death as opposed to only 1% of the compliant group. The authors concluded that non-compliance with immunosuppressant therapy is a major factor in tissue rejection, causing more transplant failures than uncontrollable rejection in compliant patients. This study illustrates a case where non-compliance to medication can have dire consequences; death. Non-compliance is also a problem with medications for chronic conditions where such immediate threats are not a concern. Table 2.1 shows a summary of nine studies that have looked at outcomes of non-compliance to various long-term drug therapies. Lack of compliance to antihypertensive, anticonvulsant, lipid-lowering, and depressive medications resulted in poor outcomes in the study populations.

The problems associated with non-compliance to medication regimens often affect more than the individual being treated. Rogers and Bullman (1995) suggest that infections may linger or become resistant to treatment and infectious diseases such as tuberculosis are spread, in part, because of the effects of non-compliance to the appropriate treatments. Thus, good health outcomes appear to be related to compliance to the appropriate medications. However, Michenbaum and Turk (1987) caution that compliance to treatment recommendations is only one factor that influences outcome.

Table 2.1: Summary of Nine Research Studies that Looked at the Relationship of Compliance and Outcomes

Reference	Study Type	Study Objective	Outcome
Psaty et al., 1990	Case Control	Looked at relative risk of first events in coronary heart disease associated with poor compliance to β-blockers in hypertensive patients	Those who stopped β-blockers had a RR of 4.5, (95%; 1.1-18.5) of first event.; Thos who were less compliant were more likely to stop therap
Bond et al., 1984	Case Control	Analyzed Effect of an intervention on improving drug compliance and documentation	Significant Correlation between compliance and Blood Pressure Control; correlation coefficients ranged from .67 to .89 for different study group:
Maronde et al., 1989	Cohort	Looked at underutilization of antihypertensive drugs and subsequent association with hospital re-admissions	Group re-admitted to hospital had significantly higher ratio of days when they were without antihypertensive agents
Gallagher et al. 1993	Random-ized Double Blind Multi-centre trial	Examined relationship between compliance to medication regimens (eg. Propranol) and mortality following MI in women	Death occurred in 13.6% of poor compliers compared with 5.6% in good compliers; RR = 2.4, (95% CI, 1.1-5.6)
Canner, Coronary Drug Project, 1980	Random-ized Double Blind, Placebo controll ed multi-	Evaluated Efficacy and Safety of several lipid-lowering drugs in the long-term treatment of coronary heart disease	Good compliers who took 80% or more of the protocol prescription during the five year study period and had a substantially lower five year mortality

	centre clinical trial		than did poor compliers (15 vs. 24.6% respectively)
McCombs et al., 1994	Cohort database	Explored association between interruption or termination of antihypertensive drug therapy and total health care costs among non-institutionalized patients	Patients with interrupted therapy consumed an addition $873 (U.S.) per pers in health care expenditures
Stanaway et al. 1985	Cohort database supple-mented by patient interv-iews)	Attempted to ascertain whether non-compliance with anticonvulsant therapy with associated with or precipitated seizures	Non-compliance was found to be instrumental in precipitating 31% of seizures for which ambulance was called, 37% of patients were not taking their medication in accordance with prescribing instructions.
Frank et al. 1992	Random-ized Clinical Trial	Examined the relationship between long-term medication compliance and to prophylaxis in recurrent unipolar depression	Medication compliance was found to be significantly associated with effective prophylaxis ($p = .04$)
Col et al. 1990	Cohort	Examined the role of medication non-compliance and adverse drug reactions in hospitalizations in the elderly	About 11% of admissions of older patients to an acute care hospital were directly related to some form of non-compliance. Total cos per patient was $2150 (US)

Another significant issue related to non-compliance is the potential associated costs. According to Rogers et al. (1995) the costs associated with non-compliance can be broken down into two categories; (1) direct costs and (2) indirect costs. Direct costs include such things as initial prescriptions which do not produce desired results because they are not taken properly and additional prescriptions which may not have been needed had the initial prescription been complied to. Also, additional physician or clinic visits, emergency room visits, hospitalizations, additional diagnostic tests, nursing home admissions, and home health care services may become necessary due to lingering problems or illnesses which could have been cured or managed had the initial prescription been complied to as recommended. Finally, additional care for the consequence of uncontrolled chronic disease such as heart attacks may become necessary if the initial preventative therapy (e.g., antihypertensive medications) is not complied to. In contrast, indirect costs of non-compliance to a prescribed regimen might include lost productivity or absenteeism in the work place, lost earnings, and employee turnover due to premature death or disability.

A number of studies have looked at direct costs of non-compliance. For example, Table 2.1 shows three studies

in which non-compliance had direct cost implications. McCombs, Nichol, Newman et al. (1994) found that non-compliance resulted in increased health care costs in patients taking antihypertensive medications. Col, Fanale, and Kronhom (1990) also found that non-compliance was related to hospital admissions in the elderly. Maronde, Chan, Larsen et al. (1989) found that re-admissions to hospital were more frequent in non-compliant patients. These studies suggest that non-compliance has significant implications for cost. Few studies have gone as far as to look at the indirect cost implications of non-compliance.

2.1.4 Methods for Studying Non-Compliance

Compliance has typically been studied in clinical trial settings through the use of such methods as patient self report through interviews or questionnaires, pill counts, electronic monitoring, or drug monitoring through blood or urine tests. A number of problems exist with these methods.

Patient self reports of medication use have been shown to be inaccurate when compared with more objective measures. Park and Lipman (1964) found that in 40% of cases, patient self reports did not match pill counts. Gordis, Markowitz, Lilienfeld (1969) also found that in children taking penicillin prophylactically, discrepancies existed between reported compliance and urine tests for the penicillin.

Responses of patients and their mothers suggested that 70% were compliant. Urine tests showed that only 33 to 42% had confirmatory urine levels of penicillin.

Pill counts or the comparison between the amount of medication remaining in a patients bottle and the amount that should have been left is a commonly employed method in compliance research. Like the other methods described this measure is not without problems. Fletcher and Pappius (1979) suggest that it is difficult to ensure that all pills are brought to the clinic for counting. This is especially true for patients who want to convince the researcher that they have been compliant to their medication regimen. Other comparative studies suggest that pill counts tend to overestimate compliance. For example, Roth and Berger (1970) found a 36% discrepancy rate between tablet counts and physiological measures in a study looking at treatment of peptic ulcer patients.

Recently a number of electronic devices have been used for such things as the monitoring of doses, self-testing, and outpatient notation of events (Cramer and Spilker, 1991). These devices use microprocessors which record the time and date that the bottle or apparatus was used to dispense a dose of medication. This method has been shown to be very useful in compliance research because it allows the

researcher to ascertain that the initiative of opening the pill bottle actually occurred. However, this method is expensive to use on a large scale basis and patients may fool the system by opening the lid an excessively large or small number of times or by putting the medication in other containers.

Drug monitoring through blood or urine tests is often considered the gold standard in compliance research (Steiner and Prochazka, 1997). It is a direct method of measurement which does not rely on patient recall. However, there are a number of problems associated with this method including the type of medication being measured and individual pharmacokinetic variations. Cramer et al.(1991) state that measurement of drug serum concentrations can indicate erratic compliance. However, she notes that, for medications with short half lives serum levels reflect only recent doses not doses missed several days before the test. Gordis(1979) states that differences in individuals in absorption, distribution, metabolism, and excretion of drugs is also an issue in measuring patient compliance with this method. Genetic differences and bioavailability, defined as the amount of the drug absorbed from a certain formulation of the drug relative to the amount of the drug absorbed from a standard reference, are thought to be a major confounders

when studying compliance via biological measurement.

As a group, these methods of measurement are very obtrusive in that patients are aware that compliance is being measured. Because compliance is a behaviourally rooted phenomenon, non-intrusive methods must be used in order to avoid the Hawthorne effect which suggests that subjects will modify their behaviour when they know that they are being studied (Forsyth, 1990). In other words, if subjects know that compliance to medication is being studied they may be more likely to comply in order to aid the researcher. In addition, it has been suggested that data from clinical trials, where compliance is not the primary research question, is not a good indication of compliance because a great deal of effort is devoted to getting subjects to comply with their medication. This is especially necessary when treatment effects of medications are being studied because effects cannot be properly evaluated if compliance is low in either group (Paykel, 1995). Recent research has used population databases as an indirect, non-obtrusive, method of studying patient compliance to medication regimens.

2.1.5 Use of Databases to Study Compliance

Use of large population databases in compliance research is a relatively new occurrence made possible by

advances in computers and data management. Patterns of utilization or prescription fill and refill can be ascertained from the database. Like several of the methods described above, inferring compliance from databases is an indirect method of measurement because one cannot observe the compliance behavior. An advantage of using databases is that they are a non-obtrusive method of studying compliance. As opposed to the methods described above, databases allow the researcher to obtain information about subjects without directly contacting or involving the subjects.

Results from a number of database studies suggest that data from randomized clinical trials may not reflect patterns observed in population-based settings. Andrade, Walker, Gottelieb et al. (1995) used computerized records from a HMO to look at discontinuation before one year in users of antihyperlipidemic drugs. They reported that the probability of discontinuing therapy within the first year ranged from 15-46% depending on drug class. This differs from previously reported discontinuation rates within the first year in clinical trials of between 4-15% (Bradford, Shear and Chremos, 1991). Similar results to the Andrade et al. (1995) study were found in several other studies. Thompson et al. (1995) looked at lipid-lowering medications and discovered that discontinuation rates after filling one

prescription ranged from 30 to 38%. Lacour and Lelorier (1995), in a population database study, found that the probability of still being on lipid-lowering medication after one year of treatment varied between 41-77.2%. Simon, Levis, and Simon (1996) looked at patients who failed to collect prescription refills for lipid-lowering drugs and found that 60% discontinued treatment in the first six months. Each of these studies suggest that the rates of discontinuation for the lipid-lowering medications may be higher in the general population than is suggested in clinical trials. This is largely due to the fact that clinical trials are not typically designed to measure compliance. In addition, much effort goes into getting subjects to comply to the medication in order to observe the effects of therapy.

Compliance outcomes from databases have been defined in a number of ways. Lacour et al. (1995) suggest that databases allow one to view compliance from two perspectives; (1) percentage of days without medication or gaps in treatment and (2) probability of a permanent treatment interruption. One criteria when inferring compliance from a database is that the treatment of interest must be of long-term duration and necessitate the filling of a number of prescriptions. Compliance to therapies with a

potential life-long duration such as lipid-lowering drugs and antihypertensive medications have been widely studied using databases (Andrade et al. ,1995; Jones et al., 1995; Maronde et.al.,1989; Thompson et al. , 1995; Bond and Monson,1984; Psaty, Koepsell, Wagner et al., 1990). Most of these studies utilized outcome measures in which either gaps in treatment or numbers of days with or without medication and total treatment discontinuations (i.e. stopping medication prematurely) were considered.

The use of databases to study compliance does have inherent problems. First, using prescription refill patterns to ascertain compliance is an indirect measurement. We assume that a person is compliant to the medication if they fill prescriptions for the recommended amount of medication over a recommended period and refill a new prescription before or at the end of that period. However, a person's refill behaviour may not necessarily reflect their actual drug-taking behaviour. Medications lost, shared with family members, or simply not taken at all may lead to an overestimation of compliance. Medications obtained from other sources not available to the researcher may cause an overestimation of non-compliance.

Databases are also limited by the accuracy of data entry. It has been suggested that administrative databases

such as those kept by pharmacies may have precision problems that occur at the data entry level (Katzelnick, Kobek, Jefferson et al., 1996).

A third problem that is often inherent in databases, administrative databases in particular, is that specific data such as diagnostic information, are usually not collected. This problem will vary depending on the database utilized and the information needed. For example, lack of diagnostic information is a problem when examining medications that may be prescribed for several different indications such as antidepressants (this will be discussed further in the next section).

A final problem involving data availability is that hospital stays during the period of treatment may create artificial gaps in treatment because medications dispensed in the hospital may not be recorded in a community (i.e. pharmacy, insurance) database (Steiner, Koepsell, Fihn, et al., 1988).

2.2 Antidepressant Medications

2.2.1 Indication

The antidepressant medications are an heterogeneous group of drugs which share major therapeutic effects; in particular, the treatment of major depressive disorder (MDD). Although utilized primarily for depressive and other

psychiatric conditions such as panic disorder and obsessive-compulsive disorder (OCD), these drugs also prove effective in the treatment of a number of other conditions (see Table 2.2). McCombs et al. (1990) found that two thirds of patients who are using antidepressants may be under treatment for problems other than MDD. Since lesser levels of depression that do not fall under the umbrella of MDD would be included in the other two thirds, it is still likely that a large portion of users are taking antidepressants for some form of depression.

There are several major classes of antidepressant drugs including (1) the tricyclic antidepressants, (2) the serotonin-selective re-uptake inhibitors (SSRI's), (3) the monoamine oxidase inhibitors (MAOI's), and the heterocyclic antidepressants, and the Serotonin - Norepinephrine Re-uptake Inhibitors (SNRI's) (see Appendix 1). This paper will focus only on the two most commonly prescribed classes, the tricyclics and the SSRI's. It should be noted that the guidelines for such things as dosing apply to those antidepressants prescribed for the indications of depression. There is a noticeable lack of specific prescribing guidelines for antidepressants for other

Table 2.2: Drug Names and Classes with Associated Indications for Use

Drug (Class)	Indication for Use
All Classes[4]	Depressive Disorders; depression, depressive phase of bipolar disorder, dysthmia
Imipramine (Tricyclic)[1] Various SSRI's[2]	Treatment of School Phobias and Panic Attacks
Imipramine[1]	Childhood enuresis
Doxepin (Tricyclic) Trimipramine (Tricyclic)[1]	Palliation of peptic ulcer in depressed patients
Doxepin (Tricyclic) Trimipramine (Tricyclic) Amitriptyline (Tricyclic) Maprotyline (MAOI)[1]	Symptomatic treatment of dermatologic allergies with pruritus
Protriptyline (Tricyclic)[1]	Hypersomnia and sleep apnea
Fluoxetine and other SSRI's Desipramine (Tricyclic)[1]	Bulimia nervosa
Desipramine (Tricyclic)[1]	Cocaine Dependence
Imipramine (Tricyclic)[1]	Narcolepsy manifesting predominantly with cataplexy
Amitriptyline (Tricyclic) Trazodone [1]	Palliation or prevention of pain syndromes and migraine
Imipramine[1]	Attention deficit disorder
Clomipramine (Tricyclic)[1] Fluoxetine (other SSRI as well)[5]	Obsessive-compulsive disorder
Amitriptyline (Tricyclic, 10-25 mg incremented[3]	Abdominal Pain caused by irritable bowel syndrome
Tricyclic (low dose)[3]	Management of angina-like chest pain of esophageal origin.

1 - Berkow (1992)
2 - Klerman (1992)
3 - Thomson and Shaffer (1994)
4 - Harris and Kurdyak (1997)
5 - Goodman, McDougle, and Price (1992)

indications such as OCD or panic disorder.

2.2.2 Mechanism of Action

It is important to understand the mechanisms by which the antidepressant medications work because of the potential role this may have on compliance to these drugs. Mood disorders are thought to be, in part, influenced by the alterations in firing patterns in certain subsets of biogenic amine-containing neurons in the central nervous system. The antidepressant drugs tend to play a role in increasing the concentrations of these biogenic amines in the brain. Although this action may occur immediately, it may take several weeks before a change or improvement in mood is observed. Chronic administration of antidepressant drugs for several weeks may result in a decreased density of postsynaptic receptors for serotonin (5-HT_2 subtype) and norepinephrine (β subtype) in the brain tissue. This phenomenon is known as down-regulation and is thought to be a reaction to the increased levels of these neurotransmitters. Much of the therapeutic effect associated with antidepressants probably occurs because of the down-regulation of receptors which may take several weeks to occur (Brody, Larner, Minneman, Neu, 1994). Thus, from the point of view of compliance, it has been suggested that the delayed onset of therapeutic effect may result in greater

levels of non-compliance in the beginning stages of therapy (Myers and Branthwaite, 1992; Maddox, Levi, and Thompson, 1994; Katzelnick et al., 1996).

2.2.3 Tricyclic Antidepressants

2.2.3.1 History and Mechanisms of Action; The tricyclics were first discovered in the 1950's and 1960's. Imipramine, the first tricyclic, was initially tested as a potential antipsychotic compound (Arana and Hyman, 1987). It is thought that the tricyclics produce their therapeutic effect by blocking, in different degrees, the re-uptake of neurotransmitters, including serotonin and norepinephrine, at the neuronal membrane (Krogh, 1994). Different tricyclics may vary in their propensity for blocking the re-uptake of either of these neurotransmitters. For example, amitriptyline shows a greater proclivity to block the re-uptake of serotonin than norepinephrine (Bernstein, 1995; Krogh, 1994).

2.2.3.2 Dosing; The tricyclics tend to have long metabolic half-lives, frequently more than 24 hours, which allows for once a day dosing. Tricyclics are typically started at a low dose with gradual increases as the therapeutic range is reached (Brody et al., 1994). This dosage can be increased by 50mg every 3-4 days as side effects allow. Most treatments should level off at

approximately 150-200mg although the maximum dosage of most tricyclics is approximately 300mg/day. (Arana et al., 1987; Practice Guidelines for MDD, 1993) A major problem with the tricyclics which often leads to treatment failure is inadequate dosing. This problem may, in part, be explained by the side effects of these drugs which are more pronounced at higher dose levels. Several studies have shown that many general practitioners do not raise the starting dose of the tricyclics to a level at which the therapeutic efficacy (for depression) has been shown to be superior to placebo in clinical trials (Tyrer, 1988; Ketai, 1976; Maddox, et al., 1994) Thus, the selection of an adequate dose takes into consideration the medications side effect profile, the typically effective dose range, as well as the patients age and health status.

2.2.3.3 Side Effects; These drugs do carry a somewhat troublesome side effect profile. Most of the side effects are a result of interactions with central and peripheral neurotransmitter receptors. Antagonism of muscarinic receptors cause such side effects as dry mouth, blurred vision, urinary retention, reduced sweating, constipation, and recent memory impairment. Sedation is caused by the blocking of the histamine (H_1) receptors. Antagonism of the α-adrenergic receptors results in orthostatic hypotension.

Cardiac toxicity is possibly the most dangerous side effect of the tricyclics which is caused, in part, by the antiarrhythmic quinidine-like side actions of the tricyclics on cardiac muscle (Arana et al., 1987). The tricyclics are also quite dangerous in overdose. A 10 day supply of antidepressants at a dose of 200mg/day, if taken at once, is most often lethal and ingestion of lesser amounts can also be quite dangerous. Some of the newer antidepressants (the SSRI's) are less dangerous in overdose. (Practice Guidelines for MDD, 1993)

2.2.4 Selective-Serotonin Re-uptake Inhibitors

2.2.4.1 History and Mechanism of Action; The first highly potent discriminative inhibitor of serotonin, fluoxetine, was first developed in the 1970's but was not marketed in North America until the 1980's (1987 in the United States). Since that time, several other antidepressants have been developed which also fall into the SSRI class including fluvoxamine, paroxetine, and sertraline. Additionally, venlafaxine is a relatively new drug which is fairly selective to serotonin but also has a potent ability to block norepinephrine (Bernstein, 1995).

2.2.4.2. Dosing; The problem of inadequate dosing is less prevalent with the SSRI's than with the tricyclics primarily because the SSRI's are manufactured in the

commonly recommended dosage whereas the tricyclics tend to come in a wider dosage range with the smaller doses being as low as 10mg. The SSRI's tend to have long half lives. Fluoxetine is notable for having a half-life of 2 to 3 days for the parent drug and up to 7 to 9 days for the active metabolite, norfluoxetine. Sertraline, a newer SSRI, has a half life of approximately 20 hours for the parent drug. The active metabolite, N-desmethylsertraline, is only active for approximately 60-100 hours. In general, the SSRI's can be administered on a one per day basis. (Brody et al., 1994)

2.2.4.3 Side Effects; Side effects with the SSRI's tend to be somewhat less severe than those associated with the tricyclics. In particular, there are a relative lack of cholinergic, histaminergic and α_1-adrenergic side effects. Essentially, this means that adverse effects such as dry mouth, constipation, cardiotoxicity, sedation, weight gain, dizziness, and orthostatic hypotension are not a major concern with the SSRI's. (Kasper, 1994) In addition, the SSRI's are relatively safe in overdose especially in comparison to the tricyclics. (Arana and Hyman, 1987) However, the SSRI's do tend to have several associated side effects. They tend to cause nausea in some people. This side effect does appear to resolve somewhat with time. A common side effect of the SSRI's that may indeed interfere with

long term compliance is sexual dysfunction. According to Bernstein (1995), up to one third of SSRI patients experience reduced libido, arousal, and organismic functioning.

2.2.5 Compliance to Antidepressants

Clinical experience suggests that patients comply poorly with psychiatric medications (Haynes, 1979). Clinical data also supports this observation. Katon, Vonkorff, Lin et al. (1992) found that only 20% of patients who had been given prescriptions for first generation antidepressants (amitriptyline, imipramine, or doxepin) filled four or more prescriptions for the antidepressants in a six month period. This compared with 34% of patients who had prescriptions issued for the newer antidepressants (nortriptyline, desipramine, trazedone, and fluoxetine). Lin, Von Korff, Katon et al. (1995) interviewed patients and found that approximately 28% of patients prescribed an antidepressant for depression stopped taking medications during the first month of therapy and 44% had stopped taking them by the third month of therapy. Maddox et al. (1994) also interviewed patients prescribed antidepressants for any reason in general practice. They found that 32% of patients had stopped the medication within six weeks and 63% of these did not inform their GP of their decision to stop. In all of

the above studies, side effect burden, at some level, was significantly associated with the decision to discontinue. Myers et al. (1992) interrogated patients and counted left-over pills after four three week periods. They also found that there was a significant reduction in compliance with the antidepressants over time. Myers and Calvert (1984) found that patients who did not comply to treatment in the first three weeks of treatment were unlikely to comply further with the same treatment regimen.

These studies suggest that compliance to antidepressant medication is a problem. As with other medications, non-compliance can have significant impact on treatment outcome. Frank et al. (1992) showed that compliance to antidepressant therapy is significantly associated with effective long-term prophylaxis in recurrent depression. In addition, Gerbino (1993) suggested that, in people prescribed antidepressants for depression, no people who took less than 80% of their medication doses recovered. Little research has been done looking at the association between compliance and outcome for other illnesses that antidepressants are prescribed for such as bulimia nervosa and obsessive compulsive disorder.

Much of the literature on antidepressants has compared the original tricyclic antidepressants with the new generation SSRI's. Research suggests that both classes are

equally efficient in the treatment of depression. However, it has been suggested that the SSRI's are better complied to because of their improved side effect profile. Montgomery and Kasper (1995) performed a meta-analysis of 67 published controlled clinical trials comparing the SSRI's and the tricyclics. They found that, although both classes were similar in efficacy for depression, the SSRI's were better tolerated as indicated by longer intervals till discontinuation. In another meta-analysis of 42 randomized controlled trials, Montgomery, Henry, McDonald et al.(1994) found that discontinuations because of side effects were greater with the tricyclics than with the SSRI's. However, discontinuations due to inefficacy were the same for both classes. This study reinforces previous literature which suggests that efficacy is similar for both classes (in terms of treatment for depression). In addition, it suggests that the classes may differ in compliance because of side effects. Maddox et al. (1994) interviewed patients who recently started courses of antidepressant therapy. They found that the SSRI's did show a slight , but not significant, compliance benefit. They suggest that this difference may have been due to side effects or due to lack of treatment efficacy with the tricyclics because of the large percentage of sub-therapeutic doses prescribed.

Simon, VonKorff, Wagner, et al. (1993) used refill records from a HMO database to look at patterns of antidepressant use in community practices. In particular, they examined two potential predictors namely inadequate dose and duration of antidepressant therapy. They found that early discontinuation of antidepressant medication (24-35% in first month) was common and that the older antidepressants (i.e. tricyclics) had slightly higher discontinuation rates. In terms of dose, they found that fewer than half of episodes of therapy had a dispensed dose that exceeded recommended standards for depression and again, this was most prevalent in the tricyclic antidepressants.

2.2.6 Use of Databases in Antidepressant Research; Problems and Benefits

Several studies have used databases to look at various aspects of antidepressant utilization. It is evident from these studies that there are a number of problems and benefits associated with the use of databases for studying antidepressants. Few database studies have actually looked at compliance to antidepressants. Several studies were identified in which utilization patterns, discontinuations, and costs of therapy were ascertained from prescription refill records. These studies were all carried out in HMO

settings in the United States (Simon et al.,1993; Katzelnick et al., 1996; McCombs, Nichol, Stimmel et al., 1990; Katon et al. 1992; Lin et al. 1995). In each of these studies, the use of databases provided access to large populations of antidepressant users. Unlike clinical trials, the use of databases allowed the researchers to unobtrusively look at compliance. Katon et al. (1992) suggest that data coming from a community setting, as is the case with the information in the databases, provides a more valid picture of utilization problems such as compliance than would clinical trial data. Patients selected for clinical trials are typically highly motivated for treatment, and are generally excluded if they have serious concurrent medical or psychiatric illnesses.

A number of problems were also identified for using databases to look at compliance to antidepressant medications. First, in several studies, the databases did not provide reasons why patients discontinued or had gaps in therapy. Thus, little information could be obtained on the influence of drug efficacy or side effects on discontinuations. Although the gaps in treatment could have been due to side effects or to lack of efficacy, this cannot be inferred from the database.

A second problem was that most databases contained no

information on other treatments such as psychotherapy that a person might be undergoing. It has been suggested that this problem can only be corrected by directly interviewing patients. (Katzelnick et al., 1996)

A third and final shortcoming that was identified was the determination of indication for treatment. Most of the databases utilized did not contain reliable information on indication (McCombs et al., 1990; Simon et al., 1993, Katzelnick et al., 1996) This presented particular concerns when studying antidepressant medication because of the wide range of illnesses that the drugs can be prescribed for. This is particularly problematic for compliance research because the illness itself may impact upon compliance. In addition, research showing standard doses and drug efficacy is often illness specific. In relation to the antidepressants, most of the research relates to depressive disorders.

2.3 Outcome Measurement

Outcome measures which utilize information from prescription refill records result in indirect measures of patient compliance to medication. The underlying assumption of such research is that prescription claims accurately reflect patient use of medication. In addition, it assumes that the information that is recorded is accurate and

reliable. The benefits of using refill records is that they can provide otherwise unavailable information concerning patterns and timing of drug exposure (Steiner et al., 1997). Also, refill records are often more easily and cheaply accessed than other information such as information from patient interviews or pill counts.

A large typology of methods for assessing refill compliance from computerized pharmacy records have been utilized in the literature. Lacour et al. (1995) have classified these measures into two distinct categories; (1) the number and pattern of days during treatment with (or without) medication and, (2) the probability of permanent interruption of treatment. The first category involves looking at refill patterns to assess whether or not gaps in treatment may exist. The second measure focuses more on compliance related discontinuations of therapy. For example, a treatment discontinuer would be defined as someone who permanently discontinues therapy before it is recommended by the health care provider. Research in this area utilizes a number of subtly different measures which attempt to measure the extent of non-compliance. Several outcome measures will be described below which reflect compliance as defined by either of these categories. These measures have been utilized in the current study.

2.3.1 Percentage of Non-compliant Days

The percentage of non-compliant days is a measurement of the number of days with no medication on hand divided by the duration of the time period of interest multiplied by 100. (A variation of this measure involves substituting the number of days with medication for the number of days without medication.) This measure (with or without the multiplication by 100) has been used in a number of studies, several of which have attempted to validate it against other measures of compliance and outcomes. Steiner et al. (1988) coined the term Med-Out to represent the ratio of days without medication to the total number of days of treatment. They attempted to validate this measure using the records of subjects taking anticonvulsant and antihypertenive medications. They compared Med-Out to several physiologic outcomes of treatment; plasma phenytoin levels (anticonvulsants) and diastolic blood pressure (antihypertensives). Results indicated that Med-Out significantly correlated with the physiological outcome measures with a Pearson 'r' ranging from 0.30 to 0.42 in the expected directions. The authors suggested that the results might be somewhat modest due to misclassification of patients as compliant who obtained but did not use the medication. Further, they propose that the relationship

between compliance and drug effect is very complex and would not be totally due to compliance.

Wandless, Mucklow, Smith et al. (1979) also attempted to validate a similar measure in which the actual number of tablets received was divided by the theoretical number of tablets required for that period. They compared this measure to results from pill counts in a population of elderly individuals and found a significant correlation between tablet counts and the ration of non-compliant days to days with medication ($r = 0.68$, $p=.0001$).

A number of other studies have also utilized this measure to determine relevant predictors or associated outcomes of non-compliance (Monane, Bohn, Gurwitz et al. 1994; Gurwitz, Glynn, Monane, et al.,1993; Hamilton et al., 1992; Steiner, Robbins, Roth et al., 1993; Maronde et al., 1989). For example, Monane et al. (1994) found that the percentage of days without medication over a 12 month period varied by such predictors as age and concurrent medications. Maronde et al. (1989) looked at the outcome of rate of readmission to hospital for hypertensive problems. They found that those with a higher rate of readmission's had a significantly higher ratio of days when they were without any antihypertensive agents relative to the length of time in the study.

One important factor which did vary between studies using this outcome measure was whether or not the measure was adjusted to account for oversupplies obtained during previous prescription intervals. For example, an individual may have returned early to refill a prescription and thus would have a surplus of pills (this will be explained further in the methods section). Several studies did account for this problem (Gurwitz et al., 1993; Steiner et al., 1988).

A general assumption that accompanied the use of this measure was that treatment gaps are due to non-compliance by the patient rather than drug discontinuation by the clinician. This is an inherent limitation of utilizing this type of data and measurement. The percentage of non-compliant days was utilized in the current study as a measure of non-compliance to antidepressants.

2.3.2 Early Medication Stoppers Versus Continuers

A second category of non-compliers are those individuals who discontinue or terminate therapy early. These patients obtain medication only for a short period of time. According to Steiner et al.(1988), the individuals identified as non-compliers by the percentage of non-compliant days measure are different from the medication stoppers in that the non-compliance index detects patients who are more difficult to

identify clinically; those people who remain in the health care system, but fill only some of their prescriptions. In other words, the percentage of non-compliant days described above, represents individuals who remain in the system and continue to get medications refilled. However, they exhibit non-compliance by not taking the medication on the recommended schedule.

Early medication stoppers have been identified based on a number of different criteria. The most popular method of recognizing early stoppers has been to identify those people who fill only one prescription (Thompson et al., 1995; Gurwitz et al., 1993; Monane et al., 1994). The assumption underlying this criteria is that if a person fails to return for further prescriptions then s/he has exhibited non-compliance to the regimen, which is assumed to be of a long-term nature. This can be viewed as primary discontinuation of therapy or the decision on behalf of the client to desist that treatment.

In most of the studies that define medication stoppers as people who fill only one prescription, a standard length of time was evident during which a person would have been on the medication. For example, Thompson et al. (1995) used prescriptions that were typically filled on a 34 day basis. Thus, a person would have had at least a 34 day supply of

medication. Antidepressant medications have unique characteristics that may influence early compliance. More specifically, because of pharmacological down-regulation, an individual will probably be taking an antidepressant for two to six weeks before any therapeutic effects occur (Arana et al., 1987; Bernstein, 1994). During this time however, side effects do occur. Consequently, it has been suggested that people may discontinue early because of side effects and lack of perceived efficacy (Katon et al., 1992; Lin et al., 1995; Thompson, Rankin, and Ashcroft, 1982). Thus, several studies have defined compliance by the duration of time spent on medication. Those who discontinue the medication early were considered non-compliers. Lin et al. (1995) looked at antidepressant stopping using a 30 day treatment duration (after initial filling) and found that 28% of people reported stopping in the first month primarily because of side effects and lack of efficacy. This also varied between the classes of antidepressants with discontinuations for the tricyclics being greatest.

