INTERRUPTED TIME SERIES ANALYSIS TECHNIQUES IN PHARMACOVIGILANCE

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December 2013

A Thesis
submitted to the School of Graduate Studies and Research
in partial fulfillment of the requirements
for the degree of
Master of Science in Mathematics[1]

[1]The M.Sc. Program is a joint program with Carleton University, administered by the Ottawa-Carleton Institute of Mathematics and Statistics

Abstract

This thesis considers an approach to evaluate the effectiveness of risk communications for prescription drugs by performing interrupted time series analysis of prescription drug volumes prior to and after the risk communication date.

The paper presents methods for detecting change in the presence of autocorrelation and techniques to reduce bias in estimation. Statistical results and data plots are presented for 63 data series. Size and power of the statistical techniques are considered, and a correspondence analysis between these statistical techniques and a small group of physicians is performed.

The methods considered in this thesis correspond weakly with physician sentiment, and exhibit inflated type I errors in the presence of significant autocorrelation.

Acknowledgements

In addition to the biostatistical things I picked up through the course of this degree, there were very many neat people I met along the way that helped me through it. Some of those people include: Don Mattison, Shirley Mills, Heather Underwood, Patricia Moretto, and Jaime Younger.

I would also like to acknowledge my family for the support they have and continue to provide in all that I do: Renée (Mum), and my sisters– Gill, Ali, and Cait[2]. There is one person that I met in this program that was so amazing I married her. Thank you Ewa for all that I have, and will have with you. Love you.

I am thankful to my committee members for requesting the changes that made this thesis quite a bit better. I am thankful to my supervisor Prof. Daniel Krewski for the sensible working relationship we had through this program and am hopeful to carry it forward.

[2]My sisters are listed in decreasing terms of distance they currently live from me. On a previous Master's thesis, they were listed according to birth order. Any ordering is necessarily unfair, they should all come in the same (just a little after Mum). My next thesis will have you listed first Cait.

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Chapter 1

Introduction

Before being approved for sale in Canada, drug manufacturers must convince Health Canada, through evidence (often from clinical trials), that their products are safe and effective. Adverse drug reactions (ADRs) are rare. It is anticipated, when a drug is first approved for market, that not every kind of ADR associated to the drug has been observed in clinical trials. As the kinds of ADRs are uncertain, so too are the frequency of these ADRs–they are generally low, but are monitored. In Canada, Health Canada manages the Canada Vigilance Program (CVP) which is a 'post-market surveillance program that collects and assesses reports of suspected adverse reactions to health products marketed in Canada'[62]. Health Canada's CVS is similar to the spontaneous reporting systems (SRS) in many other countries; they produce databases of ADRs. Many researchers have tailored statistical techniques to these databases with the intent of identifying drugs that generate proportionally more ADRs than the others for future study. Gravel[75] and Prendergast[78] have review papers of some of these techniques.

Pharmacovigilance techniques identify potentially harmful drugs from among many. Once a drug has been identified as problematic, it and the reasons it is problematic are disseminated to the healthcare community. In Canada, this dissemination is handled through Health Canada's MedEffect program[63]. One of the products of the MedEffect program are 'Dear Healthcare Professional Letters' (DHPLs) that update the healthcare community on what has been discovered about

a drug or class of drug. MedEffect distributes letters to the healthcare community thought their website, RSS feeds, email, fax, and letter mail.

It is sensible to periodically evaluate the effectiveness of this program. This thesis considers a technique for evaluating the effectiveness of the MedEffect program by analyzing prescription volumes of medications mentioned in DHPLs.

As the MedEffect program is intended to work; Health Canada distributes the DHPLs to the healthcare professionals across the country. Healthcare professionals then read and absorb the information contained in the DHPL. Healthcare professionals then make prescription decisions that incorporate this newly acquired information. Generally, DHPLs describe new ADRs that are just newly being associated with a drug; the letters tend also to limit prescribing circumstances. A drop in prescription volume is often visually observable in a plot following a DHPL issuance. Fewer prescriptions written may be attributable to healthcare professionals applying their newly acquired information from the DHPL and prescribing alternative drugs.

The methodology we employ is a simple one. We observe an outcome variable prior to the intervention and after the intervention. Differences in the variable, from before to after, are attributed to changes between the two periods– largely the intervention. This methodology has been very widely applied– sociology, psychology, biostatistics, and economics to list just a few.

Our model relies on a couple of assumptions in order for DHPL effectiveness to be linked to changes in prescription volumes. They are:

1. DHPLs should lead to a change in prescription volumes; and

2. Physicians read and respond appropriately to these DHPLs.

We consider a number of cases where the first assumption does not hold. For instance, there are a couple cases where a DHPL informs physicians of a quality control issue with a batch of a particular medication. This DHPL has no affect on the effectiveness or usefulness of the identified drug– there is no reason for prescription volumes to change. These cases are identified as they are considered in the text. We cannot evaluate the extent to which physicians read the DHPLs,

however we do assess the extent to which they agree amongst each other on a sample of DHPLs.

Chapter 2 describes the methods and techniques that will be used to assess each series for evidence of a structural break. Chapter 3 introduces the data considered in our analysis, and describes the sources of data. Plots are provided for the reader to get a visual sense of the effect of DHPLs. Chapter 4 assess the methods described in chapter 2 for size and power and evaluates agreement between the statistical techniques and among a panel of physicians. The final chapter summarizes and concludes.

Chapter 2

Methods and Analysis

In this chapter we develop the motivation and techniques for using regression methods to test for structural break. We work through Chow's paper[65]– a classic from the econometric literature. We use the work of Chow and others to develop the classic F-test.

A challenge of the applied data we are working with is autocorrelation of the dependent variable. We consider the techniques numerous authors have developed to overcome this challenge. Solutions to this challenge involve estimating a parameter to capture the nature of the autocorrelation. With these solutions, new problems present themselves– autocorrelation terms, when estimated, are often biased; particularly so in small samples. We consider techniques developed by other authors to account for both autocorrelation, and the bias of the autocorrelation term. Results are presented through the chapter as they are warranted. The final section of the chapter describes a technique for handling the case where a given medication has multiple DHPLs issued during the observation sample.

2.1 Classic F-statistic

Chow[65] begins with the linear regression

$$y_1 = X_1\beta_1 + \epsilon_1 \text{ , where} \tag{1}$$

$\boldsymbol{y}_1$ and $\boldsymbol{\epsilon}_1$ are n-element column vectors of the dependent variable and the error term (which is assumed to be normally distributed around zero with variance σ^2), $\boldsymbol{X}_1$ is an $n \times p$ matrix of regressors and $\boldsymbol{\beta}_1$ is the p-dimensional vector of model parameters. This linear regression admits a least squares estimate $\hat{\boldsymbol{\beta}}_1$[1].

Chow then considers m additional observations on variables $\boldsymbol{y}_2$ and $\boldsymbol{X}_2$, that may be thought of similarly to the first regression[2] ($\boldsymbol{\epsilon}_2$ is distributed as $\boldsymbol{\epsilon}_1$ above– normally around zero with mean σ^2), that is

$$\boldsymbol{y}_2 = \boldsymbol{X}_2\boldsymbol{\beta}_2 + \boldsymbol{\epsilon}_2 \,, \tag{2}$$

and seeks to determine if $\boldsymbol{y}_2$ and $\boldsymbol{X}_2$ can be characterized in the same way as $\boldsymbol{y}_1$ and $\boldsymbol{X}_1$. That is does $\boldsymbol{y}_2 = \boldsymbol{X}_2\hat{\boldsymbol{\beta}}_1$ appropriately describe the relation between $\boldsymbol{y}_2$ and $\boldsymbol{X}_2$.

The difference between $\boldsymbol{y}_2$ and the vector of fitted values obtained from applying $\hat{\boldsymbol{\beta}}_1$ to $\boldsymbol{X}_2$, $\boldsymbol{d}$, is constructed as follows

$$\begin{aligned} \boldsymbol{d} &= \boldsymbol{y}_2 - \boldsymbol{X}_2\hat{\boldsymbol{\beta}}_1 && (3)\\ &= \boldsymbol{X}_2\boldsymbol{\beta}_2 - \boldsymbol{X}_2\boldsymbol{\beta}_1 - \boldsymbol{\epsilon}_2 - \boldsymbol{X}_2(\boldsymbol{X}_1^\mathsf{T}\boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^\mathsf{T}\boldsymbol{\epsilon}_1 \,. && (4) \end{aligned}$$

Vector $\boldsymbol{d}$ has expectation

$$E(\boldsymbol{d}) = \boldsymbol{X}_2\boldsymbol{\beta}_2 - \boldsymbol{X}_2\boldsymbol{\beta}_1 \,, \tag{5}$$

and because of the independence of $\boldsymbol{\epsilon}_1$ and $\boldsymbol{\epsilon}_2$, vector $\boldsymbol{d}$ has covariance matrix

$$COV(\boldsymbol{d}) = \left[\boldsymbol{I} + \boldsymbol{X}_2(\boldsymbol{X}_1^\mathsf{T}\boldsymbol{X}_1)^{-1}\boldsymbol{X}_2^\mathsf{T}\right]\sigma^2 \,. \tag{6}$$

Chow considers the case where $m = 1$; here both $\boldsymbol{y}_2$ and $\boldsymbol{d}$ become scalars, and $\boldsymbol{X}_2$ a row vector[3]. Under the hypothesis that the additional observation is from the process described by $\boldsymbol{\beta}_1$, we have that $\boldsymbol{\beta}_1 = \boldsymbol{\beta}_2$, and $E(d) = 0$, d is distributed according to the following:

$$\frac{d}{\sqrt{VAR(d)}} \sim N(0,1) \quad \text{or, equivalently} \quad \frac{d^2}{VAR(d)} \sim \chi_1^2 \,. \tag{7}$$

[1]The 1 in the subscripts indicate the first part or phase of the analysis– before the break or control we are looking to measure.

[2]The 2 in the subscripts here denotes that variables $\boldsymbol{y}_2$ and $\boldsymbol{X}_2$ are the same variables as $\boldsymbol{y}_1$ and $\boldsymbol{X}_1$, but fall in the second part of the analysis– after the break.

[3]$\boldsymbol{\beta}_2$ cannot actually be estimated in an OLS sense– there aren't enough observations. But $\boldsymbol{\beta}_2$ is not needed to form d under the hypothesis that $\boldsymbol{\beta}_1 = \boldsymbol{\beta}_2$

Only there is no directly computable value for σ^2 in $VAR(d)$, σ^2 remains unknown.

The unbiased estimate of the variance of the residual, $S_1^2 = \frac{1}{n-p}\sum_{i=1}^{n} u_i^2$, where $u_i = y_{1,i} - X_{1,i}\hat{\boldsymbol{\beta}}_1$ for $i = 1 \ldots n$, is multiplied by $\frac{n-p}{\sigma^2}$ to produce a test statistic with a χ^2_{n-p} distribution. This statistic also has the unknown quantity σ^2 in it. The σ^2s cancel each other out when the quotient of the first and second statistics is taken. This ratio of two χ^2 statistics is distributed according to the F-distribution with 1 degree of freedom in the numerator, and $n - p$ degrees of freedom in the denominator.

$$\frac{d^2}{(1 + \boldsymbol{X}_2(\boldsymbol{X}_1^\intercal \boldsymbol{X}_1)^{-1}\boldsymbol{X}_2^\intercal)S_1^2} \sim F(1,\ n-p) \tag{8}$$

This test statistic is useful for determining if one additional observation is consistent with the prior sample or not. In practical settings, there will be often be many more (m) observations. To handle this, Chow extends the above tests by considering the average of m additional differences. The average of the differences and its variance are

$$\bar{d} = \frac{1}{m}\sum_{i=1}^{m} d_i \text{ , and} \tag{9}$$

$$VAR(\bar{d}) = \frac{1}{m^2} VAR\left[\sum_{i=1}^{m} d_i\right] = \frac{\sigma^2}{m^2}\left[\iota^\intercal\left(\boldsymbol{I} + \boldsymbol{X}_2(\boldsymbol{X}_1^\intercal \boldsymbol{X}_1 \boldsymbol{X}_2)^{-1}\right)\iota\right] \tag{10}$$

respectively. The test statistic of the above hypothesis, that the average difference of the m additional observations is equal to zero, is constructed as follows

$$\frac{\bar{d}^2}{\left[\iota^\intercal\left(\boldsymbol{I} + \boldsymbol{X}_2(\boldsymbol{X}_1^\intercal \boldsymbol{X}_1 \boldsymbol{X}_2)^{-1}\right)\iota\right]\frac{S_1^2}{m^2}}\text{ ,} \tag{11}$$

and is distributed $F(1,\ n-p)$. The author presents this test for completeness, but does not favour using it. $\bar{d}$ may be small because of m additional observations are consistent with the initial regression equation, but may also be small because different d_i cancel each other out, which will reduce the power of the statistic.

Instead Chow considers the quadratic form $\boldsymbol{d}^\intercal COV(\boldsymbol{d})\boldsymbol{d}$. Grouping non-stochastic

and stochastic terms together yields the following

$$\begin{aligned} \boldsymbol{d}^{\mathsf{T}} COV(\boldsymbol{d})\boldsymbol{d} &= \left[\boldsymbol{X}_2\boldsymbol{\beta}_2 - \boldsymbol{X}_2\boldsymbol{\beta}_1\right]^{\mathsf{T}} \left[\boldsymbol{I} + \boldsymbol{X}_2(\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{X}_1)^{-1}\boldsymbol{X}_2^{\mathsf{T}}\right]^{-1} \left[\boldsymbol{X}_2\boldsymbol{\beta}_2 - \boldsymbol{X}_2\boldsymbol{\beta}_1\right] \frac{1}{\sigma^2} + \\ &\quad \left[\boldsymbol{\epsilon}_2 - \boldsymbol{X}_2(\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{\epsilon}_1\right]^{\mathsf{T}} \left[\boldsymbol{I} + \boldsymbol{X}_2(\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{X}_1)^{-1}\boldsymbol{X}_2^{\mathsf{T}}\right]^{-1} \left[\boldsymbol{\epsilon}_2 - \boldsymbol{X}_2(\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{\epsilon}_1\right] \frac{1}{\sigma^2} \end{aligned} \tag{12}$$

Under the hypothesis that $\boldsymbol{\beta}_1 = \boldsymbol{\beta}_2$, the non-stochastic part of this quadratic form becomes zero, and $\boldsymbol{d}^{\mathsf{T}} COV(\boldsymbol{d})\boldsymbol{d}$ becomes equal to the second line of equation (12).

$$\boldsymbol{d}^{\mathsf{T}} COV(\boldsymbol{d})\boldsymbol{d} = \left[\boldsymbol{\epsilon}_2 - \boldsymbol{X}_2(\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{\epsilon}_1\right]^{\mathsf{T}} \left[\boldsymbol{I} + \boldsymbol{X}_2(\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{X}_1)^{-1}\boldsymbol{X}_2^{\mathsf{T}}\right]^{-1} \left[\boldsymbol{\epsilon}_2 - \boldsymbol{X}_2(\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{\epsilon}_1\right] \frac{1}{\sigma^2}$$

which is quadratic in $[\boldsymbol{\epsilon}_2 \ \ \boldsymbol{\epsilon}_1]$, and has rank m under the null hypothesis, this will follow a χ^2_m distribution ($\boldsymbol{d}^{\mathsf{T}} COV(\boldsymbol{d})\boldsymbol{d}$ will follow a non-central χ^2 distribution when $\boldsymbol{\beta}_1 \neq \boldsymbol{\beta}_2$). Here too the test statistic contains unknown quantity σ, and here again we take the quotient of two statistics containing σ in order obtain a computable statistic. The statistic

$$\frac{\boldsymbol{d}^{\mathsf{T}} COV(\boldsymbol{d})\boldsymbol{d}\frac{1}{m}}{S_1^2 \frac{n-p}{\sigma^2}\frac{1}{n-p}} = \frac{\boldsymbol{d}^{\mathsf{T}}\left[\boldsymbol{I} + \boldsymbol{X}_2(\boldsymbol{X}_1^{\mathsf{T}}\boldsymbol{X}_1)^{-1}\boldsymbol{X}_2^{\mathsf{T}}\right]\boldsymbol{d}}{S_1^2 m} \tag{13}$$

follows the $F(m,\ n-p)$ distribution.

Chow then expands his focus, and is no longer testing, just, if additional observations are consistent with the ones that came before it– he next considers all points together. Two regressions with possibly different parameters are considered,

$$\begin{aligned} \boldsymbol{y}_1 &= \boldsymbol{X}_1\boldsymbol{\beta}_1 + \boldsymbol{Z}_1\boldsymbol{\gamma}_1 + \boldsymbol{\epsilon}_1 \text{ , and} \\ \boldsymbol{y}_2 &= \boldsymbol{X}_2\boldsymbol{\beta}_2 + \boldsymbol{Z}_2\boldsymbol{\gamma}_2 + \boldsymbol{\epsilon}_2 \text{ ,} \end{aligned}$$

where $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$ are both $q-$vectors, and $\boldsymbol{\gamma}_1$ and $\boldsymbol{\gamma}_2$ are both $(p-q)$-vectors. $\boldsymbol{y}_i$ and $\boldsymbol{\epsilon}_i$ are the dependent variable and error term as they were described earlier in this section. The interest is to determine if $\boldsymbol{\beta}_1 = \boldsymbol{\beta}_2$; that is, are a subset of the regression coefficients are equal, equivalently described by the more restricted model.

$$\begin{aligned} \boldsymbol{y}_1 &= \boldsymbol{X}_1\boldsymbol{\beta}_0 + \boldsymbol{Z}_1\boldsymbol{\gamma}_1 + \boldsymbol{\epsilon}_1 \text{ , and} \\ \boldsymbol{y}_2 &= \boldsymbol{X}_2\boldsymbol{\beta}_0 + \boldsymbol{Z}_2\boldsymbol{\gamma}_2 + \boldsymbol{\epsilon}_2 \text{ ,} \end{aligned}$$

In matrix form, the unrestricted and restricted forms of the regressions, respectively, are as follows

$$\begin{bmatrix} y_1 \\ y_2 \end{bmatrix} = \begin{bmatrix} X_1 & 0 & Z_1 & 0 \\ 0 & X_2 & 0 & Z_2 \end{bmatrix} \begin{bmatrix} \beta_1 \\ \beta_2 \\ \gamma_1 \\ \gamma_2 \end{bmatrix} + \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \end{bmatrix}, \text{ and} \tag{14}$$

$$\begin{bmatrix} y_1 \\ y_2 \end{bmatrix} = \begin{bmatrix} X_1 & Z_1 & 0 \\ X_2 & 0 & Z_1 \end{bmatrix} \begin{bmatrix} \beta_0 \\ \gamma_1 \\ \gamma_2 \end{bmatrix} + \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \end{bmatrix} \tag{15}$$

Here again the motivation for the test statistic begins with the idea of differences. The unrestricted regression will always fit at least as well as the restricted regression (when the null hypothesis is true, and $\beta_1 = \beta_2 = \beta_0$), but will better fit the data when the null hypothesis is false. Chow considers the differences in the sum of squared residuals. The difference between the sum of squared residuals of the restricted model and the unrestricted model will be zero when the null hypothesis is true, but will become larger the more different β_1 and β_2 truly are from each other.

Fischer[72]'s derivation of Chow's $F-$test for structural break is done more concisely than in Chow's paper. Fisher presents 3 lemmas to motivate the statistical test– the statistical tests are a natural application of the lemmas. Fisher begins by considering a vector $\boldsymbol{\epsilon}$ of normal variables with zero-mean and covariance matrix $\sigma^2 \boldsymbol{I}$. Fisher's lemmas are as follows

Lemma 2.1.1. *Let $\boldsymbol{M}$ be any symmetric idempotent matrix. Let $\boldsymbol{u} = \boldsymbol{M}\boldsymbol{\epsilon}$. Then $(\boldsymbol{u}^\top \boldsymbol{u}/\sigma^2)$ is distributed χ^2 with $tr(\boldsymbol{M})$ degrees of freedom*[4].

Lemma 2.1.2. *Let $\boldsymbol{M}$ and $\boldsymbol{M}^*$ both be symmetric and idempotent and suppose that $\boldsymbol{M}\boldsymbol{M}^* = \boldsymbol{M}^*$ and that $\boldsymbol{M} \neq \boldsymbol{M}^*$. Define $\boldsymbol{u} = \boldsymbol{M}\boldsymbol{\epsilon}$ and $\boldsymbol{u}^* = \boldsymbol{M}^*\boldsymbol{\epsilon}$. Then the statistic*

$$F = \frac{(\boldsymbol{u}^\top \boldsymbol{u} - \boldsymbol{u}^{*\top} \boldsymbol{u}^*)/(tr(\boldsymbol{M}) - tr(\boldsymbol{M}^*))}{\boldsymbol{u}^{*\top} \boldsymbol{u}^*/tr(\boldsymbol{M}^*)}$$

is distributed as F with $(tr(\boldsymbol{M}) - tr(\boldsymbol{M}^*))$ and $tr(\boldsymbol{M}^*)$ degrees of freedom.

[4] *Where $tr(\boldsymbol{M})$ denotes the trace of matrix $\boldsymbol{M}$*

Lemma 2.1.3. *Let $\boldsymbol{X}$ be a $T \times k$ matrix of observations on a set of k variables. Let $\boldsymbol{X}^*$ be a $T \times h$ matrix of observations on a set of h variables. Suppose that the variables of $\boldsymbol{X}$ are all linear combinations of the variables of $\boldsymbol{X}^*$, so that there exists an $h \times k$ matrix $\boldsymbol{A}$ such that $\boldsymbol{X} = \boldsymbol{X}^*\boldsymbol{A}$. Define*

$$\boldsymbol{M} = \boldsymbol{I} - \boldsymbol{X}(\boldsymbol{X}^\mathsf{T}\boldsymbol{X})^{-1}\boldsymbol{X}^\mathsf{T}, \qquad \boldsymbol{M}^* = \boldsymbol{I} - \boldsymbol{X}^*(\boldsymbol{X}^{*\mathsf{T}}\boldsymbol{X}^*)^{-1}\boldsymbol{X}^{*\mathsf{T}}.$$

Then $\boldsymbol{M}$ and $\boldsymbol{M}^*$ satisfy the conditions of lemma 2.1.2.

Lemmas 2.1.1 through 2.1.3 introduce well known projection and annihilation matrices[70] and demonstrate the broad $F-$test methodology that will be used in much of the following analysis. The projection matrix, $\boldsymbol{P}_X$, projects quantities it multiplies onto the space spanned by $\boldsymbol{X}$ (the subscript of the projection matrix). The annihilation matrix, $\boldsymbol{M}_X$ ($\boldsymbol{M}$ in the notation of Fisher), projects orthogonally to the space spanned by $\boldsymbol{X}$. The $\boldsymbol{P}_X$ and $\boldsymbol{M}_X$ matrices are closely related, $\boldsymbol{M}_X = \boldsymbol{I} - \boldsymbol{P}_X$.