2.3.3 Time Till First Non-compliant Episode

Many prescription refill studies have examined non-compliance in terms of the percentage or number of non-compliant days. Only a few studies have actually looked at the duration individuals remain on medication before they

experience compliance problems as signified by 'non-compliant' gaps in treatment. Utilization of this measurement involves identifying the first 'non-compliant' period. This is accomplished by marking a gap of a specified duration as a non-compliant gap.

The idea of considering a gap of a specified duration as a non-compliant gap has been done in several studies. Bond and Monson (1984) considered a patient non-compliant when a 7 day gap in treatment occurred. Thompson et al. (1995) utilized much longer intervals of 60, 90, and 120 days to signify discontinuation of treatment to lipid-lowering medication. Hamilton et al. (1992) used a variable gap duration of which was calculated by multiplying 0.2 by the number of days supply of the previous prescription. For example, if the previous prescription was for 30 days then a non-compliant gap would be considered 6 days(30 X 0.2) between the end of the first prescription and the filling of a next prescription.

Once a first non-compliant gap has been identified, the time till this gap can be calculated. This measurement demonstrates the time course of non-compliance. In other words, it provides an indication of when during the course of therapy, individuals first become non-compliant.

2.4 Predictor Variables

Because compliance to drug regimens is such a significant predictor of outcome, it is imperative that predictors of non-compliance be identified. Previous research has presented a number of potential predictor variables of non-compliance including medication class, complexity of the medication regimen, treatment cost, and the demographic variables, age and sex. The literature presents both negative and positive results in terms of the predictive value of these variables.

2.4.1 Medication Regimen Complexity:

Christenson (1978) proposes that complexity of the medication regimen impacts on the level of compliance because of the confusion and inconvenience involved with complex regimens. Medication complexity includes such factors as number of concurrent medications and the number of doses per day.

2.4.1.1 Number of Concurrent Medications; Previous research has suggested a strong connection between the number of concurrent medications that an individual is taking and the level of compliance. More specifically, many studies have concluded and it is currently believed that the more medications that a person is taking, the less well that person complies to any particular medication. It has been

suggested that this is due to the fact that an increased number of medications are increasingly hard to keep track of and thus may lead to reduced compliance (Cramer et al., 1991). In contrast, several studies have also shown that compliance may actually increase as the number of concurrent medications increase.

Jones et al. (1995) looked at discontinuation of and changes in treatment of antihypertensive medications. They found that those patients who discontinued treatment had more concurrent medications than those who did continue the treatment. Sneddon and Farrall (1989), in a survey of an elderly population, established that compliance decreased as the number of items of medication increased. This was especially pronounced when the number of medications was greater than three. Larrat, Taubman and Willey (1990) performed interviews on a population of ambulatory individuals to ascertain compliance to a number of prescribed medications. They found that participants had at least a two times greater risk of showing compliance related problems if they were taking four or more medications than if they were taking fewer than four. Gurwitz et al. (1993) looked at prescription refill records to ascertain stop time and number of days without therapy in elderly individuals taking glaucoma treatment. They determined that patients

already taking large number of medications were less likely to comply to treatment with a new regimen. Hulka (1979) interviewed and followed charts of individuals treated for congestive heart failure and diabetes mellitus. She found that compliance, as measured by patient's reported failure to take medication as prescribed, increased as the number of concurrent medications increased.

In contrast to the studies cited above, several researchers have found that the number of concurrent medications have a direct relationship to compliance. Hamilton et al. (1992) used prescription refill records to assess gaps in treatment to a wide range of drug therapies. They found that compliance improved as the number of concurrent medications increased. Monane et al. (1994) found a similar result when they used refill records to look at the percentage of days without a prescription for congestive heart failure treatment. They also found that patients with the highest use of other medications had the least non-compliant days with cardiac therapy. These results challenge conventional beliefs concerning concurrent medications. Hamilton et al. (1992) suggest several possible explanations. First, patients taking multiple medications may be forced to develop dosage administration strategies that insure compliance. Second, patients who are perceived

by the health care provider as having complex regimens may receive more medication counseling than other patients.

2.4.1.2 Number of doses per day; The number of doses of medication that an individual takes per day has been cited as being a predictor of medication compliance (Cramer et al., 1991). Most of the literature suggests that, in general, an inverse relationship exists between the number of doses per day of a specific medication and compliance to that medication. Puller, Birtwell, and Wiles (1988) performed patient interviews and pill counts to ascertain level of non-compliance in type II diabetic patients. Patient interviews revealed that compliance was similar in once and twice daily dosing regimens but was worse with three times daily dosing. Pill counts indicated that compliance was best with once daily dosing while twice and three times were both equally inferior. Eisen, Miller, and Woodward (1990) used blister packs with electronic monitoring devices to evaluate the relationship between prescribed daily dose frequency and medication compliance in hypertensive patients. Compliance for those with one daily dose was 83.6% as compared to those with three daily doses at 59%. Gurwitz et al. (1993) looked at number of days without medication as a measure of compliance to glaucoma therapy in an elderly population. They found that people

using more than 2 administrations per day had more days without medication than those using 1 administration per day. A problem with this study was that it was assumed that medication administration patterns followed usual patterns. Number of doses per day was calculated based on the usual number of administrations per day (based on the literature) for the particular medication prescribed. Widmer, Cadoret and Troughton (1983) used refill patterns to look at compliance in antihypertensive medications in a rural area. Similar to the other studies, they determined that taking three or more pills a day was significantly related to non-compliance. Baird, Bentley-Taylor, Carruthers et al. (1984) used a randomized controlled trial to look at compliance to once versus twice daily Betaloc® (Metoprolol) therapy in hypertensive patients. They also found that compliance, as assessed by tablet counts, was significantly improved in the groups receiving once daily therapy. Each of the studies described above suggest that number of doses per day may influence compliance. It is interesting that research in this area has covered a wide range of methodologies from databases to randomized controlled trials and pill counts.

Kelloway et al. (1994) evaluated compliance and dosing frequency of two asthma medications by looking at medical and pharmacy claims records. In contrast to the studies

described above, they did not find any significant difference in compliance relative to prescribed dose frequency (twice daily or less compared with three times daily or more).

Hamilton et al (1992) utilized a prescription database to look at compliance to several types of medications. This database did not provide specific information concerning the number of administrations per day. The authors inferred doses per day from an indirect measure; the quantity of drugs dispensed divided by the days supply. This measure gave the apparent number of doses per day. In using this as a measure of number of doses per day, an assumption was made that each unit of medication was taken separately. Their finding were consistent with those of other studies, that compliance generally decreased as the number of apparent daily doses increased although the relationship was not linear. Rather, the greatest drops in compliance occurred after four doses per day. This method of looking at doses per day is very indirect and does have inherent problems. However, the authors state that the assumption that each tablet or pill represents one dose is generally reasonable for most drugs that have a wide variety of tablet strengths. Antidepressant medications do commonly come in a wide variety of strengths.

2.4.2 Demographic Variables

A great bulk of research has been dedicated, in part, to determining whether the demographic variables age and sex influence patient compliance to medication regimens.

2.4.2.1 Age; The literature shows little consensus in terms of the relationship of age to compliance. Several studies have suggested that age does have an impact on compliance. More particularly, several studies suggest that older age groups are more compliant than younger age groups. Thompson et al. (1995) found that users of lipid-lowering medications who were younger than 45 were more likely to stop medication than the most compliant group, 45-74 years. Simon et al. (1996) also found that the risk of discontinuation of lipid-lowering medication was lower in older patients (65+) than in younger patients. Rovelli et al. (1989) also found that older patients were more compliant to immunosuppressant therapy after organ transplant than were younger patients. Monane et al. (1994) looked at compliance to congestive heart failure therapy in an elderly sample and also concluded that compliance was greatest in the oldest age group (>85 years). They suggest that improved compliance in older age groups may be related to caregiver assistance.

A large number of studies have found no association between age and compliance. Frank et al. (1992) and Lin et al. (1995) attained no significant age association with discontinuation rates for antidepressant therapy. Larret et al. (1990), Sneddon et al. (1989), and Gurwitz et al. (1993) all determined that age was not a significant predictor in 60+ age groups for a variety of therapies. Stanaway et. al. (1985) found no age related association with compliance to anticonvulsant therapy. Gallagher, Viscoli, and Horwitz (1993) also failed to detect any significant age association to antihypertensive treatment in a female cohort.

As can be detected from the studies cited above, a great deal of controversy exists as to whether or not age has any predictive value for non-compliance. Overall, it would appear that most studies suggest that no association exists between the two. In addition, in several of the studies that did show an association between age and compliance, the association was weak (Monane et al., 1994).

2.4.2.2 Sex; Most of the research looking at patient gender suggests that it is not a predictor of patient compliance. Shaw, Anderson, Maloney et al. (1995) found that sex was not a significant predictor of compliance to antihypertensive medications. Larret et al. (1990) looked at

an elderly population (>60 years) and also found that sex was not a significant predictor of compliance to general medication use. Similar results were also obtained by Frank et al. (1992) and Lin et al. (1995) who looked at compliance to antidepressant medications. A number of other studies, looking at a wide variety of medications, also found that sex was not a significant predictor of compliance (O'Connor, Allen, Hilbert et al., 1981; Gurwitz, 1993; Stanaway et al., 1985)

Beardon, McGilchrist, McKendrick et al. (1993) and Andrade et al. (1995) both found slight differences between the sexes in terms of compliance, with females being more compliant. However, in both studies, the authors accounted for the differences by other variables. Thus, most of the literature does not support the notion that sex might be a predictor of non-compliance. Despite this, further study regarding the impact of patient gender on compliance should be done for antidepressants because this variable has not been studied in a database setting (with regards to antidepressants). In addition, antidepressants have a unique demographic profile. More specifically, approximately 75% of antidepressants are prescribed to females (McCombs et al., 1990).

2.4.3 Treatment Cost

The effect of the direct patient cost for prescriptions is a relatively unexplored factor in compliance research. Most of the compliance studies that have used databases have used HMO and Medicaid populations. Thompson et al. (1995) examined the effect of varying the deductible (i.e. prescription cost) on refill compliance to lipid-lowering drugs in a Saskatchewan population. They found that the odds of stopping the medication increased marginally for each $10 increase in patient cost.

Beardon et al. (1993) determined the rate of patients not redeeming their prescriptions by comparing copies of prescriptions written by general practitioners with those actually dispensed by the pharmacist in a rural area. They found that, of those who redeemed prescriptions, 17% were not exempt from prescription costs. This compared with 33% of patients who failed to redeem prescriptions. This suggests that prescription charges may be related to patient refill behaviour.

Shaw et al. (1995), in a survey of adult patients on anti-hypertensives, found that 20% of respondents stated that cost or a lack of money to buy medications was a reason for missing doses of medication. This study was based on a small sample (n=98).

O'Connor et al. (1981) looked at the number of people filling their initial prescription. In contrast to the above studies, they found that there was no difference between those who filled free prescriptions (social services recipients) and those who paid for prescriptions. A major problem with this study was that private insurance plans were not taken into account.

Most of the studies looking at prescription cost do suggest that cost might influence compliance or continuation with a medication regimen. Most studies however, have looked only at the cost of that particular medication to the consumer. A gap in the literature exists in that few studies have looked at the effect of the costs for all other medications that a person is taking on compliance.

3 METHODS

3.1 Purpose, Objectives and Hypotheses

The primary goal of the current study was to examine refill compliance behaviours and identify potential predictors of refill non-compliance in a sample of antidepressant users who were subscribers to the Atlantic Blue Cross Insurance Plans. A number of objectives and associated hypotheses were developed and are described below.

The first objective was to describe the sample of antidepressant users in terms of the problem of non-compliance as indicated by the three different non-compliance measures. The first measure, the percentage of non-compliant days allowed us to look at gaps in treatment in patients who continued to have prescriptions filled. Previous research looking at other medications has shown that the mean percentage of time without medication has ranged from 9% - 31%. (Monane et al, 1994; Gurwitz et al, 1993; Steiner et al, 1993; Steiner et al, 1988) Based on these studies, we predict a similar mean percentage of time without medication for the tricyclics and SSRI's. The second outcome measure compared early treatment stoppers to treatment continuers. Previous studies with antidepressants

have suggested that between 32% and 35% of antidepressant users discontinue treatment during the first 30 to 60 days of therapy (Simon et al, 1993; Maddox et al, 1994). We expect to find similar discontinuation rates in the current study. A final outcome measure that was utilized was the time till the first non-compliant gap. Literature on the antidepressants suggest that compliance problems may occur early in therapy due to the extended time till the onset of action of the medications as well as the side effects of the medications (Bernstein et al, 1995). Based on this information, it was hypothesized that the greatest drop in compliance would occur early in treatment in the first 1-3 months.

The second objective was to determine whether differences in compliance exist between individuals using antidepressants from the tricyclic and SSRI classes. Based on previous literature (see section 2.2.5), it was hypothesized that non-compliance would be a greater problem with the tricyclics than the SSRI's because of their worse side effect profile. Thus, it was expected that more tricyclic users than SSRI users would stop medication early. In addition, the tricyclic users would have a greater percentage of non-compliant days than the SSRI users. Also class, of medication would be a predictor of the percentage

of non-compliant days as illustrated by a regression analysis. Finally, it was expected that survival analyses would indicate that the probability of survival till a non-compliant gap in treatment would be significantly less for the tricyclics than the SSRI's.

The third objective was to ascertain whether medication complexity as demonstrated by the number of concurrent medications per day and the number of doses per day would effect compliance to the tricyclics and the SSRI's. In terms of the number of concurrent medications, conventional belief in much of the literature suggests that, as the number of concurrent medications increase, the complexity of the medication regimen also increases, and consequently compliance decreases. Consistent with the literature, we expected to find that compliance to both the SSRI's and tricyclic antidepressants would decrease as the number of concurrent medications increase. In terms of the number of doses per day, the literature suggests that increasing the number of times a medication has to be taken each day also increases the complexity of the medication regimen and thus decreases compliance. Consistent with the literature, we expected to find that compliance would decrease as the number of doses per day increase.

The fourth objective was to determine whether the

demographic variables, age and sex, are predictors of compliance to the antidepressants from the SSRI and tricyclic classes. Past literature on other drugs as well as on antidepressants (Frank et al., 1992; Lin et al., 1995) has suggested that sex does not influence compliance. We expect to obtain the same result in the current study. The literature has been quite conflicting in terms of the role of patient age on compliance. A number of studies have suggested that age has no impact on compliance (Frank et al., 1995; Gurwitz et al, 1993, Gallagher et al, 1993) while several studies have implied that as age increases, compliance increases (Monane et al., 1994; Thompson et al., 1995). In addition, in several of the studies that did show a positive association between age and compliance, the association was often weak (Monane et al (1995). Since the majority of the literature suggests that age does not impact on compliance and most of these studies have been carried out in a similar population database setting, we expect to see similar results in the current studies for users in both the SSRI and tricyclic classes

The fifth objective was to establish whether the average cost paid per prescription for the antidepressant medication as well as for any other medications an individual is taking, impact upon compliance to the

tricyclic or SSRI medication. Most of the research to date suggests that as the cost paid by the user increases compliance to the medication decreases. In the current study, the average cost paid per prescription for the antidepressant and the average cost paid per prescription for all other medications will be considered separately. The cost of other drugs was calculated separately from the cost for the antidepressants so that we could get a better idea of which direct patient costs were more likely to influence compliance; the cost for the drug itself or the other drug costs that a person was paying. Based on previous studies, it was hypothesized that increased cost in each of the two categories would decrease compliance.

A final objective of the current study was to evaluate the problems and complications involved with utilizing the Atlantic Blue Cross Database for compliance research.

3.2 Atlantic Blue Cross Database

A sample of prescriptions was taken from the database of the Atlantic Blue Cross Prescription Drug Insurance Plan based in New Brunswick, Canada. This database consisted of any clients who used community pharmacies which utilize a point of sale data system in Atlantic Canada (this includes 98% of pharmacies; 2% of pharmacies have not yet switched to

a computerized system).

Atlantic Blue Cross is utilized by individuals or families who live in Atlantic Canada and, through work or private means, have insurance coverage with Blue Cross. Typically, subscribers on group plans might work with agencies such as the federal or provincial governments, universities, or other businesses. This excludes some low income populations such as people receiving welfare and seniors who utilize provincial drug plans. Therefore, the results from this study are not necessarily applicable to the general population.

3.3 Study Design

An historical prospective study design was utilized. All beneficiaries of Atlantic Blue Cross who had at least one antidepressant prescription filled during the recruitment period of September 1995, were identified. A total of 6389 individuals fitted the criteria of having an antidepressant prescription filled during that period. All available records of all medications dispensed to each individual during the period of the database; August 15, 1994 - September 30, 1996, were obtained from Blue Cross. (Due to data storage problems, Blue Cross maintains records on each beneficiary for a period of approximately 2 years. Therefore, all data before August 15, 1994 was unavailable

for study.) The data was received from Blue Cross on diskette.

Thus, approximately two years of data was obtained. As can be seen in Figure 3.1, this time period was broken down into two study segments. The period from August 15, 1994 till February 15, 1995 was an initial screening interval. Any individual who had a prescription filled during that period was excluded. This was done to ensure that the first prescription in the database was the first prescription for that person. Six months is consistent with time intervals used for initial screening in previous compliance studies (Thompson et al., 1995; Jones et al., 1995). The second study segment was the period between February 15, 1995 and September 30, 1996, an interval of approximately one year and seven months. Any individual who started antidepressant treatment during this interval (as indicated by their first record) were included in the initial study cohort.

3.4 Ethical Considerations

The data supplied by Blue Cross contained no identifiers such as names or addresses which would allow the researchers to identify specific clients. The pseudo-identifiers, age and sex were provided for each subject. In addition, each household or family was given a pseudo-

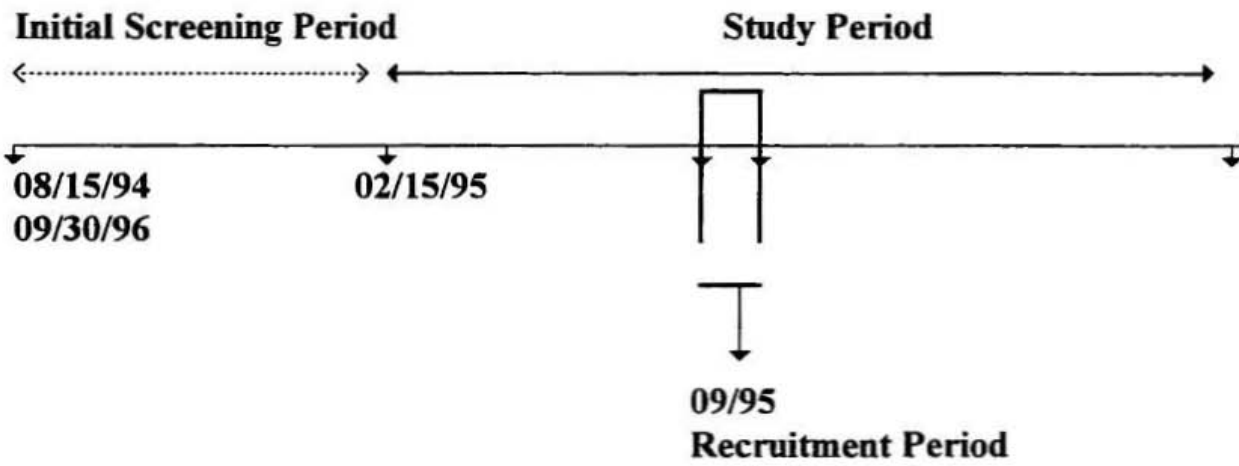


Figure 3.1: Time Line For Study; All beneficiaries of Blue Cross who had a prescription filled for an antidepressant during the recruitment period were chosen. Any records for these people which fell between 08/15/94 and 09/30/96 were obtained. Any person who had a prescription for an antidepressant filled during the initial screening phase was excluded from the study. Any person who started a course of treatment during the study period (02/15/95 - 09/30/96) was followed up to examine refill compliance.

identifier; a random four digit identification number. This project was approved by the Human Investigations Committee of Memorial University's Faculty of Medicine (see Appendices 3 and 4)

3.5 Database Management and Clean-up

Preliminary clean-up and analyses of the database received was done in Microsoft Access Version 7. The database contained 14 different fields, each of which contained specific information such as sex, date of birth, dispensing date or trade name (see table 3.1). Several of the fields were not used in the study including the 'new/refill' and the 'total cost of the drug' fields. A sample of the data can be found in Appendix 2.

3.5.1 Original Family/ Household Identification Number

The original data obtained from Blue Cross contained no individual identifiers. Rather, a four digit random number was used to identify all members sharing a family or household policy. Because this number was random, it was possible that several families may have received the same identifier. In order to identify individuals, a unique identifier had to be added to each person's set of records. The family identifier was used as a partial indicator in the attaching of a unique ID to each person.

Table 3.1: Summary of Information Contained in 14 Fields of Database

Field Name	Description of Information
Family Identification Number	Random non-exclusive 4 digit number which identified members sharing a family polic
Unique ID	Added to records by researchers; identified individual people
Counter	The unique counter identified each specific record* for each person in the database
Date Of Birth Field	Day/Month/ Year person was born
M/F	Sex of Client
Dispensing Date	Date on which drug was dispensed to clien
Quantity Dispensed	Number of pills dispensed to person on a particular dispensing date
Days Supply	Number of days that the medication supply was intended to last client.
Total Cost of Drug	Total cost of drug paid by Blue Cross
Cost of Drug to Subscriber	Price paid by subscriber (deductible)
Drug Identification Number	Standardized number which represents the specific pill dispensed
Product Therapeutic Class Code	Specific therapeutic class that drug belonged to (i.e. antidepressant, lipid-lowering etc.)
Trade Name	Specific name of the drug dispensed
New/ Refill	Indicated whether drug was a new prescription or a refill

* Record refers to one incident or drug dispensing for an individual. Each time a medication was dispensed, a new record was filled in with information entered into each of the 14 fields.

3.5.2 Adding a Unique ID Number

A new identification (ID) field containing a four digit person identifier was added to each record in the database that had similar characteristics. More specifically, if a set of records all contained the same unique combination of household ID number, sex and date of birth then a common four digit number would be added to each record in the set. This number would be unique to that particular combination of family ID, sex, and birth date and would represent or mark all records for an individual person.

By using sex and age as indicators in addition to the family identification number, the margin of error in assigning new identifiers was reduced. In order for the records of two different people to be combined as one person, the records would have to have had the same random Blue Cross four digit number, the same sex, and the same date of birth. It was impossible to distinguish the rare incidences where records meeting the study protocol actually belonged to two different individuals (as in the case of twins). Hence, there may have been some error in adding the individual identifiers.

3.5.3 Date of Birth Field

The database contained a 'Date of Birth' (DOB) field. This information was used to aid in the identification of

individuals as well as in the calculation of subject age.

The DOB field required data cleaning before the information could be utilized. The date of births were not always accurate in that an individual may have had two different dates of birth. A cleaning protocol was first developed in order to identify the records where the date of births may have been inaccurate. All birth dates that did not meet the cleaning protocol were left unchanged. The data was cleaned using a series of steps. First, each record was sorted on the basis of sex and four digit family or household identifier. If two sets of records had the same identifier, the same sex, and slightly different dates of birth then the records were inspected further. If the dispensing dates for both record sets were continuous (i.e. the dispensing dates did not overlap between the two sets of records) and the drug types (as identified by the 'trade name' field) were the same for both record sets, then the records were considered to belong to one person and the birth date was changed to the most frequently recorded date. If there were equal numbers of records with each date then the birth date was changed to the most recent date.

Dispensing date and trade name were only checked if the identification number and the sex were the same between two records but the date of birth differed by one number in

either the year, month, or day field or if the birth dates were less than ten years apart. For example, if two record sets had the same family ID number, both specified 'male' in the sex field, and the DOB's were slightly different (08/08/73 and 08/09/73) then each of the records in the set would be inspected. This process was done very methodologically and records were only changed if they met the specified criteria of having continuous dispensing date and the same trade names. Records were left unchanged (i.e. left as two separate people) if these criteria were not met. Undoubtedly there was some error in this process but it was a necessary procedure considering the errors in the database. Most of the changes made were very obvious mistakes. The birth dates may have varied by one or two numbers in either the day, month, or year fields. The errors were probably data entry problems at the pharmacy level and may have been the result of a client utilizing different pharmacies, each of which had different information on him/her. In total, 2.07% of the initial birth dates were changed.

3.5.4 M/F (Sex) Field

Sex of the subject was given as either a 'M' (Male) or 'F' (Female). A problem that was encountered in this field was the presence of a third sex identifier; 'X'.

Consultation with Blue Cross revealed that they had no record of this field value. An inspection of the birth and dispensing dates showed that, in most cases, the dispensing date was earlier than the date of birth suggesting that 'X' may have signified a fetus. In all cases where an 'X' existed in the data, the date of birth was in the year 1996. There were only 15 identification numbers which contained 'X's in the sex field. Although these subjects were not specifically eliminated because of this problem, all of these records were eliminated in the final analysis because they fell into one of the other exclusion criteria.

3.5.5 Dispensing Date

Each record for each subject contained the date on which the drug was dispensed. The dates given in the 'dispensing date' field were assumed to be accurate.

3.5.6 Days Supply

A major problem that was encountered with the Blue Cross Database was that the 'Days Supply' Field, which provided the number of days that a particular prescription was dispensed for, was not a required field for the pharmacies to complete. This field was critical to this project because it was used in the calculation of any gaps in treatment that may have existed for each subject. Several patterns were picked up in the data that suggest that some

pharmacies may have used default values for this field instead of filling in the actual number of days that the drug was supplied for. First, a number of records had '0', '1' , '999', or '365' in the 'Days Supply' field. All people with at least one record with either of these numbers in the 'Days Supply' field were eliminated from the analysis. In addition, all other records with extreme numbers (>180 or <10 days) in the 'Days Supply' Field were identified and these records were reviewed individually and adjusted or eliminated by a specified set of criteria. First, the records with the extreme values were inspected in relation to the other records for that person. If all of the records had similar values in the 'Quantity Dispensed' field and only several extreme values in the 'Days Supply' field then the extreme records were changed to the more consistent value of the 'Days Supply" field. For example, Table 3.2 depicts an instance for one person where all 'Days Supply' records but one are for 30 days. In counter row 45014 , the 'Quantity Dispensed' field did not change but the 'Days Supply' did. It is assumed that this one extreme value was the result of a data entry error. Inspection of the dispensing dates also reveal that the person returned in 30 day intervals to refill the prescription further reiterating that the 'Days Supply' for record 45014 should have been 30

Table 3.2: Example of a Record Set for a Subject With A Incorrect Value In the 'Days Supply' Row

ID	Counter	DIN	TRADE NAME	DISP DATE	DRUG QTY	DAYS
1028	13289	740802	APO-TRIMIP	15/02/95	30	30
1028	13293	740802	APO-TRIMIP	14/03/95	30	30
1028	13296	740802	APO-TRIMIP	19/04/95	30	30
1028	13299	740802	APO-TRIMIP	23/05/95	30	30
1028	13305	740802	APO-TRIMIP	29/06/95	30	30
1028	28941	740802	APO-TRIMIP	31/07/95	30	30
1028	45014	740802	APO-TRIMIP	30/08/95	30	5
1028	65122	740802	APO-TRIMIP	28/09/95	30	30
1028	81480	740802	APO-TRIMIP	30/10/95	30	30
1028	98077	740802	APO-TRIMIP	29/11/95	30	30
1028	113962	740802	APO-TRIMIP	29/12/95	30	30
1028	130427	740802	APO-TRIMIP	31/01/96	30	30
1028	145767	740802	APO-TRIMIP	29/02/96	30	30

days. Records were only changed if these patterns could be found in the data. Otherwise the values were left as they were.

3.5.7 Drug Quantity

The number of pills dispensed to a person on any particular date was recorded in the quantity field. Blue Cross required that the pharmacy complete this column each time a drug was dispensed. No default values were identified in this field. This field was essential in calculating the variable, number of doses per day

3.5.8 Cost of Drug to Subscriber

Two cost fields were included in the database; the total cost of the drug and the cost of the drug to the subscriber. The total cost of the drug was not of interest in this study and will not be discussed further. In reference to the 'Cost to the Subscriber' field, the percentage of the drug cost paid by the subscriber varied based on the benefit plan in which the person was enrolled. This was of particular interest because it allowed for comparisons of average cost paid per prescription per person within each class of drugs.

3.5.9 Drug Identification Number (DIN), Trade Name, and Product Therapeutic Class (PTC) Code

These three fields of varying specificity provided identification and information on the drugs dispensed to the subscriber. The DIN was the most specific code. This is a standardized number assigned to each different medicine available. This number provides specific information including such things as the trade name, route of administration and dosage of the medicine. The trade name is less specific and does not provide specific information about such things as dose. The most general identifier was the PTC code. This code identifies the specific therapeutic class of the drug. For example, all antidepressants have a common PTC code.

These identifiers were used for several purposes. The PTC code was used to identify all specific antidepressant records which were then separated into a new table. The DIN and trade names were used to identify the exact drug that the subject was dispensed. For the antidepressants, the Canadian Drug Identification Code (CDIC) and the Compendium of Pharmaceuticals and Specialities (CPS) were used to determine the generic name of each particular trade name in the database. Appendix 1 shows a complete listing of the DIN, trade names, and generic names of the antidepressants

found in the database

3.6 Exclusion of Subjects

46% of the initial study cohort (n=6389) was eliminated. Figure 3.2 depicts the number and chronological order of exclusions and the associated reason for each exclusion. A more detailed explanation for each of the exclusions is provided in Figure 3.2.

A number of people were excluded due to the incompleteness or contamination of records in the 'Days Supply' Field. Many pharmacies entered default values (i.e.'0','999', '1', or '365') in this field because Blue Cross did not require that the field be completed. In total, 1395 people were excluded because of default values in this field.

Any subject who received antidepressants from more than one class during the course of therapy was eliminated because of the difficulty involved in doing interclass comparisons on the study population as a whole (n= 998). This was particularly relevant for people who switched between drug classes several times during the course of therapy. It would have been extremely difficult to identify true gaps in therapy for each class separately while factoring in the possibility that a gap in therapy may have been the result of a switch in class or a period when the subject was actually taking an antidepressant from another

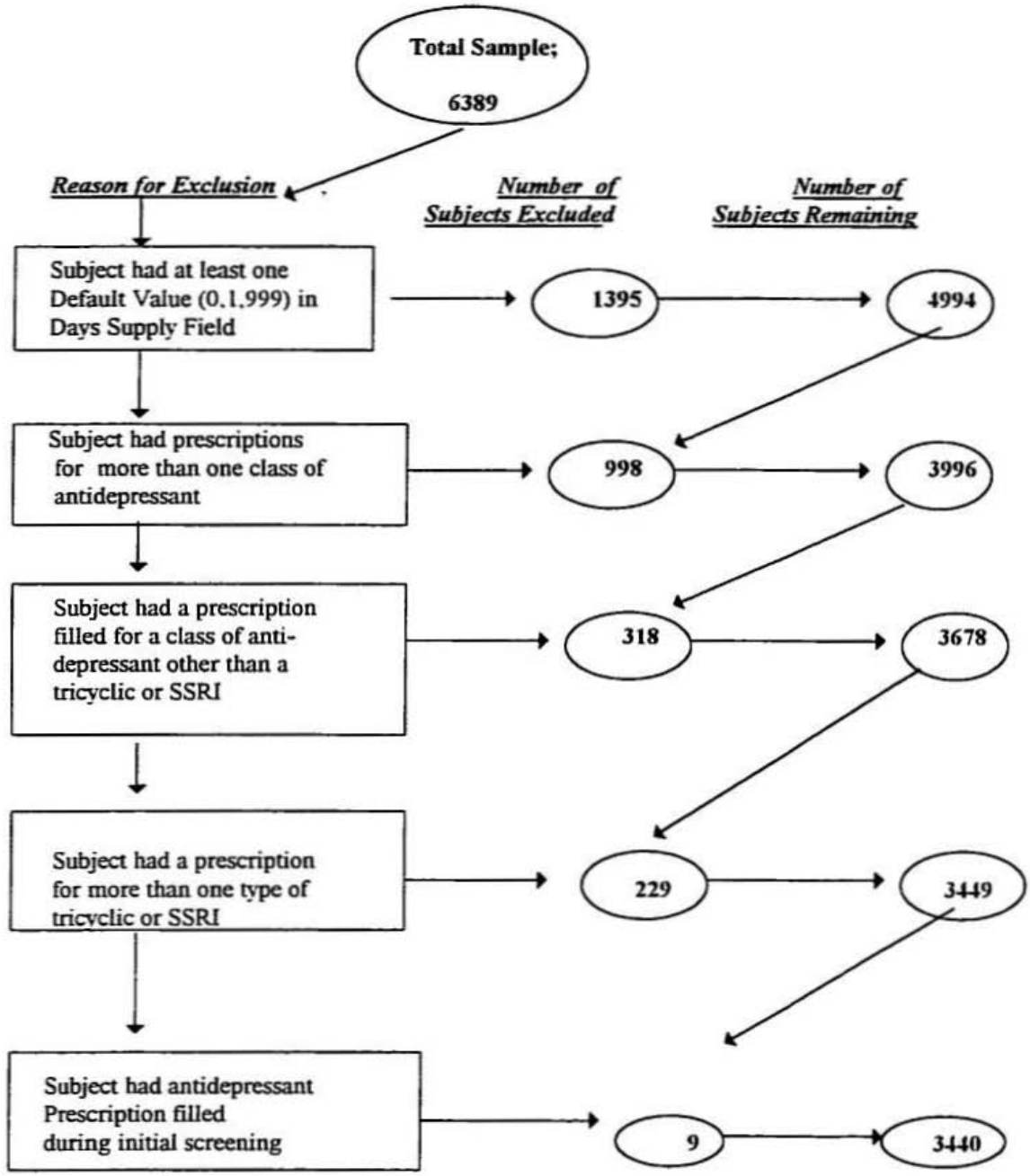


Figure 3.2: Exclusion of Subjects. Depicts the initial study cohort at the top of figure and shows the reason for each exclusion, the number excluded for that reason and the remaining number of people left. The chart flows in order of exclusions. It is possible that subjects may have fit more than one of the exclusion criteria.

class. An additional reason for excluding these subjects from the study was that switching between medication classes could possibly have impacted on compliance and thus acted as a confounder.

All individuals who were on any antidepressant drugs other than those falling into the tricyclic and SSRI classes were excluded from the analyses because the focus of the study involved only a comparison between these two classes (n=318).

Subjects were also excluded from the analyses if they filled prescriptions for more than one type of medication within a class at any time during the course of treatment (n=229). The start of a new type of medication after previously using another type in that class had potential implications for observing the gaps in treatment. For example, if a person started a new course of antidepressant therapy while still having pills left from older prescriptions, gaps in therapy would be masked because it would be assumed that the person was using the old pills to fill in the future gaps.

Several subjects were eliminated because they had prescriptions filled during the initial screening period between August 15, 1994 and February 15, 1995 (n=9). Any other people that may have had prior prescriptions were

eliminated earlier for other reasons.

Thus, the final pool of subjects included all people who were not excluded because of inter- or intra- class switching, because they fell into the first six months of data, or because of data contamination. This left 3440 people in the study group, 1582 in the SSRI group and 1858 in the tricyclic group

3.7 Predictor Variables

A number of predictor variables were calculated using various fields in the database. These variables are described below. In addition, the calculation of these variables as well as the fields that were used in the calculation are summarized in Table 3.3.

3.7.1 Number of Doses Per Day

The number of doses per day was calculated for each individual by dividing the quantity dispensed by the days supply in order to determine the apparent number of doses per day. We assumed that each unit of medication was taken separately (i.e. that the prescription did not call for taking more than one tablet per dose). This value was calculated for each antidepressant record and an average was found for all antidepressant records for that subject.

Table 3.3: Summary of Predictor Variables, Calculation of Predictor Variables and Database Fields Used in the Calculations

Predictor Variable	Calculation Summary	Database Fields Used
Age	1996 - Year of Birth	`DOB'
Sex	M/F	M/F
Antidepressant Cost	Avg Cost Per Prescription (calculated over full treatment episode)	`Cost to Subscriber'
Other Cost	Avg Cost Per Prescription (calculated for same time as antidepressant cost)	`Cost to Subscriber'
Concurrent Medications	Number of different PTC codes in subjects record in first 45 days of anti'd therapy	`PTC code'
Number/Day	Number of Pill Dispensed / Number of Days Supply	`Quantity Dispensed' `Days Supply'

3.7.2 Concurrent Medications

The number of concurrent medications was calculated by counting the number of different PTC codes in a user's file during the first 45 days of the antidepressant prescription. Trade names were not used as indicators of the number of other drugs a person was taking because they may vary for the same type of drug. For example, during the course of treatment with a particular medication, the pharmacist might switch a person from an expensive brand name to a less expensive generic brand of a drug. In this case, the trade name would change even though the drug is the same as the original. By using the PTC code as an indicator, is was assumed that a person would only be taking one drug of a particular type (i.e. antidepressant, lipid-lowering etc.) at any one time. Thus, a count of the number of different PTC codes was actually a count of the number of different therapeutic classes of drugs that the subject was issued drugs from during the first 45 day interval.

A uniform 45 day time interval was used so that the number of concurrent medications could be compared between subjects. Because treatment duration varied between people, there would have been a greater chance that subjects on the antidepressant medication for a longer interval would have taken more concurrent medications. Thus, a count of the

total number of other medications during the entire antidepressant episode for each subject would have been dependant upon duration. To ensure that the measure was independent of duration, only those medications dispensed in the first 45 day period of the antidepressant episode (i.e. first dispensing date for an antidepressant + 45 days) were counted.

3.7.3 Age and Sex;

Age was calculated for each subject by subtracting the year that the person was born from 1996. Days and months were not taken in account when calculating the age.

3.7.4 Cost to Subscriber

The cost to the subscriber was broken down into two variables; the cost paid per prescription for antidepressants and the cost paid per prescription for other drugs. The cost for antidepressant therapy was calculated as the average cost paid per prescription during the treatment episode. The average cost paid for other drugs was calculated for the time period during which the subject was dispensed an antidepressant medication. Thus, the only drug costs for other medications included in the calculation of the average cost paid for other drugs, were those where the associated dispensing date was between the start and end-date for the episode of antidepressant therapy.

3.8 Class Identification

Many of the analyses were also done separately for each class to reduce the variability due to intra- class differences. In addition, separate analyses allowed us to look at trends within each class.

Each antidepressant trade name in the database was classified into a specific class and type within that class (generic) on the basis of recommendations from several sources including the Canadian Drug Identification Codes (CDIC), the Compendium of Pharmaceuticals and Specialities (CPS), Dr. T. Kara, and Ms. Audrey Fultz of The Pharmacy Resource Centre (Memorial University of Newfoundland). All antidepressant records were first identified based on a common PTC code; 281604. In total, there were 163 different trade names included in the data. These were each divided into one of 6 classes including tricyclics, selective serotonin re-uptake inhibitors (SSRI's), serotonin-norepinephrine re-uptake inhibitor (SNRI), heterocyclics, monoamine oxidase inhibitors (MAOI's), and atypical antidepressants. A complete list of each trade name, the associated DIN, class, and generic name within each class can be found in Appendix 1.

3.9 Outcome Measurement

Several outcome measures were used including percentage of days without medication (i.e. percentage of non-compliant days), time (in days) till a first non-compliant gap, and a comparison of early medication stoppers to those who did not stop taking their medications. Detailed descriptions of the outcome measures as well as the underlying assumptions that were made in terms of treatment episodes are described below.

3.9.1 Finding Gaps In Treatment

In order to examine patterns of refill within a treatment episode it was necessary to identify gaps in treatment. This calculation was used in both the percentage of non-compliant days and the time till a first non-compliant gap outcome measures. A gap was defined as any period during treatment when a person did not have any medication in hand, based on the information in the database.

In order to calculate the treatment gaps several pieces of information were necessary. First, the dispensing date for the medication was needed. Second, the number of days that the medication was dispensed for was critical for calculating the end date or estimated stopping date when the medication from that particular prescription should have

been completely consumed. The end date, then, was calculated by adding the number of days that the medication was issued for to the original dispensing date. This end date was then compared to the next chronological dispensing date in the subject's records. For example, if a person filled a first prescription for 30 days and did not fill a second prescription until 10 days after the end date for the first prescription, then a 10 day gap in treatment would exist. However, the calculated gap between the end date of one prescription and the dispensing date of the next prescription, did not necessarily represent a true gap in treatment. For example, if a person filled two prescriptions on the same day, each for a 30 day supply of pills, negative 30 would appear as the difference between the end date of the first prescription and the dispensing date of the second prescription. However, assuming that the person filled the third prescription on time (i.e. 60 days after the first dispensing date) then the difference between the end date for the second prescription (filled on the first day) and the third prescription would be +30. This would occur because the end date for the second prescription would be the same as the end date for the first prescription because both had the same dispensing date and the same value in the 'Days Supply' field, 30 days. Thus, the difference between

the second end date and the third dispensing date would create an artificial gap in the data. This problem would occur on any occasion when a person returned to the pharmacy early (i.e. before the end date for the prescription) to obtain a refill. Therefore, negative 'gaps' in the data had to be carried forward to cancel out future positive gaps. A negative number indicated that a person had 'X' many days of extra pills on hand.

The problem of artificial gaps was remedied by starting a running total of the calculated gaps for each person. Any negative gaps would be added into the next (chronological) positive or negative gap. However, when the running sum became positive then a real gap in treatment had occurred. At this point, the subject, according to the data, could not have had extra pills on hand because all negative refill days were accounted for. Each time a positive number occurred in the running total, it was reset to the value of the next gap as calculated from the end date and dispensing date. Thus, the true gaps in treatment that occurred were the positive numbers that occurred in the running sum that was calculated from the original gap calculation. The negative numbers that occurred in the running sum column were an indication of the number of extra days of pills that a subject had on hand at that point in time.

3.9.2 Identification of Treatment Episodes

A treatment episode was defined as a period of continuous treatment with the antidepressant. Because no information on treatment duration or reasons for stopping treatment were available from the data, it was necessary to infer that a particular treatment episode had ended based on a specific algorithm. A treatment episode was considered to have ended when a gap of 90 days or greater occurred between two consecutive prescriptions. Thus, any two consecutive prescriptions fills separated in time by less than a 90 day gap in treatment were classified as part of the same treatment episode whereas any two consecutive treatment fills with a gap greater than 90 were classified as separate treatment episodes (see Figure 3.3). Simon et al.(1995) also used a 90 day or greater gap in treatment as the signal that a treatment episode had ended. This relatively long interval was chosen in order to exclude any records for a subject that may have occurred after a recent treatment failure. Any subject might have had more than one treatment episode but only the first treatment episode was utilized in this study.

3.9.3 Calculation of Treatment Duration

For the percentage of non-compliant days measure, it was necessary to calculate overall treatment duration for the episode of treatment. This was accomplished by

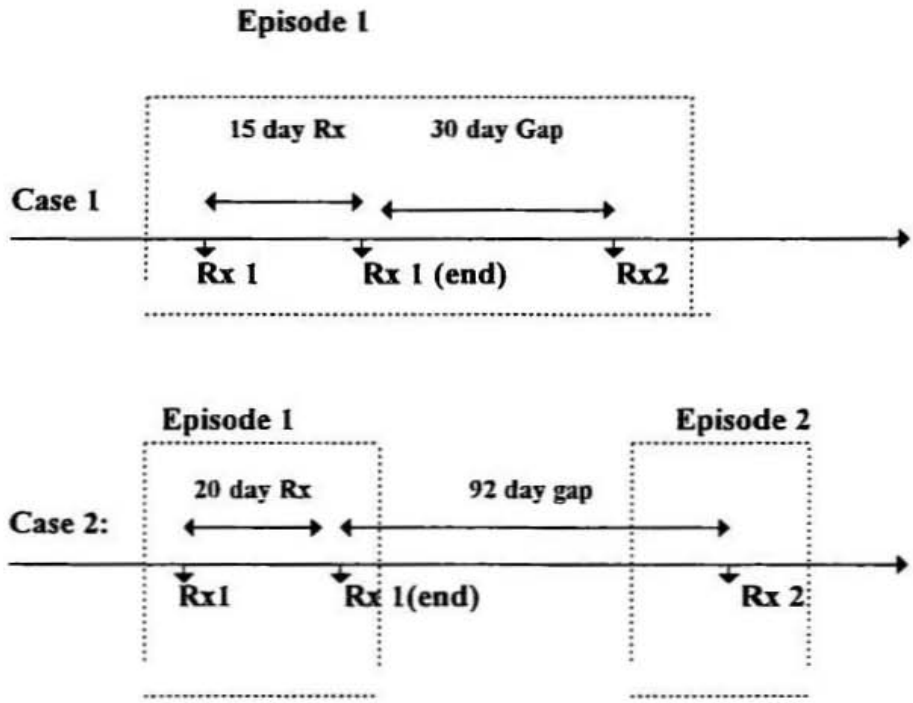


Figure 3.3: Identification of Different Treatment Episodes, Rx = the dispensing date for the prescription; Rx(End) = the end date for a prescription; In Case 1, two prescriptions were dispensed. The Gap between the end date of the first and the start date of the second was 30 days. Thus both prescriptions would be considered part of the same treatment episode. In Case 2, two prescriptions were dispensed. In this case, the gap between the end date for the first and the start date of the second was 92 days. Thus the two prescriptions were placed in different treatment episodes.

subtracting the first dispensing date in the treatment episode from the final end date for that episode. The final end date was calculated by adding the dispensing date of the last prescription in that episode to the number of days that the prescription was filled for. Accordingly, the end date was the estimated stopping date on which the last prescription fill of the episode should have been completely consumed and would have been the final date that a subject would have had any medication on hand (according to Blue Cross records). Therefore, treatment duration, as was used in several of the outcome measures described below, was actually the duration of the full treatment episode.

3.9.4 Percentage of Non-compliant Days

This outcome variable measured the percentage of medication free or non-compliant days during the treatment episode. The percentage of days that a person was without medication during the first treatment episode was calculated by summing the number of positive gaps during treatment and dividing it by the treatment duration.

The function of the statistical analysis done on this variable was to determine whether or not the predictor variables could predict the extent of non-compliance.

It should also be noted that all people who filled only one prescription for an antidepressant and then stopped

(i.e. did not return for a refill) were also not included in this analysis because they would not have had any discernible gaps in treatment. Individuals who stopped medication after only a short interval or after one prescription were considered in another analysis which specifically compared medication 'stoppers' to those who continued pass a specified period.

3.9.5 Early Medication Stoppers versus Continuers

In the previous outcome measure, compliance was viewed from the perspective of gaps in treatment. Very little emphasis was actually placed on the duration that individuals remained on treatment. A second outcome measure was used which was similar to that used in study by Thompson et al. (1995) on lipid-lowering medications They classified individuals who filled one prescription as stoppers as compared to those who filled more than one prescription who were deemed treatment continuers. In the current study stoppers were defined in two ways, (1) those who filled only one prescription and (2) the total duration of antidepressant use.

Subjects who filled only one prescription were identified as having only one antidepressant record in the database. These subjects were compared to the remainder of the sample who had more than one prescription filled.

In terms of duration of use, medication users were classified as stoppers if their total duration on the medication was less than a critical length of time. Two critical stopping times were used, 30 and 60 days. In most cases subjects who filled only one prescription would have fallen into these categories. It should be noted however, that in some cases several prescriptions may have been filled before this duration was reached. To clarify this scenario further, if the duration was less than or equal to 30 or 60 (depending on the analysis) then the subject was classified as a medication stopper. If the total duration for a subject was greater than the specified critical time then the person was considered a non-stopper. (see Figure 3.4)

The Blue Cross database utilized in this study did not have standard refill times. Hence, it was possible that the first prescription may have ranged in duration from as little as 10 days to as high as 100 days. By setting specific duration cutoffs (30 or 60 days), we were able to look at all people who stopped at approximately the same time As was discussed in the introduction, the assumptions of 30 and 60 days were made based on two criteria; outcome measures used in previous studies and theoretical ideas concerning compliance to antidepressant medications.

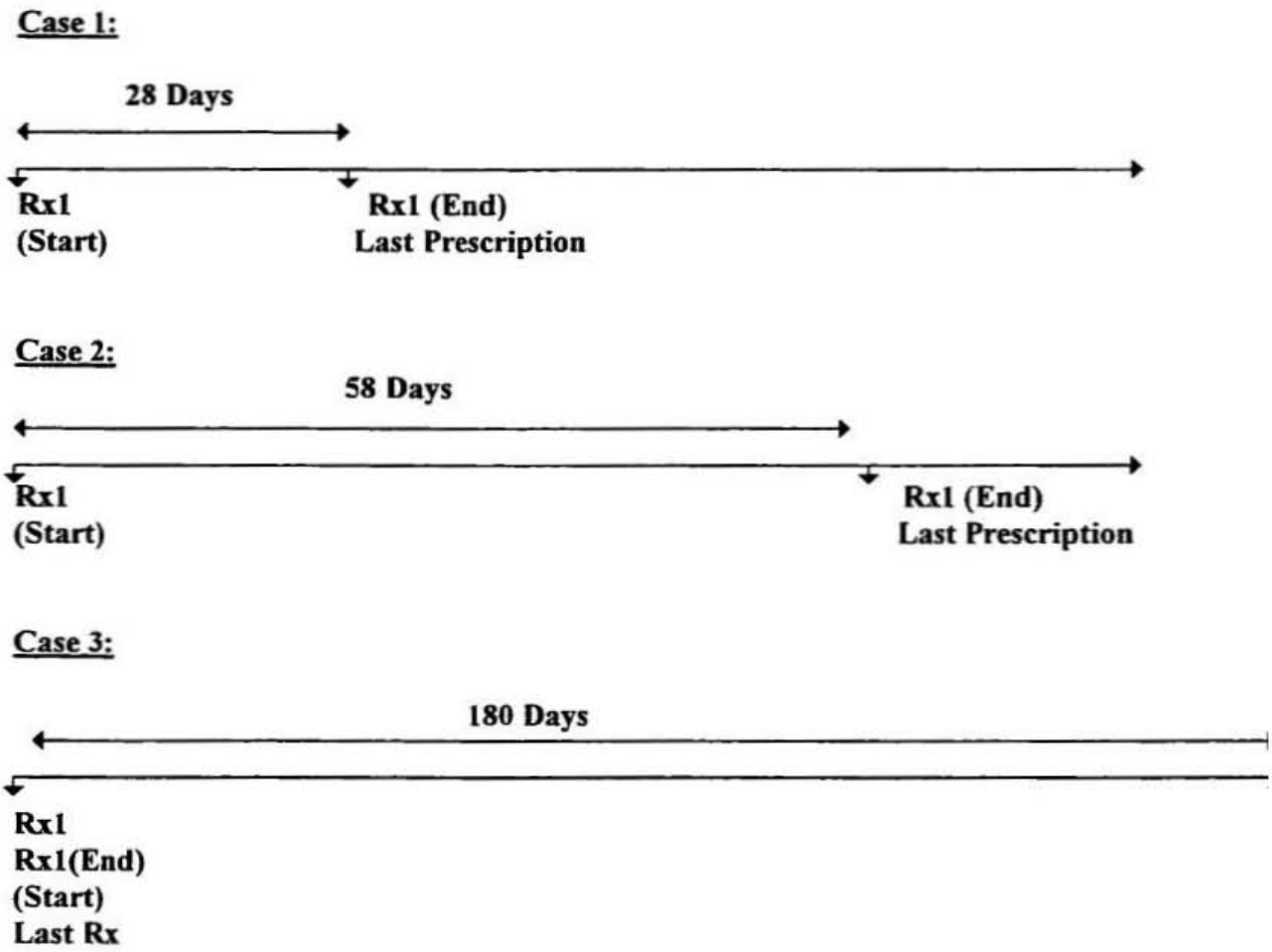


Figure 3.4: Classification of Subjects as Stoppers or Non-stoppers based on 30 and 60 day assumptions. Rx(Start) = Dispensing date of first prescription in episode; Rx(End) = End Date of last prescription in episode.

In Case 1, the treatment duration was 28 days. Thus, this subject would be classified as a stopper under the 30 and 60 day assumptions.

In case 2, the treatment duration was 58 days. This subject would be classified as a stopper under the 60 day assumption but as a continuer under the 30 day analysis.

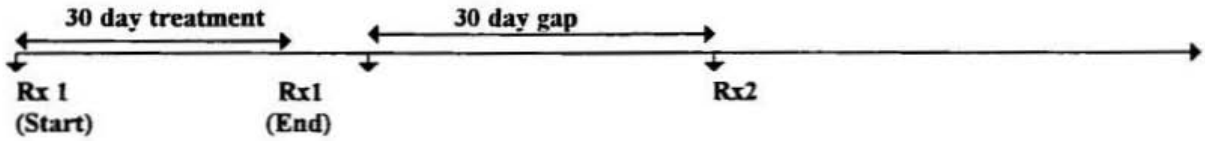
Finally, in case 3 , the treatment duration is 180 days. This subject would be classified as a continuer under both assumptions.

3.9.6 Time Till First Non-compliant gap

The duration of time that a person remained on the antidepressant before they became non-compliant was compared among levels of the predictor variables. For the purposes of this study, a non-compliant gap was defined based on two different assumptions or definitions; (1) that a 15 day gap in treatment represented a non-compliant episode and (2) that a 30 day gap in treatment represented a non-compliant episode (see Figure 3.5).

It was necessary to define what magnitude or gap size would be considered a non-compliant period. In the previously discussed percentage of non-compliant days, the compliance measure was a continuous variable. Thus, it was appropriate to view smaller treatment gaps as part of that continuum in order to get a full picture of non-compliance. In contrast, in this measure, the goal was to identify the first significant non-compliant episode. It was assumed that smaller gaps in treatment represented lesser magnitudes of non-compliance. Gaps of 15 and 30 days were used because they represent more significant gaps in treatment and thus, are more significant periods of non-compliance. Thompson et al.(1995) looked at duration till stopping treatment and used 30, 60 and 90 day assumptions to ascertain whether or not the subject had actually stopped medication. In the

Case 1:



Case 2:

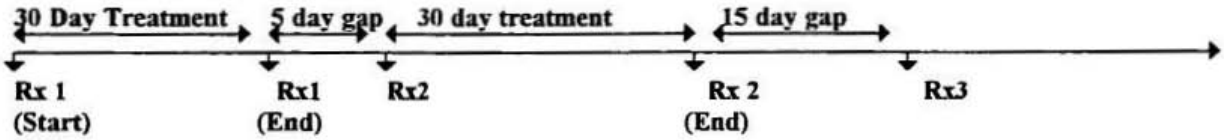


Figure 3.5: Calculation of survival duration till first non-compliant episode for >=15 and >=30 day assumptions. Rx(Start) = first prescription in episode; Rx(end) = end date for each individual prescription; Rx = dispensing date for prescription.

In Case 1, a treatment episode of 30 days was followed by a 30 day gap in treatment. Thus, the survival duration till the first gap is 30 days. This is true for both the >=15 day and >=30 assumptions.

In case 2, a 30 day treatment episode is followed by a 5 day gap, another 30 day treatment episode, and then a gap of 15 days. This 15 day gap would fulfil the >=15 day assumption not but the >=30 day assumption. Thus the survival duration for the >=15 day assumption would be 65 days (30 + 5 + 30 days). The survival duration by the >=30 day assumption would be the duration until the first gap >=30 days.

Thompson et al. (1995) study, the time intervals were longer because the authors were attempting to ascertain whether the subject stopped medications. In the current study, the gaps are considered non-compliant periods or breaks in treatment and do not represent the stopping or discontinuing of treatment.

3.10 Data Analysis

Data was analysed using SPSS Version 7.1. The purpose of the data analysis was to evaluate the study objectives. Additional analysis were used to describe the sample in terms of utilization patterns.

A number of frequencies and cross tabulations were done to describe patterns of antidepressant utilization in terms of class use, and the other predictor variables; demographic (age, sex), medication complexity (number of pills per day, and number of concurrent medications), and the cost to the subject.

Each of the three outcome measures; percentage of non-compliant days, the early medication stoppers versus continuers and the time till a first non-compliant gap measure were analyzed separately in terms of the appropriate objectives. Descriptive statistics were done in order to describe the extent of non-compliance (objective 1) as well as to compare compliance between the SSRI's and Tricyclic

antidepressants (objective 2). Descriptive statistics, regression analysis, and survival analysis were utilized to look at the changes in compliance at various levels of the predictor variables (objectives 3-5)

3.10.1 Percentage of non-compliant days

Frequencies and cross tabulations were used to describe the sample in terms of the percentage of non-compliant days. Frequencies were calculated for various groupings of the percentage of non-compliant days. These statistics allowed us to get a picture of non-compliance as measured by the percentage of non-compliant days (objective 1) and to see how the percentage differed between the SSRI's and tricyclics (objective 2). The mean percentage of non-compliant days was found for each level of the predictor variable (objectives 3-5).

A multiple regression analysis was performed to ascertain whether differences in class or in levels of the various predictor variables could account for any of the variance in the percentage of non-compliant days. Because of the large number of predictor variables used, a backwards stepwise regression was utilized. This analysis regressed all of the variables against the outcome measure and eliminated variables at each step in the regression if they did not meet the standard SPSS specified inclusion criteria

for elimination of variables at each step in a backwards regression (p=.10).

3.10.2 Stoppers Versus Continuers

The proportion of the sample stopping after one prescription or after either 30 or 60 days was calculated in order to determine the magnitude of the problem of discontinuing medication in the sample.

Frequencies and percentages of users in each group (stoppers or continuers) were compared to determine the extent of non-compliance as indicated by the number of stoppers (objective 1). This was also done for each class so that comparisons could be made between classes (objective 2). Means and confidence intervals were calculated for all levels of the continuous predictor variables; age, number/day, concurrent medications, and cost. Frequencies and percentages were calculated for the categorical variable, sex (objectives 3-5).

3.10.3 Time Till First Non-compliant Episode

Survival analysis was utilized to determine whether survival curves differed between classes (objective 2) and among various levels of the predictor variables (objectives 3-5). A life tables analyses was chosen instead of the Kaplan Meier approach because of the large numbers involved. The first analysis was stratified by class. This was done in

order to determine whether there was a difference in the survival curves between classes. Further analysis were done separately for the tricyclic and SSRI classes and were stratified by various levels of the predictor variables. Overall and Pairwise comparisons of survival curves were done for each analysis using the Wilcoxan (Gehan) statistic. The use of multiple pairwise comparisons necessitated the reduction of the significance levels for a number of comparisons. This was done by dividing the standard α level of 0.05 by the number of pairwise comparisons done. A table documenting these calculations can be found in the results section.

4 RESULTS

4.1 General Utilization Patterns

4.1.1 Class Breakdown

The antidepressants were divided into 6 classes based upon recommendations from several sources (Krogh, 1994; Arana et al., 1987; Bernstein, 1995). The classes included the tricyclics, the SSRI's, the MAOI's, the heterocyclics, the SNRI's, and the atypical antidepressants. Appendix 1 shows the DIN, trade name, generic name, and associated class for each medication available in the database.

The breakdown of people into class of antidepressant use presented difficulties because of the number of people who switched between classes of medication. 1380 people out of the total sample (n=6389) had prescriptions for drugs from more than one class. This number is larger than that given in Figure 3.2 because it represents the entire sample before any other exclusions. In Figure 3.2, a number of subjects (n=1395) had already been excluded because of default or missing values in the 'Days Supply' Field which was the first exclusion done. Some of the people who were excluded in this initial exclusion had prescriptions from more than one class.

A person was counted in each class that s/he had a prescription for. This resulted in a total 'N' which was greater than the actual 'N'.

Table 4.1 shows the number of people who had a least one prescription from each of the classes before any exclusions. As can be seen, the tricyclics and the SSRI classes were the most commonly used classes.

4.1.2 Demographics and Patient Treatment Characteristics

After all exclusions (see section 3.6), the final sample contained 3440 individuals. Table 4.2 shows a breakdown in terms of the variables utilized in the study; age, sex, average cost per prescription (antidepressant and other), number of concurrent medications, and number of doses per day. Percentages for each class are given within each level of the demographic variables (age, sex) or the patient's treatment characteristic. Overall, a slightly higher percentage of the sample was using medication from the tricyclic class than the from the SSRI class (54% and 46% respectively).

The sex ratio of males to females was 1:2.1 respectively. This ratio was approximately upheld within each class.

Table 4.1: Number of People who had at least one prescription filled from each of the Classes of Antidepressants

Antidepressant Class	Number of People who had a least one prescription filled
Tricyclic	3360
SSRI	3413
MAOI	367
Heterocyclic	407
SNRI	281
Atypical	240
Total*	8068

*The total over-counting can be broken down in terms of the number of classes that each individual had a prescription from.

Total Over-counting;

# of People;	
5009	X 1 Class = 5009
1127	X 2 Classes = 2254
213	X 3 Classes = 639
35	X 4 Classes = 140
4	X 5 Classes = 20
1	X 6 Classes = 6
	TOTAL = 8068

Table 4.2: Frequencies and Percentages of Users in Terms of Demographic and Patient Treatment Characteristics

Variable	SSRI	Tricyclic	Total
Sex			
Male	517 (32.7%)	593 (31.9%)	1110 (32.2)
Female	1065 (67.3%)	1265 (68.1%)	2330 (67.8)
Age			
<=20 Years	51 (3.2%)	70 (3.8%)	121 (3.5%)
21-35 Years	265 (16.8%)	174 (9.4%)	439 (12.7%)
36-50 Years	801 (50.6%)	794 (42.7%)	1595 (46.4)
51-65 Years	410 (25.9%)	702 (37.8%)	1112 (32.3%)
>65 Years	55 (3.5%)	118 (6.3%)	173 (5.1%)
Concurrent Medications			
0	415 (26.2%)	387 (20.8%)	802 (23.4%)
1	424 (26.8%)	470 (25.3%)	894 (26.0%)
2	305 (19.3%)	377 (20.3%)	682 (19.9%)
3-4	310 (19.6%)	397 (21.4%)	707 (20.5%)
>=5	128 (8.1%)	227 (12.2%)	355 (10.2%)
Average Cost for All Other Prescriptions			
<=$4.00	654 (41.3%)	685 (36.9%)	1339 (38.9%)
$4.01-8.00	717 (45.3%)	865 (46.6%)	1582 (45.9%)
>=$8.01	211 (13.4%)	308 (16.5%)	519 (15.2%)
Average Cost for antidepressant			
<=$4.00	262 (16.6%)	944 (50.8%)	1206 (35.0%)
$4.01-8.00	843 (53.3%)	735 (39.6%)	1578 (45.9%)
>=$8.01	477 (30.1%)	179 (9.6%)	656 (19.1%)
Number of Doses Per Day			
1	1041 (65.8%)	536 (28.8%)	1577 (45.8%)
>1	541 (34.2%)	1322 (71.2%)	1863 (54.2%)
Totals	1582 (46.0%)	1858 (54.0%)	3440 (100%)

The mean age for the sample was 46.75 years (95%CI; 46.33-47.17). 79% of the sample fell in the '36-50' and '51-65' age groups. The '<=20' and '>65' age groups had the smallest percentages of subjects (3.5 and 5.1% respectively). The percentage of people within each age group did differ somewhat by class. In the younger age groups, '21-35' and '36-50', the percentage of people on SSRI's was slightly higher. In contrast, in both the '51-65' and '>65' age groups, the tricyclics had higher percentages than did the SSRI's.