In much of the analysis to come we will be interested in testing the equality of parameter vectors from separate regressions. Let $\boldsymbol{y}_1 = \boldsymbol{X}_1\boldsymbol{\beta}_1 + \boldsymbol{\epsilon}_1$ and $\boldsymbol{y}_2 = \boldsymbol{X}_2\boldsymbol{\beta}_2 + \boldsymbol{\epsilon}_2$ be the two regressions we are looking to assess. The regressions may be jointly written as

$$\begin{bmatrix} \boldsymbol{y}_1 \\ \boldsymbol{y}_2 \end{bmatrix} = \begin{bmatrix} \boldsymbol{X}_1 & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{X}_2 \end{bmatrix} \begin{bmatrix} \boldsymbol{\beta_1} \\ \boldsymbol{\beta_2} \end{bmatrix} + \begin{bmatrix} \boldsymbol{\epsilon}_1 \\ \boldsymbol{\epsilon}_2 \end{bmatrix}, \tag{16}$$

which may be written as, $\boldsymbol{y} = \boldsymbol{X}^*\boldsymbol{\beta}_* + \boldsymbol{\epsilon}$, to invoke notation suggestive of Fisher's lemmas. To restrict these regressions, and require their parameter vectors to be identical, we regress the following

$$\begin{bmatrix} \boldsymbol{y}_1 \\ \boldsymbol{y}_2 \end{bmatrix} = \begin{bmatrix} \boldsymbol{X}_1 \\ \boldsymbol{X}_2 \end{bmatrix} \begin{bmatrix} \boldsymbol{\beta_0} \end{bmatrix} + \begin{bmatrix} \boldsymbol{\epsilon}_1 \\ \boldsymbol{\epsilon}_2 \end{bmatrix}, \tag{17}$$

which may be written as , $\boldsymbol{y} = \boldsymbol{X}\boldsymbol{\beta}_0 + \boldsymbol{\epsilon}$, again to invoke the notation of Fisher. The least squares estimates of $\boldsymbol{\beta}_*$ and $\boldsymbol{\beta}_0$ are $\hat{\boldsymbol{\beta}}_* = (\boldsymbol{X}^{*\mathsf{T}}\boldsymbol{X}^*)^{-1}\boldsymbol{X}^{*\mathsf{T}}\boldsymbol{y}$ and $\hat{\boldsymbol{\beta}}_0 = (\boldsymbol{X}^\mathsf{T}\boldsymbol{X})^{-1}\boldsymbol{X}^\mathsf{T}\boldsymbol{y}$ respectively. From this we can know the fitted values of these regressions; $\boldsymbol{X}^*\hat{\boldsymbol{\beta}}_* =$

$\boldsymbol{X}^*(\boldsymbol{X}^{*\mathsf{T}}\boldsymbol{X}^*)^{-1}\boldsymbol{X}^{*\mathsf{T}}\boldsymbol{y} = \boldsymbol{P}_{X^*}\boldsymbol{y}$, and $\boldsymbol{P}_X\boldsymbol{y}$ similarly. The residuals of these regressions are

$$\begin{aligned} \boldsymbol{u}^* &= \boldsymbol{y} - \boldsymbol{X}^*\hat{\boldsymbol{\beta}}_* \\ &= \boldsymbol{y} - \boldsymbol{X}^*(\boldsymbol{X}^{*\mathsf{T}}\boldsymbol{X}^*)^{-1}\boldsymbol{X}^{*\mathsf{T}}\boldsymbol{y} \\ &= \left(\boldsymbol{I} - \boldsymbol{X}^*(\boldsymbol{X}^{*\mathsf{T}}\boldsymbol{X}^*)^{-1}\boldsymbol{X}^{*\mathsf{T}}\right)\boldsymbol{y} \\ &= \boldsymbol{M}_{X^*}\boldsymbol{y} \\ &= \boldsymbol{M}_{X^*}\boldsymbol{\epsilon}\ , \end{aligned} \tag{18}$$

and $\boldsymbol{M}_X\boldsymbol{\epsilon}$ similarly. Direct application of the 3 lemmas allows one to construct an $F-$statistic to test the hypothesis that $\boldsymbol{\beta}_* = \boldsymbol{\beta}_0$.

$$F = \frac{(\boldsymbol{u}^{\mathsf{T}}\boldsymbol{u} - \boldsymbol{u}^{*\mathsf{T}}\boldsymbol{u}^*)/k}{\boldsymbol{u}^{*\mathsf{T}}\boldsymbol{u}^*/n - 2k} \tag{19}$$

Similar application of the lemmas allow one to test the equality of subsets of regression coefficients as well.

We will be interested to test the linear trend of prescription volumes before and after a DHPL is issued. When there is no difference between the periods prior to and after the DHPL, we expect the F-statistic to be relatively small, and are inclined to accept that the DHPL had no effect on prescription volumes. When there is a difference in the linear trend prior to and after the DHPL, we anticipate the F-statistic to be more extreme, and are inclined to accept that the DHPL did have an effect on prescription volumes.

For each series of drug prescription volumes of length T, the first $D-1$ observations denote the observations prior to the the issuance of the DHPL. The $D+1$ to T observations index the observations after the the issuance of the DHPL[5].

We are interested to know if $\boldsymbol{\beta}_{t<D}$ from the following regression

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\imath} & \boldsymbol{t} \end{bmatrix}\boldsymbol{\beta}_{t<D} + \boldsymbol{\epsilon}_t \quad t = 1 \ldots D\ ,$$

is the same as $\boldsymbol{\beta}_{t\geq D}$ from the following regression

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\imath} & \boldsymbol{t} - D \end{bmatrix}\boldsymbol{\beta}_{t\geq D} + \boldsymbol{\epsilon}_t \quad t = D+1 \ldots T\ .$$

[5]DHPLs occur at any point within the month. Ones that occur later in the month naturally have less opportunity to create an observable effect in that month. We handle all DHPLs as becoming effective in the month they were issued, regardless of when in the month they were issued.

In the above some new notation has been introduced, and other notation has been adapted. The dependent variable and error term are now subscripted with a t to denote their time dependent nature; t's relation to D is what now determines if a data point is from the period prior to or after the issuance of the DHPL. The vector $\boldsymbol{\iota}$ is used to indicate a vector of ones– in a typical least squares regression $\boldsymbol{\iota}$'s parameter would be the regression's constant. Variable $\boldsymbol{t}$ is the time trend which may sometimes be differenced by D so that both time trends start at 1.

To build an $F-$statistic to assess the hypothesis that $\boldsymbol{\beta}_{t<D} = \boldsymbol{\beta}_{t\geq D}$, we need a restricted and an unrestricted model. Those models, respectively, are the following

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\iota} & \boldsymbol{t} \end{bmatrix} \boldsymbol{\beta}_0 + \boldsymbol{\epsilon} \quad t = 1 \dots T \,,$$

and,

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\iota} & \boldsymbol{t} & \boldsymbol{0} & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{\iota} & \boldsymbol{t} - D \end{bmatrix} \boldsymbol{\beta}_A + \boldsymbol{\epsilon} \quad t = 1 \dots T^{6} \,.$$

Several of the competing techniques taken up in the following sections are similar to this statistical test, and will be described in terms of their matrices of variables, or design matrices. The sum of squared residuals from the restricted regression and the unrestricted regression are combined to produce the F-statistic, as described in equation 19.

2.2 Autocorrelation Techniques for Interrupted Time Series Analysis

2.2.1 Autocorrelation in the Data Series

The nature of the data we are working with brings to doubt the F-statistic constructed in the previous section. For the statistic in the previous section to be appropriate, successive observations must be independent of one another. Time

[6] We use this notation for many of the unrestricted models we consider. It is succinct and intuitive. To be clear: the top row of the design matrix contains only D elements, and the bottom row contains $T - D$ elements.

trend data of the type we are considering are often not independent of each other, but rather quite correlated amongst themselves.

Crosbie[68] and Gottman[74] describe a technique for obtaining sample estimates of autocorelation coefficients. The centered dependent variable is regressed against lagged versions of itself. The coefficient on the k^{th} lag is the k^{th} autocorrelation coefficient. In the case where our interest is obtaining the first order correlation coefficient, the regression is

$$\boldsymbol{y}_t = \rho_1 \boldsymbol{y}_{t-1} + \boldsymbol{\epsilon}_t \quad t = 2 \ldots N. \tag{20}$$

Where $\boldsymbol{y}_t$ and $\boldsymbol{y}_{t-1}$ are the centered and lagged centered variables respectively, and $\boldsymbol{\epsilon}_t$ is the error which is assumed to be normally distributed around zero with mean σ^2. This regression admits $\hat{\rho}_1$ as the estimate of the first order autocorrelation coefficient.

We perform this regression for all of the data series we have, and summarize the p-values in figure 1. Over 98% of the p-values are in the 0-0.05 range, which suggests that autocorrelation is present in the data, and must be taken under consideration when building an appropriate test statistic. The estimated autocorrelation coefficients are plotted in figure 2, and seem to be concentrating around values just less than one.

2.2.2 Gottman (1981) Interrupted Time Series Experiment (ITSE)

Gottman[74] describes a technique for accounting for autocorrelation in an interrupted time series analysis setting. His technique is to include a lagged version of the dependent variable among the regressors in a manner similar to how the autocorrelation coefficient was estimated. The unrestricted model becomes

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\imath} & \boldsymbol{t} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{y}_{t-1} \\ \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{\imath} & \boldsymbol{t} - D & \boldsymbol{y}_{t-1} \end{bmatrix} \boldsymbol{\beta}_O + \boldsymbol{\epsilon}_t \quad t = 2 \ldots T\,, \tag{21}$$

and the restricted model becomes

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\imath} & \boldsymbol{t} & \boldsymbol{y}_{t-1} \end{bmatrix} \boldsymbol{\beta}_A + \boldsymbol{\epsilon} \quad t = 2 \ldots T\,, \tag{22}$$

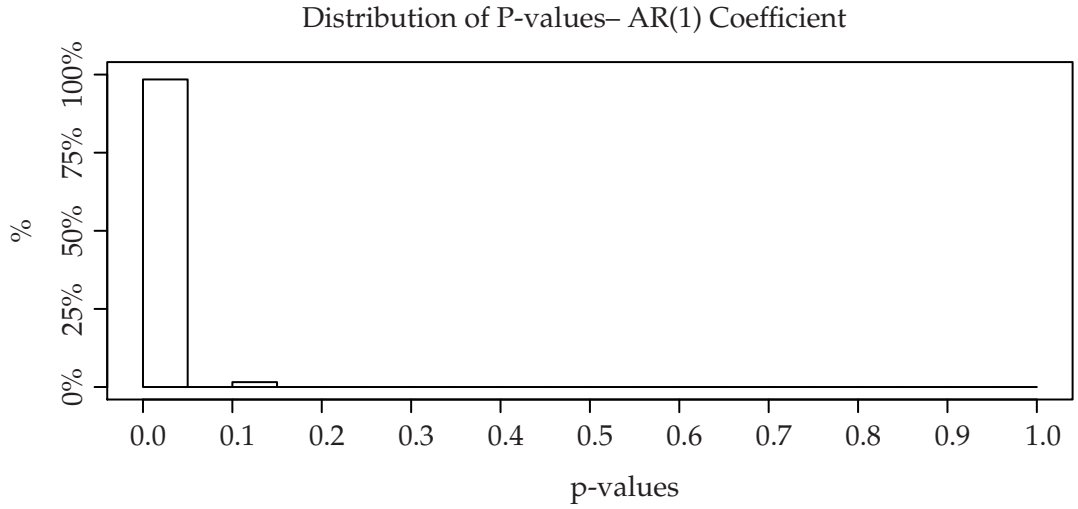

Figure 1: Distribution of p-values of First Order Autocorrelation Coefficients

where $\boldsymbol{\beta}$ in each case is of conformable dimension to the design matrix.

Gottman[74]'s specification is more general that what has just been described. Instead of a single lagged dependent variable, Gottman's technique specified an arbitrary (k) number of lags. We choose to limit our analysis to first order autocorrelation. Because our samples are small ($T = 36$ usually), each additional autocorrelation term is costly– a degree of freedom is lost when the sample size is reduced, and another degree of freedom is lost in estimating an additional autocorrelation parameter. The evidence to support inclusion of second order autocorrelation coefficients is weaker– there are fewer p-values for the second order autocorrelation coefficients in the 0-0.05 range than there were for the first order autocorrelation coefficients (figure 3).

2.2.3 Ramsey and Ramsey (2006)

Ramsey and Ramsey[82] consider the interrupted time series analysis problem in a manner similar to Gottman[74]. They choose a different design matrix for their

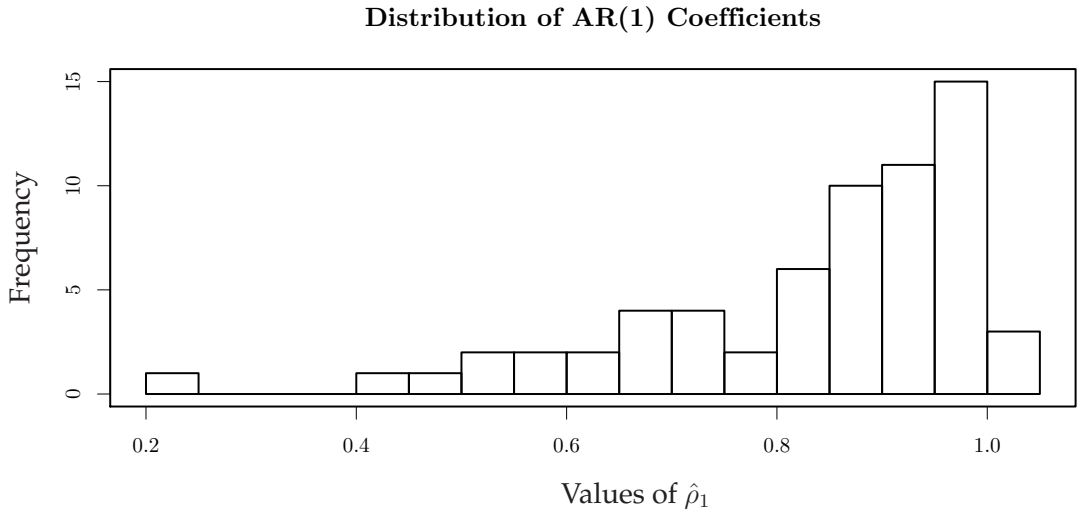

Figure 2: Distribution of First Order Autocorrelation Coefficients

analysis. Their design matrix differs only in terms of the post DHPL variables. Instead of beginning their index variable at 1, they choose to begin the index variable at D. Ramsey and Ramsey recommend accounting for autocorrelation in the same way as Gottman, that is with a lagged version of the dependent variable. Also, their restricted version of the regression is the same as Gottman's, regression (22). Their unrestricted regression is

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\imath} & \boldsymbol{t} & \mathbf{0} & \mathbf{0} & \boldsymbol{y}_{t-1} \\ \mathbf{0} & \mathbf{0} & \boldsymbol{\imath} & \boldsymbol{t} & \boldsymbol{y}_{t-1} \end{bmatrix} \boldsymbol{\beta}_A + \boldsymbol{\epsilon}_t \quad t = 2 \dots T \,, \tag{23}$$

The design matrix is very similar between regressions (21) and (23). The only difference is the post-DHPL time-trend variable which begins at 1 in regression (21), and at $D + 1$ in regression (23). Ramsey and Ramsey claim that Gottman[74]'s post DHPL trend variable produces bias in the estimates of the level effect. The two models will yield different estimates of $\boldsymbol{\beta}_A$ surely, but we prove that these are otherwise identical techniques.

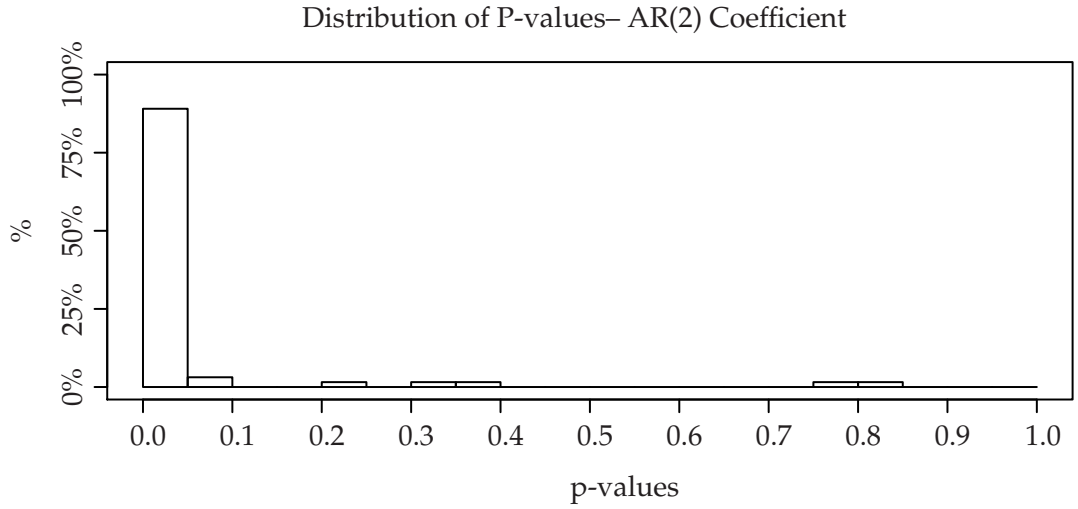

Figure 3: Distribution of Second Order Autocorrelation Coefficients

Proof. Recall that the alternative hypothesis under the ITSE model may be expressed as

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\iota} & \boldsymbol{t} & \mathbf{0} & \mathbf{0} & \boldsymbol{y}_{t-1} \\ \boldsymbol{\iota} & \boldsymbol{t} & \boldsymbol{\iota} & \boldsymbol{t} - (D+1) & \boldsymbol{y}_{t-1} \end{bmatrix} \boldsymbol{\beta}_A + \boldsymbol{\epsilon}_t, \quad t = 2 \dots T. \tag{24}$$

Which can be separated and rearranged as follows:

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\iota} & \boldsymbol{t} & \boldsymbol{y}_{t-1} \\ \boldsymbol{\iota} & \boldsymbol{t} & \boldsymbol{y}_{t-1} \end{bmatrix} \boldsymbol{\beta}_{A^-} + \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ \boldsymbol{\iota} & \boldsymbol{t} - (D+1) \end{bmatrix} \begin{bmatrix} \beta_{A,2} \\ \beta_{A,3} \end{bmatrix} + \boldsymbol{\epsilon}_t, \quad t = 2 \dots T, \tag{25}$$

Where $\beta_{A,2}$ and $\beta_{A,3}$ are the components of $\boldsymbol{\beta}_A$ that have been removed to give $\boldsymbol{\beta}_{A^-}$. This is further simplified according to the following

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\iota} & \boldsymbol{t} & \boldsymbol{y}_{t-1} \\ \boldsymbol{\iota} & \boldsymbol{t} & \boldsymbol{y}_{t-1} \end{bmatrix} \boldsymbol{\beta}_{A^-} + \begin{bmatrix} \mathbf{0} \\ \boldsymbol{\iota} \end{bmatrix} \begin{bmatrix} \beta_{A,2} \end{bmatrix} + \begin{bmatrix} \mathbf{0} \\ \boldsymbol{t} \end{bmatrix} \begin{bmatrix} \beta_{A,3} \end{bmatrix} - \begin{bmatrix} \mathbf{0} \\ (D+1) \end{bmatrix} \begin{bmatrix} \beta_{A,3} \end{bmatrix} + \boldsymbol{\epsilon}_t, \quad t = 2 \dots T. \tag{26}$$

Because $D + 1$ is a constant, equation 26 may be expressed as

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\imath} & \boldsymbol{t} & \boldsymbol{y}_{t-1} \\ \boldsymbol{\imath} & \boldsymbol{t} & \boldsymbol{y}_{t-1} \end{bmatrix} \boldsymbol{\beta}_{A^-} + \begin{bmatrix} \boldsymbol{0} \\ \boldsymbol{\imath} \end{bmatrix} \left[\beta_{A,2} - (D+1)\beta_{A,3} \right] + \begin{bmatrix} \boldsymbol{0} \\ \boldsymbol{t} \end{bmatrix} \left[\beta_{A,3} \right] + \boldsymbol{\epsilon}_t, \quad t = 2 \dots T. \tag{27}$$

If we let $\beta_{A,2^*} = \beta_{A,2} - (D+1)\beta_{A,3}$, and combine the design matrix and parameter vector back together, we get the following

$$\boldsymbol{y}_t = \begin{bmatrix} \boldsymbol{\imath} & \boldsymbol{t} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{y}_{t-1} \\ \boldsymbol{\imath} & \boldsymbol{t} & \boldsymbol{\imath} & \boldsymbol{t} & \boldsymbol{y}_{t-1} \end{bmatrix} \boldsymbol{\beta}_{A^*} + \boldsymbol{\epsilon}_t, \quad t = 2 \dots T. \tag{28}$$

Which is exactly the design matrix under the alternative hypothesis of Ramsey and Ramsey[82]. □

Models estimated under the alternative hypotheses of the ITSE model and the Ramsey and Ramsey[82] model produce numerically identical fitted values and residuals. Level effects likely seem higher in the ITSE model, by approximately $(D+1)\hat{\beta}_{A,3}$. In what follows, these two models will be treated as one, and shall be referred to as the ITSE-Ramsey model.

2.3 Autocorrelation and Bias Controlling Techniques for Interrupted Time Series Analysis

Gottman[74] and Ramsey and Ramsey[82] of the previous section presented techniques that control for autocorrelation of the dependent variable. What they have chosen not to address is the difficulty in properly estimating the autocorrelation coefficient. The final two techniques considered in this paper account for both autocorrelation of the dependent variable, and the bias one obtains in estimating autocorrelation coefficients– particularly in small samples. The two techniques correct for bias in near opposite approaches. Crosbie[67]'s approach uses a theoretical approximation of the bias to correct with, whereas the bootstrap based technique of McKnight *et al*[77] find a way to simulate the bias and iteratively remove it until estimates are nearly unbiased.

2.3.1 Crosbie (1993) ITSACORR

Crosbie[67] begins with the initial ITSE model as proposed by Gottman[74] his restricted and unrestricted models are (22) and (21) respectively. Crosbie then uses a result from Shaman and Stine[83] to approximate the bias of the autocorrelation term. Shaman and Stine[83] derive bias correction vectors for up to the sixth correlation coefficient. In the ITSACORR work of Crosbie[67, 68] there is no mention of any other bias correction vector other than the first order correlation term. Crosbie seems inclined to, as we are, consider only the first order autocorrelation of the series he is working with. The approximately unbiased correlation coefficient $\hat{\boldsymbol{\beta}}^{*}_{y_{t-1}}$ is obtained from the biased $\hat{\boldsymbol{\beta}}_{y_{t-1}}$ (which was obtained through least squares estimation) through the following transformation

$$\hat{\boldsymbol{\beta}}^{*}_{y_{t-1}} = \frac{T\hat{\boldsymbol{\beta}}_{y_{t-1}} + 1}{T - 3}$$

With an unbiased value for the autocorrelation term in both the restricted and unrestricted models, the slope and intercept parameters are re-estimated holding the correlation terms fixed. The unrestricted and restricted models then admit an F-statistic in their usual way.

2.3.2 McKnight *et al* (2000) Double Bootstrap

McKnight *et al*[77] model autocorrelation in the error term instead of lagging the dependent variable. They begin by considering

$$\boldsymbol{y}_t = \boldsymbol{X}_t\boldsymbol{\beta} + \boldsymbol{u}_t \text{ where,} \tag{29}$$

$$\boldsymbol{u}_t = \rho\boldsymbol{\epsilon}_{t-1} + \boldsymbol{\epsilon}_t, \tag{30}$$

where $\boldsymbol{\epsilon}_t$ is assumed to be identically and independently distributed with zero mean and finite variance, and $\boldsymbol{X}$, their design matrix, is defined according to the following

$$\boldsymbol{X} = \begin{bmatrix} \boldsymbol{\imath} & \boldsymbol{t} & \boldsymbol{0} & \boldsymbol{0} & \boldsymbol{y}_{t-1} \\ \boldsymbol{\imath} & \boldsymbol{t} & \boldsymbol{\imath} & \boldsymbol{t} - (D+1) & \boldsymbol{y}_{t-1} \end{bmatrix}. \tag{31}$$

When the specification in equation 30 is combined into equation 29, one obtains a non-linear regression that contains lagged variables $\boldsymbol{X}_{t-1}$ and $\boldsymbol{y}_{t-1}$. A non-linear least squares (NLS) routine is used to obtain estimates for $\boldsymbol{\beta}$ and ρ. McKnight *et al* then use $\hat{\rho}$ to generate another set of variables

$$\begin{aligned} \boldsymbol{v}_t(\hat{\rho}) &= \boldsymbol{y}_t - \hat{\rho}\boldsymbol{y}_{t-1} \text{ , and} \\ \boldsymbol{W}_t(\hat{\rho}) &= \boldsymbol{X}_t - \hat{\rho}\boldsymbol{X}_{t-1}. \end{aligned}$$

Here $\boldsymbol{W}_t(\hat{\rho})$ is a matrix with dimensions equal to $\boldsymbol{X}_t$. $\boldsymbol{v}_t(\hat{\rho})$ is then regressed on $\boldsymbol{W}_t(\hat{\rho})$ to obtain least squares parameter estimate $\hat{\boldsymbol{\gamma}}$. McKnight *et al* bring $\hat{\boldsymbol{\gamma}}$ and $\hat{\rho}$ together to produce their initial $\hat{\boldsymbol{\beta}}$ vector,

$$\hat{\boldsymbol{\beta}} = \begin{bmatrix} \frac{\hat{\gamma}_1}{1-\hat{\rho}} & \hat{\gamma}_2 & \dots \end{bmatrix}$$

With this, McKnight *et al* are able to begin generating data. They obtain residuals from the model by constructing fitted values. The residuals are then rescaled to correct for deflation that may have occurred during model fitting, and centred at zero. The authors sample with replacement from the vector of errors, using the first observation of $\boldsymbol{y}$ and $\hat{\boldsymbol{\beta}}$ and $\hat{\rho}$ to generate bootstrap data sets. The same estimation is applied to each of the N generated bootstrap data sets, which yields N vectors of estimates $[\hat{\boldsymbol{\beta}}_i^* \quad \hat{\rho}_i^*]$, $i = 1 \dots N$.

The author's main purpose with this bootstrap is to gather information about the bias of ρ. This bootstrap is re-sampling from a population whose autocorrelation term is known to be $\hat{\rho}$. Thus, each of the N quantities, $\hat{\rho}_i^* - \hat{\rho}$, is a random variable whose expectation approximates the true bias of ρ.

The authors then take the average of these variables to get the average bias of $\hat{\rho}$

$$\text{bias}(\hat{\rho}) = \frac{1}{N}\sum_{i=1}^{N} \hat{\rho}_i^* - \hat{\rho}$$

Here begins the author's iterative procedure for eliminating the bias of ρ. A new estimate of the autocorrelation term is constructed by removing the bias from the previous estimate

$$\hat{\rho}_{(2)} = \hat{\rho} - \text{bias}(\rho) \, .$$

The new autocorrelation term is used to generate $v_t(\hat{\rho}_{(2)})$ and $W_t(\hat{\rho}_{(2)})$, which are used to produce $\hat{\boldsymbol{\beta}}_{(2)}$. $\hat{\boldsymbol{\beta}}_{(2)}$ and $\hat{\rho}_{(2)}$ allow the authors to produce a vector of residuals and generate new bootstrap samples. The bias of $\hat{\rho}_{(2)}$ is estimated (same way as above) and subtracted from $\hat{\rho}_{(2)}$ to produce $\hat{\rho}_{(3)}$. This procedure is iterated until the bias becomes acceptably (arbitrarily) small

$$|\hat{\rho}_{(j)} - \hat{\rho}_{(j-1)}| < \varepsilon \quad \text{or} \quad |\text{bias}(\hat{\rho}_{(j)})| < \varepsilon \,,$$

at which point $[\hat{\boldsymbol{\beta}}_{j-1} \quad \hat{\rho}_{j-1}]$ are taken to be the model parameters. McKnight *et al* recommend setting $\epsilon = 0.01$.

This bootstrap technique is typically recommended for samples larger than 40 observations[82]. Our largest sample has 36 observations– several of our bootstraps did converge, but not all of them. Because of this, we do not report bootstrap results, nor do we consider the bootstrap in chapter 4, the chapter on simulation studies.

Full results of these techniques are presented in tables 55 and 56 as well as throughout chapter 3, our application chapter. Each row of tables 55 and 56 reports the *F*-statistic and p-value for each of the methods. The numbers of degrees of freedom for these statistics are not all the same– they change based on number of observations in the sample, number of observations dropped from the sample, and number of parameters estimated. The statistics and p-values are computed using the appropriate numbers of degrees of freedom in each case. Bold text indicates, for each technique, that a significant difference was detected between the pre and post DHPL periods at the $\alpha = 0.05$ level using the omnibus *F*-statistic.

There are a number of statistical test that can be used to assess the break between periods of a sample. Using an *F*-test statistic between a restricted and an unrestricted model is the way we have chosen to proceed. Other techniques may have included assessing the *t*-test statistics produced from a fully specified regression model. These techniques offer more choice to the researcher; one could observe a slope change but not an intercept change, vice versa, neither or both. Simplicity of hypothesis is the reason we have chosen, as others call it, the omnibus *F*-test– it tests the joint hypothesis that (slope and intercept) are different against the null hypothesis that (slope and intercept) are not different between periods.

There is also no treatment of the extensive time series literature in this analysis. This is consistent with the typical approach to modelling structural break in *short* time series. McKnight *et al* and Ramsey and Ramsey[82] write that they do not consider autoregressive moving average (ARMA) techniques because they do not have sufficient observations for the techniques, and are primarily concerned with quickly applying an effective test and not modelling the dependent variable.

2.3.3 Non-Linear Data Series

Slope and intercept make clear the kind of functional form expected of the data series– a simple straight line (disjointed if there is a structural break). The actual data series may be reasonably well described by this functional form; or they may not be. In cases where the data series are not well described by a linear functional form, it is less than appropriate to use a linear specification to model the relationship.

How one handles this depends on the nature of the non-linearity. If the plotted data appears suggestive of a polynomial relationship, then higher orders of the independent variable can be included in the regression to capture the polynomial relationship of the dependent variable to the independent variable. If the data plot is highly erratic and demonstrates severe corrections to trend, then it is less clear how to proceed– there would appear to be no relationship with the dependent variable.

There are a couple data series that do appear quite non-linear. To all of these series we apply the first approach to handling non-linear series described in this section– that is we consider a square term of the time dependent variable as a possible specification.

To determine which specification to choose, we perform an F-test between the unrestricted linear model[7] and the unrestricted model with squared time variables. In general, this test is essentially between the restricted and unrestricted models, respectively, below:

[7] Unrestricted in the sense that it models structural break at the DHPL date.

$$y_t = \begin{bmatrix} \imath & t & 0 & 0 \\ 0 & 0 & \imath & t \end{bmatrix} \beta_R + \epsilon_t, \text{ and}$$

$$y_t = \begin{bmatrix} \imath & t & 0 & 0 \\ 0 & 0 & \imath & t \end{bmatrix} \beta_R + \begin{bmatrix} t^2 & 0 \\ 0 & t^2 \end{bmatrix} \beta_U + \epsilon_t.$$

The restricted and unrestricted models are used to determine which functional form to accept[8], after which it is compared against is corresponding restricted form that does not model the structural break. P-values less than 0.05 were taken as suggestive of a squared specification, and greater than 0.05 suggested a linear specification.

Series that have had this additional consideration applied to them can be identified in chapter 3 by the linear/squared designation in the table– 'linear' indicates that the linear specification was suggested by the *F*-test, and 'squared' indicates that the squared specification was suggersted by the *F*-test. Tables 55 and 56 convey this information through daggers (†) and double daggers (‡). A dagger on the series number indicates that the higher order consideration was performed on the series, a double dagger by the statistic indicates that the squared specification was chosen.

2.4 Drugs with Multiple DHPLs Issued

For 8 of the drug considered in this analysis, more than one DHPL was issued over the course of the data sample. Testing each DHPL separately at each of the separate DHPLs is something that can be and is still done. Interpreting these statistics is a little more problematic. Consider rosiglitazone, which had 3 DHPLs issued on its behalf in 2007. The DHPL in February of 2007 informed physicians of a clinical trial that found increased rates of bone fractures among women taking rosiglitazone. The second DHPL in June of 2007 informed physicians of an article

[8]The variables, coefficients, and error terms are all as they have been previously defined.

in a peer-reviewed journal[9], that found increased rates of bone fractures among women taking rosiglitazone– similar information to the first letter. The second letter also informed of upcoming changes to the product's monograph. The third DHPL in November of 2007 informed physicians of changes to prescribing practices and to the product monograph as a result of the findings related to bone fractures among women. Each letter delivers very similar information about bone fractures in women. Visually, from figure 4, it seems to be the second letter that has the observable effect on prescription volumes– it is nearest to the point where the series seems to turn. In general, and without clear visual cues, it is difficult to know when the information disseminated in a DHPL becomes reflected in the series of prescription volumes.

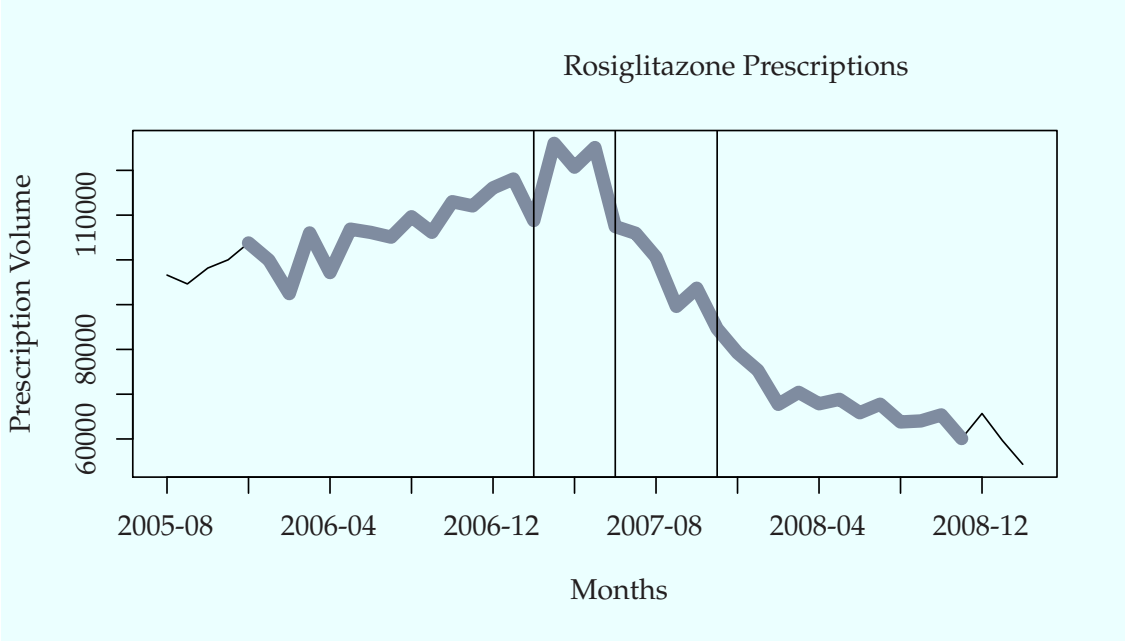

Figure 4: Rosiglitazone Prescriptions

The structural break methodology was extended by Quandt[79, 80] to test for

[9]Nissen S, Wolski K. Rosiglitazone Revisited. An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality. Arch Intern Med 2010; 170 (14). 1191-1201.

structural break at an unknown position. Quandt[79] proposed to take the maximal *F*-test from the set of *F*-tests that tested structural break at every point in the sample– this largest *F*-test was to be used to perform the typical *F*-test. Quandt[80] later reported that the distribution of this maximal *F*-statistic was not the conventional *F*-statistic as earlier reported. Andrews [1] developed a statistic and its distribution that brings together the ideas in the vein of Quandt. Sup-*F* statistics, as they are called, are computed similarly to the Quandt maximal *F*-statistic, only the Sup-*F* Statistics are calculated over sub samples of the sample, not the whole sample.

The Andrews Sup-*F* statistic requires a trimming parameter to define the sub sample of the sample for which possible largest *F*-statistics will be computed. A trimming parameter of $\pi_0 = 0.15$, following the notation of Andrews [1], implies the first and last 15% of the sample will not be used to generate *F*-statistics[10]

When no information is known about the break point, Andrews recommends using $\pi_0 = 0.15$ as the trimming parameter. Andrews finds that the sup-*F* statistics converge in distribution when $\pi_0 \neq 0$, but diverge in probability to infinity when $\pi_0 = 0$. When information is known about where a break is likely to have occurred, a more restrictive sub sample may be chosen (π_0 larger), and a more powerful test statistic results.

We may reasonably expect that any time after the issuance of a data series' first DHPL is a good point to begin considering the possibility of structural break. We might also accept that a break may occur sometime after the issuance of the last DHPL. We choose the tightest band that captures the first DHPL and some data points after the last DHPL. All of the trimming parameters are symmetric, and are multiples of 5, per the tables of critical values produced by Andrews [1, 2]

Table 1 lists the drugs that have had more than one DHPL issued on their behalf over the sampling period, and the trimming parameters used for the sup-*F* statistics.

The critical values of Andrews'[1, 2] tables includes trimming parameters, size, and degrees of freedom. Andrews requires that sup-*F* statistics be asymptotically

[10]The data in these parts of the sample are still used to compute *F*-statistics. What this means is that the sup-*F* statistic will not come from the first or last 15% of the sample.

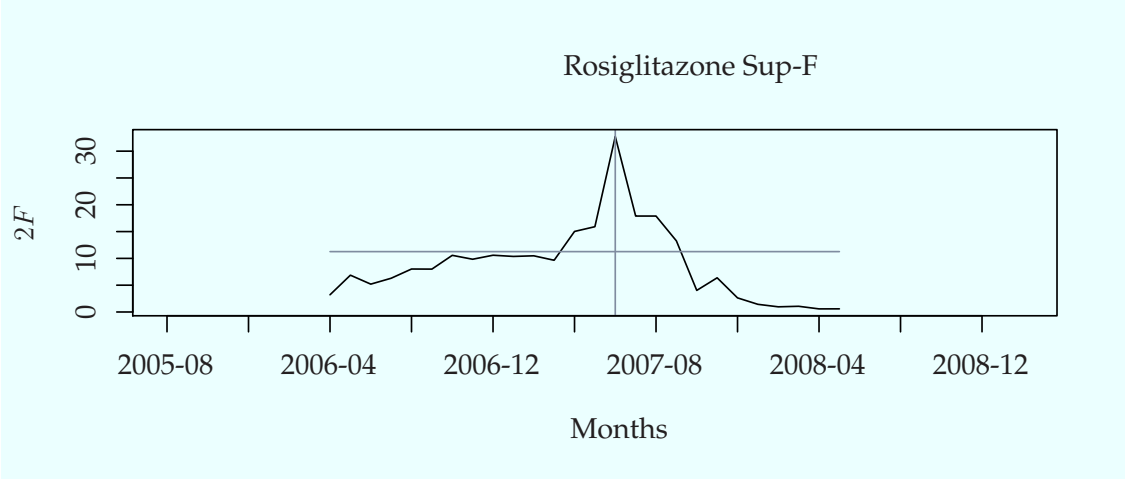

Figure 5: Rosiglitazone Sup-F Statistic

Drug	Range	Drug	Range
Deferasirox	0.10–0.90	Telithromycin	0.30–0.70
Getfitinib	0.15–0.85	Bevacizumab	0.25–0.75
Rosiglitazone	0.20–0.80	Rituximab	0.25–0.75
Paroxetine	0.35–0.65	Gatifloxacin	0.25–0.75

Table 1: Drug Series Number Concordance

approximated to χ^2 distributions by multiplying by the number of degrees of freedom in the numerator. The *F*-tests performed in this paper test two parameters equal to zero, and so twice the sup-*F* statistic will be compared to the critical value for two degrees of freedom with the appropriate trimming parameter and level.

Figure 5 is the plot of *F*-stats corresponding to figure 4. The *F*-statistics are only plotted within the trimmed range. The sup-*F* is indicated by the vertical gray bar[11]. The horizontal gray bar indicates the critical value at which we reject the hypothesis of no structural break. The value of the series is greater than the horizontal gray

[11]The *F*-statistics were calculated using the ITSACORR technique, and are so through the rest of the paper.

line at the value of the sup-F statistic, indicating that this is most likely, according to the data, where a break occurred. For rosiglitazone, it is close to the issuing of the second DHPL.

Chapter 3

Application

Data for our analysis come from two sources; the DHPL letters issued by Health Canada, and the prescription volume data from the IMS Health CompuScript database.

The DHPL letters are issued and distributed through Health Canada's MedEffect program, often in conjunction with the pharmaceutical company that manufactures the drug mentioned in the DHPL. The decision to produce and release a DHPL is determined by the performance of the drug–either ADRs are detected through Canada's SRS, the SRS of other (often larger) nations, or in published medical journals.

The prescriptions are calculated from IMS Health CompuScript database. IMS Health maintains a panel of over 4,700 retail pharmacies across Canada– this represents approximately $^2/_3$ of all retail pharmacies across Canada[63]. The panel is stratified according to province, store type (chain or independent), and store size in such a way that calculations derived from it can be thought of as representative of Canada.

Our analysis borders on the historical. We must wait 18 months after a given DHPL before we can extract prescription volumes from the IMS Health CompuScript database. As much as was possible, 18 months of data prior to and after the release of a DHPL were extracted[1]

[1]I am very appreciative of Rick Fry (Health Canada) for providing this data.

In the sections that follow, we consider the substance of the DHPLs, observe the plotted values of each series, and present statistical results of the interrupted time series analysis. The first section considers only drugs that had a single DHPL issued through the observation period. There are two subsections here: one that describes DHPLs without risk of future ADRs, and one that describes DHPLs that do impact future ADRs. The second section considers drugs that have multiple DHPLs issued through the observation period. Graphs of prescription volume in the single DHPL section (3.1) feature, in addition to the plotted value of the series, a vertical line that indicates the date at which the DHPL was issued. Graphs in the multiple DHPL section feature both prescription volume and the sup-*F* statistic plots. The prescription plots here have vertical bars at all the dates at which a DHPL was issued. In segments, the line that plots prescription volumes will be thicker and gray; this serves to indicate points at which the two (or more) drug series that have been combined shared overlapping values. The sup-*F* plots are as they were described in section 2.4.

3.1 Single DHPLs

3.1.1 DHPLs without Risk of Future ADRs

The following 2 cases describe DHPLs that involve quality control issues (QC issues). These are different than typical DHPLs in the sense that the information contained in these DHPLs should not impact upon the perscribing decisions of physicians going forward. Granted, patients should not be administered mislabelled or mismanufactured medications; but more importantly, barring the few affected lots shipped to market, a physician's choice to prescribe these medications, based on drug effectiveness and patient safety, remains unchaged.

RATIO-METFORMIN

On 2008-07-18 Health Canada issued a DHPL concerning RATIO-METFORMIN (metformin)[58]. The letter advised healthcare professionals that a quality control

problem has been discovered– some other pills had made it into packages of RATIO-METFORMIN. The letter describes the differences between what the correct and the misplaced pills look like, and directs pharmacists to check their auto-dispensing machines if they have them. Prior to the DHPL, there appears to be a modest but

Statistical Test	Value Of *F*-statistic	P-value
Naive F (Squarred)	**10.57**	$<$ **0.01**
ITSE-Ramsey (Squarred)	**3.74**	**0.01**
ITSACORR (Linear)	0.73	0.49

Table 2: Statistical Findings of Structural Break for Metformin

persistent upward trend in prescription volumes (figure 6). This trend appears to continue after the DHPL for a couple months before abruptly dropping and then increasing sharply.

This is a case where the linear/non-linear *F*-test was performed on the data series to choose a specification[2]. The test is applied to this series because of the abrupt disruption on the post-DHPL period of the series. Table 2 shows that the Naive-*F* and ITSE-Ramsey favoured a squared specification, whereas the ITSACORR favored a linear specification.

From the graph, there does appear to be an event that changes prescription patterns 5-6 months beyond the DHPL date. It would be feasible to perform a rolling *F*-test of unknown break point, as we do for the multiple DHPL series; but this is akin to trading interpretation for methodology. How could a break 5-6 months following a DHPL date be explained? These considerations are summarized in the concluding chapter.

[2]Tables indicate that the specification test was performed by having either 'linear' or 'squared' in the statistical test column.

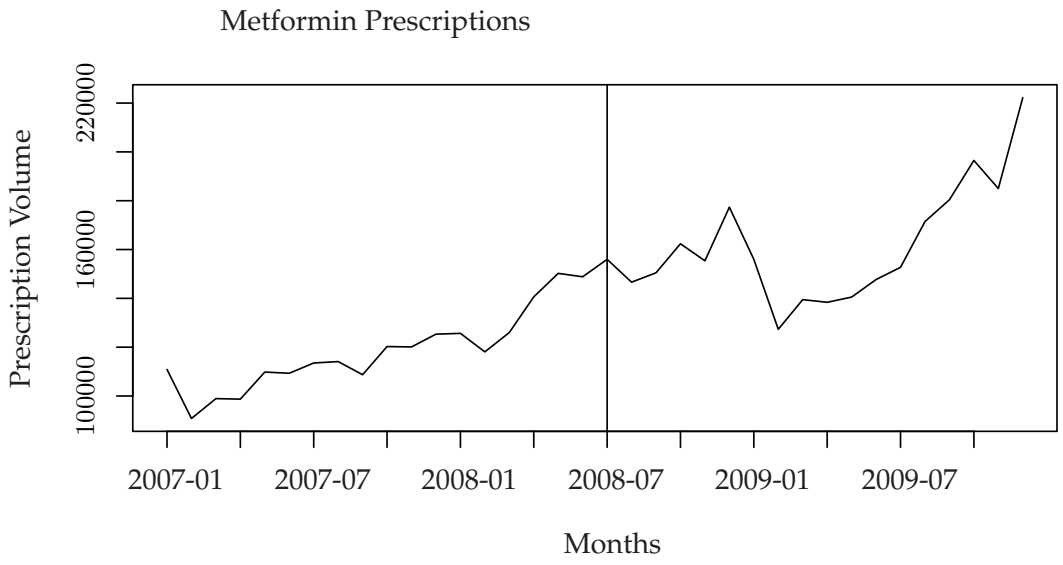

Figure 6: Metformin Prescriptions

OCTREOTIDE

On 2006-01-26 Health Canada issued a DHPL concerning OCTREOTIDE (octreotide)[29]. The letter advises healthcare professionals of a quality control issue that has the potential for serious harm or death. Some vials labelled as OCTREOTIDE might actually contain FLUPHENAZINE. FLUPHENAZINE is intended to be delivered intramuscularly or subcutaneously, not intravenously as OCTREOTIDE is. Pharmacists are instructed to notify all physicians that have prescribed this medication immediately. The letter goes on to describe the treatments likely required in the event that these two drugs were incorrectly administered. Prescription volumes

Statistical Test	Value Of *F*-statistic	P-value
Naive F (Squarred)	**3.25**	**0.04**
ITSE-Ramsey (Linear)	0.63	0.6
ITSACORR (Linear)	0.97	0.39

Table 3: Statistical Findings of Structural Break for Octreotide

(figure 7) are highly volatile with low volume throughout the entire sample. This is a series that appeared sufficiently non-linear to consider assessing it with square terms. Only the Naive-*F* selects the squared model, and only the Naive-*F* finds evidence of structural break (table 3).