In terms of concurrent medications, the mean for the sample was 1.99 (95%CI; 1.92-2.05). 23.4% of the sample were taking no concurrent medications, as opposed to 76.6% of the sample who fell into the '1', '2', '3-4', and '>=5' groups. The largest percentage of people fell into the '1' concurrent medication group (26.0%). The number of concurrent medication did not vary greatly among classes. Small percentage differences existed between all concurrent medication groups. The greatest differences were between the lowest (0) and the highest (>=5) groups with the SSRI's having slightly higher percentages of users in the lowest group and the tricyclics in the highest group.

The mean average cost paid per prescription for other drugs that an individual was using was $4.68 (95%CI; 4.57-

4.79). 84.8% of the sample were paying less than or equal to $8.00 per prescription. Only 15.2% of the sample were paying more than $8.00 per prescription. This breakdown did not vary greatly between classes.

The mean average cost paid per prescription for antidepressants reflect the price differences that exist between the two types of medications (i.e. the SSRI's are more costly). The mean cost per prescription for the SSRI's was $7.19 (95%CI; $6.93-7.44) as opposed to $4.37 (95%CI; $4.24-4.49) for the tricyclics. 50.8% of those on tricyclics fell into the <=$4.00 group as opposed to 16.6% in the SSRI group. In contrast, 30.2% of those taking SSRI's fell into the >=8.01 prescription group as opposed to 9.6% in the tricyclic group.

4.2 Non-compliance Outcome Measurement

4.2.1 Percentage of Non-compliant Days

Percentage of non-compliant days was calculated by dividing the days without medication by the total duration for the treatment episode multiplied by 100. The total 'N' involved in this measurement was less than the total 'N' for the sample. Three hundred and twenty seven subjects were excluded from the frequency analyses because they had only one prescription in the database and thus had no discernible gaps in treatment between refills. The total 'N' for the

frequency analyses was 3113. The mean percentage of non-compliant days for these 3113 subjects was 8.4% (95% CI; 7.9-8.9).

A multiple regression analysis was performed in order to ascertain whether class and the other predictor variables; age, sex, number of concurrent medications, number of doses per day, and the two cost variables had an impact on extent of non-compliance. This analysis was used to determine whether the predictor variables could predict the extent of non-compliance among subjects who exhibited some level of non-compliance. The analysis involved only those subjects who had a percentage of non-compliant days greater than zero (n=1454). Thus all subjects who had no gaps in treatment (percentage of non-compliant days = 0%) were not included (n=1659). Because the group with a percentage of non-compliant days of zero was so large it skewed the distribution to a point that regression analysis could not have been utilized. Even after exclusion of the 0% group, the values were still not normally distributed. Thus, the log of each data point was found in order to make the data suitable for analysis by parametric regression analysis. The distribution of the original and logarithmically transformed data can be found in Appendix 5.

4.2.1.1 Extent of Non-compliance/ Tricyclics Versus SSRI's; Tables 4.3 and 4.4 present the distribution of patients by percentage of non-compliant days. For both the tricyclic and SSRI classes, the largest percentage of all users (55.4% and 50.9% respectively) had no non-compliant days between refills. Also, addition of the percentages in the first five rows of the table shows that 88% of all SSRI users and 85.5% of all tricyclic users had less than or equal to 25% of days without medication. That left only 12.0% of the SSRI sample and 14.5% of the tricyclic sample who had more than 25% of days without medication. As can be seen from these numbers, the extent of non-compliance did not vary a great deal between the SSRI and tricyclic classes. Class was also included as a predictor in the multiple regression that is presented later in section 4.2.1.2.2 of the results. Class was not a significant predictor of the extent of non-compliance among users with a percentage non-compliance greater than zero.

4.2.1.2 Predictor Variables; Table 4.5 shows the mean percentage of non-compliant days for each level of the predictor variables stratified by class. In the following commentary, the only differences that were described were cases when the mean percentage of non-compliant days between different variable levels were

Table 4.3: Distribution and Percentage of Users by Percentage of Non-Compliant Days for Tricyclics

Percentage of Days Without Medication	Frequency	Percentage of Total (%) ; n=1459
0%	917	55.5
<=5%	144	8.7
>5 and <=10%	143	8.6
>10 and <=15%	82	5.0
>15% and <=25%	128	7.7
>25 and <=50%	209	12.6
>50 and <=75%	29	1.8
>75%	2	0.1
Total	1654	100

Table 4.4: Distribution and Percentage of Users by Percentage of Non-Compliant Days for Subjects taking SSRI's

Percentage of Days Without Medication	Frequency	Percentage of Total (%) ; n=1459
0%	742	50.9
<=5%	151	10.3
>5 and <=10%	130	8.9
>10 and <=15%	116	8.0
>15% and <=25%	144	9.9
>25 and <=50%	162	11.0
>50 and <=75%	14	1
>75%	0	0
Total	1459	100

Table 4.5: Mean Percentages of Non-compliant Days by Patient Treatment Characteristic (Stratified by Class)

Variable	SSRI Mean Percentage of Non-compliant Days (%) (95% Confidence Interval, N)	Tricyclic Mean Percentage of Non-compliant Days (%) (95% Confidence Interval, N)
Sex Male	8.06 (6.99-9.13) n=477	8.41 (7.19-9.62) n=519
Female	8.33 (7.53-9.14) n=982	8.66 (7.83-9.48) n=1135
Age (Years)		
<=20	9.84 (6.50-13.17) n=44	13.82 (9.53-18.10) n=54
21-35	9.08 (7.4210.74) n=237	7.93 (5.93-9.93) n=140
36-50	8.12 (7.23-9.02) n=739	8.65 (7.59-9.71) n=706
51-65	7.83 (6.57-9.09) n=386	8.85 (7.73-9.97) n=644
>65	7.82 (4.25-11.41) n=53	4.76 (2.57-6.95) n=110
Concurrent Medications		
0	10.01 (8.69-11.3) n=376	11.22 (9.48-12.97) n=329
1	8.38 (7.11-9.66) n=385	10.36 (8.86-11.87 n=407
2	7.77 (6.32-9.22) n=283	7.66 (6.28-9.04) n=342
3-4	6.92 (5.53-8.31) n=296	6.72 (5.44-8.00) n=362
>=5	6.63 (4.67-8.56) n=119	5.72 (4.11-7.33) n=214
Doses Per Day		
1	8.46 (7.66-9.27) n=944	6.46 (5.32-7.61) n=442
>1	7.84 (6.77-8.92) n=515	9.35 (8.52-10.18) n=1212
Aver Cost for Other Drugs		
<=$4.00	7.77 (6.82-8.73) n=597	8.87 (7.75-10.00) n=606
$4.01-8.00	8.44 (7.45-9.42) n=667	8.06 (7.09-9.04) n=770
>=$8.01	9.03 (7.17-10.89) n=195	9.36 (7.55-11.17) n=278
Aver Cost for anti'd		
<=$4.00	6.78 (5.26-8.30) n=244	9.35 (8.33-10.37) n=831
$4.01-8.00	7.74 (6.92-8.56) n=780	7.76 (6.74-8.78) n=658
>=$8.01	9.96 (8.64-11.29) n=435	7.92 (5.93-9.91) n=165

different and the corresponding 95% confidence intervals of the mean did not overlap.

4.2.1.2.1 SSRI Group; Among the SSRI users, there was little difference in the percentage of non-compliant days between males and females. There were however, differences between the age groups. As age increased, mean percentage of non-compliant days decreased. The difference in means was greatest between the '<=20' and '50-65' age groups (9.84% and 7.82% respectively). It should be noted that these differences were not large and in all cases, the confidence intervals for the means over-lapped between the groups. In terms of medication complexity, the mean percentage of non-compliant days decreased as the number of concurrent medications increased. The difference in the means was greatest between the "0" and "3-4" and the "0" and '>=5' groups. These differences were complemented by non-overlapping confidence intervals suggesting that a real difference in the means of these groups does exist. A difference in means existed between those taking one pill per day and those taking more than one pill per day (8.46% and 7.84% respectively). However, the confidence intervals between these groups overlapped each other.

The mean percentage of non-compliant days increased as the cost for the other medications that a person was taking increased. However, the confidence intervals between these groups overlapped. This trend was evident for the cost of the antidepressant medication as well. More specifically, as level of cost of the antidepressant increased the mean percentage of non-compliant days also increased. This difference in mean non-compliance was greatest between the group paying <=$4.00 and the group paying >=$8.01 as was evidenced by non-overlapping confidence intervals.

4.2.1.2.2. Tricyclic Users; Among the tricyclic users, there was very little difference in the sexes in terms of percentage of non-compliant days. Age differences were evident between the '<20' and the '>65' groups (13.82% and 4.76% respectively). The confidence intervals between these two groups did not overlap.

As the number of concurrent medications increased the mean percentage of non-compliant days decreased. Significant differences, as evidenced by non-overlapping confidence intervals, existed between the '0'concurrent medications and the '2', '3-4' and '>=5' groups. In terms of the number of doses per day, people taking one dose per day had a lower mean percentage of non-compliant days as opposed to those taking more than one dose per day (6.46% and 9.35%

respectively). Confidence intervals for these means did not overlap.

No pronounced differences in mean percentage of non-compliant days existed for either the average cost of other or of antidepressant medications.

4.2.1.2.3 Regression Analysis; In a multiple regression analysis with percentage of days without medication as the dependent variable, none of the predictor variables were significant predictors of the extent of non-compliance among subjects who exhibited some level of non-compliance (i.e. percentage of non-compliant days > 0). In a backward regression model initially involving the predictor variables, class, sex, age, average cost for other medications, average cost for antidepressant medications, number of concurrent medications, and number of medications per day, very little of the variance in the percentage of non-compliant days measure was accounted for by the predictors in the final model. (R^2 = .017, $F(2, 1453)$ = 13.47, $p > .05$). The final model contained only two of the predictor variables; number of concurrent medications and number of doses per day. The respective Beta's were -0.097 (SE; 0.016) and 0.099 (SE.; 0.025). The other predictor variables were eliminated in earlier steps of the model.

4.2.2 Early Stoppers Versus Continuers

Based on several definitions of 'medication stopper', the sample was divided into dichotomous groups of either early medication stoppers or medication continuers. First, all individuals who had only one prescription filled for an antidepressant were classified as early medication stoppers. Second, all individuals who had a total treatment duration less than (1) 30 days or (2) 60 days were also classified as medication stoppers. Separate analyses were done for each of these assumptions.

4.2.2.1 Extent of Non-Compliance; Table 4.6 summarizes the numbers of subjects who fell into each group for each of the three assumptions. The number of stoppers was quite low for each assumption with the greatest percentage of stoppers in the 60 Day assumption (11.4%).

Table 4.6; Frequencies and Percentages of Sample Who Fell Into Either the Stoppers or Continuers Group by the three definitions of stoppers

Assumption	Number of Subjects (N=3440)	Percentage (%)
One Prescription		
One Pres.	327	9.5
> One Pres.	3113	90.5
30 Day		
<=30 Days	279	8.1
>30 Days	3161	91.9
60 Day		
<=60 Days	391	11.4
>=60 Days	3049	88.6

4.2.2.2 Tricyclics Versus SSRI's; Table 4.7 shows the percentages and frequencies for individuals in each group within each assumption stratified by medication class. The percentage of tricyclic users who stopped was slightly higher than the percentage of SSRI users who stopped medication. This pattern was true for all assumptions.

Table 4.7: Frequencies and Percentages (Within each cell) of Individuals in each group by the assumption and class

Variable	One Prescription		30 Day Assumption		60 Day Assumption	
Class	1 Pres.	>1 Pres	<=30 Days	>30 Days	<=60 Days	>60 Days
SSRI	123 (7.0)	1459 (93.0)	106 (6.7)	1476 (93.9)	152 (9.6)	1430 (90.4)
Tricyclic	204 (11.0)	1654 (89.0)	173 (9.3)	1685 (90.7)	239 (12.9)	1619 (87.1)

4.2.2.3 Predictor Variables; The relatively small number of 'stoppers' as compared to 'continuers' made analyses using this group very difficult. Logistic regression was the method of choice, but due to the small numbers in the 'stoppers' group, this test could not be used. Instead, the data was described using means, frequencies, and

percentages. Means and confidence intervals were calculated for the continuous predictor variables (age, number of concurrent medications, number per day, and both cost variables) for each class. Frequencies were provided for the nominal variable, sex.

4.2.2.3.1 SSRI Users; For the sample of SSRI users, the mean age of 'stoppers' was less than for the 'continuers' and the confidence intervals did not overlap between the'stoppers' and 'continuers' group. This was true for all three assumptions (see table 4.8). The frequencies of users in the 'stoppers' and 'continuers' group did not vary greatly by gender for either assumption (see table 4.9). The mean number of concurrent medications was less for the 'stoppers' across all assumptions. However, the confidence interval overlapped between the two groups for the 30 and 60 day assumptions. In addition, the number of doses taken per day did not differ between the 'stoppers' and 'continuers' for either assumption. The average cost paid for antidepressants did not differ significantly between the 'stoppers' and 'continuers' for either assumption. However, the mean cost paid for other medications was greater in the 'continuers' group for each of the three assumptions. This was complemented with non-overlapping confidence intervals between the 'stoppers' and 'continuers' for each assumption.

Table 4.8: Means and Confidence Intervals for each variable by assumption and group (stopper or continuer) for SSRI Users

Variable	One Prescription Assumption (mean, 95% Confidence interval)		30 Day Assumption (Mean, 95% Confidence Interval)		60 Day Assumption (Mean, 95% Confidence Interval)	
	1 Pres.	>1 Pres	<=30 Days	>30 days	<=60 Days	>=60 days
Age	42.06 (39.85-44.26)	44.87 (44.27-45.48)	41.73 (39.26-44.19)	44.86 (44.27-45.46)	41.74 (39.75-43.72)	44.96 (44.36-45.57)
Concurrent Med	1.45 (1.17-1.72)	1.84 (1.75-1.94)	1.58 (1.28-1.89)	1.83 (1.73-1.92)	1.61 (1.35-1.86)	1.83 (1.74-1.93)
Avg Cost per Anti.	$7.16 ($6.47-7.86)	$7.19 ($6.92-7.46)	$7.35 ($6.59-8.11)	$7.17 ($6.91-7.44)	$6.79 ($6.15-7.43)	$7.23 ($6.96-7.50)
Avg Cost per Other	$3.13 (2.54-3.72)	$4.64 (4.50-4.79)	$3.31 ($2.66-3.95)	$4.61 ($4.47-4.76)	$3.28 (2.78-3.79)	$4.66 (4.51-4.81)
Number per day	1.27 (1.15-1.39)	1.28 (1.25-1.31)	1.28 (1.15-1.42)	1.28 (1.25-1.31)	1.25 (1.15-1.35)	1.29 (1.26-1.32)

Table 4.9 Frequency and Percentage (within each Assumption by sex) of SSRI Users in Each Group by the Three Assumptions and Subject Sex

Variable	One Prescription		30 Day Assumption		60 Day Assumption	
Sex	1 Pres.	>1 Pres	<=30 Days	>30 Days	<=60 Days	>60 Days
Female	83 (7.8)	982 (92.2)	71 (6.7)	994 (93.3)	101 (9.5)	964 (90.5)
Male	40 (7.7)	477 (92.3)	35 (6.8)	482 (93.2)	51 (9.9)	466 (90.1)

4.2.2.3.2 Tricyclic Group; The age pattern was consistent across all three assumptions in that the mean age for the 'continuers' group was greater than that for the 'stoppers' group. The confidence intervals for the groups did not overlap suggesting that a real difference in the means for the groups did exist (see table 4.10). The frequencies of users in the 'stoppers' and 'continuers' group did not vary greatly by gender for either assumption (see table 4.11). A similar pattern was evident in the mean number of concurrent medications. The 'continuers' had a higher mean number of concurrent medications than the 'stoppers' and this was also complemented by non-overlapping confidence intervals. In addition, the number of doses taken per day did not differ between the 'stoppers' and

Table 4.10: Means and Confidence Intervals for each variable by assumption and group (stopper or continuer) for Tricyclic Users

Variable	One Prescription Assumption (mean, 95% Confidence interval)		30 Day Assumption (Mean, 95% Confidence Interval)		60 Day Assumption (Mean, 95% Confidence Interval)	
	1 Pres.	>1 Pres	<=30 Days	>30 days	<=60 Days	>60 days
Age	43.35 (41.39-45.31)	49.17 (48.56-49.78)	42.42 (40.37-44.46)	49.16 (48.55-49.77)	43.04 (41.28-44.80)	49.34 (48.73-49.96)
Concurrent Med	1.62 (1.39-1.85)	2.20 (2.10-2.29)	1.55 (1.31-1.80)	2.19 (2.10-2.29)	1.62 (1.40-1.83)	2.21 (2.11-2.31)
Avg Cost per Anti.	$4.09 ($3.71-4.47)	$4.40 (4.26-4.54)	$4.20 ($3.78-4.61)	$4.38 ($4.25-4.52)	$4.17 ($3.82-4.53)	$4.39 ($4.25-4.53)
Avg Cost per Other	$3.81 ($3.11-4.52)	$4.94 ($4.79-5.09)	$3.42 ($2.84-4.00)	$4.96 ($4.80-5.11)	$3.65 ($3.01-4.27)	$4.98 ($4.83-5.14)
Number per day	2.18 (1.94-2.42)	2.21 (2.15-2.27)	2.30 (2.02-2.57)	2.20 (2.13-2.26)	2.13 (1.92 3.34)	2.22 (2.15-2.28)

Table 4.11 Frequency and Percentage (within each Assumption by sex) of Tricyclic Users in Each Group by the Three Assumptions and Subject Gender)

Variable	One Prescription		30 Day Assumption		60 Day Assumption	
Sex	1 Pres.	>1 Pres	<=30 Days	>30 Days	<=60 Days	>60 Days
Female	130 (10.3)	1135 (89.7)	113 (8.9)	1152 (91.1)	153 (12.1)	1112 (87.9)
Male	74 (12.5)	519 (87.5)	60 (10.1)	533 (89.9)	86 (14.5)	507 (85.5)

'continuers' for either assumption. In terms of the average cost of other drugs, the 'stoppers' had a lower mean cost per prescription than the 'continuers'. This was consistent across the three assumptions and the confidence intervals between the 'stoppers' and 'continuers' did not overlap. No mean differences in the average cost paid for the tricyclic was evident between the groups.

4.2.3 Time Till First Non-compliant gap

Life tables survival curves were used to look at the time till the first non-compliant gap stratified by different levels of the predictor variables. Overall and pairwise comparisons of the strata of survival curves for each variable were competed using the Wilcoxan Gehan statistic. Survival curves as well as tables documenting

each comparison and the associated alpha level are presented below. In most cases, only the survival curves for the 15 day assumption are shown. The associated curve for the 30 day assumption can be found in the Appendix 7. Survival curves for all non-significant comparisons are presented in the Appendix 8.

Since multiple pairwise comparisons were often performed for each variable, the α level was lowered to decrease the probability of type II error. This was calculated by dividing the standard α level of 0.05 by the number of pairwise comparisons performed. Table 4.12 shows the modified α level for each predictor variable.

Table 4.12; Modified α-levels calculated from ratio of standard α=.05 to number of possible comparisons

Variable	Number of levels of Variable*	Number of Possible Comparisons	Modified α-level
Class	2	1	0.050
Doses per Day	2	1	0.050
Sex	2	1	0.050
Cost of Other Drugs	3	3	0.017
Cost of Anti'd	3	3	0.017
Age	5	10	0.005
Concurrent Medications	5	10	0.005

*Variable levels can be seen in Tables 4.8 and 4.10

4.2.3.1 Tricyclics Versus SSRI's; A preliminary survival analysis was stratified by class. Figures 4.1 and 4.2 present the preliminary survival curves comparing subjects on SSRI's to those on tricyclics on the basis of time till first non-compliant episode. For both the 15 and 30 day non-compliance assumptions, the difference in survival curves was not significant ($W(1)=0.23$, $p=.8798$ and $W(1)= 3.80$, $p=.051$ respectively). However, examination of the curves does show that, although both classes show a drop-off in compliance early in treatment, the tricyclics show a greater drop in compliance at about 50 days into treatment. This pattern changes when the SSRI's have a lower cumulative probability of survival than the tricyclics at approximately the 200^{th} day of treatment by the 15 day assumption and at the 300^{th} day of treatment by the 30 day assumption.

4.2.3.2 Predictor Variables

4.2.3.2.1 Tricyclic Users; Table 4.13 shows the overall comparisons for each variable for the sample who were tricyclic users. Only significant pairwise comparisons are shown. A complete table showing all pairwise comparisons can be found in Appendix 9. Age differences existed between strata in the sample of tricyclic users.

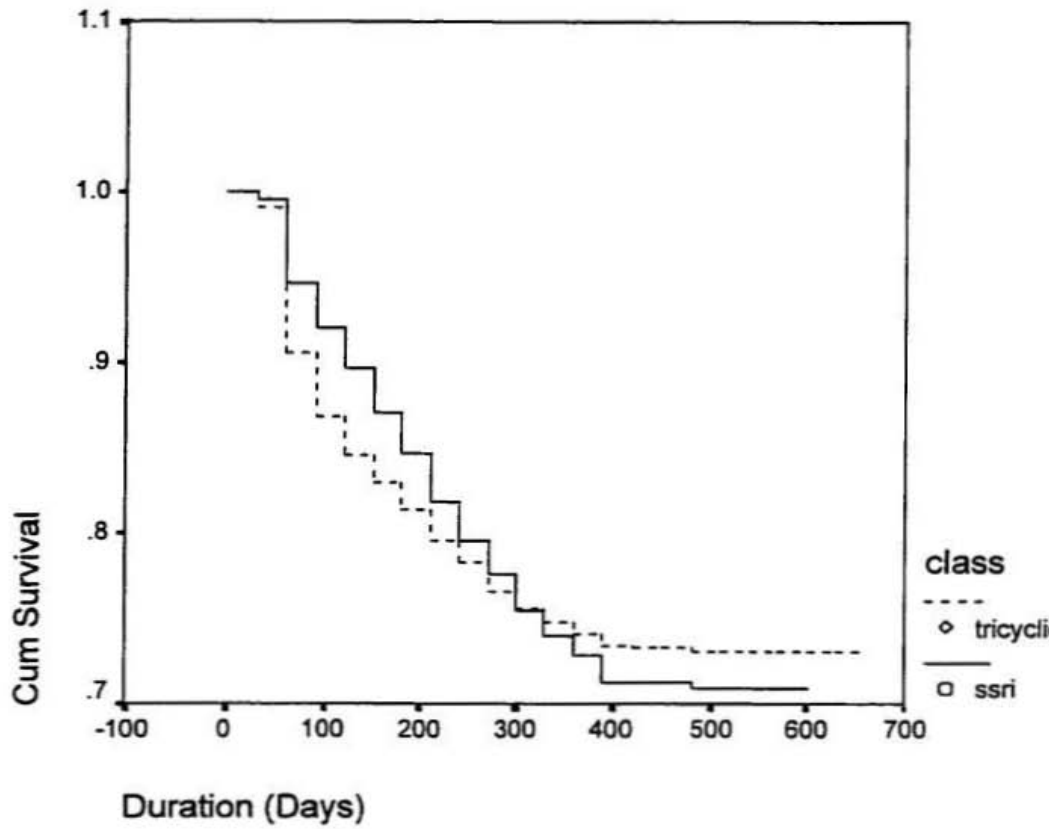


Figure 4.1: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Between the Tricyclic and SSRI Users by the 30 Day Assumption

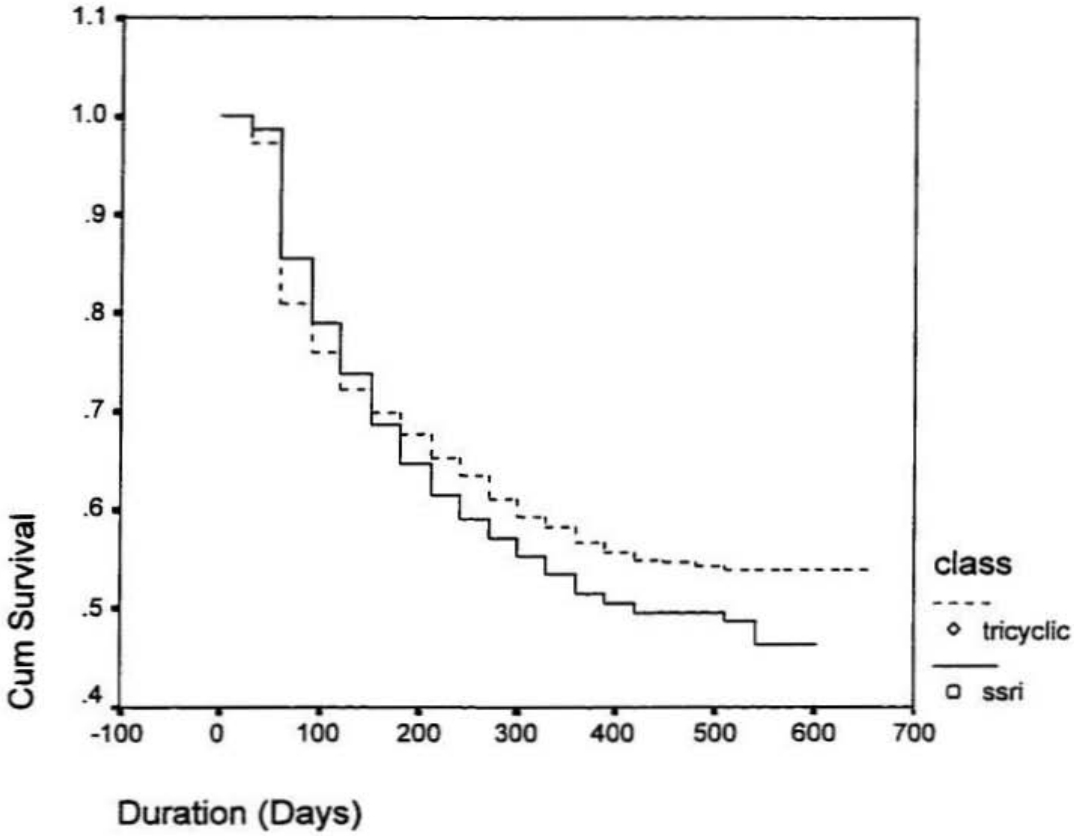


Figure 4.2: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Between the Tricyclic and SSRI Users by the 30 Day Assumption

Table 4.13: Pairwise and Overall Comparisons of time to non-compliance for the Various Levels of the Predictor Variables for the Tricyclic Class

Variable	Comparison Type	Wilcoxan for 15 day assumption	Wilcoxan for 30 Day assumption
Sex	Overall (2 pairs)	W(1)=0.003, p=.959	W(1)=0.793, p=.373
Age	Overall (10 pairs)	W(4)=15.72, p=.003	W(4)=13.48, p=.009
<20 and 21-35	Pairwise	W(1)=1.16, p=.281	W(1)=9.88, p=.002*
<20 and 36-55	Pairwise	W(1)=5.68, p=.017	W(1)=8.18, p=.004*
<20 and 51-65	Pairwise	W(1)=5.34, p=.021	W(1)=8.22, p=.004*
<20 and >65	Pairwise	W(1)=13.96, p=.000*	W(1)=10.88, p=.001*
21-35 and >65	Pairwise	W(1)=9.18, p=.002*	W(1)=0.18, p=.676
Concurrent Drugs Comparisons;	Overall (10 pairs)	W(4)=26.03, p=.000*	W(4)=15.24, p=.004*
0 and 3-4	Pairwise	W(1)=8.87, p=.003*	W(1)=4.39, p=.036
0 and >=5	Pairwise	W(1)=17.32, p=.000*	W(1)=7.72, p=.005
1 and >=5	Pairwise	W(1)=15.73, p=.000*	W(1)=10.27, p=.001*
Number/Day	Overall (2 pairs)	W(1)=30.21, p=.000*	W(1)=17.79, p =.000*
Avg cost of Other Drugs	Overall (3 pairs)	W(2)=4.00, p=.135	W(2)=2.63, p=.268
Avg cost of anti'd	Overall (3 Pairs)	W(2)=2.69, p=.26	W(2)=1.83, p=.401

*Significant at the modified alpha level (see table 4.12)

Figure 4.3 shows the survival curves for the 15 day assumption stratified by age group. The '>65' group showed the greatest cumulative probability of survival till the first non-compliant gap. The curves actually descend in order of age group suggesting that the younger age groups had a greater probability of having a non-compliant episode early in treatment. Only two pairs of curves were significantly different by the 15 day assumption, the '<20' and '>=65 and the '21-35' and '>=65' age groups. The '<20' and the '>=65' day curves were also significantly different by the 30 day assumptions (see Appendix 8 for survival curves). In addition, the '<20' curve was significantly different from the '21-35', the '36-55', and the '51-65' age groups by the 30 day assumption.

In terms of the number of concurrent medications, several patterns were evident in the survival curves. As can be seen in Figure 4.4, the survival curves for the 15 day assumption descended in order from '>=5' to '0' suggesting that the those taking more concurrent medications had a greater probability of surviving longer till a non-compliant gap than did those taking less concurrent medications. This same pattern was also evident in the curves for the 30 day assumption (see Appendix 8). Several of the pairwise comparisons were also significant. For the 15 day

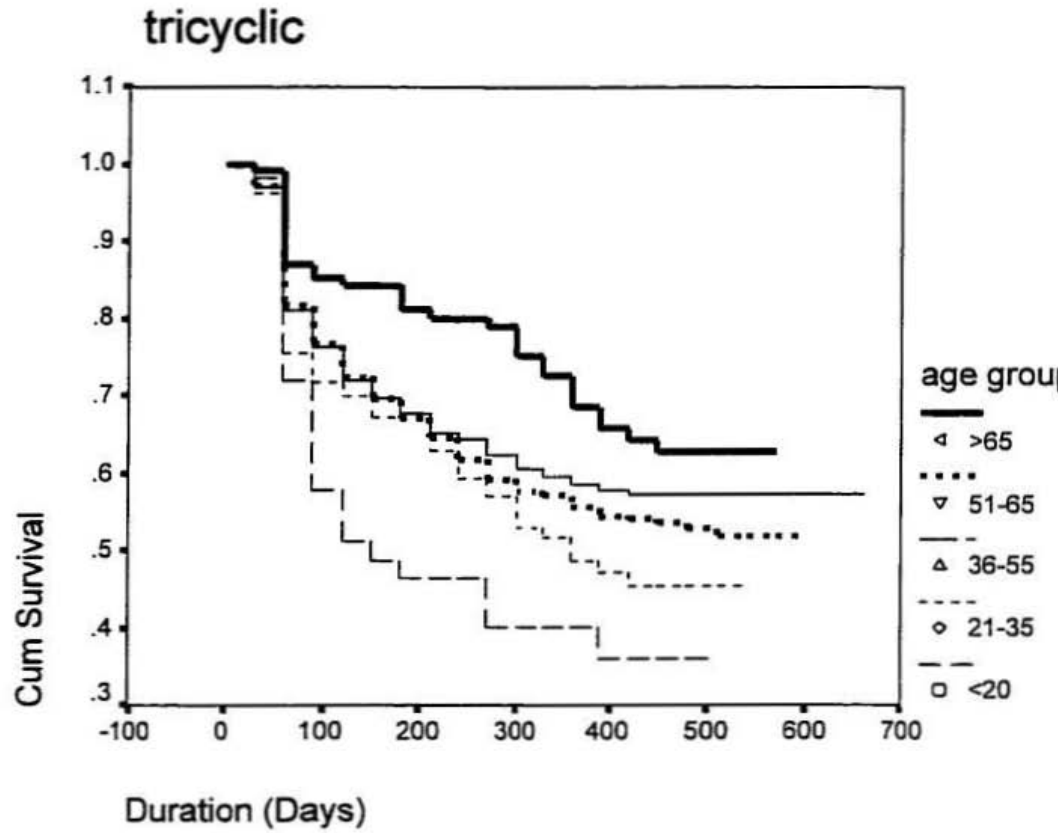


Figure 4.3: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Between the Different Age Groups of Tricyclic Users by the 15 Day Assumption

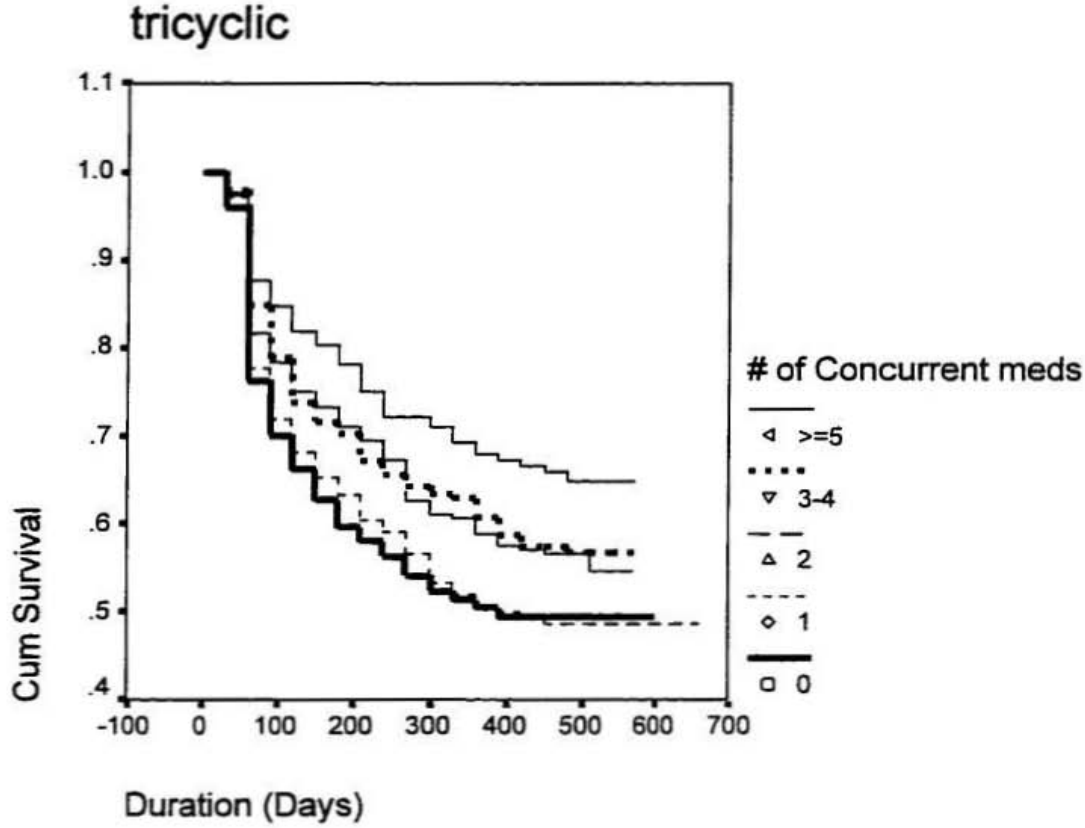


Figure 4.4: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Between Various Levels of Concurrent Medication Use for Tricyclic Users by the 15 Day Assumption

assumption, the survival curves for the '0' and '3-4', '0' and '>=5', and the '1' and '>=5' groups were significantly different. Only the '1' and '>=5' comparison was significant by the 30 day assumption. The other two groups did approach significance but were not significant because of the stringent alpha values utilized (see Appendix 8).

Figure 4.5 shows the survival curves stratified by number of doses per day. As can be seen from the survival curves, the survival times till a first non-compliant gap were shorter for the group taking more then one tricyclic dose per day. The difference in these curves is statistically significant by both the 15 and 30 day assumptions.

No trends or significant differences were noted in the survival curves stratified by levels of both cost variables and sex (see Appendix 9). This was consistent for both the 15 and 30 day assumptions.

4.2.3.2.2 SSRI Users; Table 4.14 shows the overall and pairwise comparisons for each predictor variable for the SSRI users.

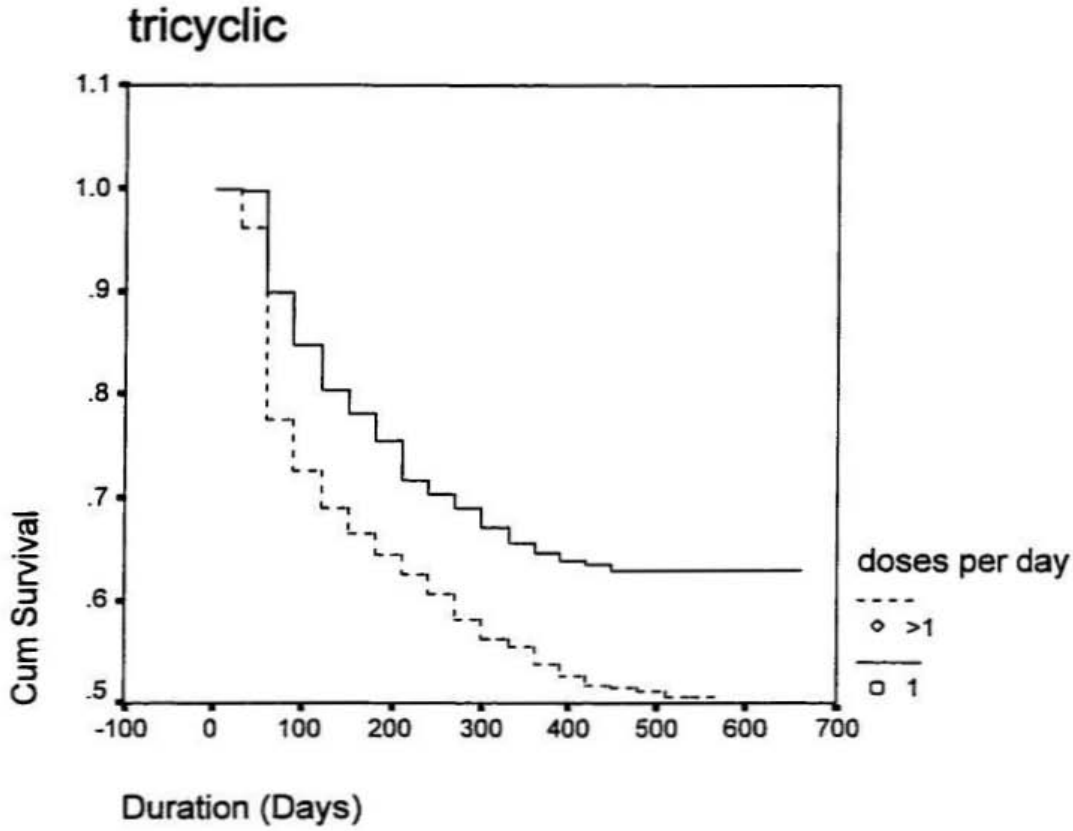


Figure 4.5: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Between Users Taking One Dose Per Day and Users Taking More Than One Dose Per Day for the Tricyclic Users by the 15 Day Assumption

Table 4.14: Pairwise and Overall Comparisons of time to non-compliance for the Various Levels of the Predictor Variables for the SSRI Class

Variable	Comparison Type	Wilcoxan for 15 day assumption	Wilcoxan for 30 Day assumption
Sex	Overall (2 pairs)	W(1)=0.05, p=.82	W(1)=0.31, p=.58
Age	Overall (10 pairs)	W(4)=4.37, p=.36	W(4)=2.68, p=.61
Concurrent Drugs Comparisons;	Overall (10 pairs)	W(4)=18.18, p=.001*	W(4)=6.30, p=.178
0 and 2	Pairwise	W(1)=10.11, p=.002*	W(1)=1.84, p=.175
0 and 3-4	Pairwise	W(1)=12.75, p=.000*	W(1)=4.44, p=.035
Number/Day	Overall (2 pairs)	W(1)=8.10, p=.00*	W(1)=6.47, p =.01*
Avg cost of Other Drugs	Overall (3 pairs)	W(2)=0.40, p=.84	W(2)=3.47, p=.18
Avg cost of antidepressant	Overall (3 Pairs)	W(2)=6.80, p=.033	W(2)=6.36, p=.042
$4.01-8.00 and >$8.00	Pairwise	W(1)=6.00, p=0.014*	W(1)=5.54, p=.019

*Significant at the modified alpha level (see Table 4.12)

No significant differences between survival curves were noted for sex or age. Inspection of the survival curve in Figure 4.6 (15 day assumption) shows that although the age curves do not differ significantly, they do follow the same trend as the tricyclics. More specifically, they descend by age with the older age groups having a greater probability of longer survival times till the first non-compliant gap. This was the case for both the 15 and 30 day assumptions.

In terms of concurrent medications, significant differences did exist between the survival curves for the '0' and '2' and the '0' and '3-4' groups. These differences were significant only for the 15 day assumption. Inspection of the survival curves reveals that those with greater number of concurrent medications had a greater probability of survival or longer survival times that those with less concurrent medications (see Figure 4.7). This trend mirrored the results from the tricyclic analysis.

Figure 4.8 shows the survival curves stratified by number of doses per day. As can be seen, the probability of becoming non-compliant sooner is greater for the group taking more then one dose per day. The difference in these curves is statistically significant by both the 15 and 30 day assumptions.

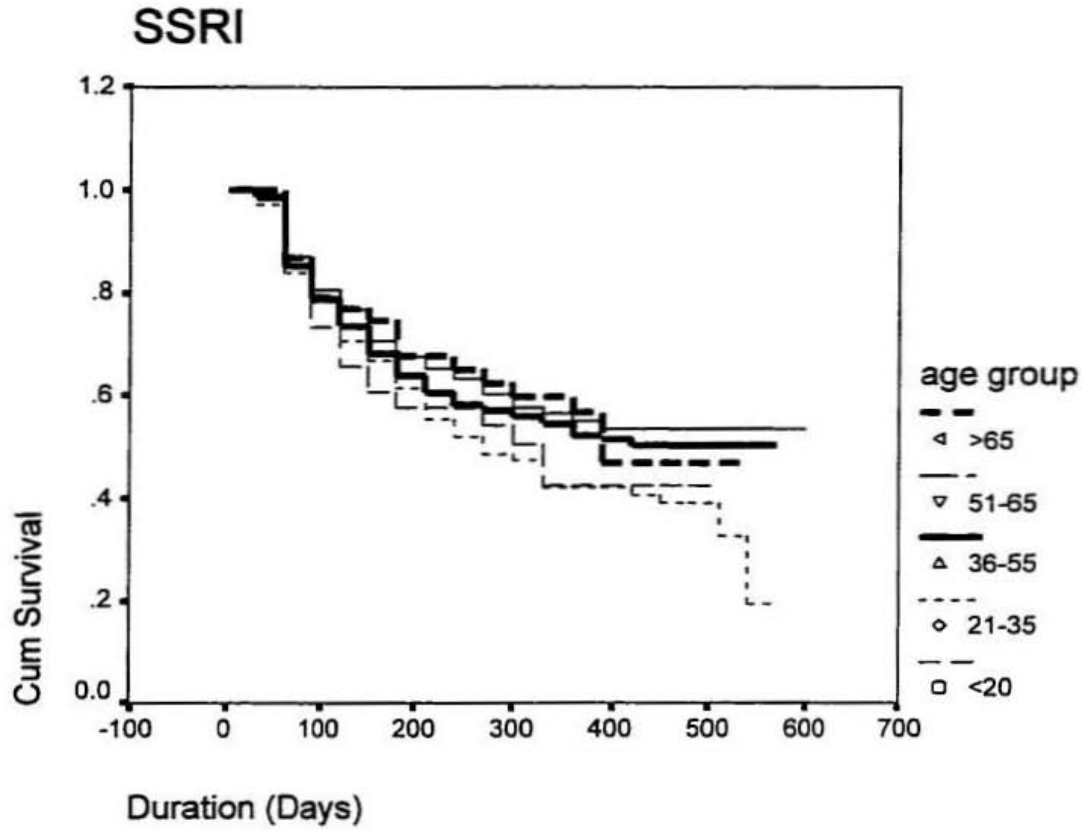


Figure 4.6: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-Adherent Gap Between the Different Age Groups of SSRI Users by the 15 Day Assumption

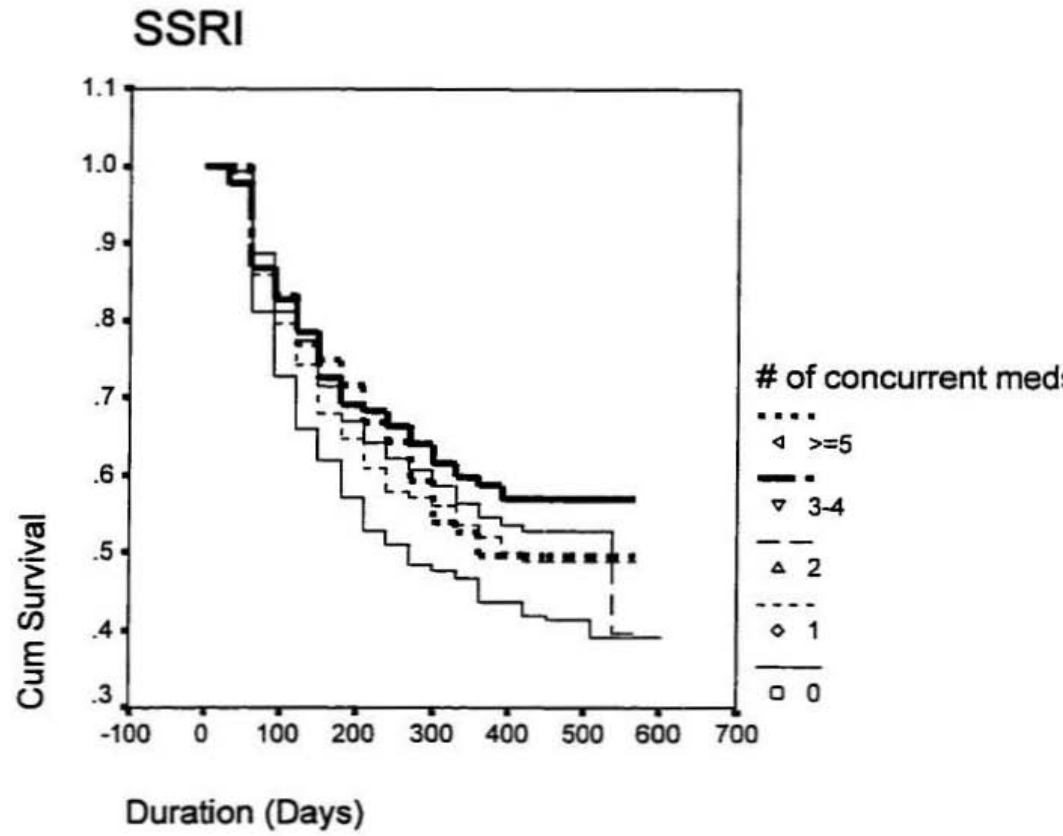


Figure 4.7: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap by Different Levels of Concurrent medication Use for the SSRI Users by the 15 Day Assumption

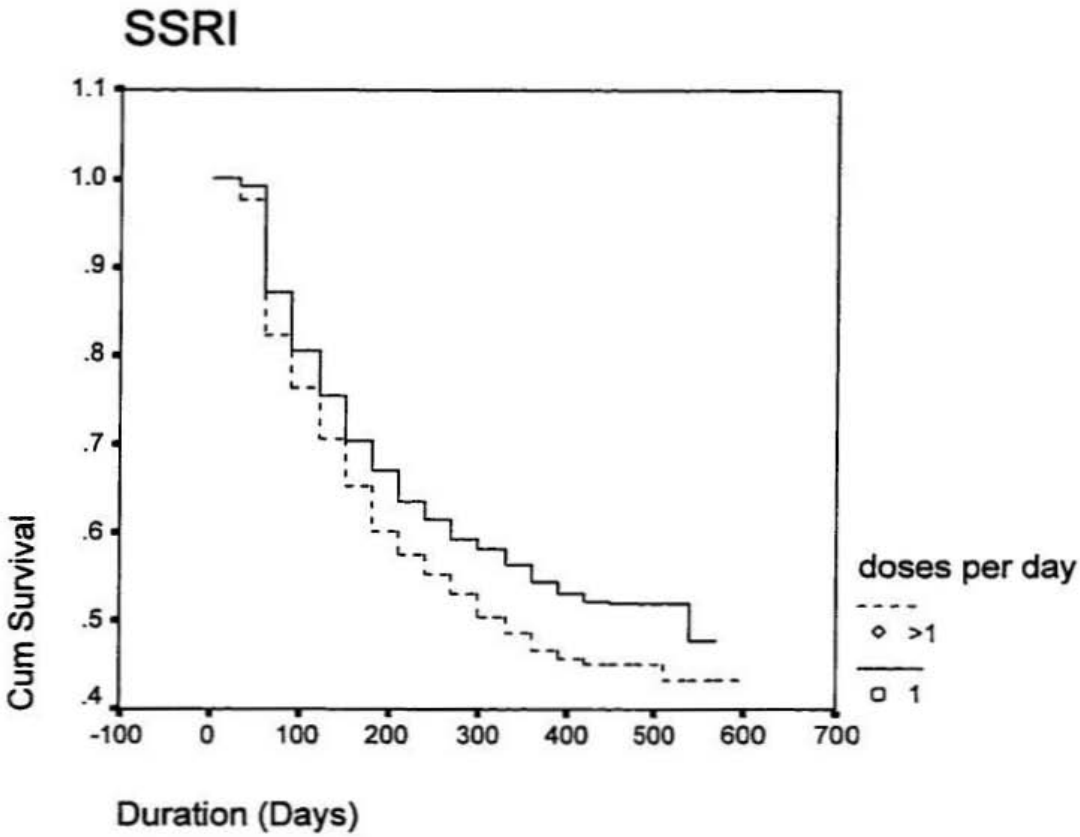


Figure 4.8: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Between Those Having One Dose Per Day and Those Having More Than One Dose Per Day Among the SSRI Users for the 15 Day Assumption

The survival curves stratified by cost paid per prescription for other drugs did not differ significantly. A significant difference was found between the '>$8.00' and the '$4.00-8.00' groups for the cost paid for antidepressants for the 15 day assumption. This comparison approached significance for the 30 day assumption. In addition, the difference between the '<$4.00' and the '>$8.00' curves also approached significance for both the 15 and 30 day assumptions. An inspection of the survival curves in Figure 4.9 shows that the >$8.00' group had a greater probability of having a non-compliant gap than those paying less that $8.00 per prescription. The difference between these curves was especially pronounced around the 200 day mark suggesting that continued treatment at high cost to the consumer may adversely effect compliance.

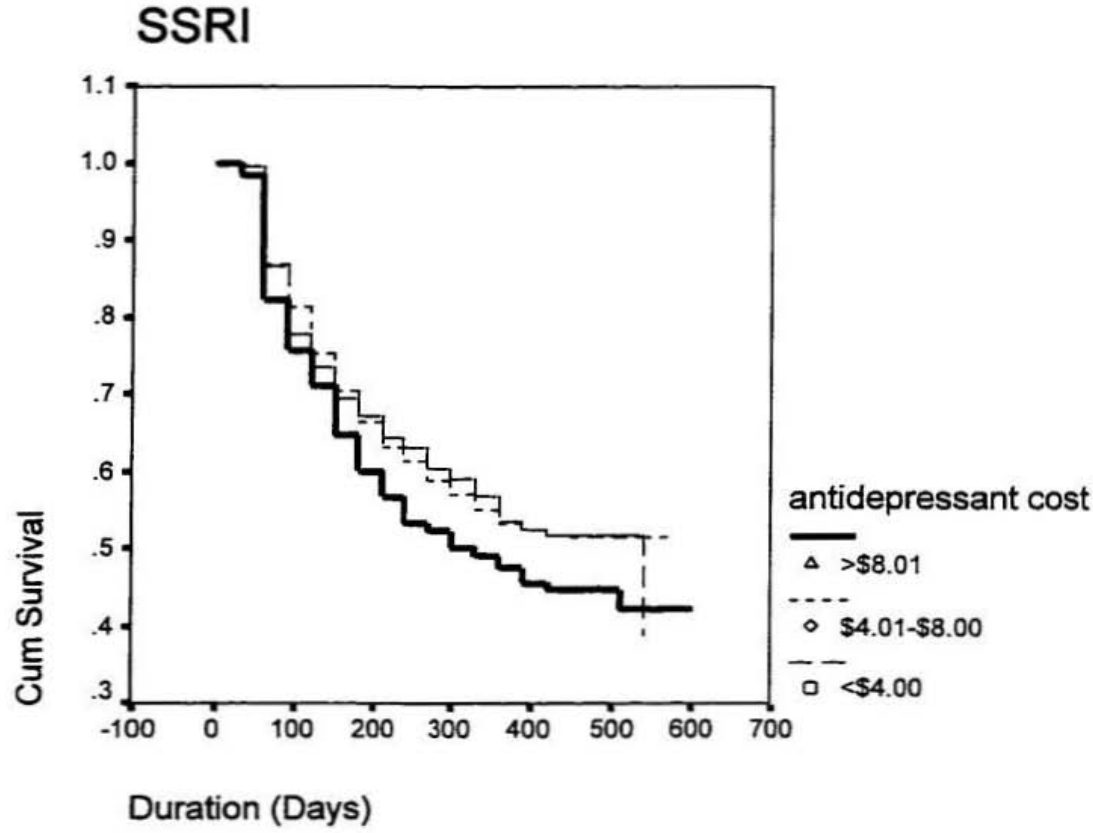


Figure 4.9: Survival Function Comparing the Cumulative Survival Till the First Non-adherent Gap Among Varying Levels of Cost Per Prescription for the Antidepressant Medication for SSRI Users By the 15 Day Assumption

5 DISCUSSION

The current study utilized an administrative prescription drug database to examine patient fill-refill behaviours as well as to determine potential predictors of non-compliance to antidepressant medications

5.1 The Problem of Non-compliance

Non-compliance was measured in several ways. Calculation of the percentage of non-compliant days allowed for the examination of patterns of fill-refill in non-compliant patients who are difficult to identify clinically because they remain under the care of their physician as evidenced by continuous refills of medication. However, they are non-compliant to the extent that they fail to fill some of their prescriptions and thus have treatment gaps in their fill-refill records (Steiner et al., 1988).

In the current study, 99.0% of SSRI users and 85.5% of tricyclic users were greater than 75 percent compliant by the percentage of non-compliant days measure. This is consistent with results from other studies that also utilized a similar measure. Steiner et al. (1993) also used this measure to determine the extent of non-compliance to antihypertensive medications. They found that 75% of the sample reached 80 percent compliance. Kelloway et al.

(1994) state that the percentage of non-compliant days measure may overestimate compliance because it assumes that gaps in treatment are due to non-compliance. They suggest that other events such as lost medications, sharing medication with family members, or simply not taking the medication at all will lead to an overestimation of compliance.

As discussed above, a large percentage of users were greater than 75% compliant. Although this result is consistent with other studies that have used the same measure, Gerbino (1993) suggests 75% compliance is not good enough for antidepressant medications. He suggests that for depression, 90% of patients who take 90 percent of their prescribed doses improve. In contrast, patients who take less than 80 percent of doses will probably not improve. In this study, 72.8% of the SSRI users and 70.1% of the tricyclic users had less than 10 percent of days without medications or were greater than or equal to 90 percent compliant to their medication by this definition of compliance. Thus, 27.2% of SSRI and 29.9% of tricyclic users had more than 10% of days without medication. According to Gerbino (1993), this is the group who will not get therapeutic value from the antidepressant (assuming that it is prescribed for depression).

The percentage of non-compliant days measure ignores an entire sub-population of users who prematurely discontinue therapy. The second outcome measure compared early medication stoppers to medication continuers. In the current study, the early medication stoppers were not a large group. The first definition of medication stopper, which defined medication stoppers as those people who filled only one prescription, classified only 9.5% of users as medication stoppers. The second and third definitions, which defined stoppers as those who were on the antidepressant for only 30 or 60 days respectively, classified 8.1% and 11.4% of users as medication stoppers. Other studies looking at antidepressant medications have suggested that early medication stoppers actually account for a much larger portion of the entire population of users. Simon et al. (1993) found that 35% of depressed patients in a primary care setting discontinued treatment after 30 days. Maddox et al. (1994) found that 32% of depressed patients had stopped antidepressant medication at 6 weeks into therapy. The results from this study may show a smaller number of early treatment stoppers for several reasons. First, the population of clients using the Blue Cross program tends to be primarily middle class individuals. Characteristics of this sample such as higher education levels, employment

status, or social economic status may affect continuation rates. Second, other studies looking at discontinuation have primarily used patients who are using the antidepressant for the indication of depression. No such information was available in the current study. Thus, it is possible that discontinuation rates are different for the antidepressants as a whole than they are for those prescribed only for depression.

The survival curves did give some indication of the time course of non-compliant behaviours in the population of antidepressant users. The initial curves for each class show that the greatest probability of having a first non-compliant episode occurs early in therapy for both classes at approximately 40 to 50 days. The survival curves depict a fairly uniform decline in the cumulative probability of survival (of not-having a non-compliant episode) over the remainder of therapy. Examination of these survival curves provided information on exactly when during therapy compliance problems may occur. These results may be helpful in determining when during the course therapy, interventions which aim to increase compliance would be most effective.

5.2 Medication Class and Compliance

Although the comparisons of the SSRI's and tricyclics did not show significantly different patterns of compliance between the two, several interesting patterns were noted. First, the tricyclics did have a slightly greater discontinuation rate by each of the three assumptions of 'early stopper'. This is consistent with information from clinical trials and other population studies that suggest that the tricyclics are not as well tolerated as the SSRI's, especially early in therapy, because of a worse side effect profile (Simon et al., 1993; Anderson et al., 1995).

A comparison of the survival curves directly comparing the classes was not significant but several patterns did exist. More specifically, the tricyclics showed a greater drop than the SSRI's at the 50 day mark. In contrast, the SSRI's showed a greater decrease in the cumulative probability of survival between the 200-300 day marks. This decline was consistent across the remainder of the time course of therapy. These differences may actually be related to the differing side effect profiles of the two classes. The tricyclics tend to have more troublesome side effects such as constipation, blurred vision, and urinary retention which might result in early discontinuations or reductions in compliance (Lin et al., 1993). The SSRI's showed a

greater drop in compliance than the tricyclics later in treatment. This may possibly be related to the fact that the SSRI's tend to cause sexual dysfunction in approximately one third of users (Bernstein, 1995). This side effect may be tolerated when the illness is being treated but once a person goes into maintenance and is generally asymptomatic, this side effect may be more troublesome and possibly result in decreased compliance later in therapy.

5.3 Predictors of Non-compliance

Several of the variables were consistently associated with each compliance measure. In particular, age, the number of concurrent medications, and the number of doses per day all varied as a function of compliance. Patient cost and sex were not consistently associated with compliance.

5.3.1 Age

Subject age showed specific trends in terms of compliance. More specifically, as age decreased, non-compliance increased. Although this trend was evident in the descriptive statistics (means and frequencies), more stringent statistical tests of significance showed that this association was weak with the greatest difference existing between the youngest and oldest age groups. The age association was stronger for the tricyclic class than the SSRI class.

Previous literature has been conflicting in terms of age (see section 2.4.2.2). A very limited number of studies have looked specifically at the antidepressants. Last and Thase (1985) and Lin et al. (1995) both found that age was not associated with early termination from pharmacologic treatments in depressed patients. Many population database studies that have looked at age in relation to other medications including antihypertensive, lipid-lowering, and anticonvulsant medications have found no or weak associations with age (Monane et al., 1994; Larret et al., 1990; Stanaway et al., 1985). Although the results from the current study, like several previous studies, do suggest an age related trend in compliance the association is very weak. Lorenc and Branthwaite (1993) suggest that the age related association to non-compliance may actually be the result of separate factors which might correlate with age which are actually related to compliance. For example, accurate knowledge of the regimen, belief in the importance of taking tablets exactly as prescribed, low resentment of time spent waiting to see doctor, less fear of illness, and living with a relative may all correlate with age and actually be predictors of compliance.

5.3.2 Regimen Complexity

The complexity of the medication regimen as indicated by the number of concurrent medications and the number of doses per day did show specific patterns in terms of patient compliance.

Compliance increased as the number of concurrent medications increased. This result was consistent across outcome measures and drug classes. The medication stoppers had a lower mean number of concurrent medications than those who continued on the antidepressant. The mean percentage of non-compliant days also decreased as the number of concurrent medications increased. Although these patterns were quite evident in the data, more stringent statistical tests (i.e. confidence intervals, regression analysis) showed that the differences between levels were not large with only a weak association between the number of concurrent medications and compliance.

Current opinion regarding the effect of the number of concurrent medications on compliance is that compliance decreases as the number of concurrent medications increase. This pattern is thought to be due to the increase in complexity of the medication regimen. The current study, as well as similar studies in population settings by Hamilton et al. (1992) and Monane et al. (1994) suggest that the

opposite trend may exist. Hamilton et al. (1992) found that compliance to a wide range of drug therapies improved as the number of concurrent medications increased. Monane et al. found that the percentage of non-compliant days to cardiac therapy decreased as the number of concurrent medications increased. Hamilton et al. (1992) suggest several possible explanations. First, because of the complexity of the regimen, subjects may be forced to develop dosage administration schedules that ensure compliance. Second, people with more medications may be perceived as having a greater risk of non-compliance because of the complex regimen and thus, may receive more medication counseling. Although this research does not absolutely confirm that past studies are wrong, it does reiterate the need for further research in this area, predominantly in settings where compliance is not influenced by the researcher. One problem with this measure, which is also true of most of the predictors used, is that it may be related to another variables. For example, the number of concurrent medications often increase as age increases and thus it is difficult to ascertain what factor is actually influencing compliance.

The second measure of medication complexity, the number of doses per day, also showed distinct trends in terms of compliance. The mean percentage of non-compliant days was

greater in the group taking more than one dose per day. This was consistent for both the tricyclic and SSRI classes. However, regression analysis suggested that the percentage of the variance accounted for by this measure was not great. In addition, the early medication stoppers did not differ from the medication continuers in the mean number of doses per day. This may indicate that the number of doses per day may be a barrier to compliance for those people who continue on with the medication. In addition, survival analysis showed that individuals taking more than one administration per day were significantly more likely to have a non-compliant gap earlier in therapy than those taking one administration per day. Again, these findings were significant for both classes.