The following 7 cases describe DHPLs that involve withdrawal of drug from market. The graphs of these drug series often show an abrupt halt of all prescription volumes. The statistical techniques presented will often find very significant evidence of structural break. However, these breaks occur regardless of whether the DHPL is effective or not. Had not a single physician read the issued DHPLs, the data series would look much the same– no drugs are available to be dispensed, and the series drops off.

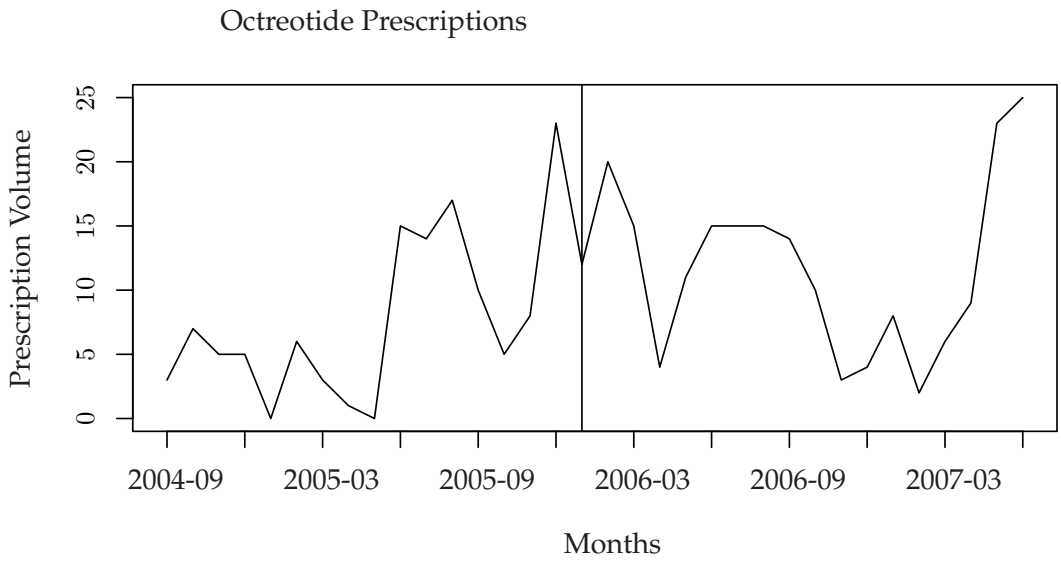

Figure 7: Octreotide Prescriptions

SANDOZ

On 2008-07-17 Health Canada issued a DHPL concerning SANDOZ (timolol)[59]. The letter informed healthcare professionals of a quality control problem that had been discovered. It was discovered that SANDOZ had shipped with greater concentrations than what is reported on the product's packaging. The letter informed healthcare professionals that no replacements would be available in the near future. The prescription volumes (figure 8) demonstrate a slow decline up to the DHPL at

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**84.16**	$<$ **0.01**
ITSE-Ramsey	**35.04**	$<$ **0.01**
ITSACORR	**52.74**	$<$ **0.01**

Table 4: Statistical Findings of Structural Break for Timolol

which point the series drops to zero for the majority of the post-DHPL period. All of the statistical techniques find evidence of structural break (table 4).

PREXIGE

On 2007-10-03 Health Canada issued a DHPL concerning PREXIGE (lumiracoxib)[45]. The letter informed healthcare professionals that, after having reviewed the manufacturer supplied health and safety data, Health Canada has decided that the risk of serious hepatotoxicity associated with the use of PREXIGE cannot be safely or effectively managed, and that sales and manufacture of PREXIGE must cease. prescription volumes (figure 9) grow steadily over the pre-DHPL period of the sample, then drop off drastically to zero following the DHPL. All of the statistical techniques find evidence of structural break (table 5).

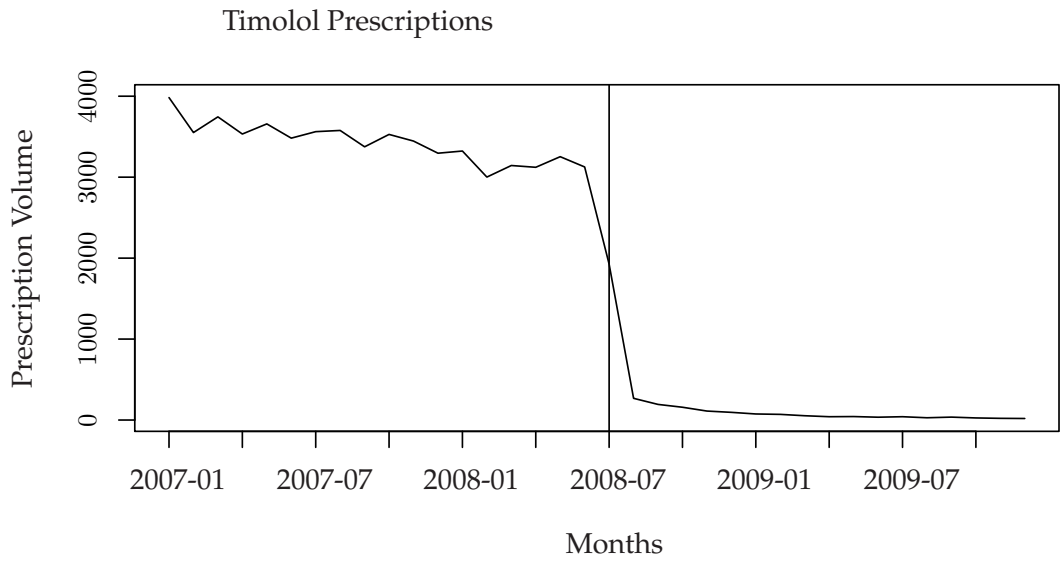

Figure 8: Timolol Prescriptions

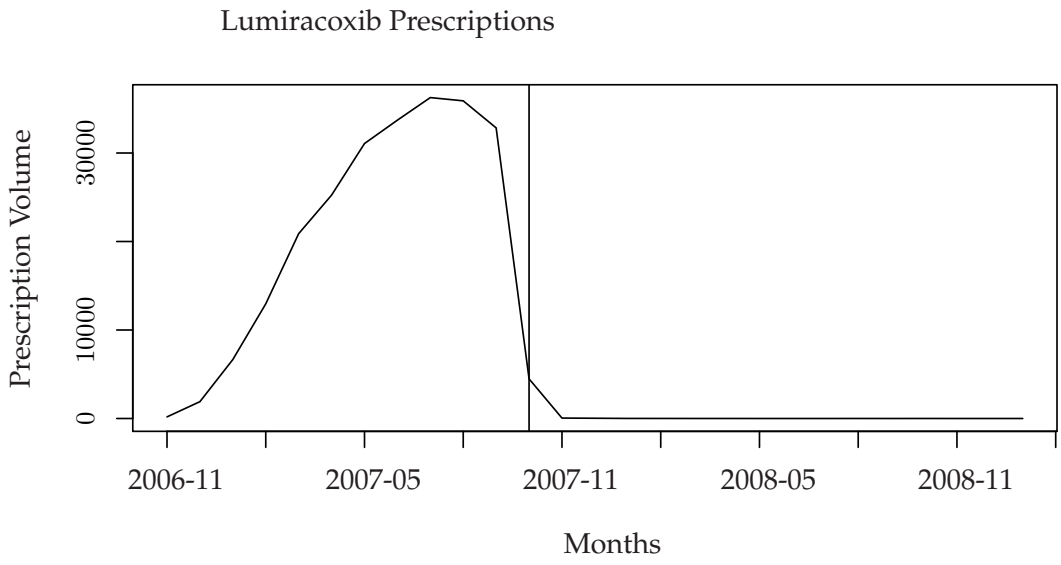

Figure 9: Lumiracoxib Prescriptions

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**198.01**	$<$ **0.01**
ITSE-Ramsey	**33.19**	$<$ **0.01**
ITSACORR	**53.3**	$<$ **0.01**

Table 5: Statistical Findings of Structural Break for Lumiracoxib

PERMAX

On 2007-08-10 Health Canada issued a DHPL concerning PERMAX (pergolide)[51]. The letter describes Health Canada's decision that there is insufficient evidence to support the continued safe use of PERMAX in Canada. The letter also informs healthcare professionals that sales of PERMAX will cease at the end of the month. Prescription volumes (figure 10) maintain a relatively constant (declining slightly)

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**26.39**	$<$ **0.01**
ITSE-Ramsey	**5.36**	$<$ **0.01**
ITSACORR	**8.59**	$<$ **0.01**

Table 6: Statistical Findings of Structural Break for Pergolide

level throughout the pre-DHPL period, after which point prescription volumes drop abruptly to zero. All of the statistical techniques find evidence of structural break (table 6).

FLUOTIC

On 2007-06-21 Health Canada issued a DHPL concerning FLUOTIC (sodium fluoride)[42]. The letter advised healthcare professionals of a quality control issue with FLUOTIC– the disintegration time of samples of the product were faster than usual. Because of this, the generally low level of FLUOTIC sales, and a manufacturer review of its

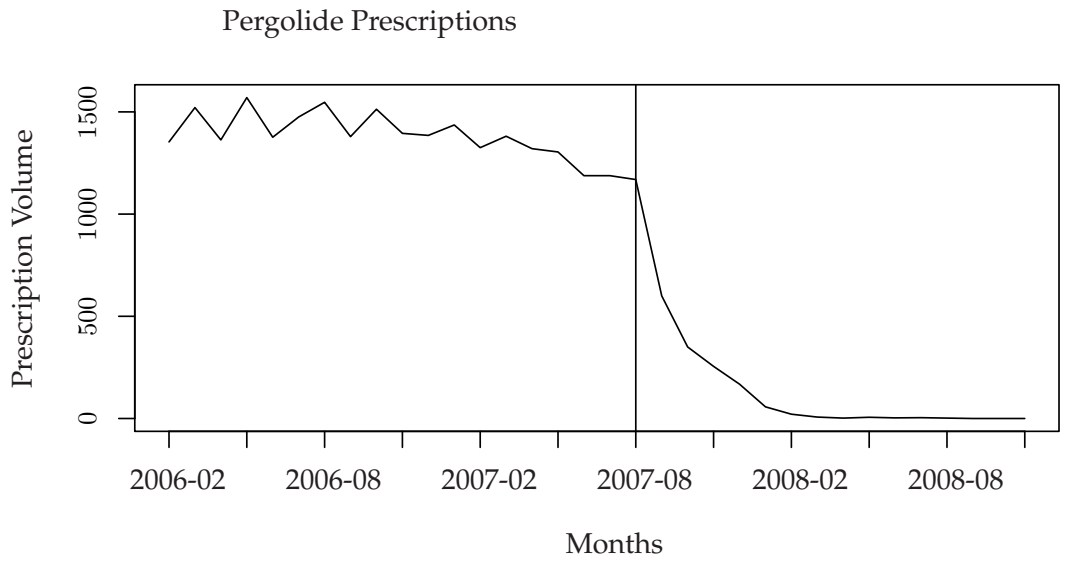

Figure 10: Pergolide Prescriptions

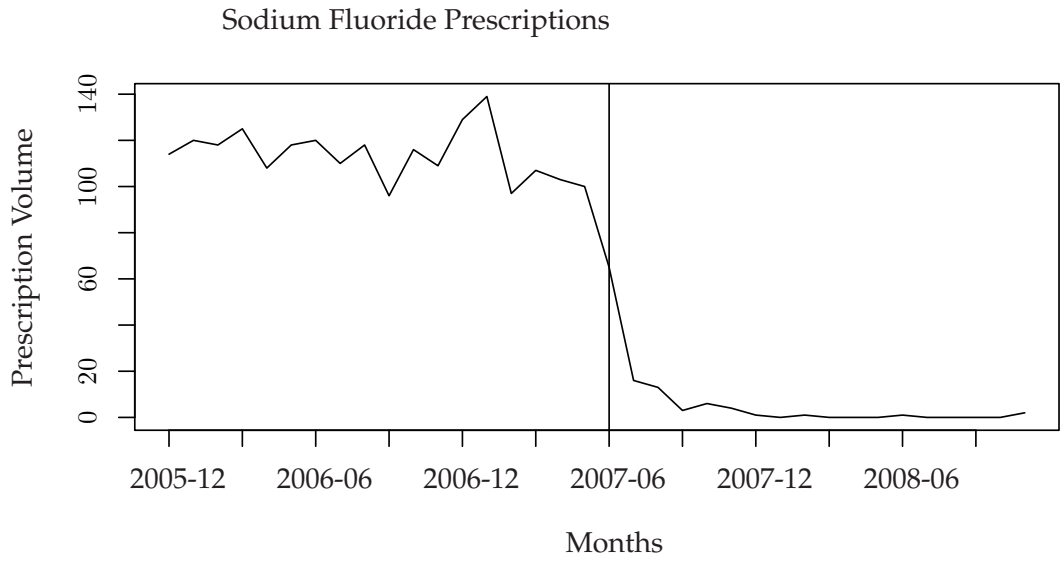

Figure 11: Sodium Fluoride Prescriptions

business lines FLUOTIC is being withdrawn from the market, and will no longer be manufactured or marketed. Prescription volumes (figure 11) maintain a level

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**58.92**	$<$ **0.01**
ITSE-Ramsey	**12.62**	$<$ **0.01**
ITSACORR	**19.63**	$<$ **0.01**

Table 7: Statistical Findings of Structural Break for Sodium

trend in the period prior to the DHPL, after which prescription volumes drop to near-zero. All of the statistical techniques find evidence of structural break (table 7).

ZELNORM

On 2007-03-30 Health Canada issued a DHPL concerning ZELNORM (tegaserod hydrogen maleate)[50]. The letter informed healthcare professionals of a retrospective analysis that found greater incidence of cardiovascular ischemic events among patients taking ZELNORM than among the controls. The manufacturer of ZELNORM is ceasing production and distribution of ZELNORM in Canada, and patients taking ZELNORM should discontinue use. Prescription volumes (figure

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**31.27**	$<$ **0.01**
ITSE-Ramsey	**5.72**	$<$ **0.01**
ITSACORR	**9**	$<$ **0.01**

Table 8: Statistical Findings of Structural Break for Tegaserod

12) demonstrate a level (increasing slightly) trend in the period prior to the DHPL. Immediately following the DHPL, prescription volumes drop to zero for the entire post-DHPL period of the sample. All of the statistical techniques find evidence of structural break (table 8).

CLIMACTERON

On 2005-11-23 Health Canada issued a DHPL concerning CLIMACTERON (estradiol dienanthate)[5]. The letter advises healthcare professionals that CLIMACTERON has been discontinued due to safety reasons, and will no longer be available once current stocks are depleted.

Prescription volumes (figure 13) demonstrate a level trend (decreasing slightly) in the period prior to the DHPL. Immediately following the DHPL, prescription volumes drop to near zero for the entire post-DHPL period of the sample. All of the statistical techniques find evidence of structural break (table 9).

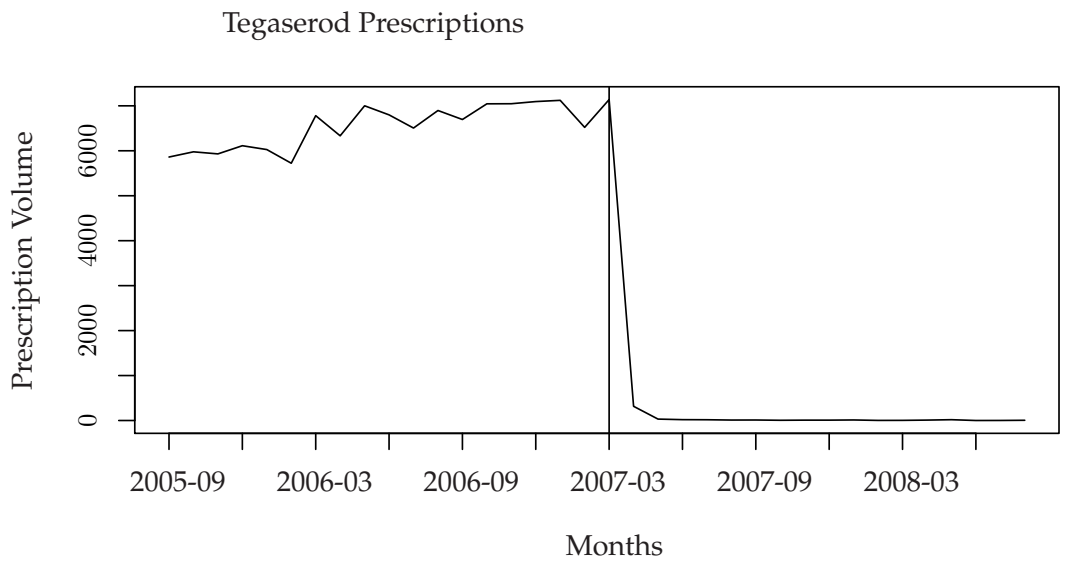

Figure 12: Tegaserod Prescriptions

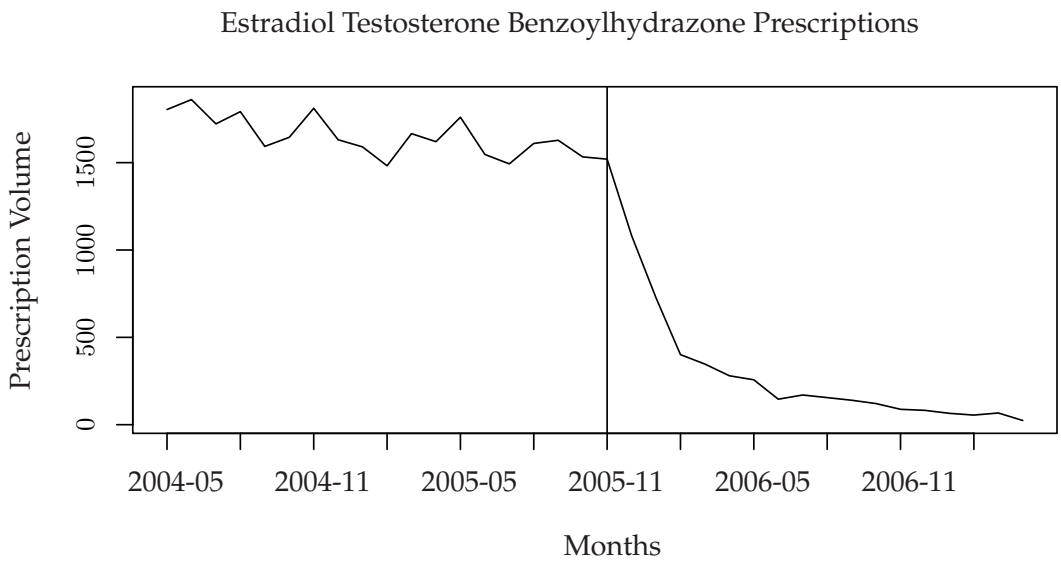

Figure 13: Estradiol Testosterone Benzoylhydrazone Prescriptions

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**21.02**	< **0.01**
ITSE-Ramsey	**5.31**	< **0.01**
ITSACORR	**8.41**	< **0.01**

Table 9: Statistical Findings of Structural Break for Estradiol!Testosterone Benzoylhydrazone

Thioridazine

On 2005-08-31 Health Canada issued a DHPL concerning Thioridazine[16]. In July 2001 MELLARIL (Thioridazine) was volountarily withdrawn from the Canadian market by its manufacturer. Several generic manufacturers have continued to manufacture and sell Thioridazine into the Canadian market because of a lack of evidence to support the cessation of sales. Thioridazine is now known to be associated with QT prolongation, which predisposes patients to life threatening cardiac arrhythmias. As such, Thioridazine will no longer be sold into the Canadian market. Prescription volumes (figure 14) demonstrate a modest decreasing trend

Statistical Test	Value Of *F*-statistic	P-value
Naive F (Squarred)	**34.19**	< **0.01**
ITSE-Ramsey (Squarred)	**3.64**	**0.02**
ITSACORR (Linear)	2.81	0.08

Table 10: Statistical Findings of Structural Break for Thioridazine

up to the DHPL, after which the series tapers off quickly to zero. The Naive-*F* and ITSE-Ramsey find evidence of break at the 5% level, and the ITSACORR statistic is nearly significant (table 10).

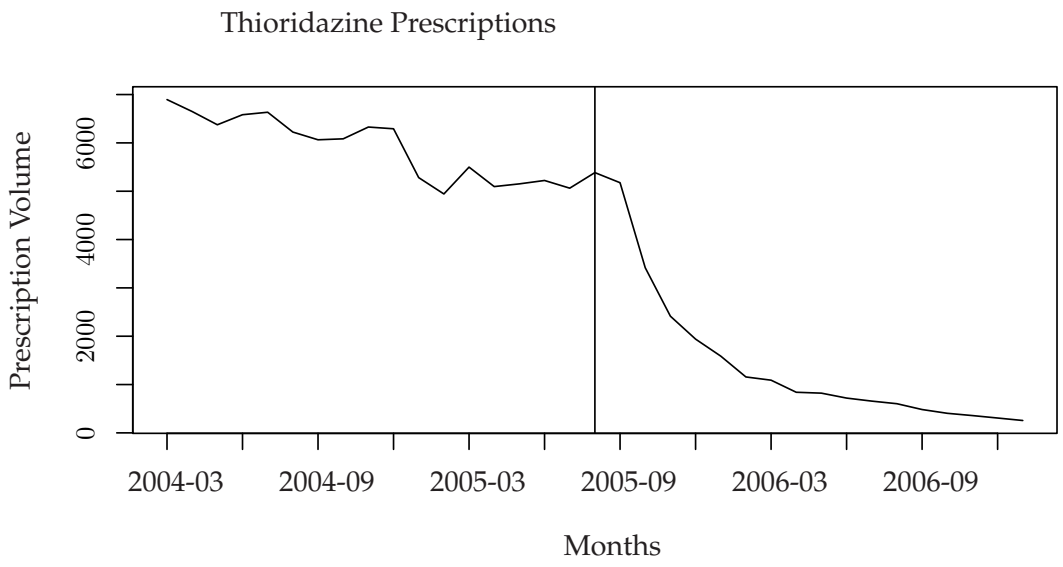

Figure 14: Thioridazine Prescriptions

3.1.2 DHPLs with Risk of Future ADRs

The following DHPLs are ones whose values may be influenced by the actions of physicians through their prescribing behaviors. Additionally, these DHPLs can be considered on their own, without concern for other similar and closely released DHPLs possibly confounding the effect (as we do in the following section).