As discussed in section 2.4.1.2, most of the literature suggests that the number of doses per day increases the complexity of the medication regimen and thus lead to a decrease in patient compliance. This study is generally consistent with these findings.

This measure does have a number of inherent problems. First, the number of doses per day was calculated from the number of medication dispensed and the number of days supply. Problems with data contamination in the 'Days Supply' field in the database may have resulted in incorrect

calculations for the number of doses per day. In addition, it was inferred that, because a person was taking more than one pill per day, that each unit of medication was taken separately. According to Hamilton et al. (1992) this is a generally reasonable assumption for drugs that come in a wide variety of tablet strengths as do most of the antidepressants. However, it should be reiterated that this was an indirect measure of the number of doses per day.

5.3.3 Patient Cost

Neither average patient cost for the antidepressants nor average patient cost for other drugs appeared to be consistently associated with compliance for either class. One noticeable trend did exist for the average patient cost of the SSRI in both the percentage of non-compliant days and the survival analysis. More particularly, there was a significant difference in the mean percentage of non-compliant days between the group paying $8.01 or more per SSRI prescription and those paying $4.00 or less per SSRI prescription. In addition, those paying $8.00 or more per prescription had a greater probability of having a non-compliant gap earlier in therapy than those paying an average of $4.00 or less per prescription.

Previous studies have suggested that increased cost to the patient negatively impacts on compliance (Thompson et

al., 1995; Beardon et al., 1993). The current study suggests that the average cost that an individual pays for the other medication that s/he takes does not effect compliance to the antidepressant medication. However, the direct cost that a patient is paying for the antidepressant medication itself may effect compliance to the antidepressant especially if that cost exceeds a certain level (in this study >$8.00). Although several other outcome measures did not indicate any association with cost, this significant association does indicate that further research should attempt to ascertain whether greater magnitudes of cost impact on compliance. In the current study, the function of studying the antidepressant and other costs separately was to ascertain which cost components (direct cost of antidepressant or costs associated with other drugs) influenced non-compliance to the antidepressants. Future research should probably look at impact of the total cost of all treatments upon non-compliance. In addition, future research should look at overall costs to a family. For example, a measure of total costs could have looked at the total cost per family and whether or not high family costs impact on fill-refill compliance.

A problem that existed with the measurement of the average cost per prescription in this database involved the

fact that prescriptions were not filled for uniform time periods. Thus, cost was dependent on prescription duration. One person may have paid more for the same drug than another person because they had the prescription filled for a longer duration not because they were actually paying more for the drug itself. The cost measure is valid in as much as it allows us to ascertain whether the cost to an individual at one point in time (i.e. when they pick up their prescription) affects compliance. However, the lack of significant outcomes in this measure may, in part, be due to the fact that the average price paid for a prescription was dependent on duration.

5.4 Evaluation of the Blue Cross Database

Examination of the Blue Cross administrative database revealed a number of problems. Contamination of the data, missing data values, as well as inherent limitations in the database itself resulted in problems that may have affected the results.

Errors in data entry presented problems for the analysis of compliance. Default values in the 'Days Supply' field and errors in date of birth entries were only two instances where problems existed. In these cases, strict protocols were initiated to clean the data. It is possible

that contaminated information might have existed in other fields as well.

A number of problems were identified which were beyond the control of the researchers. For example, a small percentage of the male subjects (3.5%) were identified who had prescriptions for a birth control pill of some kind. Investigation of this phenomenon with Blue Cross revealed that, a women's birth control prescription could have accidentally been entered into her husband's file if he had filled the prescription. This was not a standard practice by the pharmacy but a result of accidental data entry. It is unknown to what extent this problem existed in the data.

Another problem that was encountered was a result of a confidentiality measure taken by Blue Cross. Because names could not be issued, the data was presented to the researchers with only family ID numbers. This necessitated the correction of files to add individual identifiers. Although a strict protocol was followed in the adding of the individual identifiers, not enough information was available to ensure that individuals were always identified correctly. For example, in the case of twins, because the family ID number, the date of birth, and the sex would all be the same, the records of both twins would be combined as one person.

In general, although a number of problems were identified through careful inspection of the data, it is possible that other problems may have existed that were not addressed through any data cleaning process such as the problem of a prescription fill being placed in the wrong person's file (i.e. a husbands or wives file). The problems encountered in this study, as well as potentially unidentified problems, should be seriously considered in future studies that use this and similar databases as a source of information.

An inherent characteristic of the Blue Cross Database that was problematic was the lack of documentation regarding drop-outs or starters to the Blue Cross Program. An individual may have been misclassified as an 'early medication stopper' when, in fact, they had switched to another insurance plan. Also, the first medication reported in the Blue Cross Database may not have been the first antidepressant in that course of therapy for an individual who had recently switched into the Blue Cross Program.

Also, if a person had two sets of coverage under the Blue Cross program, that person would be considered two different people in the Blue Cross records. For example, if a women had coverage under her husband's family plan but also had individual coverage through an employer, then she

would have had two separate sets of records in the database. This problem could have led to one person being counted as two separate people in the analysis.

Private administrative insurance claims databases are designed to allow insurance companies to monitor their spending and costs incurred for each client and their dependents. Although they contain specific details, the information may be contaminated or incorrect. Compliance research such as that carried out in the current study requires very specific information concerning the exact dates and quantities of medication dispensed. On the surface, the Blue Cross Database provided some of this information. However, close inspection of the data revealed that it contained many data entry errors. An indication of the magnitude of this problem is the 21.8% of the original 6389 subjects who were eliminated from the study because of contaminated (eg default values such as '999' or'0') or missing records in the "Days Supply" field.

5.5 Problems Associated with Using Databases to Study Compliance

The use of population databases have many advantages in the study of compliance. They allow the researcher access to a wide body of data for a specific population. They are often less expensive than studies where large amounts of

data have to be collected through surveys or clinical trials. In addition, patient behaviours are not influenced by the intervention of the researcher. However, the Blue Cross database as well as any other administrative databases of its kind have inherent limitations for compliance research.

First, no information is available on indications for use of the medication. This is particularly problematic for the antidepressants because of the wide range of indications they can be prescribed for. This wide range of indications is associated with varying treatment characteristics such as optimal doses or duration of treatment. Thus, in the current study, an assumption was made that individuals starting new courses of therapy would be taking the medication for an extended duration as would be the case for an individual prescribed an antidepressant for depression; the most common indication that the antidepressants are used for (McCombs et al., 1990; Wagner et al., 1992, Simon et al., 1993). However, individuals using the medication for other indications may have been using it for a shorter duration of time. Thus, they may have been wrongly classified as 'early medication stoppers'.

Another problem related to the study of antidepressants in a database is the varying time course of the dosing of

medication. A person may be on a full dose of an the antidepressant while s/he is in a depressive episode. However, if the person remains on the medication for prophylactic reasons (referred to as a maintenance period), the dose may be tapered. In some cases the physician may not change the prescription. S/he may only tell the patient to take half the dose (eg. one pill per day instead of two). This change would not be reflected in the pharmacy's records and thus would result in apparent gaps in treatment.

The problem of incorrect classification of non-compliance is a issue as well. Because most drug plan databases do not perceive a need to gather information on reasons for discontinuations or gaps in therapy, no information is documented on why gaps in treatment occur. In this study, it was assumed that non-compliance was the reason for gaps in treatment less than 90 days in length. In fact, this may not have been the reason for the gaps. For example, subjects may have been hospitalized and thus had their medications provided by the hospital, they may have received medication from other sources such as another insurance plan or a family member, or the health care provider may have stopped or interrupted the therapy. A more comprehensive database with links to hospital records, physician records, or other sources of prescription

medication would allow for a greater deal of certainty in the assumption of non-compliance.

In addition, drug plan databases do not provide information on other non-pharmaceutical therapies that a person might be using. This is particularly important for the study of compliance to therapies for disorders like depression where a person might be using other therapies to complement the antidepressant therapy such as psychotherapy.

Finally, the study of refill compliance measures from databases looks only at the subset of the population who actually fill their first prescription. Those who do not fill a first prescription are lost to database researchers.

5.6 Recommendations for Database Improvement

Several improvements or additions to the Blue Cross database would increase the usefulness of the data for compliance research. The use of common patient identifiers (e.g. MCP Numbers) would allow for increased linkages with other databases from hospitals, clinics, or other coverage plans that would provide necessary information on indication, hospital admission times, and number of doses per day.

In addition, because data entry was such a large problem in terms of data reliability, educating pharmacists, pharmacy technicians, or data entry staff in the importance

of accurate data entry is essential. Some form of marker to indicate that a subject has just joined the Blue Cross program or to signify that they have dropped out of the program would also prove useful. Linkages of records belonging to an individual who has separate policies is also an essential improvement.

Many researchers and agencies such as governments are interested in studying or monitoring drug utilization, patient compliance, post marketing surveillance of new drugs, drug interactions, benefit and risks of medications, and drug use information (West, 1993). Improvement of administrative databases as described above would have great value in these research initiatives.

It would be in the best interests of private agencies such as Blue Cross to set up data sources that not only monitor expenditures, but which also allow for research opportunities. For example, research in cost-benefit and over utilization could result in more effective use of medications and thus potentially lead to cost savings for private insurance plans. In terms of compliance, it is in the best interests of insurance companies to facilitate research in this area because of the proven effect of compliance on patient outcomes (see section 2.1.3). Increased information on compliance could lead to improved

interventions to improve patient compliance. Improved compliance by subscribers may reduce the costs incurred by insurance agencies because of the ramifications of non-compliance.

Increased linkages through the use of common patient identifiers and agreements between governments and private agencies would avoid duplication of information and would maximize the potential for high caliber research particularly in the area of compliance. A major condition of such unions between various agencies would be universal standards which would ensure reliability of the data sources.

5.7 Future Compliance Research Recommendations

Future research on antidepressant compliance needs to utilize data sources that are very comprehensive and which contain accurate and reliable information on such things as indication. The Saskatchewan population database which links records via common patient identifiers between various segments of the health sector (i.e. hospitals etc.) would be an example of a comprehensive source of data. Use of comprehensive data sources where all information on any particular client is readily linked through common identifiers would allow researchers to access all pertinent information such as indications for use. For example,

prescription refill records would be available via insurance companies such as Blue Cross and information on indication would be available through computerized files in clinics. These records would optimally be linked via a common identification number.

It would be interesting to compare compliance among those taking the medication for different indications. Another group that may prove interesting to study are the group of people who switch between classes of antidepressants (this group was eliminated from the current study). It would be interesting to look at compliance in a population that engages in medication switching in order to view the possible effects of this factor on compliance. In terms of predictors of compliance, further research should explore cost and regimen complexity as predictors. Although regimen complexity has been studied widely for other medications, research on antidepressants is lacking in this area. This is probably due to the fact that most antidepressant regimens involve once or twice daily dosing. More specific research could help in tailoring prescribing guidelines in order to maximize both compliance and therapeutic benefit. The age and sex variables have been widely studied with no consistent patterns found across studies. The idea put forward by Lorenc et al. (1993) that

age might actually appear to be related to other variables which effect compliance should be studied further. This suggestion also reiterates the problems associated with determining predictors of compliance behaviours. All behaviours are very complex and it is highly probable that a combination of many highly complex factors impact upon an individuals decision to comply to a prescribed regimen. Thus, as was evident in the regression analysis, individual predictors will probably only account for a small portion of the variance in compliance behaviours. Research should probably focus on developing more complex models of compliance which consider multiple factors such as individual patient characteristics (e.g., behaviours, attitudes) as well as external factors such as patient-health care provider interactions, family and social influences, as well as specific disease states (e.g.. severity of depression). Only when this is done can effective interventions aimed at improving compliance be developed.

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APPENDICES

Appendix 1
Complete List of Antidepressants in Database

Table A1; Complete List of All Antidepressants Found in database

TRADE NAME	CLASS	TYPE	DIN	DOSE
SERZONE	ATYPICAL	Nefrazodone	2087383	150
SERZONE	ATYPICAL	Nefrazodone	2087375	100
SERZONE	ATYPICAL	Nefrazodone	2087391	200
NOVO-MAPROTILINE	HETER	Maprotiline	2158639	75
LUDIOMIL	HETER	Maprotiline	641855	10
NOVO-MAPROTILINE	HETER	Maprotiline	2158612	25
LUDIOMIL	HETER	Maprotiline	360481	25
LUDIOMIL	HETER	Maprotiline	360503	50
LUDIOMIL	HETER	Maprotiline	360511	75
NOVO-TRAZODONE	HETER	Trazodone	2144298	150
SYN-TRAZODONE	HETER	Trazodone	2053209	150
DESYREL	HETER	Trazodone	579351	50
DESYREL	HETER	Trazodone	579378	100
DESYREL	HETER	Trazodone	702277	150
SYN-TRAZODONE	HETER	Trazodone	2053187	50
SYN-TRAZODONE HCL	HETER	Trazodone	2053195	100
NOVO-TRAZODONE	HETER	Trazodone	2144271	100
APO-TRAZODONE	HETER	Trazodone	2147637	50
APO-TRAZODONE	HETER	Trazodone	2147645	100
APO-TRAZODONE	HETER	Trazodone	2147653	150
PMS-TRAZODONE	HETER	Trazodone	1937227	50
PMS-TRAZODONE	HETER	Trazodone	1937235	100
NOVO-TRAZODONE	HETER	Trazodone	2144263	50
MANERIX	MAOI	Moclobemide	899356	150
MANERIX	MAOI	Moclobemide	899348	100
MANERIX	MAOI	Moclobemide	2166747	300
NARDIL	MAOI	Phenelzine	476552	15
PARNATE	MAOI	Tranylcypromine	27111	10
PARNATE	MAOI	Tranylcypromine	1919598	10
EFFEXOR	SNRI	Venlfaxine	2103702	75
EFFEXOR	SNRI	Venlfaxine	2103680	37.5
PMS-FLUOXETINE	SSRI	Fluoxetine	2177587	20
NOVO-FLUOXETINE	SSRI	Fluoxetine	2216582	10
PROZAC	SSRI	Fluoxetine	2018985	10
APO-FLUOXETINE	SSRI	Fluoxetine	2216361	20
PROZAC	SSRI	Fluoxetine	636622	20
PMS-FLUOXETINE	SSRI	Fluoxetine	2177579	10
NOVO-FLUOXETINE	SSRI	Fluoxetine	2216590	20
PROZAC	SSRI	Fluoxetine	1917021	20
NU-FLUOXETINE	SSRI	Fluoxetine	2192764	20
NU-FLUOXETINE	SSRI	Fluoxetine	2192756	10
LUVOX	SSRI	Fluvoxamine	1919342	50

LUVOX	SSRI	Fluvoxamine	1911872	100
LUVOX	SSRI	Fluvoxamine	1911856	50
LUVOX	SSRI	Fluvoxamine	1919369	100
PAXIL	SSRI	Paroxetine	1940473	30
PAXIL	SSRI	Paroxetine	1940481	20
ZOLOFT	SSRI	Sertraline	1962817	50
ZOLOFT	SSRI	Sertraline	1962779	100
ZOLOFT	SSRI	Sertraline	2132702	25
NOVO-TRIPTYN	TRICYCLIC	Amitriptyline	37427	50
NOVO-TRIPTYN	TRICYCLIC	Amitriptyline	37400	10
APO-AMITRIPTYLINE	TRICYCLIC	Amitriptyline	335088	50
ELAVIL	TRICYCLIC	Amitriptyline	16330	25
APO-AMITRIPTYLINE	TRICYCLIC	Amitriptyline	335061	25
APO-AMITRIPTYLINE	TRICYCLIC	Amitriptyline	335053	10
PMS-AMITRIPTYLINE	TRICYCLIC	Amitriptyline	654515	25
ELAVIL	TRICYCLIC	Amitriptyline	16349	50
ELAVIL	TRICYCLIC	Amitriptyline	354295	75
PMS-AMITRIPTYLINE	TRICYCLIC	Amitriptyline	654523	10
NOVO-TRIPTYN	TRICYCLIC	Amitriptyline	37419	25
LEVATE	TRICYCLIC	Amitriptyline	405612	75
APO-AMITRIPTYLINE	TRICYCLIC	Amitriptyline	754129	75
ELAVIL	TRICYCLIC	Amitriptyline	16322	10
ELAVIL	TRICYCLIC	Amitriptyline	16306	10
ASENDIN	TRICYCLIC	Amoxapine	527084	25
ASENDIN	TRICYCLIC	Amoxapine	527092	50
ASENDIN	TRICYCLIC	Amoxapine	527106	100
GEN-CLOMIPRAMINE	TRICYCLIC	Clomipramine	2139340	10
GEN-CLOMIPRAMINE	TRICYCLIC	Clomipramine	2139359	25
APO-CLOMIPRAMINE	TRICYCLIC	Clomipramine	2040778	25
GEN-CLOMIPRAMINE	TRICYCLIC	Clomipramine	2139367	50
ANAFRANIL	TRICYCLIC	Clomipramine	402591	50
ANAFRANIL	TRICYCLIC	Clomipramine	324019	25
APO-CLOMIPRAMINE	TRICYCLIC	Clomipramine	2040751	50
ANAFRANIL	TRICYCLIC	Clomipramine	330566	10
APO-CLOMIPRAMINE	TRICYCLIC	Clomipramine	2040786	10
PERTOFRANE	TRICYCLIC	Desipramine	893765	50
NORPRAMIN	TRICYCLIC	Desipramine	2024888	10
NORPRAMIN	TRICYCLIC	Desipramine	2024896	25
DESIPRAMINE	TRICYCLIC	Desipramine	1948792	50
DESIPRAMINE	TRICYCLIC	Desipramine	1948784	25
DESIPRAMINE HYDROCHLORIDE	TRICYCLIC	Desipramine	1948776	10
NORPRAMIN	TRICYCLIC	Desipramine	425265	75
NORPRAMIN	TRICYCLIC	Desipramine	776157	10
PMS DESIPRAMINE HYDRO	TRICYCLIC	Desipramine	1946277	50
PMS DESIPRAMINE HYDRO	TRICYCLIC	Desipramine	1946269	25

NORPRAMIN	TRICYCLIC	Desipramine	2103583	10
NORPRAMIN	TRICYCLIC	Desipramine	353876	50
NORPRAMIN	TRICYCLIC	Desipramine	2099144	75
NORPRAMIN	TRICYCLIC	Desipramine	2099128	25
PMS DESIPRAMINE HYDRO	TRICYCLIC	Desipramine	1946242	75
NORPRAMIN	TRICYCLIC	Desipramine	2024918	50
PERTOFRANE	TRICYCLIC	Desipramine	10448	25
NORPRAMIN	TRICYCLIC	Desipramine	2024926	75
DESIPRAMINE	TRICYCLIC	Desipramine	1948806	75
NORPRAMIN	TRICYCLIC	Desipramine	2024934	100
NORPRAMIN	TRICYCLIC	Desipramine	353868	25
PMS DESIPRAMINE HYDRO	TRICYCLIC	Desipramine	1946250	10
TRIADAPIN	TRICYCLIC	Doxepin	629308	100
TRIADAPIN	TRICYCLIC	Doxepin	629294	75
SINEQUAN	TRICYCLIC	Doxepin	584274	150
SINEQUAN	TRICYCLIC	Doxepin	400750	75
SINEQUAN	TRICYCLIC	Doxepin	24325	10
SINEQUAN	TRICYCLIC	Doxepin	24341	50
NOVO-DOXEPIN	TRICYCLIC	Doxepin	1913476	150
SINEQUAN	TRICYCLIC	Doxepin	326925	100
SINEQUAN	TRICYCLIC	Doxepin	24333	25
NOVO-DOXEPIN	TRICYCLIC	Doxepin	1913433	50
APO-DOXEPIN	TRICYCLIC	Doxepin	2049996	10
APO-DOXEPIN	TRICYCLIC	Doxepin	2050005	25
APO-DOXEPIN	TRICYCLIC	Doxepin	2050013	50
APO-DOXEPIN	TRICYCLIC	Doxepin	2050021	75
APO-DOXEPIN	TRICYCLIC	Doxepin	2050048	100
APO-DOXEPIN	TRICYCLIC	Doxepin	2050056	150
NOVO-DOXEPIN	TRICYCLIC	Doxepin	1913441	75
NOVO-DOXEPIN	TRICYCLIC	Doxepin	1913468	100
NOVO-DOXEPIN	TRICYCLIC	Doxepin	1913425	25
TRIADAPIN	TRICYCLIC	Doxepin	842753	25
RHO-DOXEPIN	TRICYCLIC	Doxepin	2144158	50
KENRAL-DOXEPIN	TRICYCLIC	Doxepin	2140071	10
KENRAL-DOXEPIN	TRICYCLIC	Doxepin	2140098	25
TRIADAPIN	TRICYCLIC	Doxepin	842745	10
NOVO-PRAMINE	TRICYCLIC	Imipramine	21504	10
APO-IMIPRAMINE	TRICYCLIC	Imipramine	326852	50
APO-IMIPRAMINE	TRICYCLIC	Imipramine	360201	10
NOVO-PRAMINE	TRICYCLIC	Imipramine	21520	50
APO-IMIPRAMINE	TRICYCLIC	Imipramine	312797	25
NOVO-PRAMINE	TRICYCLIC	Imipramine	21512	25
TOFRANIL	TRICYCLIC	Imipramine	10472	25
TOFRANIL	TRICYCLIC	Imipramine	10464	10
TOFRANIL	TRICYCLIC	Imipramine	306487	75

APO-IMIPRAMINE	TRICYCLIC	Imipramine	644579	75
TOFRANIL	TRICYCLIC	Imipramine	10480	50
AVENTYL	TRICYCLIC	Nortriptyline	15237	25
AVENTYL	TRICYCLIC	Nortriptyline	15229	10
TRIPTIL	TRICYCLIC	Protriptyline	322741	10
SURMONTIL	TRICYCLIC	Trimipramine	1926330	50
APO-TRIMIP	TRICYCLIC	Trimipramine	740799	12.5
APO-TRIMIP	TRICYCLIC	Trimipramine	740802	25
APO-TRIMIP	TRICYCLIC	Trimipramine	740810	50
APO-TRIMIP	TRICYCLIC	Trimipramine	740829	100
RHOTRIMINE	TRICYCLIC	Trimipramine	761605	12.5
RHOTRIMINE	TRICYCLIC	Trimipramine	761613	25
RHOTRIMINE	TRICYCLIC	Trimipramine	761621	50
SURMONTIL	TRICYCLIC	Trimipramine	442437	75
APO-TRIMIP	TRICYCLIC	Trimipramine	2070987	75
RHOTRIMINE	TRICYCLIC	Trimipramine	761656	75
NU-TRIMIPRAMINE	TRICYCLIC	Trimipramine	2020602	25
SURMONTIL	TRICYCLIC	Trimipramine	1926322	25
SURMONTIL	TRICYCLIC	Trimipramine	1926349	75
SURMONTIL	TRICYCLIC	Trimipramine	1926357	12.5
SURMONTIL	TRICYCLIC	Trimipramine	25828	17.43
SURMONTIL	TRICYCLIC	Trimipramine	25836	34.86
SURMONTIL	TRICYCLIC	Trimipramine	25844	69.72
NOVO-TRIPRAMINE	TRICYCLIC	Trimipramine	1940430	25
NOVO-TRIPRAMINE	TRICYCLIC	Trimipramine	1940449	50
NOVO-TRIPRAMINE	TRICYCLIC	Trimipramine	1940457	100
NU-TRIMIPRAMINE	TRICYCLIC	Trimipramine	2020610	50
NU-TRIMIPRAMINE	TRICYCLIC	Trimipramine	2020599	12.5
SURMONTIL	TRICYCLIC	Trimipramine	1926284	100

Heter = Heterocyclic
SSRI = Selective Serotonin Re-uptake Inhibitors
SNRI = Selective Norepinephrine Re-uptake Inhibitors
MAOI = Monoamine Oxidase Inhibitors

Appendix 2
Sample of Data Obtained From Blue Cross

Table A2; Sample of Data Found In Files Obtained From Blue Cross							
ID	Counte	DIN	TRADE	DISP	DRUG	DAYS	PAID BY
2	24572	16322	ELAVIL	24/07/95	60	60	$2.40
2	62362	16322	ELAVIL	23/09/95	60	60	$2.40
2	95610	16322	ELAVIL	22/11/95	60	60	$2.40
2	128015	16322	ELAVIL	22/01/96	60	60	$2.40
2	158849	16322	ELAVIL	21/03/96	60	60	$2.40
3	24612	2018985	PROZAC	26/07/95	60	60	$5.00
3	62384	2018985	PROZAC	22/09/95	60	60	$5.00
3	95644	2018985	PROZAC	23/11/95	60	60	$5.00
3	128040	2018985	PROZAC	25/01/96	60	60	$5.00
3	158868	2018985	PROZAC	20/03/96	60	60	$5.00
3	180672	2018985	PROZAC	13/05/96	60	60	$5.00
3	208664	2018985	PROZAC	14/07/96	60	60	$5.00
3	222066	2018985	PROZAC	05/08/96	60	60	$5.00
3	228827	2018985	PROZAC	20/08/96	60	60	$5.00
3	241738	2018985	PROZAC	24/09/96	60	60	$5.00
4	28189	306487	TOFRANIL	19/07/95	30	30	$7.90
4	44612	306487	TOFRANIL	16/08/95	30	30	$7.90
4	44614	306487	TOFRANIL	16/08/95	36	36	$7.90
4	64657	306487	TOFRANIL	18/09/95	30	30	$7.90
4	81065	306487	TOFRANIL	17/10/95	30	30	$7.90
4	97654	306487	TOFRANIL	16/11/95	30	30	$7.90
4	113592	306487	TOFRANIL	16/12/95	30	30	$7.90
4	121556	306487	TOFRANIL	11/01/96	30	30	$7.90
4	138107	306487	TOFRANIL	14/02/96	30	30	$7.90
4	152882	306487	TOFRANIL	15/03/96	30	30	$7.90
4	167627	306487	TOFRANIL	13/04/96	30	30	$7.90
4	182172	306487	TOFRANIL	09/05/96	30	30	$7.90
4	196749	306487	TOFRANIL	11/06/96	30	30	$7.90
4	236537	1940481	PAXIL	13/09/96	15	30	$7.90

Appendix 3
Letter of Approval From Blue Cross

BLUE CROSS
OF ATLANTIC CANADA

644 Main St PO Box 220 Moncton NB E1C 8L3 · 644 rue Main CP 220 Moncton NB E1C 8
Tel: (506) 853-1811 Fax: (506) 867-4651

07 October 1996

Ms. Lynette Powell
Research Assistant
Graduate Student
Memorial University of Newfoundland
Division of Community Medicine
Faculty of Medicine
The Health Sciences Centre
St. John's, Newfoundland
A1B 3V6

Dear Lynette:

This letter is to confirm that Blue Cross is willing to provide data in support of the study to determine whether refill compliance to antidepressant medication varies in relation to different factors.

To ensure confidentiality of the data, we will require an agreement to be signed by Memorial University. A copy of the agreement will be sent to you as soon as possible.

I apologize for the delays experienced thus far in obtaining the requested data. We will endeavour to provide you with the data as quickly as possible. If you have any questions, please do not hesitate to contact me.

Yours truly.

Aliesje MacInnis
Health Care Professional & Provider Relations

BLUE CROSS
OF ATLANTIC CANADA

ALIESJE MACINNIS BBA
Health Care Professional and Provider Relations
(506) 867-4774
Fax: (506) 867-4666

644 Main St PO Box 220 644 rue Main CP 220
Moncton NB E1C 8L3 Moncton NB E1C 8L3

Appendix 4
Human Investigations Committee Approval

University of Newfoundland

Office of Research and Graduate Studies (Medicine)
Faculty of Medicine
The Health Sciences Centre

21 October 1996

TO: Ms. Lynette Powell

FROM: Dr. Verna M. Skanes, Assistant Dean
Research & Graduate Studies (Medicine)

SUBJECT: Application to the Human Investigation Committee - #96.144

The Human Investigation Committee of the Faculty of Medicine has reviewed your proposal for the study entitled **"Factors Affecting Refill Adherence After the Start of New Courses of Selective Serotonin Reuptake Inhibitors and Tricyclic Antidepressants"**.

Full approval has been granted for one year, from point of view of ethics as defined in the terms of reference of this Faculty Committee.

For a hospital-based study, it is **your responsibility to seek necessary approval from the Health Care Corporation of St. John's**.

Notwithstanding the approval of the HIC, the primary responsibility for the ethical conduct of the investigation remains with you.

Verna M. Skanes, Ph.D.
Assistant Dean

cc Dr. K.M.W. Keough, Vice-President (Research)
Dr. E. Parsons, Vice-President, Medical Services, HCC
Dr. R. West, Supervisor

St. John's, NF, Canada A1B 3V6 • Tel.: (709) 737-6762 • Fax: (709) 737-5033 • email: rgs@morgan.ucs.mun.ca

University of Newfoundland

Human Investigation Committee
Research and Graduate Studies
Faculty of Medicine
The Health Sciences Centre

21 October 1996

Reference #96.144

Ms. Lynette Powell
Division of Community Medicine

Dear Ms. Powell:

At a meeting of the Human Investigation Committee held on **October 10, 1996**, your application entitled **"Factors Affecting Refill Adherence After the Start of New Courses of Selective Serotonin Reuptake Inhibitors and Tricyclic Antidepressants"** was considered and approval recommended.

We take this opportunity to wish you every success with your research study.