ZIAGEN, KIVEXA, and TRIZIVIR

On 2008-06-18 Health Canada issued a DHPL concerning ZIAGEN, KIVEXA, and TRIZIVIR (abacavir containing medical products)[53]. These products are antiretrovirals, often used in combination with other retrovirals, in the treatment of human immune deficiency syndrome virus (HIV). The letter describes a journal article that found an association between increased risk of myocardial infarction and the use of abacavir containing medical products. The letter provides information, and no prescriptive guidance.

The plotted prescription volumes (figure 15) appear to be increasing in the period prior to the issuance of the DHPL, though noisily. Prescription volumes appear to be decreasing in the period after the DHPL. Table 11 shows that all statistical techniques find evidence of a break around the DHPL.

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**24.06**	$<$ **0.01**
ITSE-Ramsey	**9.6**	$<$ **0.01**
ITSACORR	**14.63**	$<$ **0.01**

Table 11: Statistical Findings of Structural Break for Abacavir

APO-DESMOPRESSIN SPRAY

On 2008-07-31 Health Canada issued a DHPL concerning APO-DESMOPRESSIN SPRAY (desmopressin ddavp)[54]. The letter advises that APO-DESMOPRESSIN

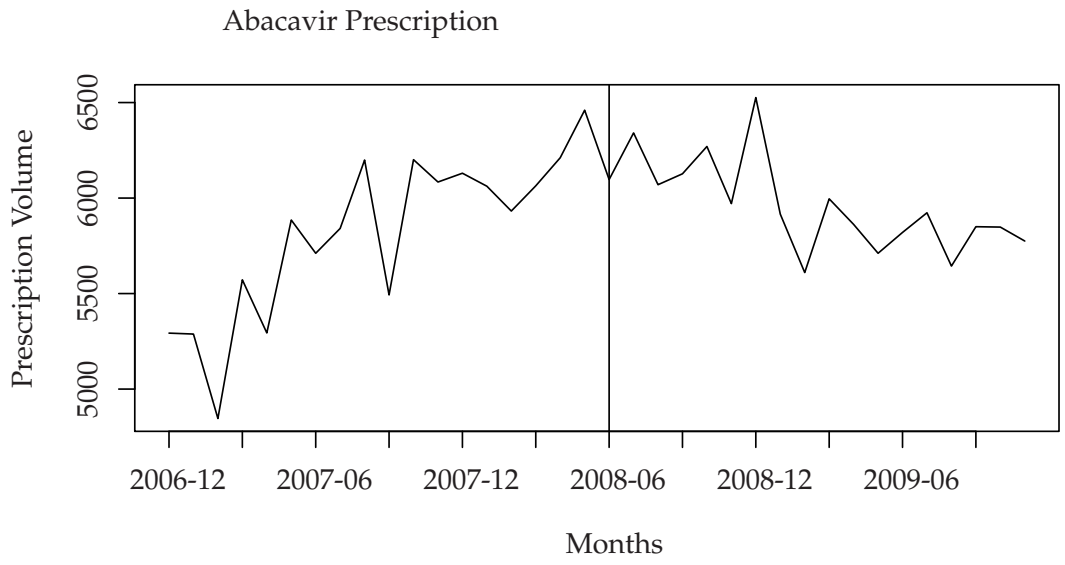

Figure 15: Abacavir

SPRAY is now contraindicated for the treatment of Primary Nocturnal Enuresis because post market surveillance has shown greater risk of hyponatremia, a serious potentially fatal reaction caused by water retention,than oral formulations. The

Statistical Test	Value Of *F*-statistic	P-value
Naive F	1.62	0.21
ITSE-Ramsey	0.92	0.44
ITSACORR	1.39	0.27

Table 12: Statistical Findings of Structural Break for Desmopressin Ddavp

plotted prescription volumes (figure 16) appear quite noisy. There does seem to be a drop in the prescription volume immediately following the DHPL, and the prescription volumes seem lower in the post-DHPL period. Table 12 shows that none of the statistical techniques were able to detect a structural break.

TYSABRI

On 2008-06-02 Health Canada issued a DHPL concerning TYSABRI (natalizumab)[61]. The letter informed healthcare professionals of post-market clinically significant liver injuries that have been observed, and recommends that treatment with TYSABRI be discontinued if a patient shows symptoms of jaundice or any other significant liver injury. For about $^2/_3$ of the period prior to the DHPL, prescription volumes

Statistical Test	Value Of *F*-statistic	P-value
Naive F (Squarred)	**12.2**	$<$ **0.01**
ITSE-Ramsey (Squarred)	**3.33**	**0.02**
ITSACORR (Linear)	2.08	0.14

Table 13: Statistical Findings of Structural Break for Natalizumab

remain flat near zero. Following this, prescription volumes (figure 17) demonstrate an abrupt increase that fades slightly through the DHPL. The only statistical

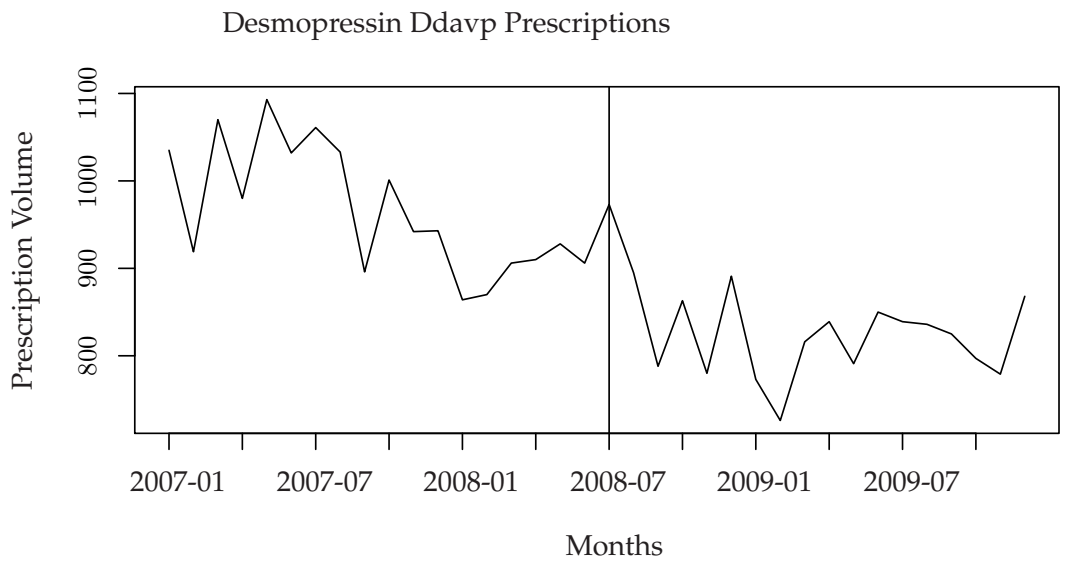

Figure 16: Desmopressin Ddavp Prescriptions

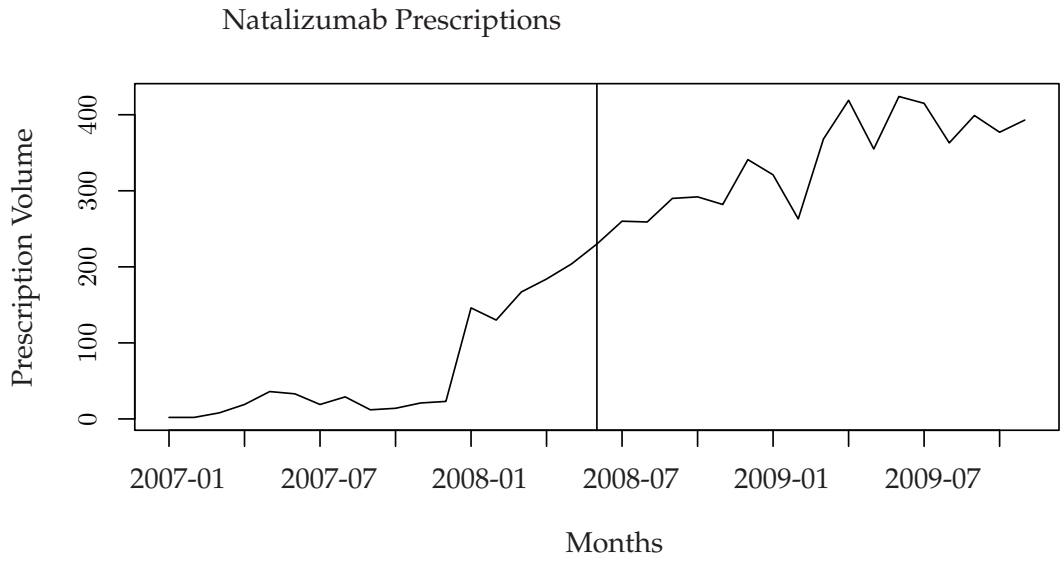

Figure 17: Natalizumab Prescriptions

technique that detects structural break is the naive-*F* (table 13).

SOMAVERT

On 2008-06-02 Health Canada issued a DHPL concerning SOMAVERT (pegvisomant)[60]. The letter informs healthcare professionals of findings from a post marketing study, which found a marked increase in heptatic enzyme levels in patients that were taking SOMAVERT (> 10 times the upper limit of normal) in combination with a somatostatin analogue (octreotide acetate). The letter goes on to state that using these two drugs in combination is not an approved treatment of acromegaly as neither the safety nor the efficacy of these drugs together has been established. For about $^2/_3$ of the period prior to the DHPL, prescription volumes remain flat near zero. Following this, prescription volumes (figure 18) demonstrate an abrupt increase that fades slightly through the DHPL, and then begins to decline. All 3 techniques find evidence of structural break (table 14).

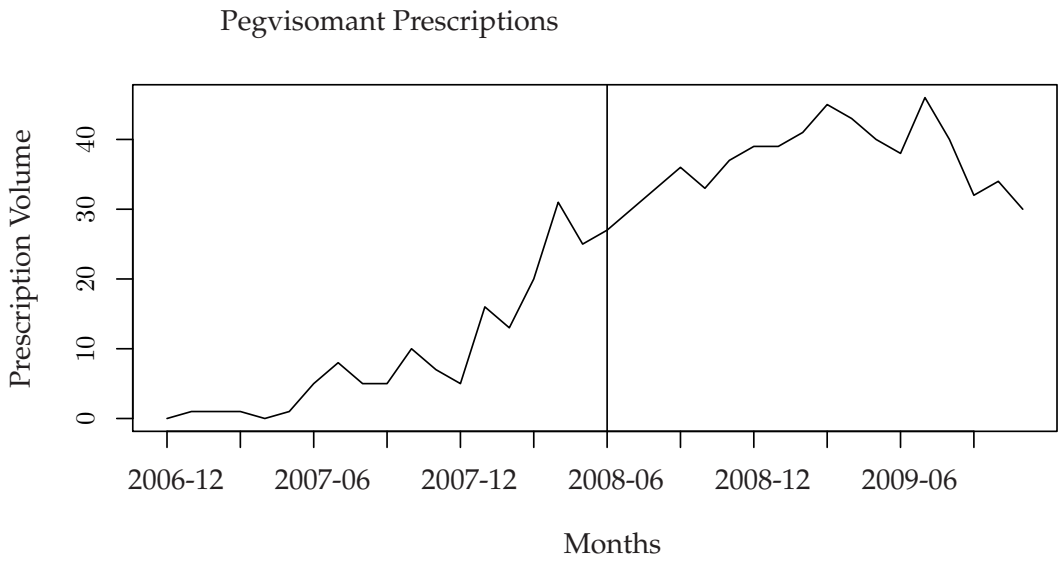

Figure 18: Pegvisomant Prescriptions

Statistical Test	Value Of *F*-statistic	P-value
Naive F (Squarred)	**28.43**	$<$ **0.01**
ITSE-Ramsey (Squarred)	**5.66**	$<$ **0.01**
ITSACORR (Linear)	**4.4**	**0.02**

Table 14: Statistical Findings of Structural Break for Pegvisomant

CHAMPIX

On 2008-06-13 Health Canada issued a DHPL concerning CHAMPIX (varenicline)[55]. CHAMPIX is a smoking cessation aid. The DHPL concerning CHAMPIX informed healthcare professionals of results from post marketing studies that showed increased risk of neuropsychiatric events among patients taking CHAMPIX. The letter also recommends that physicians supervise their patients with psychiatric conditions, even well controlled conditions, very closely. prescription volumes

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**157.91**	$<$ **0.01**
ITSE-Ramsey	**7.92**	$<$ **0.01**
ITSACORR	**16.07**	$<$ **0.01**

Table 15: Statistical Findings of Structural Break for Varenicline

(figure 19) demonstrate a dramatic increase in the period prior to the DHPL. Just before the issuance of the DHPL, prescription volumes begin to decline. In the post-DHPL period, prescription volumes demonstrate a steady downward trend. All of the statistical techniques find evidence of structural break (table 15).

ALERTEC

ON 2007-12-18 Health Canada issued a DHPL concerning ALERTEC (modafinil)[36]. The letter informed healthcare professionals of updates to the product monograph.

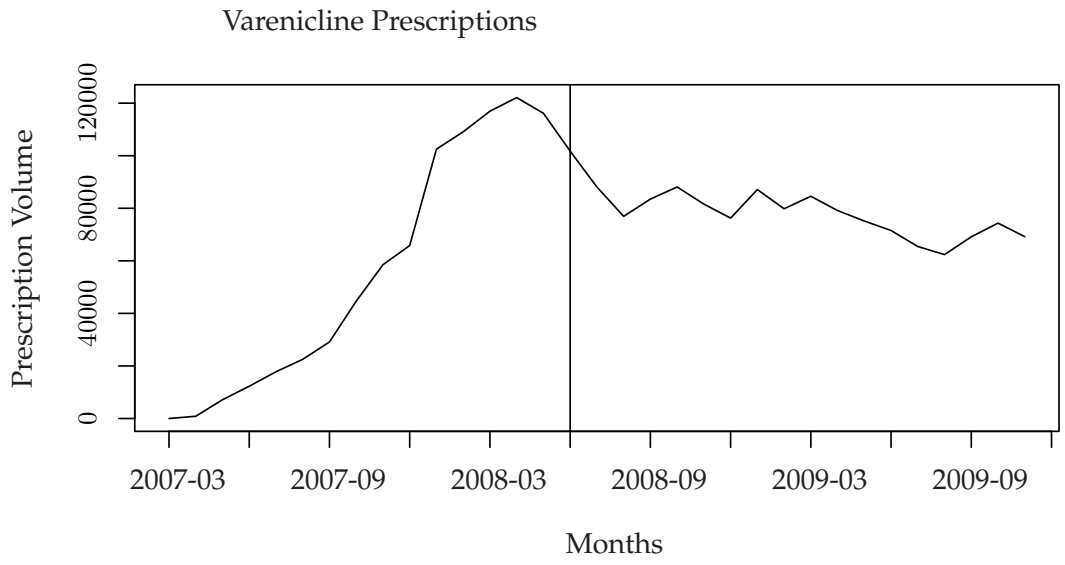

Figure 19: Varenicline Prescriptions

The changes included the possibility of life threatening skin and other hypersensitivity reactions, that the product is not approved for pediatric use, and that the medication can cause psychiatric symptoms. Prescription volumes (figure 20) in-

Statistical Test	Value Of *F*-statistic	P-value
Naive F	3.26	0.05
ITSE-Ramsey	1.89	0.16
ITSACORR	2.85	0.07

Table 16: Statistical Findings of Structural Break for Modafinil

crease, though noisily, through the pre-DHPL period of the sample. Prescription volumes seem to shift downward immediately after the issuance of the DHPL, after which they resume their same linear trend with similar noise. None of the statistical techniques were able to find evidence suggestive of a structural break (table 16).

VIRACEPT

On 2007-09-10 Health Canada issued a DHPL concerning VIRACEPT (nelfinavir)[49]. The letter informs healthcare professionals of a process related impurity found in VIRACEPT, a treatment for HIV, that has been shown to be carcinogenic in animal studies. Physicians are encouraged to consider the risk and benefits of prescribing VIRACEPT to their HIV patients, and Health Canada recommends changing to alternative medication where possible. Prescription volumes (figure 21) decline mildly through the pre-DHPL period, and then drop off considerably following the DHPL. All of the statistical techniques find evidence of structural break (table 17).

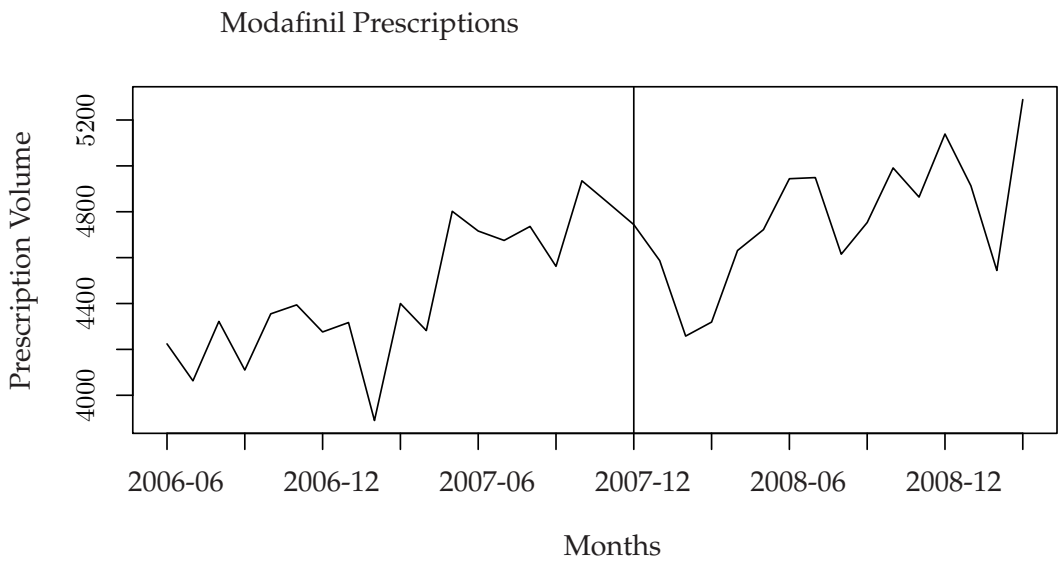

Figure 20: Modafinil Prescriptions

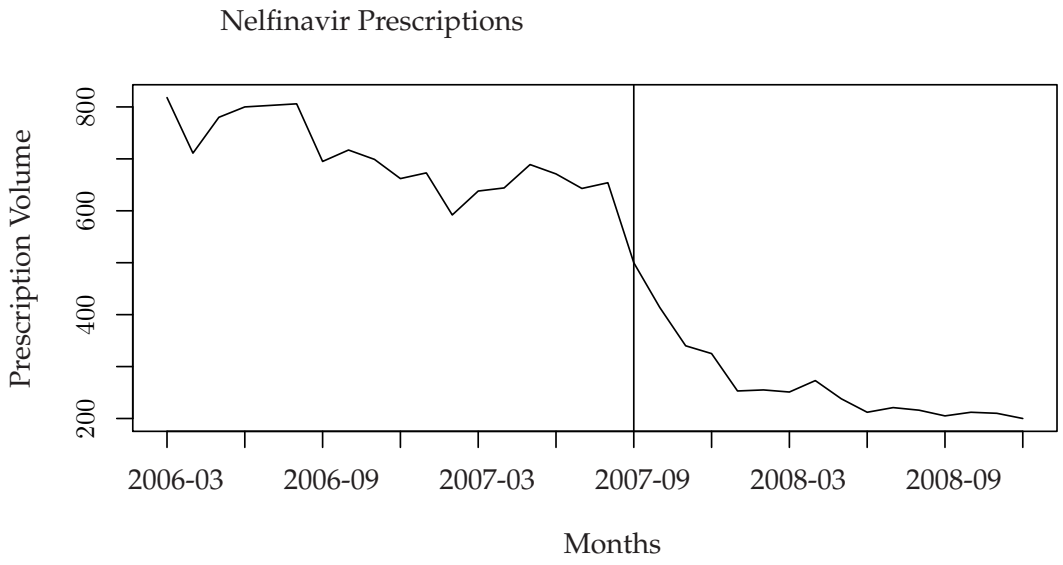

Figure 21: Nelfinavir Prescriptions

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**28.44**	**< 0.01**
ITSE-Ramsey	**10.23**	**< 0.01**
ITSACORR	**15.59**	**< 0.01**

Table 17: Statistical Findings of Structural Break for Nelfinavir

ARANESP and EPREX

On 2007-04-16 Health Canada issued a DHPL concerning ARANESP and EPREX (darbepoietin alfa and epoetin alfa)[40]. The letter informs healthcare professionals of changes of use for these medications. ARANESP remains a treatment for both anaemia associated with chronic renal failure as well as anaemia resulting from chemotherapy; EPREX is no longer indicated for the treatment of anaemia associated with chronic renal failure, it is only indicated for anaemia resulting from chemotherapy. Prescription volumes (figure 22), overall, establish an increasing

Statistical Test	Value Of *F*-statistic	P-value
Naive F (Linear)	**14.36**	**< 0.01**
ITSE-Ramsey (Linear)	**3.61**	**0.02**
ITSACORR (Linear)	**5.57**	**0.01**

Table 18: Statistical Findings of Structural Break for Both Darbe+ Erythro

trend over the pre-DHPL period, but the data is very noisy. Following the DHPL there appears to be a decreasing trend, but here too, the data is very noisy. Based on the information contained in the DHPL, it is entirely reasonable that physicians shift between prescriptions for ARANESP and EPREX (particularly for anaemia associated with chronic renal failure). We have no way of capturing this degree of change with our data aggregated as it is. We discuss this and other limitations of the data in our discussion and conclusions section. All of the statistical techniques find evidence of structural break (table 18).

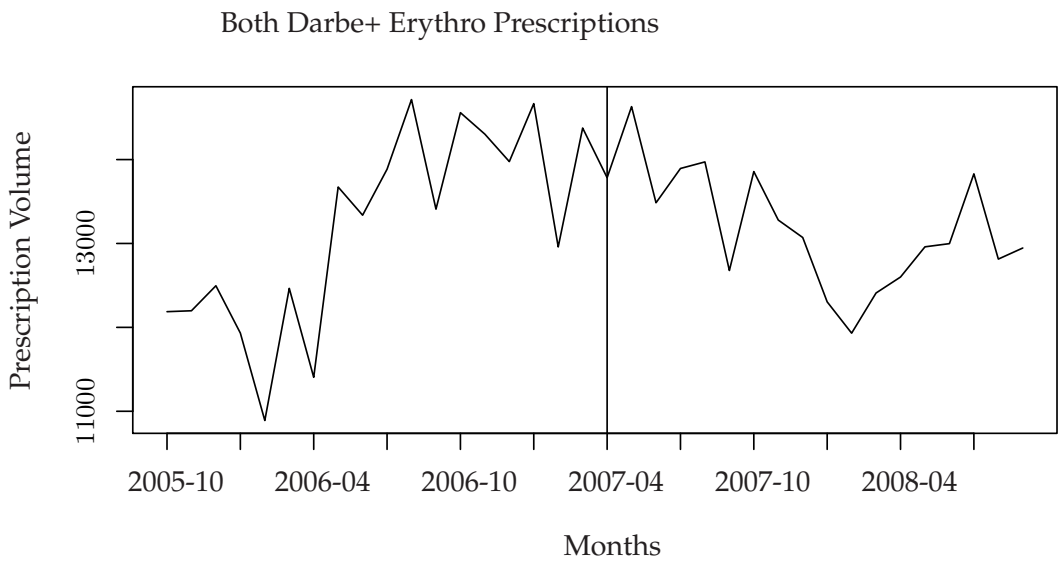

Figure 22: Both Darbe+ Erythro Prescriptions

ACTOS

On 2007-04-18 Health Canada issued a DHPL concerning ACTOS (pioglitazone)[35]. The letter informs healthcare professionals of the findings of several post market studies. The studies found increased bone fracture risk among women taking ACTOS in the trials, and no increased bone fracture risk among similar men in the trials. The letter recommends that physicians consider bone fracture risk in prescribing ACTOS to female patients. Prescription volumes (figure 23) demonstrate

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**5.89**	**0.01**
ITSE-Ramsey	2.27	0.1
ITSACORR	**3.46**	**0.04**

Table 19: Statistical Findings of Structural Break for Pioglitazone

an increasing trend over the sample window. It is reasonable to expect that a medication causing increased bone fracture risk in female patients should be prescribed differently once information about the increased risk is made public. What is less reasonable is the direction of the change– it appears that prescription volumes go up following the DHPL (figure 23). We may have other factors at play here. ACTOS is used to improve glucose regulation among adults with type 2 diabetes. What we may be observing in the data series is increased rates of type 2 diabetes, and the drugs to control it, among an ageing and increasingly sedentary population (obese), that is mitigated by being prescribed less to women. The naive-*F* and the ITSACORR techniques find evidence of structural break, and the ITSE-Ramsey technique is just on the cusp of significance (table 19).

BARACLUDE

On 2007-02-21 Health Canada issued a DHPL concerning BARACLUDE (entecavir)[52]. BARACLUDE is a treatment for chronic hepatitis B (HBV) that is administered to

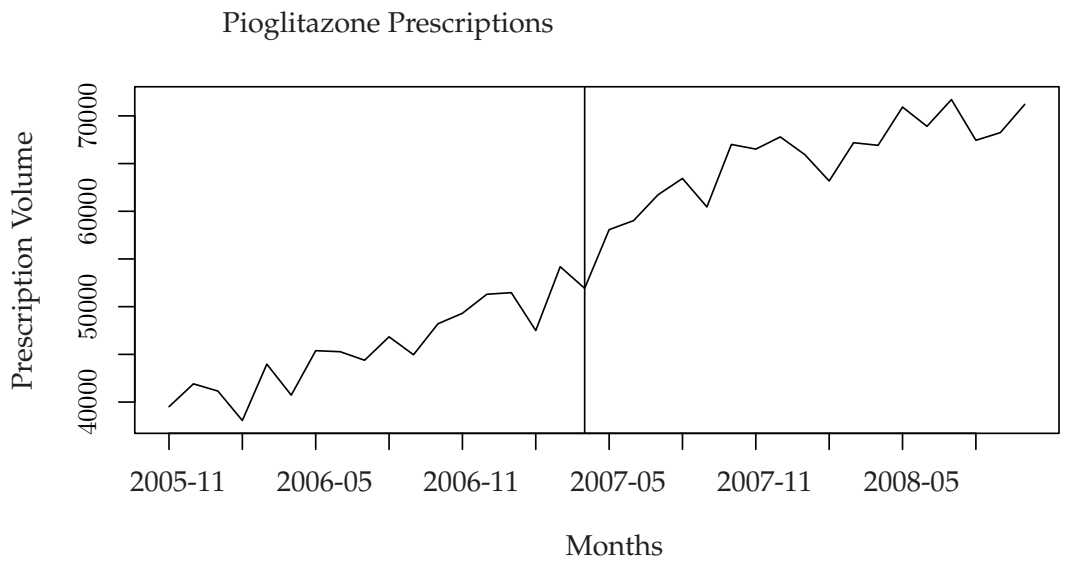

Figure 23: Pioglitazone Prescriptions

HIV patients. It is preferable for patients taking BARACLUDE to also be receiving highly active anti-retroviral therapy (HAART). The letter informs healthcare professionals of a case in which a patient was being treated with BARACLUDE for HBV, but not with a HAART for HIV, developed HIV resistance. Throughout

Statistical Test	Value Of *F*-statistic	P-value
Naive F	2.57	0.1
ITSE-Ramsey	0.43	0.73
ITSACORR	0.72	0.5

Table 20: Statistical Findings of Structural Break for Entecavir

the sample window prescription volumes (figure 24) exhibit a consistent and clear increasing trend. There does not appear to be any change after the DHPL. Moreover, because there are few data points prior to the DHPL, it is unclear that the statistical techniques will have enough sample to pick up a significant statistical effect if there is one. Not all of the drug series have their DHPL occurring in the middle of the sample, table 58 describes how many observations before and after the DHPL there are for each series. None of the statistical techniques were able to find evidence suggestive of a structural break (table 20).

EVRA

On 2006-11-21 Health Canada issued a DHPL concerning EVRA (norelgestromin and ethinyl estradiol)[23]. The letter informed healthcare professionals of new safety information that was being added to the product's monograph. The safety information concerned the increased risk of venous thromboembolism (VTE) with EVRA compared with other oral contraceptives. It was found that obesity is a risk factor for VTE associated with EVRA. Physicians are advised to consider a patient's risk profile in prescribing EVRA. Prescription volumes (figure 25) demonstrate a steep increase then a noisy decrease in the pre-DHPL period of the sample. In the post-DHPL period of the sample, prescription volumes demonstrate a noisy

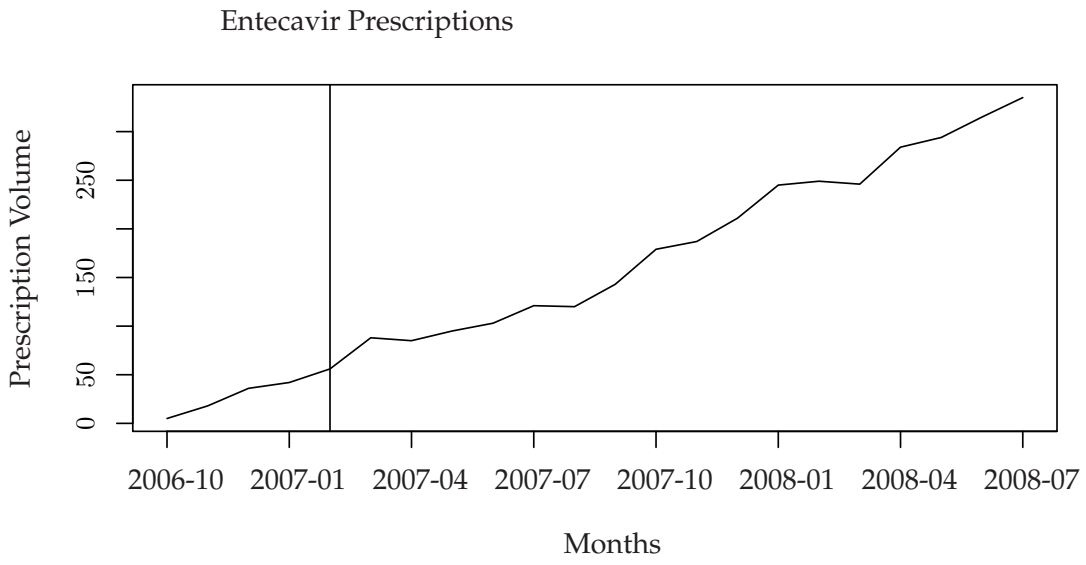

Figure 24: Entecavir Prescriptions

Statistical Test	Value Of *F*-statistic	P-value
Naive F (Squarred)	**7.78**	$<$ **0.01**
ITSE-Ramsey (Squarred)	2.52	0.06
ITSACORR (Linear)	1.34	0.28

Table 21: Statistical Findings of Structural Break for Ethinylestradiol!Norelgestromin

decreasing linear trend. Only the naive-*F* test finds evidence of a structural break (table 21).

HYDREA

On 2006-03-01 Health Canada issued a DHPL concerning HYDREA (hydroxyurea)[24]. The letter informed healthcare professionals of post market case reports of cutaneous vasculitis toxicities, including vasculitic ulcerations and gangrene, among patients with myeloproliferative disorders receiving treatment with HYDREA. Physicians are cautioned to discontinue HYDREA treatments if symptoms of cutaneous vascular toxicities appear. Physicians are made aware that cutaneous vascular toxicities occurred most often in HYDREA patients that were receiving interferon therapy. Prescription volumes (figure 26) demonstrate an increasing

Statistical Test	Value Of *F*-statistic	P-value
Naive F	0.44	0.65
ITSE-Ramsey	0.82	0.49
ITSACORR	1.23	0.31

Table 22: Statistical Findings of Structural Break for Hydroxyurea

trend over the entire sample window. None of the statistical techniques were able to find evidence suggestive of a structural break (table 22).

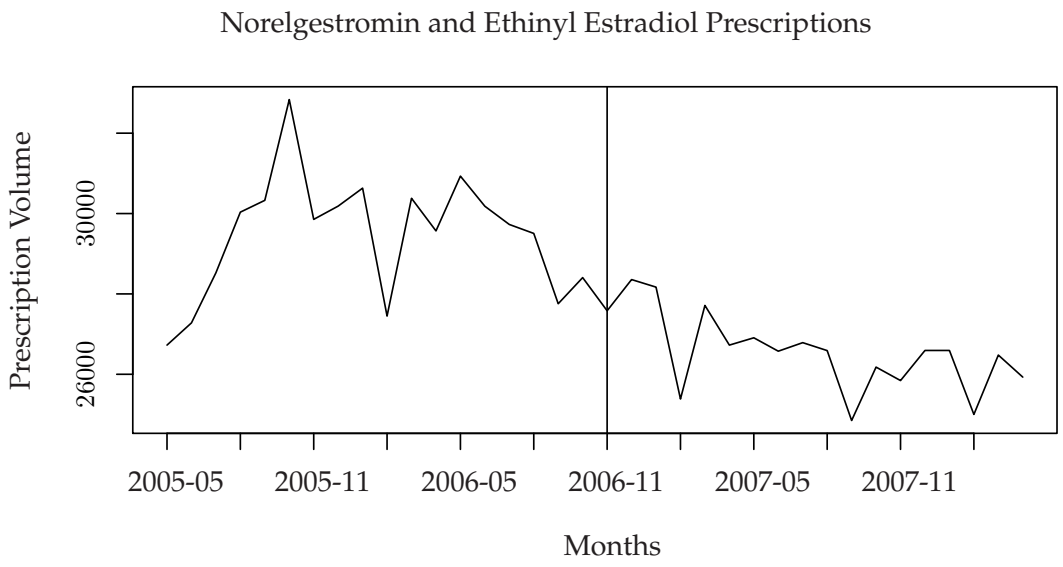

Figure 25: Norelgestromin and Ethinyl Estradiol Prescriptions

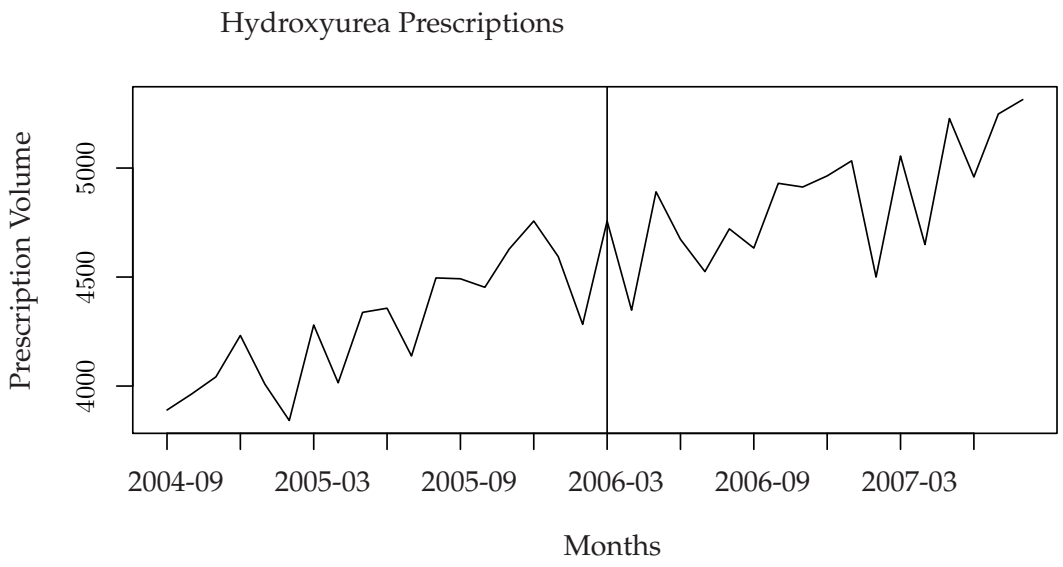

Figure 26: Hydroxyurea Prescriptions

EVISTA

On 2006-05-18 Health Canada issued a DHPL concerning EVISTA (raloxifene)[22]. The letter informs healthcare professionals of a large placebo controlled study that found increased mortality risk due to stroke among patients taking EVISTA relative to the control patients. Physicians are encouraged to consider the risk profiles of their patients before prescribing EVISTA, as EVISTA remains an effective and preventative treatment for osteoporosis. Prescription volumes (figure 27)

Statistical Test	Value Of *F*-statistic	P-value
Naive F	1.05	0.36
ITSE-Ramsey	0.47	0.7
ITSACORR	0.71	0.5

Table 23: Statistical Findings of Structural Break for Raloxifene

demonstrate a decreasing trend throughout the sample window. None of the statistical techniques were able to find evidence suggestive of a structural break (table 23).

RAPAMUNE

On 2006-08-18 Health Canada issued a DHPL concerning RAPAMUNE (sirolimus)[30]. The letter informs healthcare professionals in the proper use of RAPAMUNE. Per the DHPL, RAPAMUNE's use is limited to the prevention of renal transplant rejection in combination with cyclosporine and steroids. Physicians are reminded that the safety and efficacy of RAPAMUNE, as immunosuppressant, for liver and lung transplants has not been established and is not recommended. Prescription volumes (figure 28) demonstrate an overall increasing trend over the sample window. The period prior to the DHPL seems to be characterized by more volatility and greater increase in prescription volumes. In the period after the DHPL, by contrast, prescription volumes are less volatile and appear to be increasing at a lesser rate. Only the naive-*F* test finds evidence of a structural break (table 24).

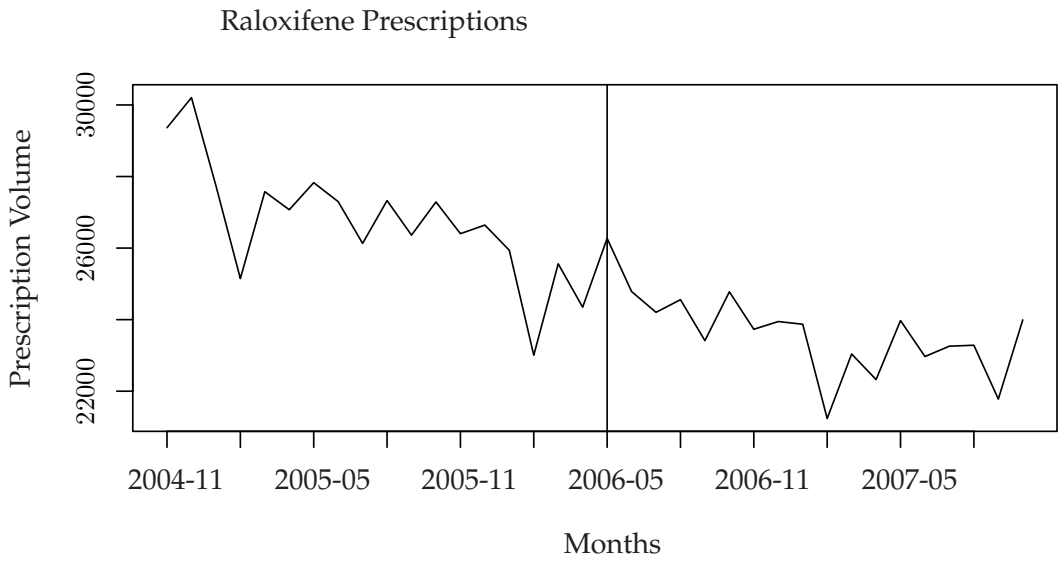

Figure 27: Raloxifene Prescriptions

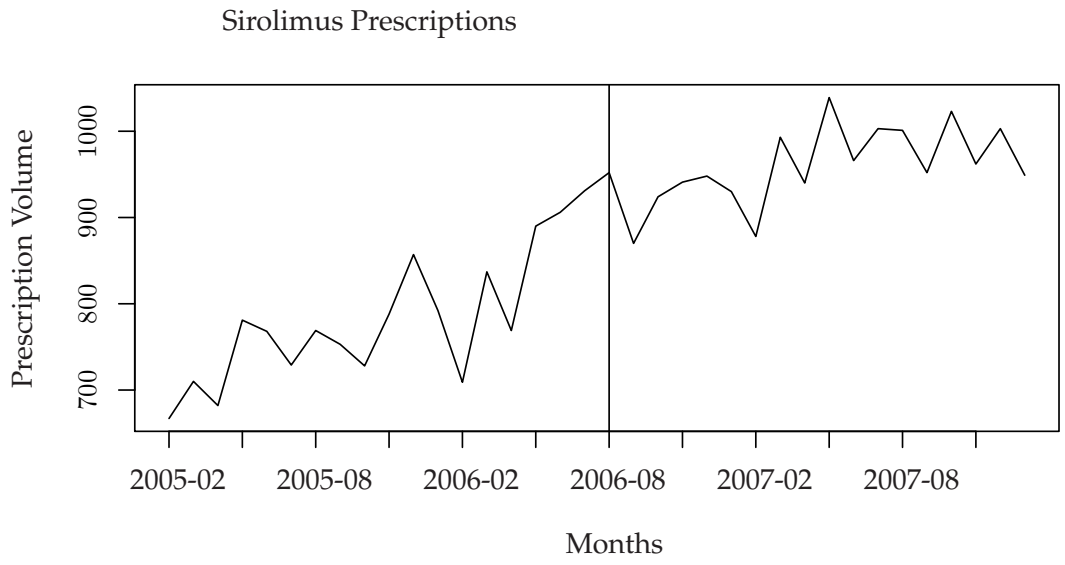

Figure 28: Sirolimus Prescriptions

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**3.51**	**0.04**
ITSE-Ramsey	2.14	0.12
ITSACORR	3.23	0.05

Table 24: Statistical Findings of Structural Break for Sirolimus

APTIVUS

On 2006-06-29 Health Canada issued a DHPL concerning APTIVUS (tipranavir)[19]. The letter informed healthcare professionals of new safety information related to the product. In the wake of reports of cases of intercranial haemorrhages, APTIVUS should be used cautiously with patients at increased risk of bleeding from trauma, surgery, or other medical conditions, or who are receiving medications known to increase the risk of bleeding. Prescription volumes (figure 29) demonstrate a sharply increasing trend in the pre-DHPL period of the sample. Increases in prescription volumes continue in the post-DHPL period of the sample but at a lesser rate and with greater volatility. All of the statistical techniques find evidence of structural break (table 25).

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**9.44**	$<$ **0.01**
ITSE-Ramsey	**4.15**	**0.02**
ITSACORR	**6.39**	**0.01**

Table 25: Statistical Findings of Structural Break for Tipranavir

ADHD

On 2006-05-25 Health Canada issued a DHPL concerning all drugs indicated for the treatment of ADHD[34] including

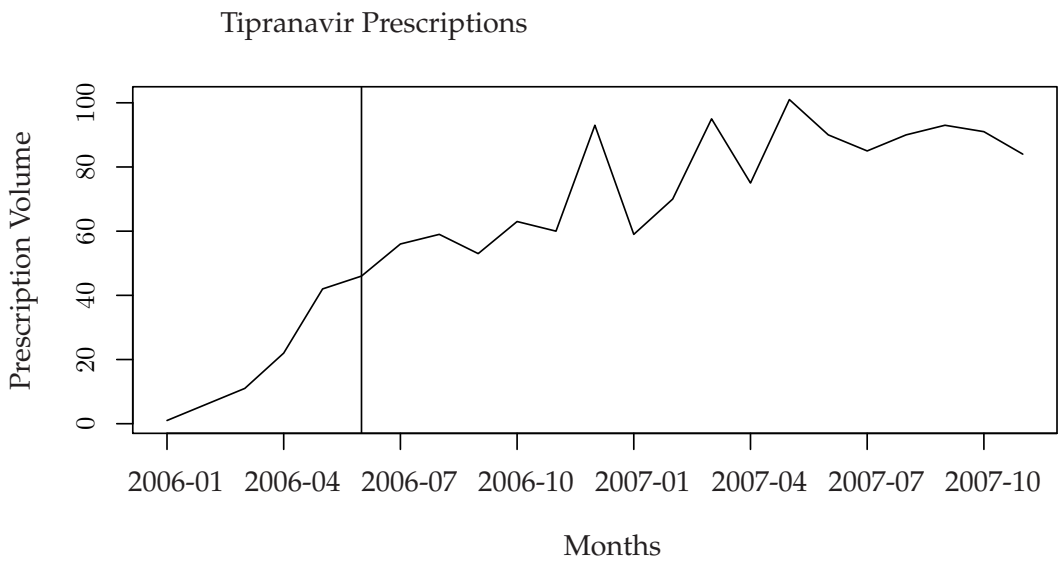

Figure 29: Tipranavir Prescriptions

- ADDERALL XR (mixed salts amphetamine extended-release);
- ATTENADE (dextromethylphenidate);
- BIPHENTIN (methylphenidate controlled release);
- CONCERTA (methylphenidate extended release);
- DEXEDRINE (dextroamphetamine);
- RITALIN (methylphenidate);
- RITALIN SR (methylphenidate extended release); and
- STRATTERA (atomoxetine).

The letter advises healthcare professionals of updated cautionary prescribing practices. These new prescribing practices aim to reduce the number of cardiac related adverse events. The changes include:

- Starting patients at the lowest possible dose;
- Contraindicated for use if patient has symptomatic cardiac disease, hypertension, or structured cardiac anomalies; and
- Performing periodic cardiovascular evaluation of patients who will be treated with ADHD medication on a long term basis.