Sincerely yours,

H.B. Younghusband, Ph.D.
Chairman
Human Investigation Committee

HBY\jglo

cc Dr. K.M.W. Keough, Vice-President, Research
Dr. Eric Parsons, Vice-President, Medical Services, HCC
Dr. Roy West, Supervisor

St. John's, NF, Canada A1B 3V6 • Tel.: (709) 737-6974 • Fax: (709) 737-5033

Appendix 5
Normal and Logarithmic Transformation of Percentage of Non-compliant Days

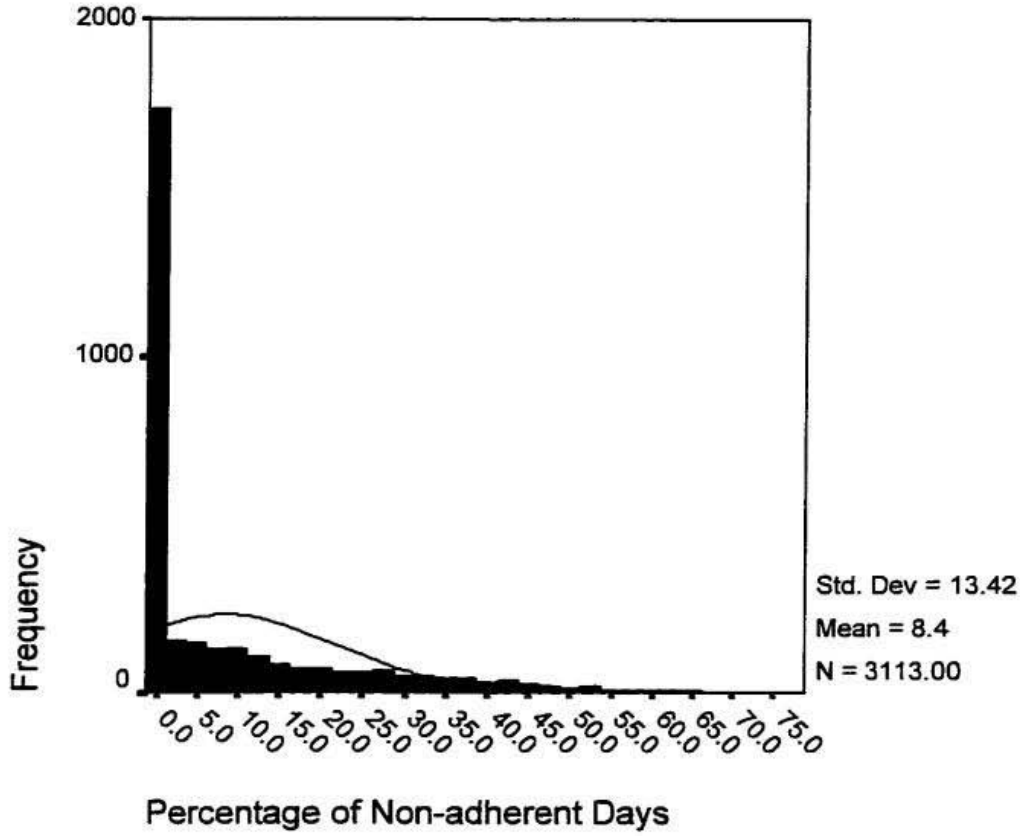

Figure A1: Distribution of the Percentage of Non-adherent Days Measure Including All 3113 Subjects

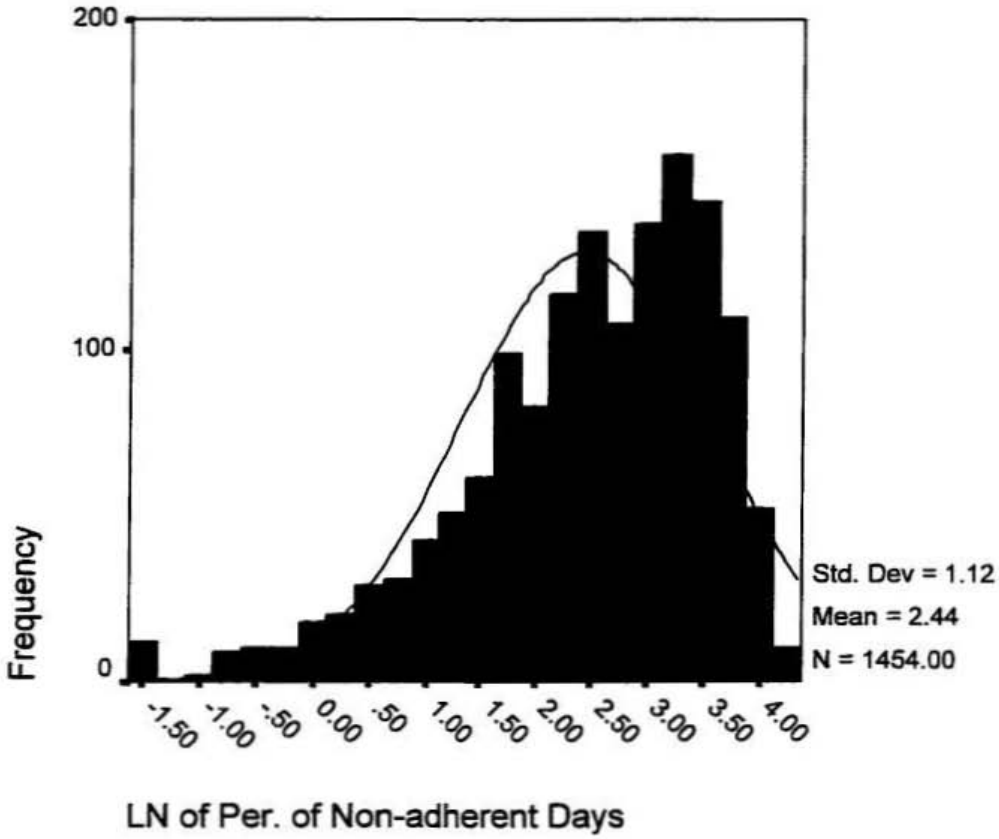

Figure A2: Logarithmic Transformation of the Percentage of Non-adherent Days Measure. All Subjects who had a percentage of non-adherent days equal to Zero were excluded from this distribution

Appendix 6
Regression Model for Percentage of Non-compliant Days Analysis

Table A3; Regression Model for Tricyclic and SSRI users with percentage of non-compliant days >0

Model	R Square	F (df)	Sign
1	0.008	F(1,1452)=12.96	.000
2	0.017	F(2,1451)=13.47	.000

Model 1; Predictors; Number of doses per day

Model 2; Predictors; Number of doses per day and number of concurrent medications

Appendix 7
Survival Curves for 30 Day Assumption

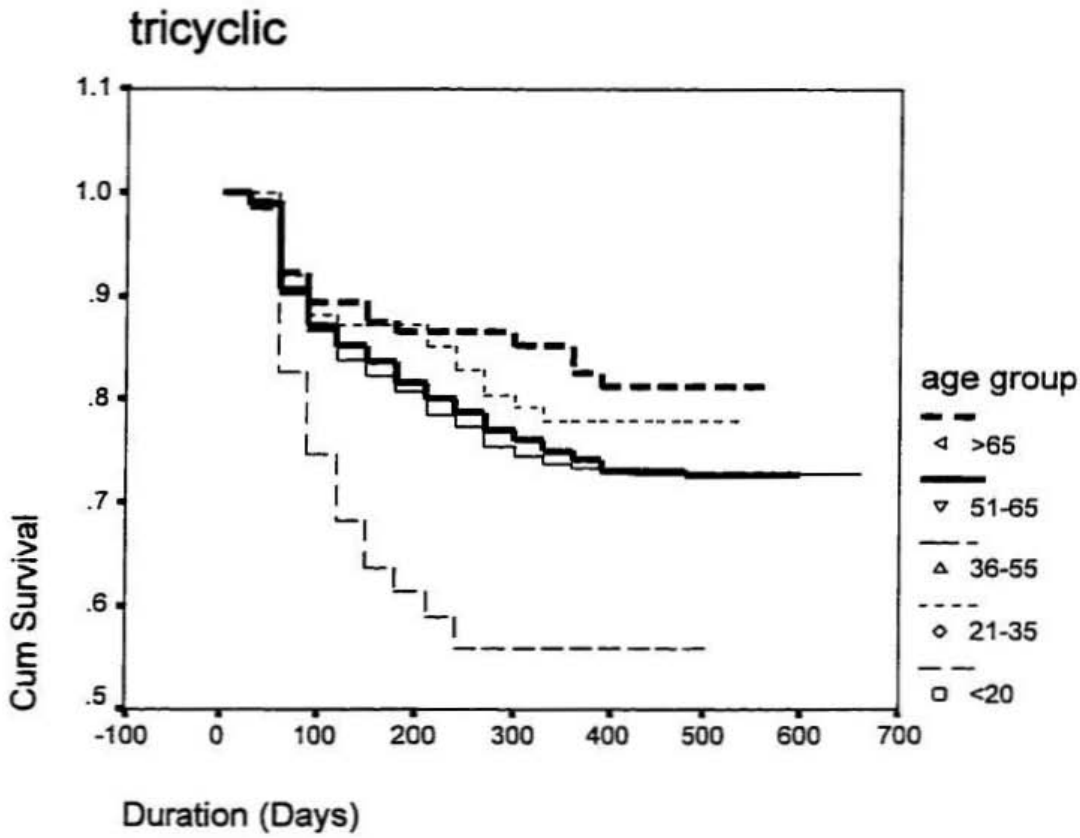

Figure A3: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Among the Different Age Groups of Tricyclic Users by the 30 Day Assumption

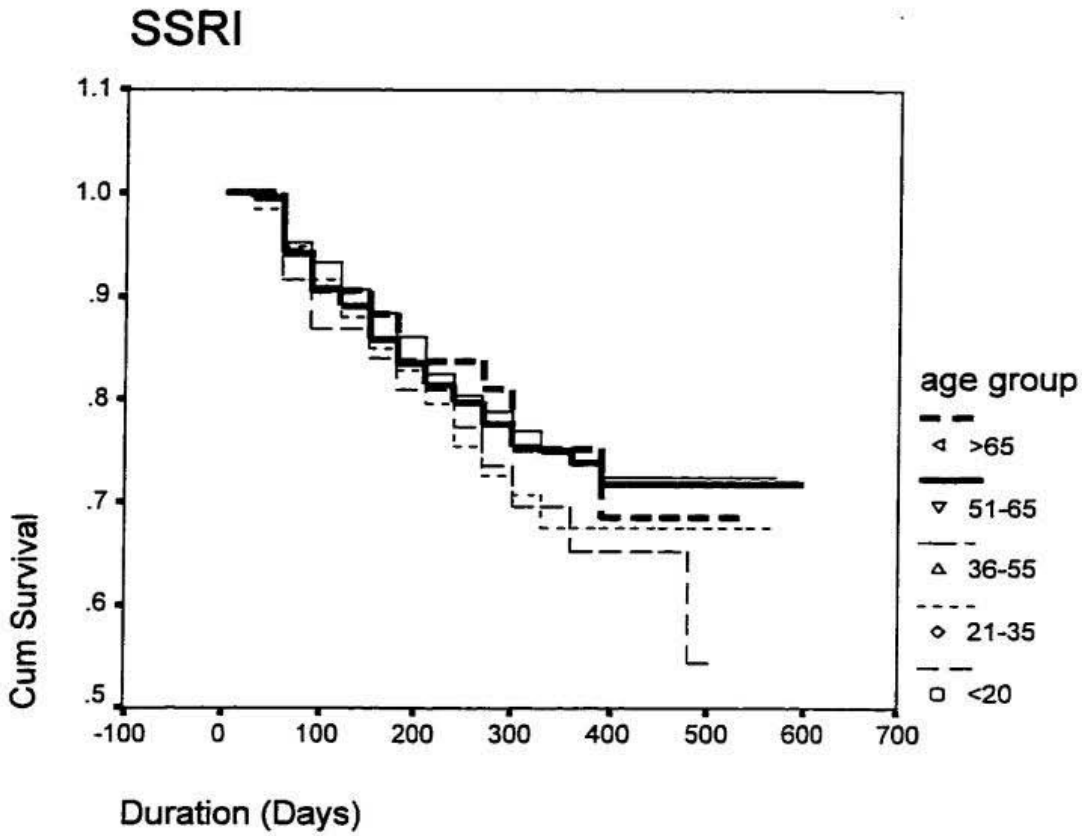

Figure A4: Survival Function Comparing Cumulative Probability of Survival Till a First Non-adherent Gap Among Various Age Groups of SSRI Users by the 30 Day Assumption

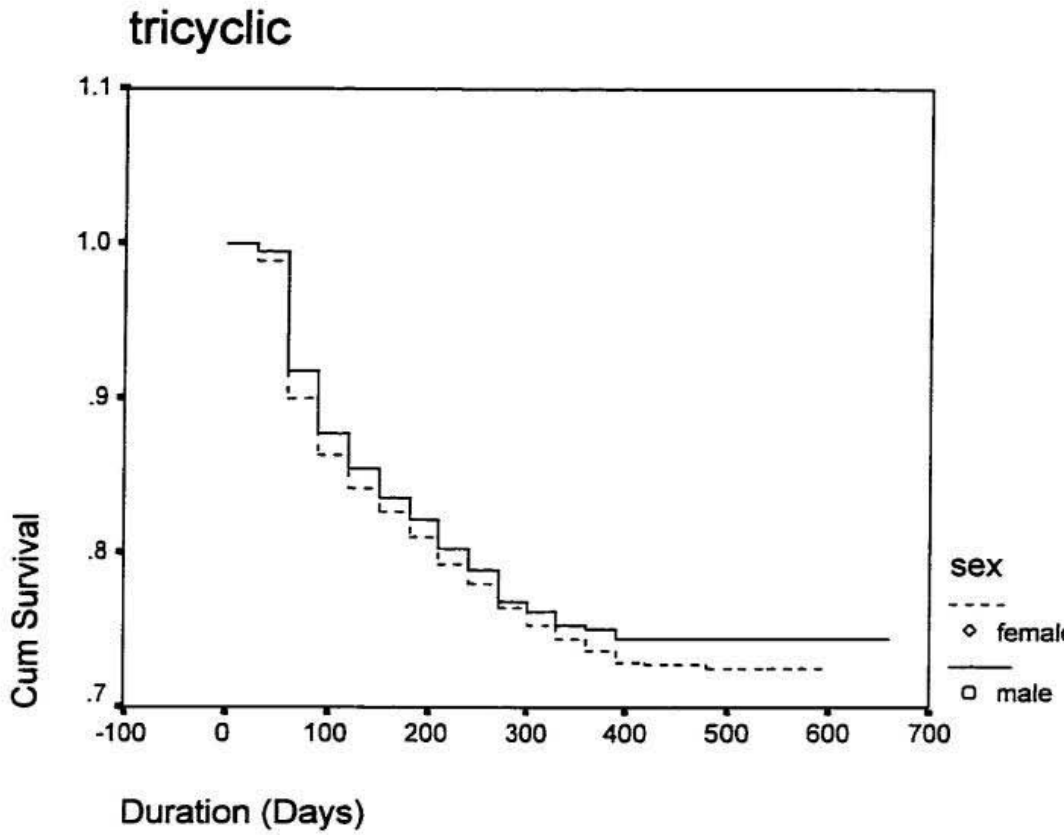

Figure A5: Survival Function Comparing Cumulative Probability of Survival Till a First Non-adherent Gap Among Male and Female Tricyclic Users by the 30 Day Assumption

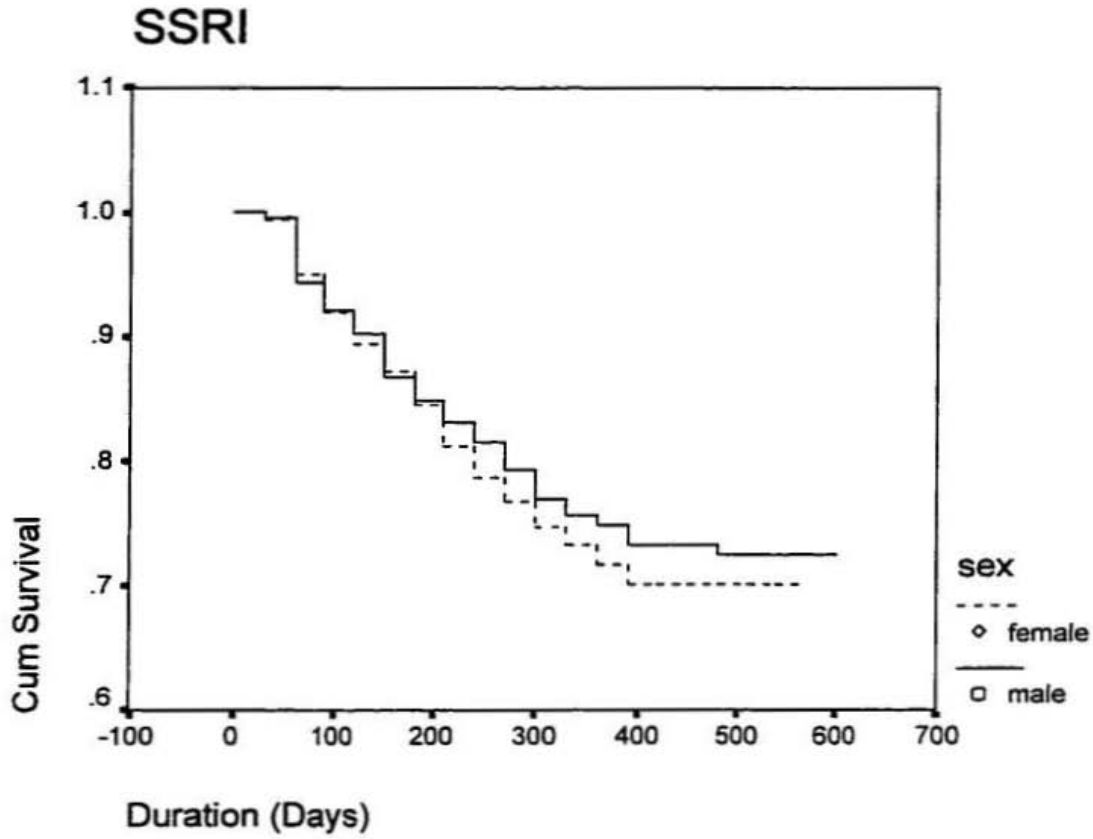

Figure A6: Survival Function Comparing the Cumulative Probability of Survival Till A First Non-adherent Gap Between Male and Female SSRI Users By the 30 Day Assumption

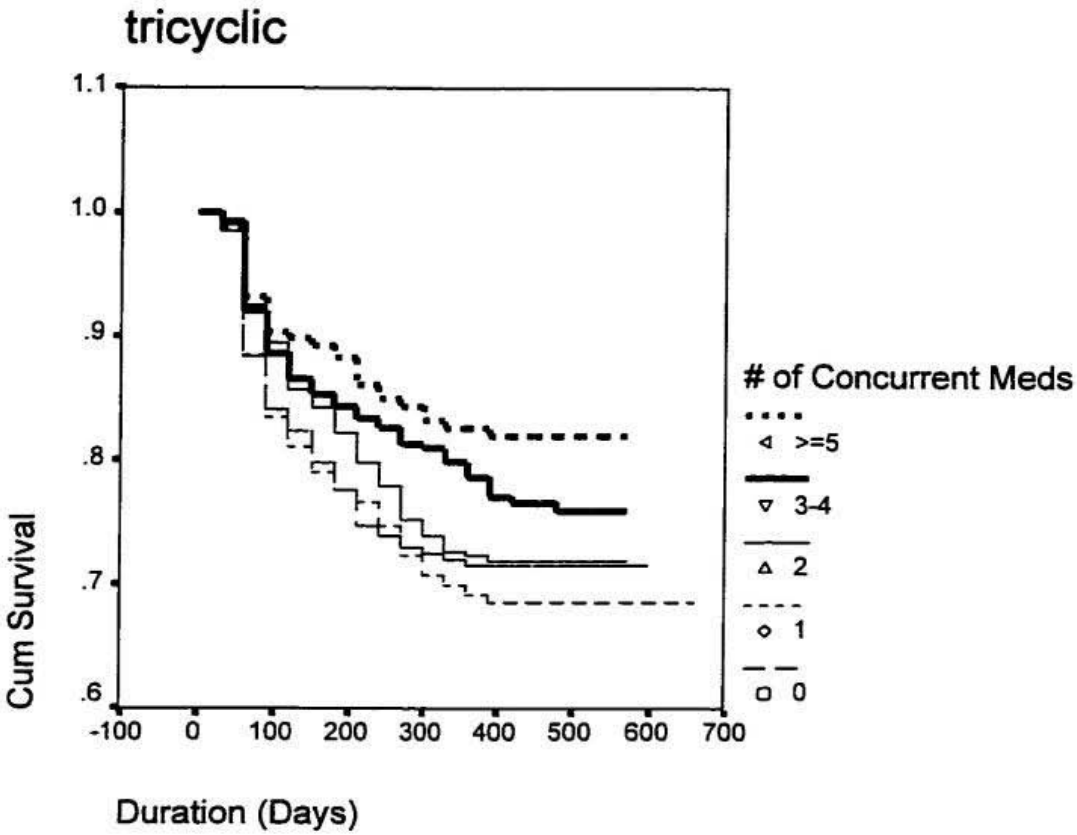

Figure A7: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Among Tricyclic Users Taking Varying Numbers of Concurrent Medications by the 30 day Assumption

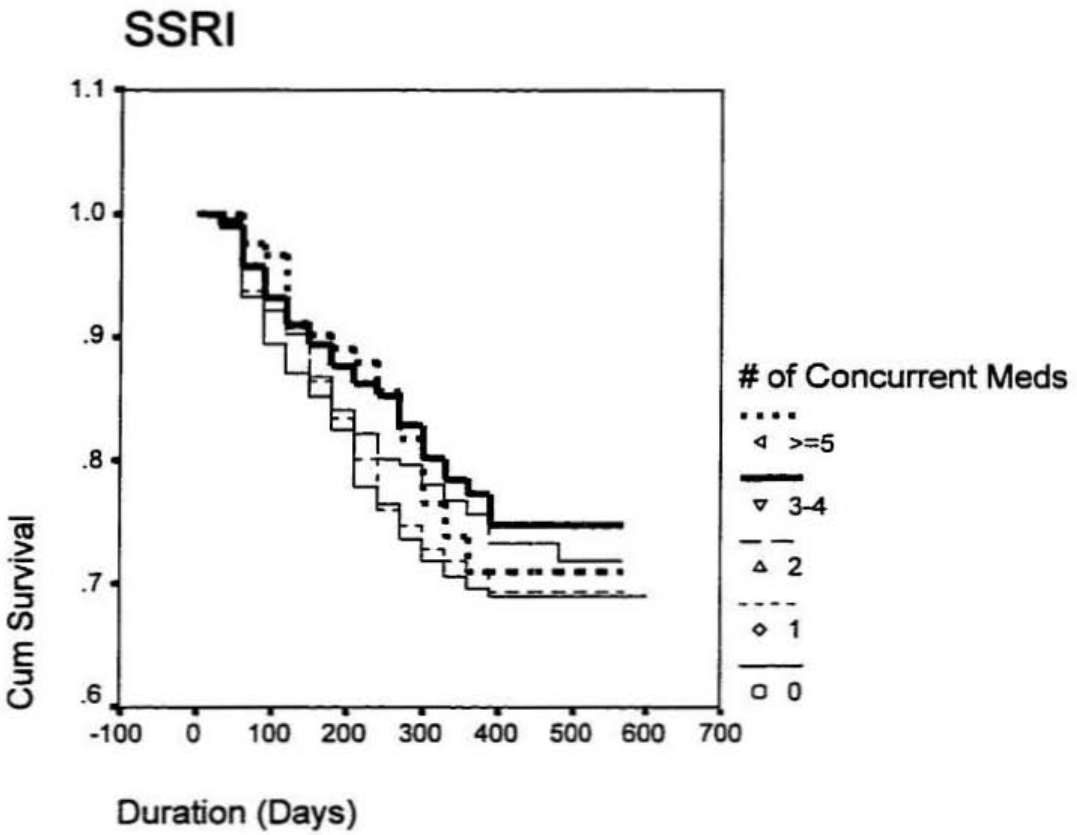

Figure A8: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap In SSRI Users Taking Varying Numbers of Concurrent Medications By the 30 Day Assumption

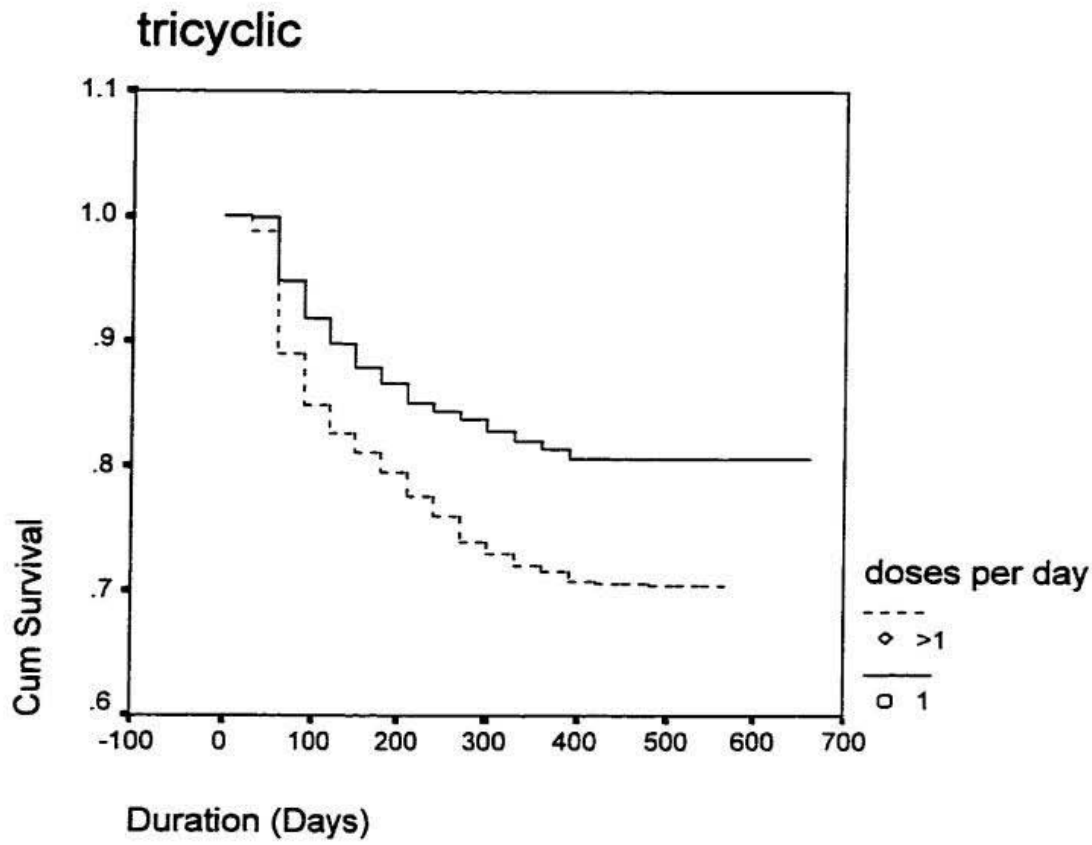

Figure A9: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Between Tricyclic Users Taking One Dose Per Day and Those Taking More Than One Dose Per Day by the 30 Day Assumption

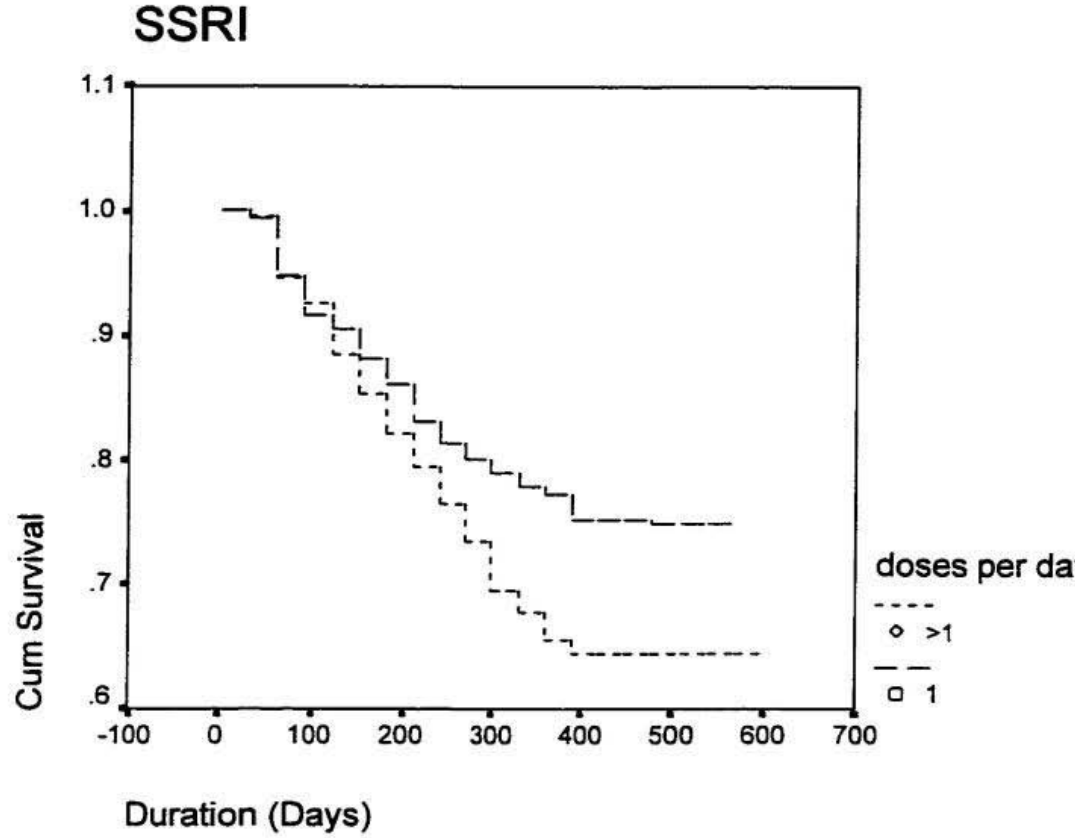

Figure A10: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Among SSRI Users Who Take One Dose Per Day and SSRI Users Who Take More than One Dose Per Day by the 30 Day Assumption

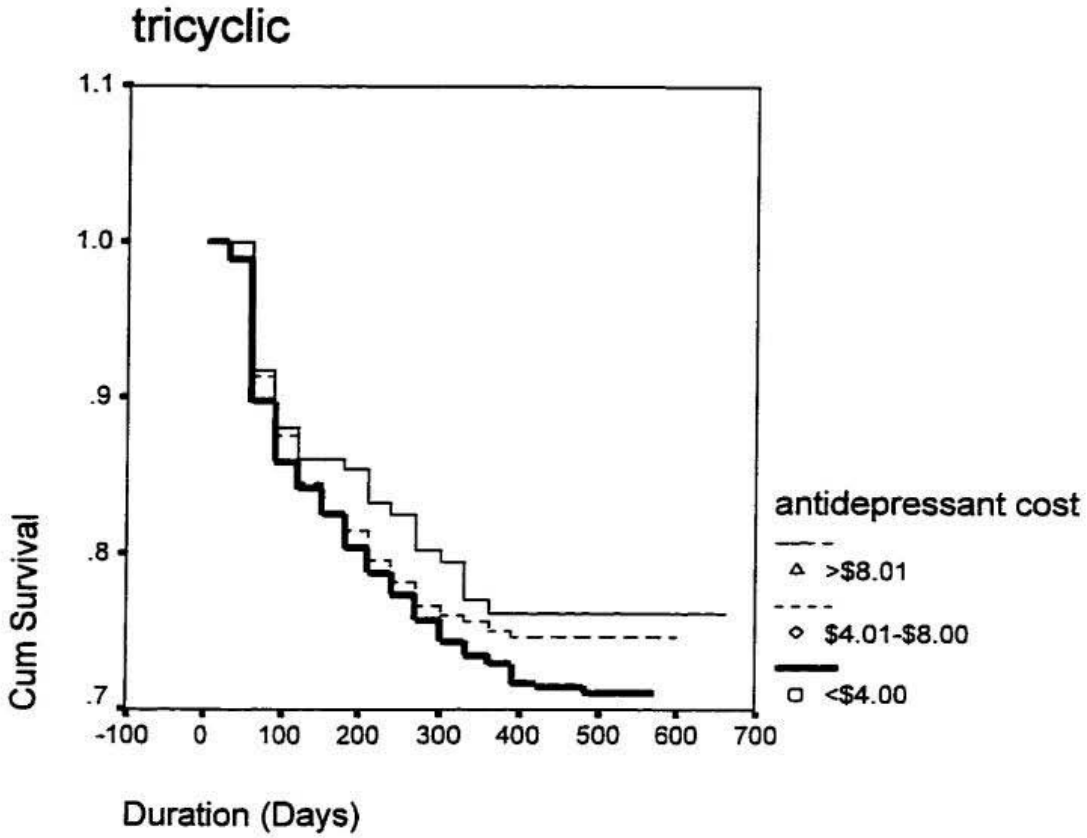

Figure A11: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Among Varying Average Cost Per Antidepressant Prescription for Tricyclic Users by the 30 Day Assumption