Statistical Test	Value Of *F*-statistic	P-value
Naive F	0.15	0.86
ITSE-Ramsey	0.09	0.97
ITSACORR	0.13	0.87

Table 26: Statistical Findings of Structural Break for Adhd

Prescription volumes (figure 30) demonstrate an overall increasing trend over the sample window. There does appear to be a considerable drop in prescription

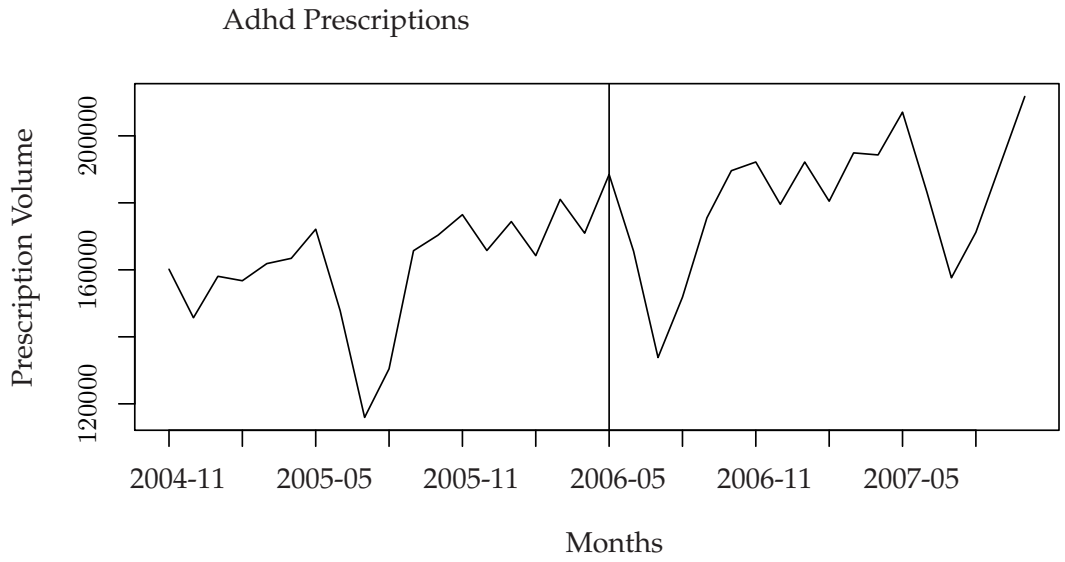

Figure 30: Adhd Prescriptions

volume immediately following the issuance of the DHPL, but this seems more likely to do with the annual prescription trends of ADHD medications and the academic school year– prescription volumes drop in June, once school is out, and pick up again with the new school year.

There is clearly a seasonal pattern of variation in this data. If our objective were to best model prescription volumes through time, we would surely consider techniques for capturing this variation. However, our objective is to assess, in as general a way possible, all of the drug series in our sample for evidence of structural break. Using the techniques and specifications described, the techniques find no evidence of structural break (table 26).

CIALIS , LEVITRA, and VIAGRA

On 2006-06-19 Health Canada issued a DHPL concerning CIALIS , LEVITRA, and VIAGRA (tadalafil, vardenafil hydrochloride, and sildenafil citrate respectively)[21].

This letter is the second DHPL Health Canada has issued to healthcare professionals on this matter. Sudden temporary or permanent loss of vision has been experienced by patients taking these erectile dysfunction medications. Healthcare professionals are encouraged to remind their patients to stop taking these medications and promptly get themselves if any vision loss symptoms present.

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**4.2**	**0.02**
ITSE-Ramsey	1.05	0.39
ITSACORR	1.60	0.22

Table 27: Statistical Findings of Structural Break for Cialis, Levitra, Viagara

Prescription volumes (figure 31) demonstrate a noisily increasing series over the entire sample window. Here too, like with the ADHD medications previously, we observe a seasonal pattern. It appears that many prescriptions are filled in the month of December, and very few are filled in January. This likely owes to many prescriptions being filled before the insurance deductible resets in the new year. Only the naive-*F* test finds evidence of a structural break (table 27).

ARANESP

On 2005-11-25 Health Canada issuead a DHPL concerning ARANESP (darbepoetin alfa)[3]. The letter advises healthcare professionals to discontinue use of ARANESP and asses patients for the presence of binding and neutralizing antibodies if a patient appears to be showing signs of antibody-mediated pure red cell aplasia, as a small number of patients have been reported to do. Prescription volumes (figure 32) appear relatively constant through the pre-DHPL period of the sample. Following the DHPL, prescription volumes demonstrate an increase through the post-DHPL period of the sample. All of the statistical techniques find evidence of structural break (table 28).

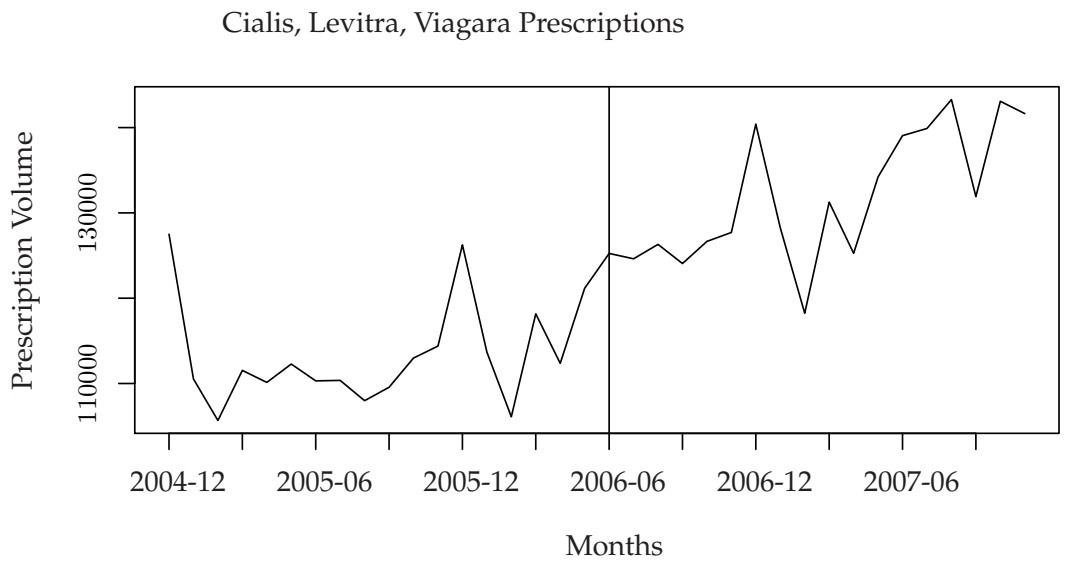

Figure 31: Cialis, Levitra, Viagara Prescriptions

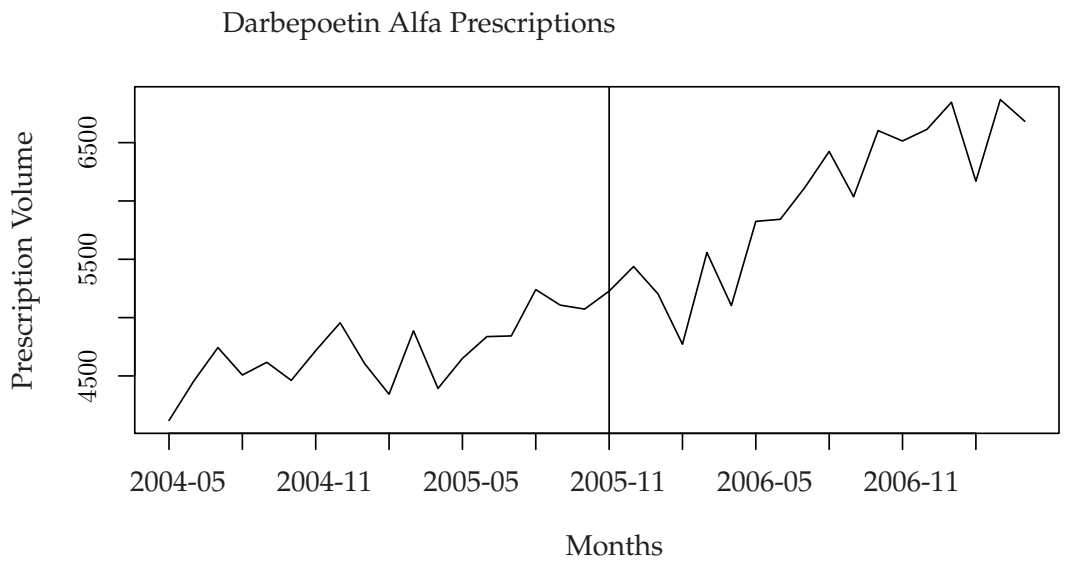

Figure 32: Darbepoetin Alfa Prescriptions

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**8.57**	**< 0.01**
ITSE-Ramsey	**4.12**	**0.01**
ITSACORR	**6.26**	**0.01**

Table 28: Statistical Findings of Structural Break for Darbepoetin Alfa

MACUGEN

On 2005-09-29 Health Canada issued a DHPL concerning MACUGEN (pegaptanib sodium injection)[28]. The letter advises opthamologists of safety information related to post marketing reports. A number of hypersensitivity reports have been reported with MACUGEN– both anaphylaxis and anaphylactoid reactions. Opthamologists are advised to be prepared for the procedures involved with handling hypersensitivity reactions. The letter also indicates that MACUGEN is contraindicated for patients with known hypersensitivity to any components of the MACUGEN preparation.

Statistical Test	Value Of *F*-statistic	P-value
Naive F (Squarred)	1.76	0.2
ITSE-Ramsey (Linear)	0.26	0.86
ITSACORR (Linear)	0.42	0.67

Table 29: Statistical Findings of Structural Break for Pegaptanib

Prescription volumes (figure 33) here again appear highly volatile and have low volume. Also there are very few observations prior to the DHPL. None of the statistical techniques were able to find evidence suggestive of a structural break (table 29).

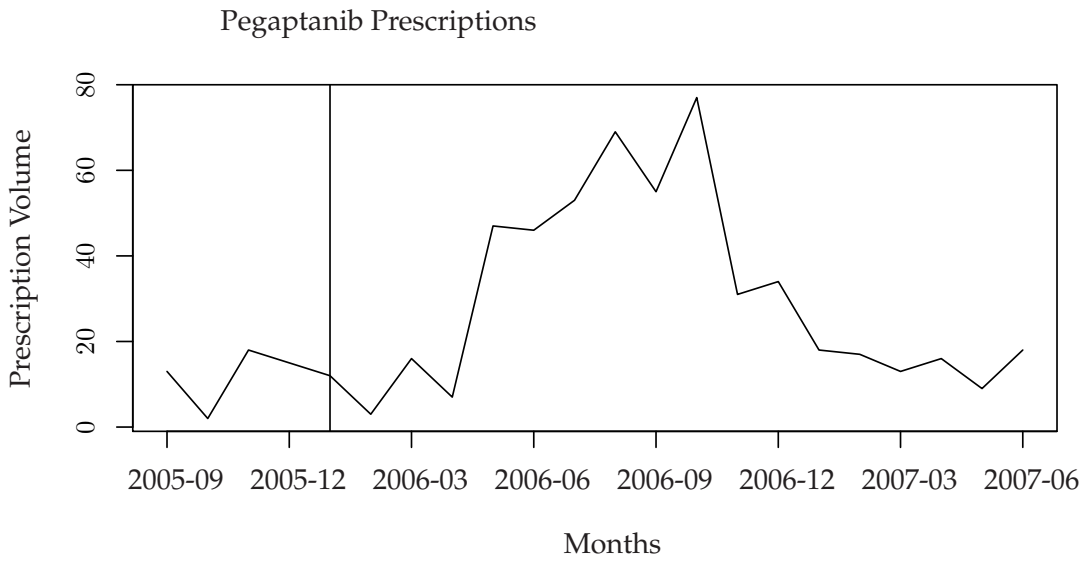

Figure 33: Pegaptanib Prescriptions

STRATTERA

On 2005-09-28 Health Canada issued a DHPL concerning STRATTERA (atomoxetine hydrochloride)[13]. The letter brings important new safety information to the attention of healthcare professionals. The results of a placebo controlled clinical trial show increased suicidal ideation among adolescents taking STRATTERA. Rigorous clinical monitoring for suicidal ideation of patients of all ages taking STRATTERA is recommended. Prescription volumes (figure 34) demonstrate a

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**52.6**	$<$ **0.01**
ITSE-Ramsey	1.49	0.25
ITSACORR	3.52	0.05

Table 30: Statistical Findings of Structural Break for Atomoxetine

consistent increasing trend over the sample window. The series begins at zero in the pre-DHPL period of the sample and increases rapidly up to the DHPL date, which occurs earlier than it typically does in these series (there are no data points available prior to prescription volume being equal to zero). After the DHPL, prescription volumes continue to increase, but at a lesser rate. Only the naive-*F* test finds evidence of a structural break (table 30).

CELEBREX

On 2005-09-21 Health Canada issued a DHPL concerning CELEBREX (celecoxib)[4]. The letter brought to the attention of healthcare professionals important new safety information that was also being added to the product's monograph. Prior to this letter being disseminated, it was known that selective COX-2 inhibitor NSAIDS, of which CELEBREX is one, had been associated with increased risk of cardiovascular events. The letter describes the more nuanced language changes in the monograph concerned with cardiovascular adverse events. Prescription volumes (figure 35) behave erratically in the period prior to the DHPL. The series holds mostly steady

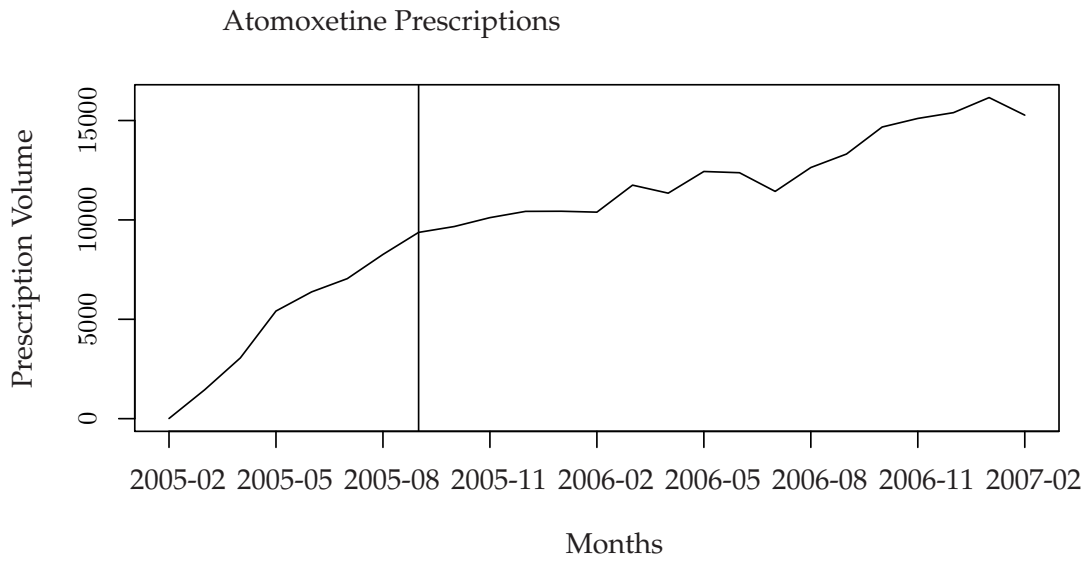

Figure 34: Atomoxetine Prescriptions

Statistical Test	Value Of *F*-statistic	P-value
Naive F (Linear)	**9.51**	$<$ **0.01**
ITSE-Ramsey (Linear)	1.22	0.32
ITSACORR (Linear)	2.03	0.15

Table 31: Statistical Findings of Structural Break for Celecoxib

before an abrupt increase then an abrupt decrease. Once the prescription volume achieves this new lower level, it maintains it (slight increasing trend) through the DHPL date. We apply the linear/non-linear specification test to this series because of the large abrupt discontinuity in the period before the DHPL. This discontinuity will not likely be well explained by including squared terms for the time variable (it isn't). This is a stark example of a non-linearity that cannot be well handled by these regression techniques. We include it for completeness in treatment of DHPL cases. Only the naive-*F* test finds evidence of a structural break (table 31).

DURAGESIC

On 2005-09-13 Health Canada issued a DHPL concerning DURAGESIC (fentanyl transdermal system)[7]. The letter informs healthcare professionals that the product monograph has been updated. DURAGESIC is a transdermal pain reliever, as with other pain relievers, the potential for abuse is high. The letter informs healthcare professionals of safety information and expands on the potential for misuse and abuse as a couple deaths have recently been reported concerning the medication. Prescription volumes (figure 36) demonstrate a broadly increasing trend through the sample window. The data is noisy, but there appears to be a greater slope in the post-DHPL period of the sample. None of the statistical techniques were able to find evidence suggestive of a structural break (table 32).

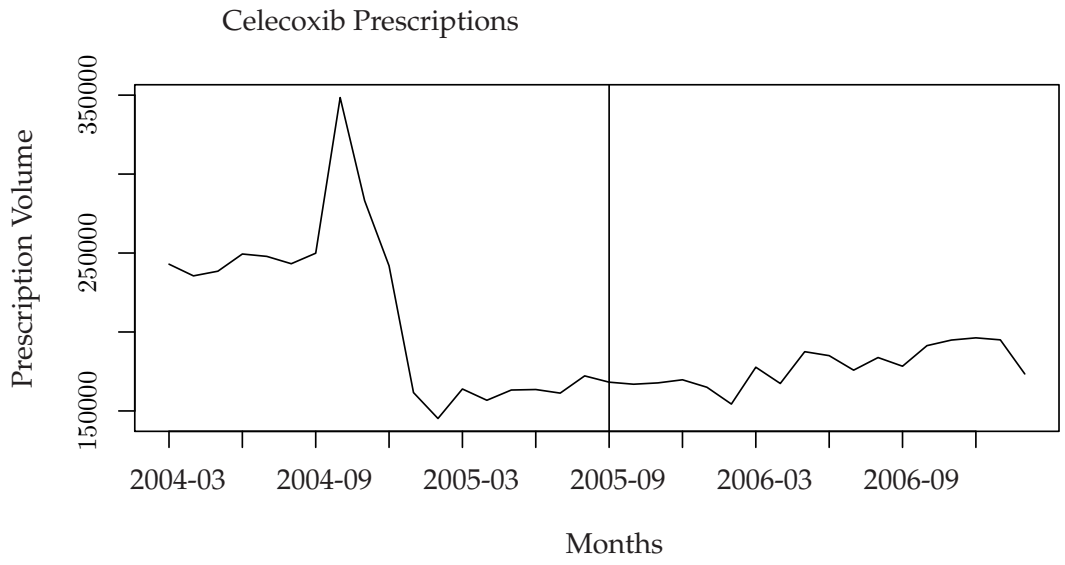

Figure 35: Celecoxib Prescriptions

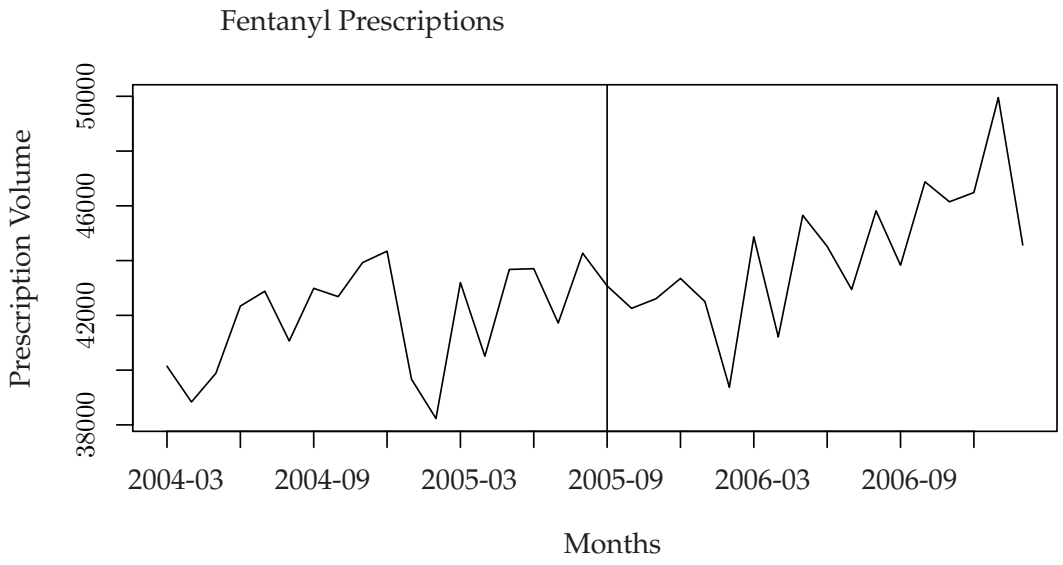

Figure 36: Fentanyl Prescriptions

Statistical Test	Value Of *F*-statistic	P-value
Naive F	2.05	0.15
ITSE-Ramsey	1.43	0.25
ITSACORR	2.15	0.13

Table 32: Statistical Findings of Structural Break for Fentanyl

Long-Lasting β_2 Agonist

On 2005-09-07 Health Canada issued 3 similar DHPLs concerning the following long-lasting β_2 agonists[10]

- FORADIL (formoterol fumarate);
- OXEZE (formoterol fumarate dihydrate); and
- SEREVENT ADVAIR (salmeterol and formoterol).

The letter advises healthcare professionals of the findings of the US Food and Drug Administration's Pulmonary-Allergy Drugs Advisory Committee meeting. The committee was presented the findings of a large placebo controlled study done in the US that showed increased risk of asthma-related death in patients using salmeterol. The committee's position was that this increased risk could apply to all long-lasting β_2 agonists. The committee agreed unanimously that the long-lasting β_2 agonists should continue to be available. Prescription volumes (figure 37)

Statistical Test	Value Of *F*-statistic	P-value
Naive F (Linear)	2.33	0.11
ITSE-Ramsey (Linear)	0.79	0.51
ITSACORR (Linear)	1.20	0.31

Table 33: Statistical Findings of Structural Break for Formoterol (Oxeze)

demonstrate a slight decreasing trend over the sample window. The prescription

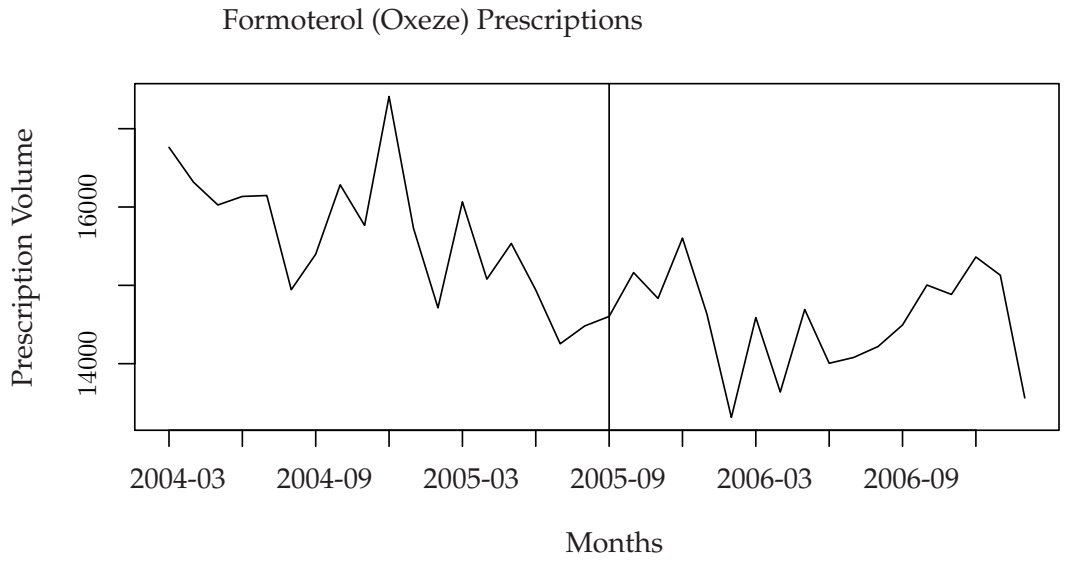

Figure 37: Formoterol (Oxeze) Prescriptions

volumes are quite noisy, and the decreasing trend persists into the post-DHPL period of the sample. None of the statistical techniques were able to find evidence suggestive of a structural break (table 33).