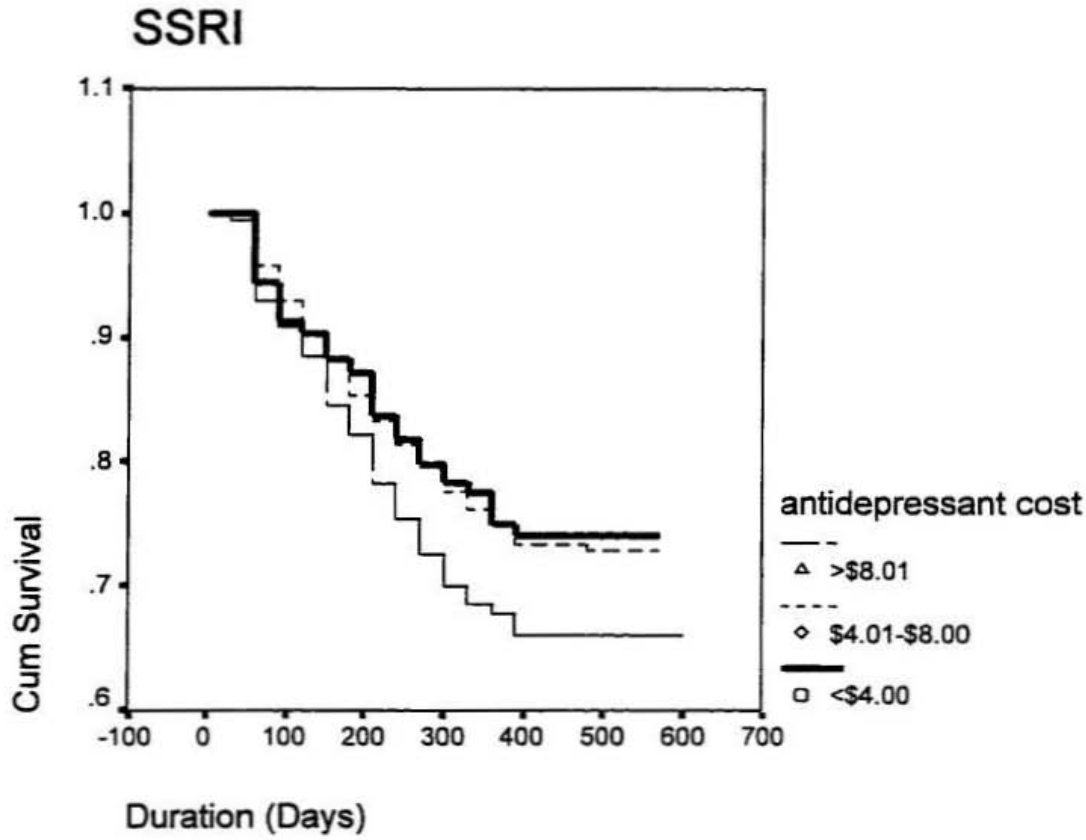

Figure A12: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Among Varying Average Cost Per Antidepressant for The SSRI Users by the 30 Day Assumption

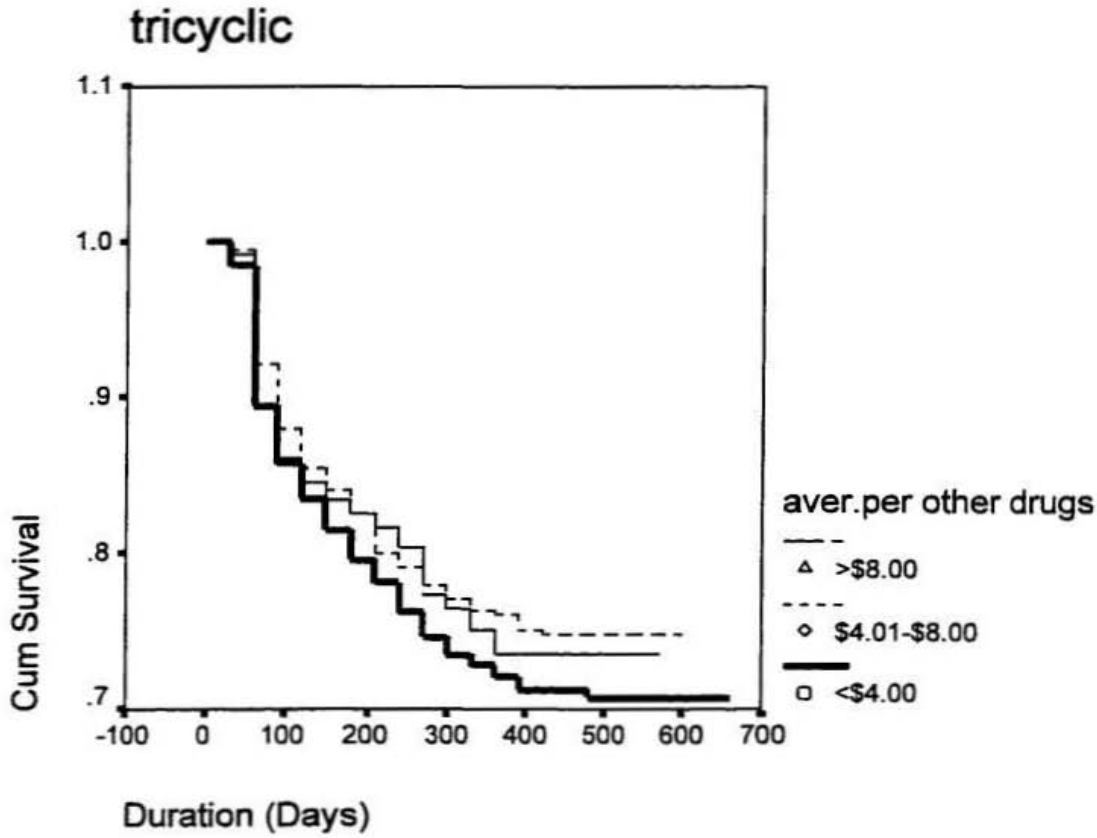

Figure A13: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Among Varying Average Cost Per Prescription for Other Drugs for Tricyclic Users by the 30 Day Assumption

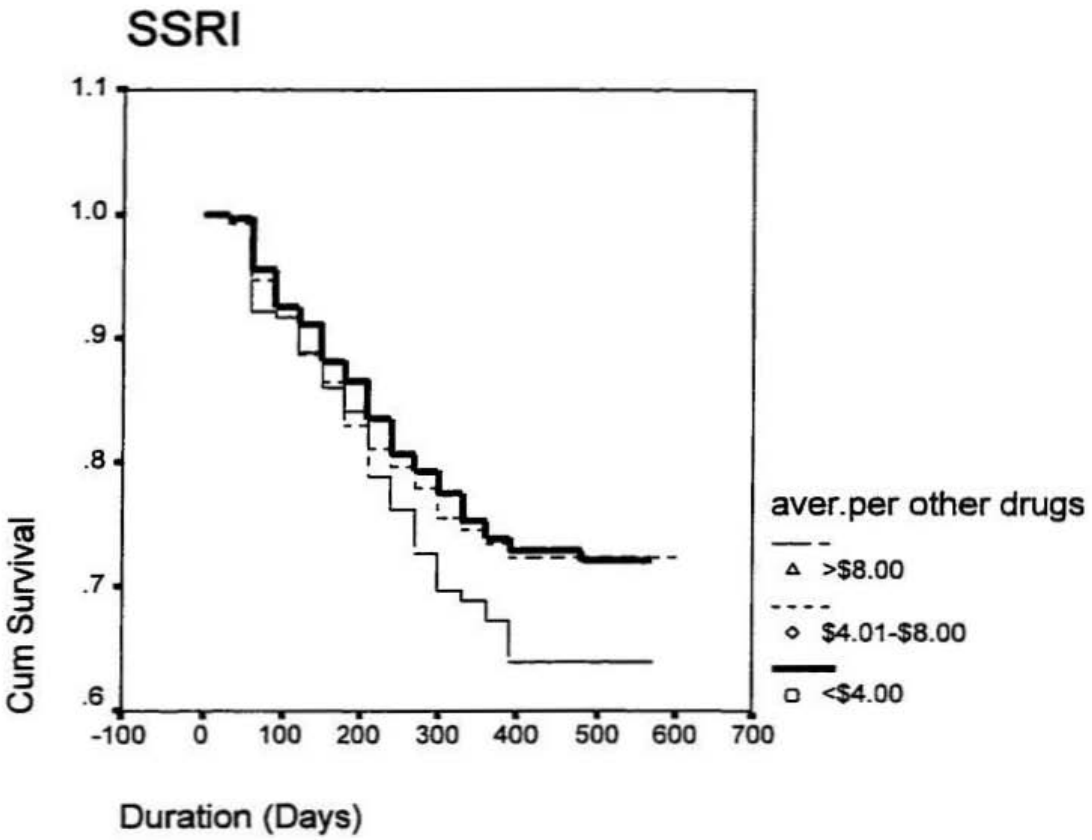

Figure A14: Survival Function Comparing The Cumulative Probability of Survival Between Varying Average Levels of Cost Per All Other Prescriptions for Users of the SSRI Class by the 30 Day Assumption

Appendix 8
Survival Curves for Non-significant Variables for 15 Day Assumption

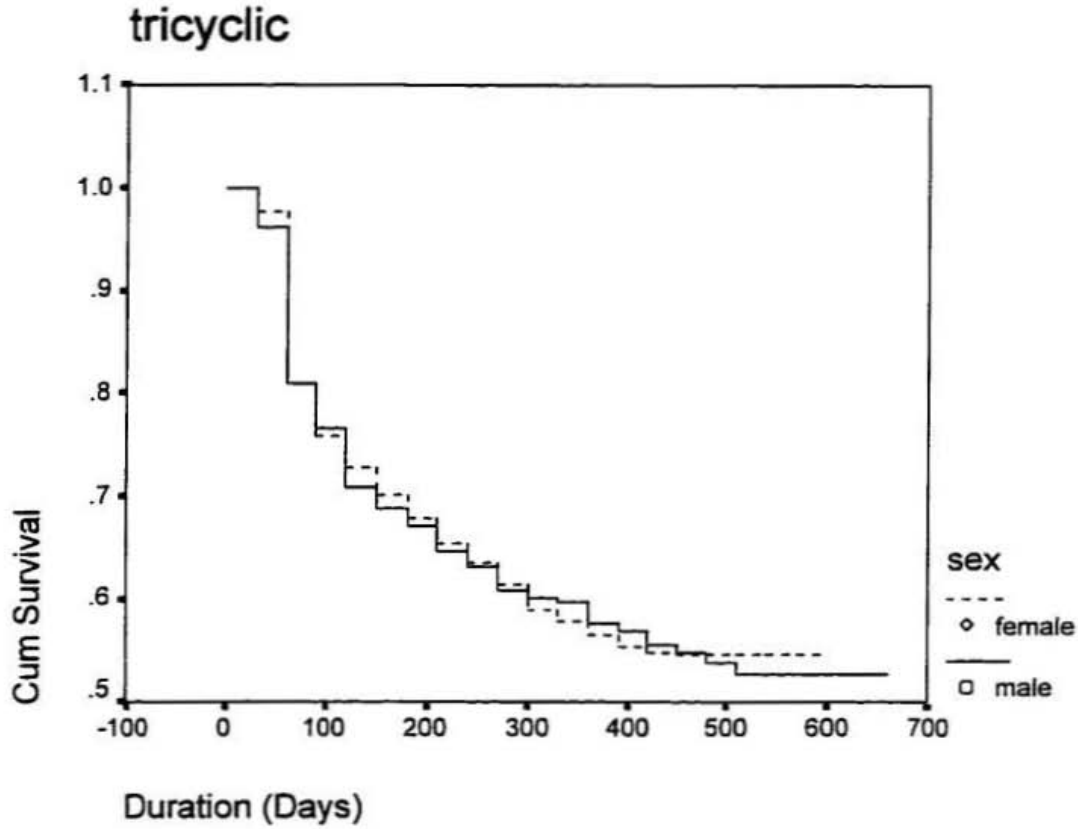

Figure A15: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Among Male and Female Tricyclic Users by the 15 Day Assumption

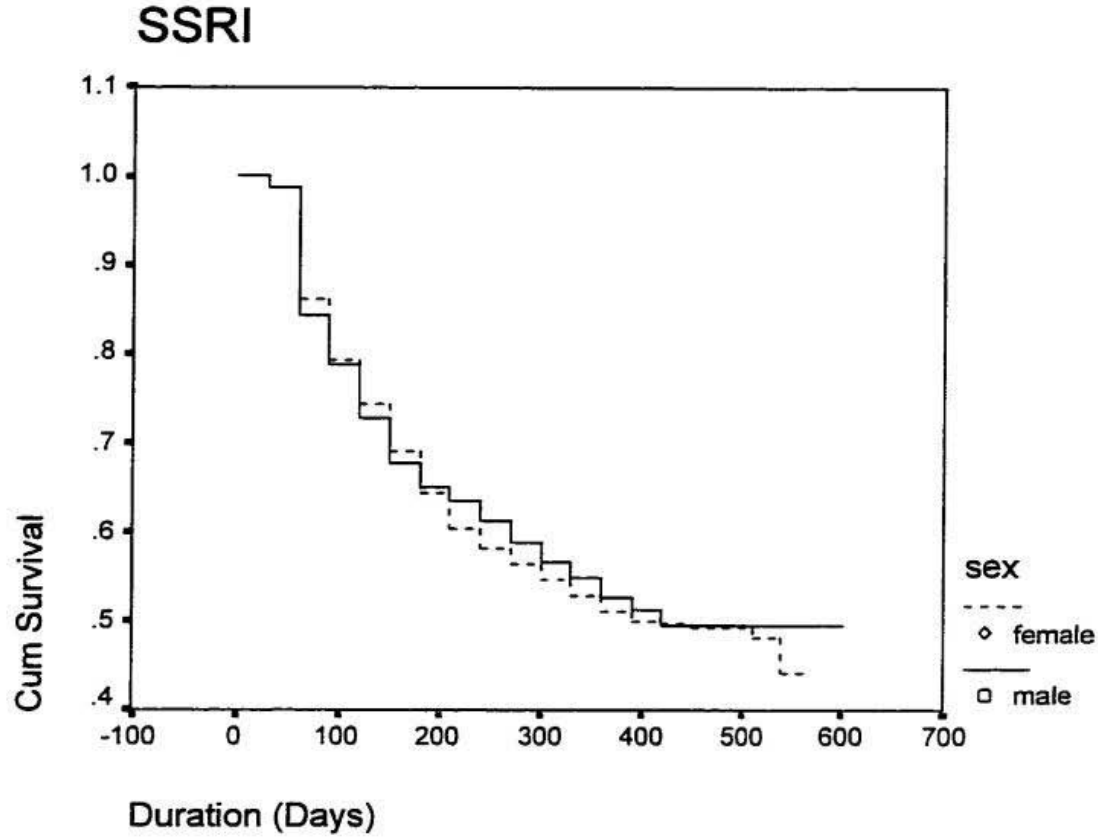

Figure A16: Survival Function Comparing the Cumulative Probability of Survival Before a First Non-adherent Gap Between Male and Female SSRI Users By the 15 Day Assumption

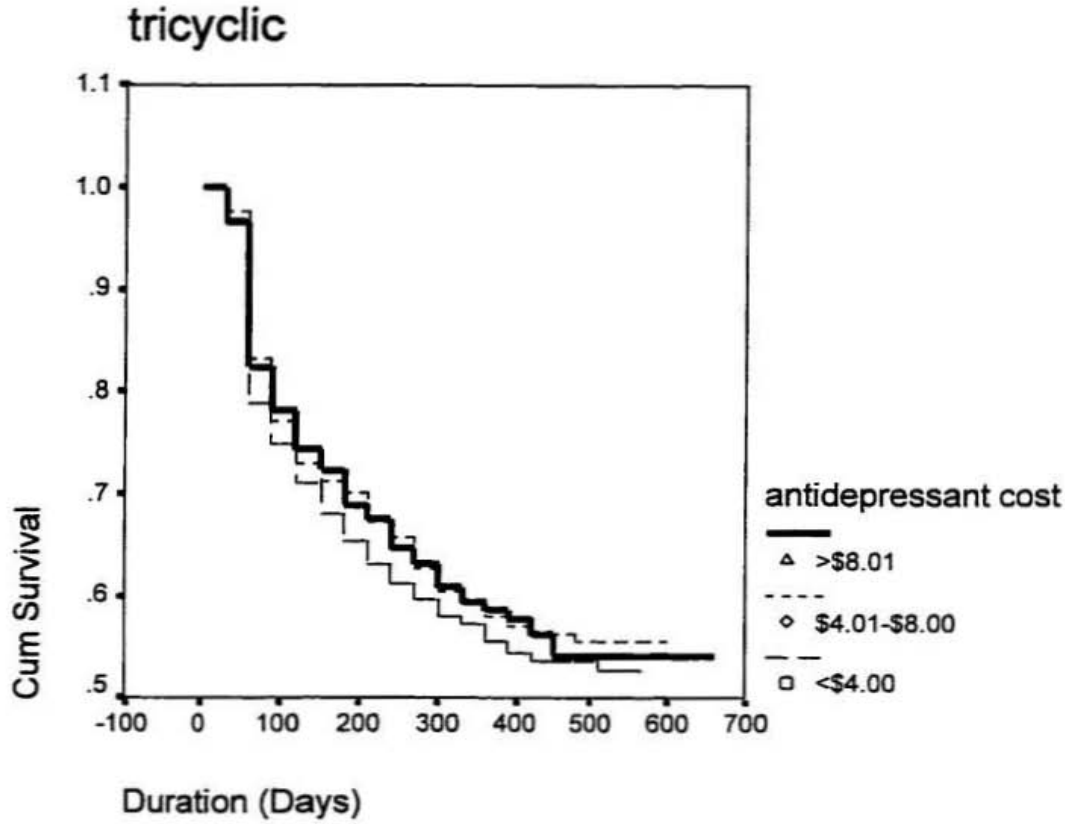

Figure A17: Survival Function Comparing the Cumulative Probability of Survival Till A First Non-adherent Gap Among Varying Levels of Cost Per Antidepressant Prescription for the Tricyclic Users By the 15 Day Assumption

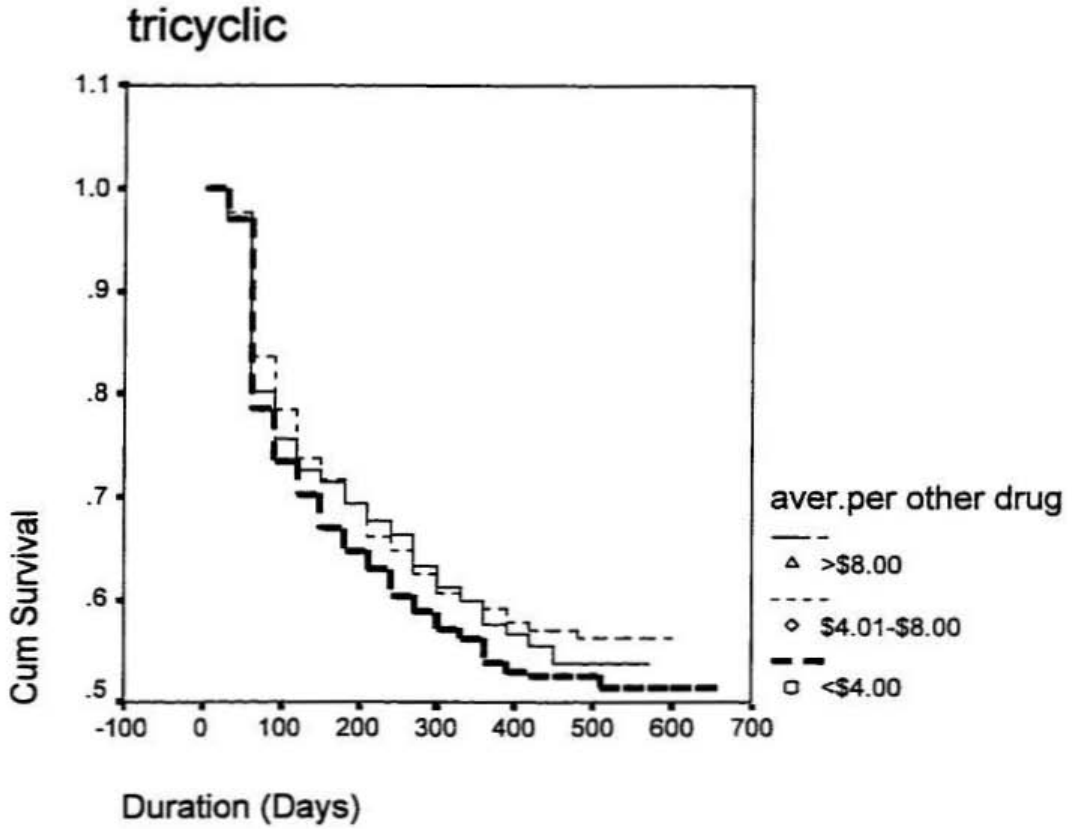

Figure A18: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Among Varying Levels of Average Cost for Other Medications for Tricyclic Users By the 15 Day Assumption

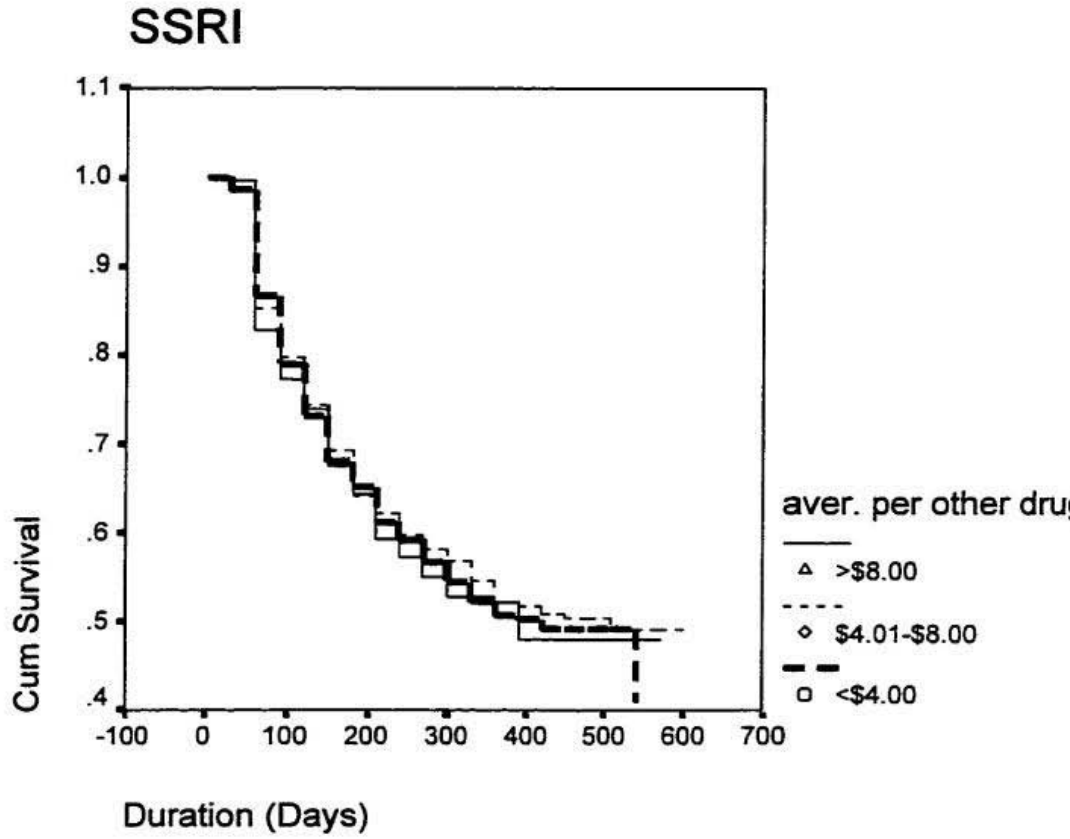

Figure A19: Survival Function Comparing the Cumulative Probability of Survival Till a First Non-adherent Gap Between Varying Levels of Average Cost Per Prescription for SSRI Users by the 15 Day Assumption

Appendix 9
Complete Tables of All Wilcoxan-Gehan Comparisons of Survival Curves

Table A4 Pairwise and Overall Comparisons of time to non-compliance for the Various Levels of the Predictor Variables for the Tricyclic Class

Variable	Comparison Type	Wilcoxan for 15 day assumption	Wilcoxan for 30 Day assumption
Sex	**Overall (2 pairs)**	**W(1)=0.003, p=.959**	**W(1)=0.79, p=.373**
Age	**Overall (10 pairs)**	**W(4)=15.72, p=.003**	**W(4)=13.48, p=.009**
<20 and 21-35	Pairwise	W(1)=1.16, p=.281	W(1)=9.88, p=.002*
<20 and 36-55	Pairwise	W(1)=5.68, p=.017	W(1)=8.18, p=.004*
21-35 and 36-55	Pairwise	W(1)=1.95, p=.163	W(1)=1.22, p=.270
<20 and 51-65	Pairwise	W(1)=5.34, p=.021	W(1)=8.22, p=.004*
21-35 and 51-65	Pairwise	W(1)=1.54, p=.215	W(1)=1.00, p=.317
36-55 and 51-65	Pairwise	W(1)=0.23, p=.633	W(1)=0.04, p=.847
<20 and >65	Pairwise	W(1)=13.96, p=.000*	W(1)=10.88, p=.001*
21-35 and >65	Pairwise	W(1)=9.18, p=.002*	W(1)=0.18, p=.676
36-55 and >65	Pairwise	W(1)=5.82, p=.016	W(1)=2.90, p=.089
51-65 and >65	Pairwise	W(1)=7.22, p=.007	W(1)=2.52, p=.113
Concurrent Drugs Comparisons;	**Overall (10 pairs)**	**W(4)=26.03, p=.000***	**W(4)=15.24, p=.004***
0 and 1	Pairwise	W(1)=0.34, p=.559	W(1)=0.48, p=.827
0 and 2	Pairwise	W(1)=6.40, p=.011	W(1)=1.36, p=.243
1 and 2	Pairwise	W(1)=4.60, p=.032	W(1)=2.15, p=.143
0 and 3-4	Pairwise	W(1)=8.87, p=.003*	W(1)=4.39, p=.036
1 and 3-4	Pairwise	W(1)=6.85, p=.009	W(1)=6.54, p=.010
2 and 3-4	Pairwise	W(1)=0.13, p=.723	W(1)=1.26, p=.263
0 and >=5	Pairwise	W(1)=17.32, p=.000*	W(1)=7.72, p=.005
1 and >=5	Pairwise	W(1)=15.73, p=.000*	W(1)=10.27, p=.001*
2 and >=5	Pairwise	W(1)=4.38, p=.036	W(1)=4.37, p=.037
3-4 and >=5	Pairwise	W(1)=3.50, p=.061	W(1)=1.34, p=.247
Number/Day	**Overall (2 pairs)**	**W(1)=30.21, p=.000***	**W(1)=17.79, p =.000***
Avg cost of Other Drugs	**Overall (3 pairs)**	**W(2)=4.00, p=.135**	**W(2)=2.63, p=.268**
<$4.00 and $4.01-8.00	Pairwise	W(1)=4.08, p=.043	W(1)=2.67, p=.102
<$4.00 and >$8.00	Pairwise	W(1)=0.64, p=.423	W(1)=0.53, p=.468
$4.01-8.00 and >$8.00	Pairwise	W(1)=0.48, p=.489	W(1)=0.25, p=.616
Avg cost of antidepressants	**Overall (3 Pairs)**	**W(2)=2.69, p=.26**	**W(2)=1.83, p=.401**
<$4.00 and $4.01-8.00	Pairwise	W(1)=2.56, p=0.109	W(1)=0.88, p=.347
<$4.00 and >$8.00	Pairwise	W(1)=0.62, p=0.432	W(1)=1.43, p=.233
$4.01-8.00 and >$8.00	Pairwise	W(1)=0.04, p=0.839	W(1)=0.34, p=.556

Table A5: Pairwise and Overall Comparisons of time to non-compliance for the Various Levels of the Predictor Variables for the SSRI Class

Variable	Comparison Type	Wilcoxan for 15 day assumption	Wilcoxan for 30 Day assumption
Sex	**Overall (2 pairs)**	**W(1)=0.05, p=.82**	**W(1)=0.31, p=.575**
Age	**Overall (10 pairs)**	**W(4)=4.37, p=.36**	**W(4)=2.68, p=.61**
<20 and 21-35	Pairwise	W(1)=0.04, p=.85	W(1)=0.29, p=.59
<20 and 36-55	Pairwise	W(1)=0.53, p=.47	W(1)=1.44, p=.23
21-35 and 36-55	Pairwise	W(1)=1.14, p=.29	W(1)=1.59, p=.21
<20 and 51-65	Pairwise	W(1)=1.40, p=.24	W(1)=0.64, p=.43
21-35 and 51-65	Pairwise	W(1)=3.54, p=.06	W(1)=0.24, p=.63
36-55 and 51-65	Pairwise	W(1)=1.23, p=.27	W(1)=0.57, p=.45
<20 and >65	Pairwise	W(1)=1.03, p=.31	W(1)=0.49, p=.48
21-35 and >65	Pairwise	W(1)=1.24, p=.26	W(1)=0.18, p=.67
36-55 and >65	Pairwise	W(1)=0.27, p=.61	W(1)=0.07, p=.79
51-65 and >65	Pairwise	W(1)=0.00, p=.99	W(1)=0.00, p=.96
Concurrent Drugs Comparisons;	**Overall (10 pairs)**	**W(4)=18.18, p=.001***	**W(4)=6.30, p=.178**
0 and 1	Pairwise	W(1)=6.15, p=.013	W(1)=0.38, p=.539
0 and 2	Pairwise	W(1)=10.11, p=.002*	W(1)=1.84, p=.175
1 and 2	Pairwise	W(1)=0.91, p=.342	W(1)=0.66, p=418
0 and 3-4	Pairwise	W(1)=12.75, p=.000*	W(1)=4.44, p=.035
1 and 3-4	Pairwise	W(1)=1.86, p=.172	W(1)=2.47, p=.116
2 and 3-4	Pairwise	W(1)=0.17, p=.684	W(1)=0.45, p=.503
0 and >=5	Pairwise	W(1)=5.87, p=.015	W(1)=2.49, p=.115
1 and >=5	Pairwise	W(1)=0.62, p=.433	W(1)=1.51, p=.220
2 and >=5	Pairwise	W(1)=0.01, p=.951	W(1)=0.25, p=.617
3-4 and >=5	Pairwise	W(1)=0.08, p=.772	W(1)=0.01, p=.942
Number/Day	**Overall (2 pairs)**	**W(1)=8.10, p=.00***	**W(1)=6.47, p =.01***
Avg cost of Other Drugs	**Overall (3 pairs)**	**W(2)=0.40, p=.84**	**W(2)=3.47, p=.18**
<$4.00 and $4.01-8.00	Pairwise	W(1)=0.01, p=.94	W(1)=0.90, p=.34
<$4.00 and >$8.00	Pairwise	W(1)=0.30, p=.60	W(1)=3.48, p=.06
$4.01-8.00 and >$8.00	Pairwise	W(1)=0.33, p=.57	W(1)=1.42, p=.23
Avg cost of antidepressants	**Overall (3 Pairs)**	**W(2)=6.80, p=.033**	**W(2)=6.36, p=.042**
<$4.00 and $4.01-8.00	Pairwise	W(1)=0.01, p=0.941	W(1)=0.01, p=.926
<$4.00 and >$8.00	Pairwise	W(1)=3.55, p=0.059	W(1)=3.23, p=.072
$4.01-8.00 and >$8.00	Pairwise	W(1)=6.00, p=0.014*	W(1)=5.54, p=.019

*Significant at the modified alpha level (see Table 4.12)