FEMARA

On 2005-11-17 Health Canada issued a DHPL concerning FEMARA (letrozole)[8]. FEMARA is indicated for the treatment of breast cancer among postmenopausal women. The letter informs healthcare professionals that Health Canada and FEMARA's manufacturer are aware and concerned that FEMARA is being used as an ovulation induction treatment for infertility in premenopausal women. There have been post market reports of congenital anomalies in infants of mothers who were exposed to FEMARA for the treatment of infertility. The letter reiterates that FEMARA is not an infertility treatment. Prescription volumes (figure 38) demonstrate a similar increasing trend in both the pre and post-DHPL sections of the sample.

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**8.46**	**< 0.01**
ITSE-Ramsey	**3.17**	**0.04**
ITSACORR	**4.81**	**0.02**

Table 34: Statistical Findings of Structural Break for Letrozole

There appears to be a marked drop in prescription volumes immediately following the issuance of the DHPL, which seems to shift the post-DHPL prescription volume line downwards. All of the statistical techniques find evidence of structural break (table 34).

ZOMETA and ACLASTA

On 2005-08-09 Health Canada issued a DHPL concerning ZOMETA and ACLASTA (both zoledronic acid)[15]. The letter informs healthcare professionals of a change in dosage for cancer patients with renal impairment taking ZOMETA. The recommended concentrations have been reduced to improve renal safety. Also, the letter informs healthcare professionals that ACLASTA can now be used as a single-dose intravenous treatment for Paget's disease of the bone for both men and women. Prescription volumes (figure 39) decline steadily throughout the pre-DHPL period

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**108.6**	**< 0.01**
ITSE-Ramsey	**7.3**	**< 0.01**
ITSACORR	**12.81**	**< 0.01**

Table 35: Statistical Findings of Structural Break for Zoledronic Acid

of the sample. The series levels at its lowest point just prior to the DHPL. There are clearly two separate and different processes on each side of the DHPL. All of the statistical techniques find evidence of structural break (table 35).

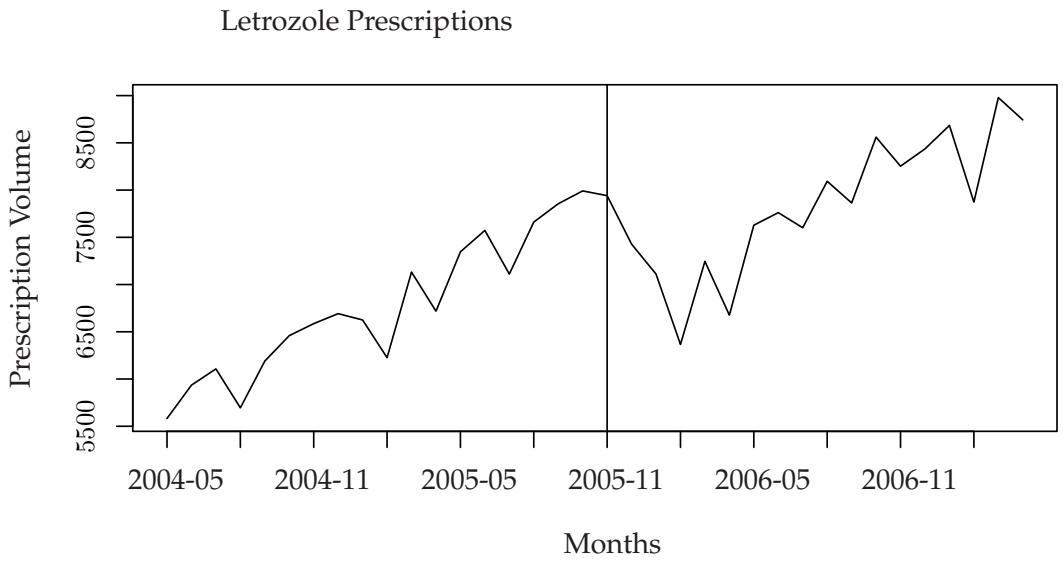

Figure 38: Letrozole Prescriptions

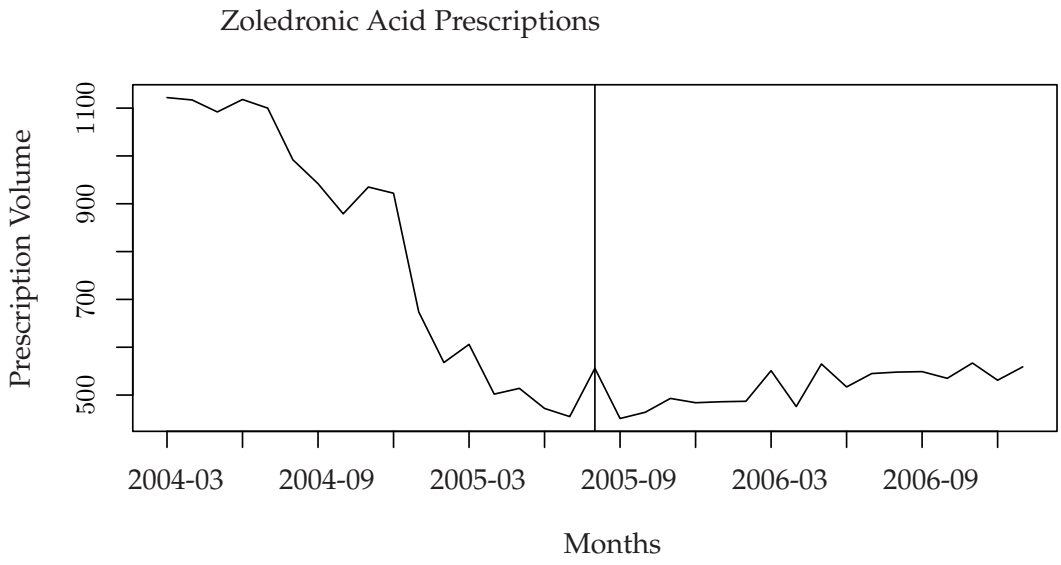

Figure 39: Zoledronic Acid Prescriptions

The remaining single DHPL cases, 6 of them, are so grouped because they highlight a disconcerting phenomenon. As we apply these methods, generally, we can visually observe a change in trend in the plotted series points and then confirm that this break is statistically significant. In the following DHPLs, a linear trend extends itself through the DHPL date seemingly unaffected by the DHPL, but returns a significant test for break. The results are disconcerting because it is difficult to reconcile the visual intuition is at odds with the statistical findings. We note the discord and proceed along with the statistical results, while acknowledging that some practitioners would instead give more credence to the more intuitive visual interpretation.

PREZISTA

On 2008-05-12 Health Canada issued a DHPL concerning PREZISTA (darunavir)[57]. The letter presents new safety information about the medication. PREZISTA is used in the treatment of patients with HIV. This letter informs of reported cases of patients using PREZISTA and experiencing drug induced hepatitis. The plotted

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**7.39**	$<$ **0.01**
ITSE-Ramsey	**3.48**	**0.03**
ITSACORR	**5.29**	**0.01**

Table 36: Statistical Findings of Structural Break for Darunavir

prescription volumes (figure 40) appear to be firmly trending upwards through the DHPL point. Table 36 shows that all of the 3 statistical techniques find evidence of a structural break around the DHPL.

SENSIPAR

On 2007-06-19 Health Canada issued a DHPL concerning SENSIPAR (cinacalcet)[48]. The letter brings to the attention of healthcare providers changes to the clinical use

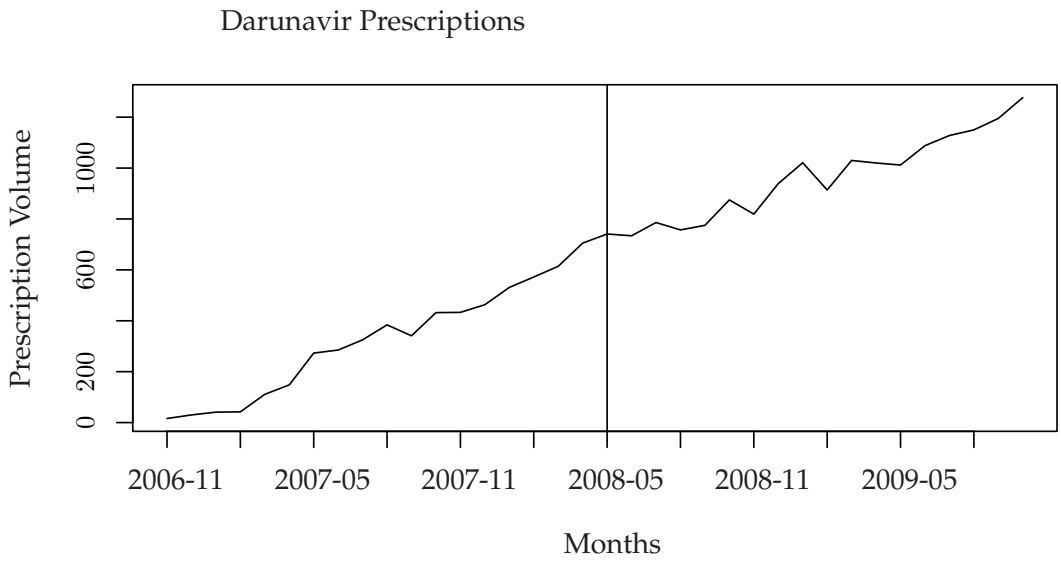

Figure 40: Darunavir Prescriptions

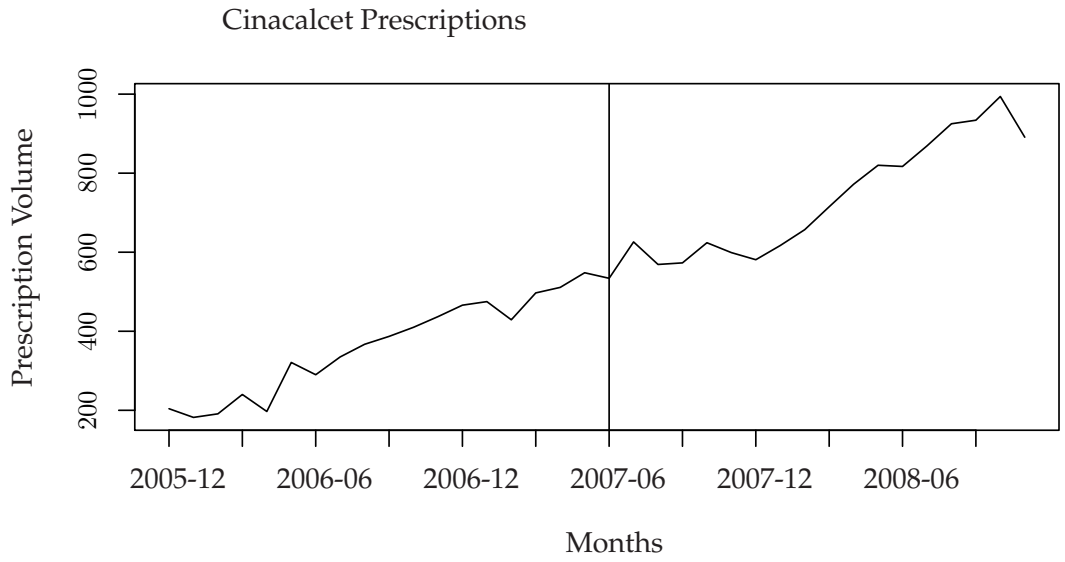

Figure 41: Cinacalcet Prescriptions

of SENSIPAR that are being updated in the product monograph. SENSIPAR is no longer indicated for patients with secondary hyperparathyroidism and Chronic Kidney Disease (CKD) who are not receiving dialysis. Prescription volumes (figure 41) maintain a consistent increasing trend through the pre-DHPL period that appears to continue through the post-DHPL period. Only the naive-*F* test finds evidence of a structural break (table 37).

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**4.5**	**0.02**
ITSE-Ramsey	1.14	0.35
ITSACORR	1.76	0.19

Table 37: Statistical Findings of Structural Break for Cinacalcet

REMICADE

On 2006-07-24 Health Canada issued a DHPL concerning REMICADE (infliximab)[31]. The letter advises healthcare professionals of new safety information related to the use of REMICADE. Among the information is the following: a number of rare lymphomas have been reported among paediatric and young patients taking REMICADE for Crohn's disease. REMICADE is not authorized for paediatric use in Canada. Prescription volumes (figure 42) demonstrate an increasing trend over the

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**5.05**	**0.01**
ITSE-Ramsey	**7.55**	$<$ **0.01**
ITSACORR	**11.32**	$<$ **0.01**

Table 38: Statistical Findings of Structural Break for Infliximab

entire sample window. All of the statistical techniques find evidence of structural break (table 38).

LAMICTAL

On 2006-08-01 Health Canada issued a DHPL concerning LAMICTAL (lamotrigine)[27]. The letter informs healthcare professionals of emerging data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry that suggest an association between LAMICTAL and an increased risk of non-syndromic oral clefts in children of patients. Physicians are encouraged to talk to and monitor their patients on LAMICTAL, particularly the ones that could become pregnant. Prescription volumes (figure 43) demonstrate an increasing trend over the entire sample window. ITSE-Ramsey and the ITSACORR techniques find evidence of structural break (table 39).

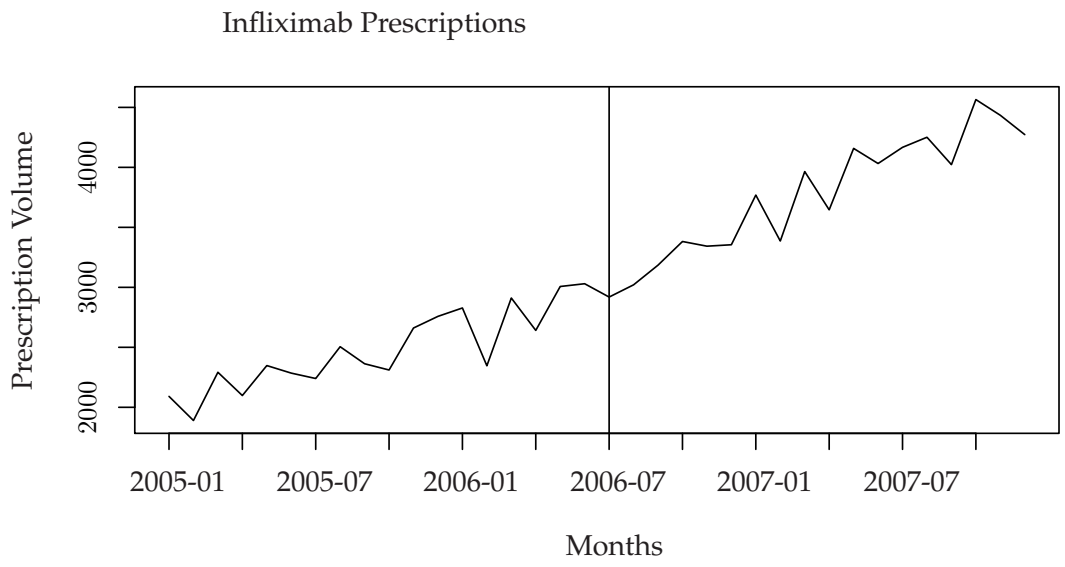

Figure 42: Infliximab Prescriptions

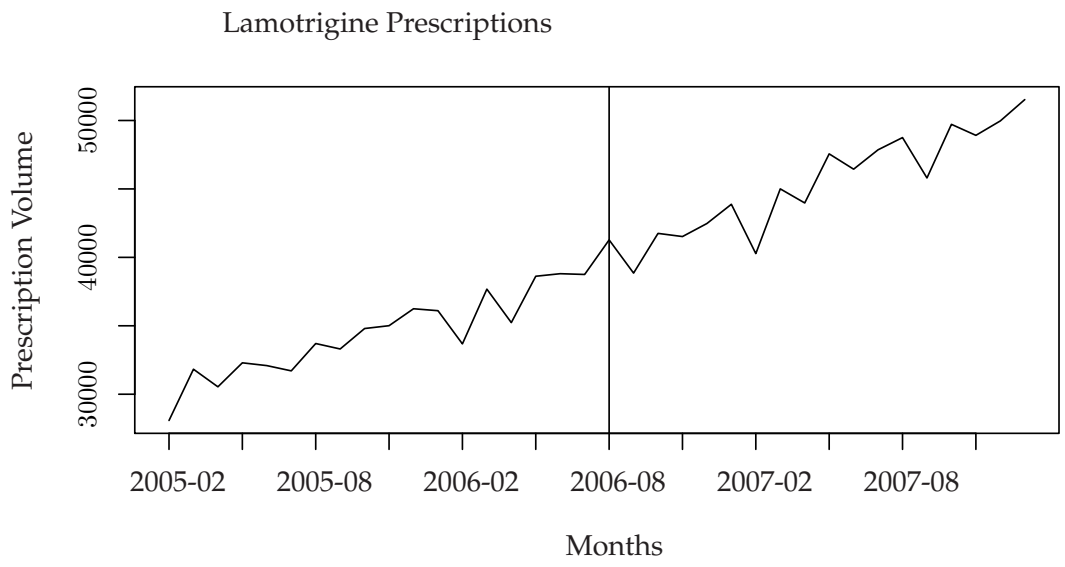

Figure 43: Lamotrigine Prescriptions

Statistical Test	Value Of *F*-statistic	P-value
Naive F	1.28	0.29
ITSE-Ramsey	**3.03**	**0.04**
ITSACORR	**4.54**	**0.02**

Table 39: Statistical Findings of Structural Break for Lamotrigine

Anti-TNFα

On 2006-01-13 Health Canada issued a DHPL concerning Anti-TNFα products ENBREL (etanercept), HUMIRA (adalimumab), and REMICADE (infliximab)[18]. Patients with a chronic hepatitis B infection receiving the listed medications, in a number of cases, have experienced HBV reactivation. Patients identified as chronic HBV carriers should be monitored for signs and symptoms of active HBV infection throughout the course of therapy and for several additional months. The letter clarifies that reactivation of HBV is not unique to Anti-TNFα agents, and has been reported with other immunosuppressive drugs. Prescription volumes (figure 44)

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**8.2**	$<$ **0.01**
ITSE-Ramsey	**4.05**	**0.02**
ITSACORR	**6.12**	**0.01**

Table 40: Statistical Findings of Structural Break for Enbrel Humira Remicade

demonstrate an increasing trend through the sample window. There appears to be a drop immediately after the DHPL, but this does not seem to affect the overall trajectory of the prescription volumes. All of the statistical techniques find evidence of structural break (table 40).

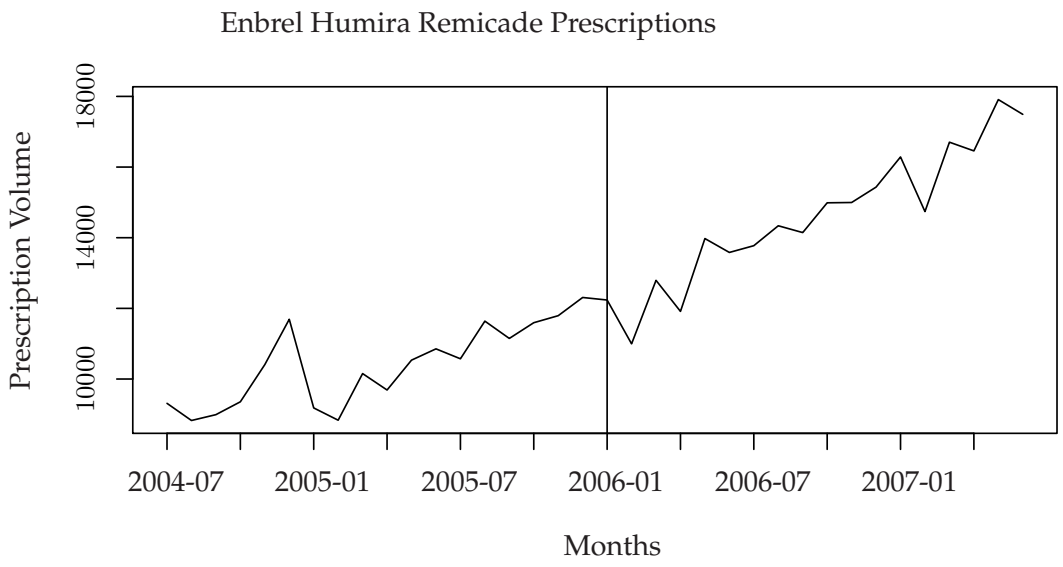

Figure 44: Enbrel Humira Remicade Prescriptions

DEPO-PROVERA

On 2005-06-30 Health Canada issued a DHPL concerning DEPO-PROVERA (medroxyprogesterone acetate injectable suspension)[6]. The letter informs healthcare professionals of new safety information that is being applied to DEPO-PROVERA's product monograph. It has been found through clinical trials that DEPO-PROVERA may significantly reduce bone mineral density (BMD) in women taking the medication for conception control. Also, the longer a patient is on DEPO-PROVERA, the more BMD tends to be lost. Prescription volumes (figure 45) demonstrate a

Statistical Test	Value Of *F*-statistic	P-value
Naive F	**6.67**	$<$ **0.01**
ITSE-Ramsey	2.51	0.08
ITSACORR	**3.83**	**0.03**

Table 41: Statistical Findings of Structural Break for Medroxyprogesterone

decreasing trend through the sample window. Visually, there appears to be little change in the prescription volumes trajectory resulting from the DHPL. All three techniques find evidence of structural break (table 41).

3.2 Multiple DHPLs

AVANDIA

On 2007-02-23 Health Canada issued a DHPL concerning AVANDIA (rosiglitazone)[37]. The letter describes the findings of a clinical trial on type 2 diabetes progression. The study found that significantly more female patients experienced fractures when taking AVANDIA that the female patients who were not. Physicians are advised to consider the risk of fracture among their patients that are being prescribed AVANDIA, specifically female patients.

On 2007-06-01 Health Canada issued a second DHPL concerning AVANDIA[38].

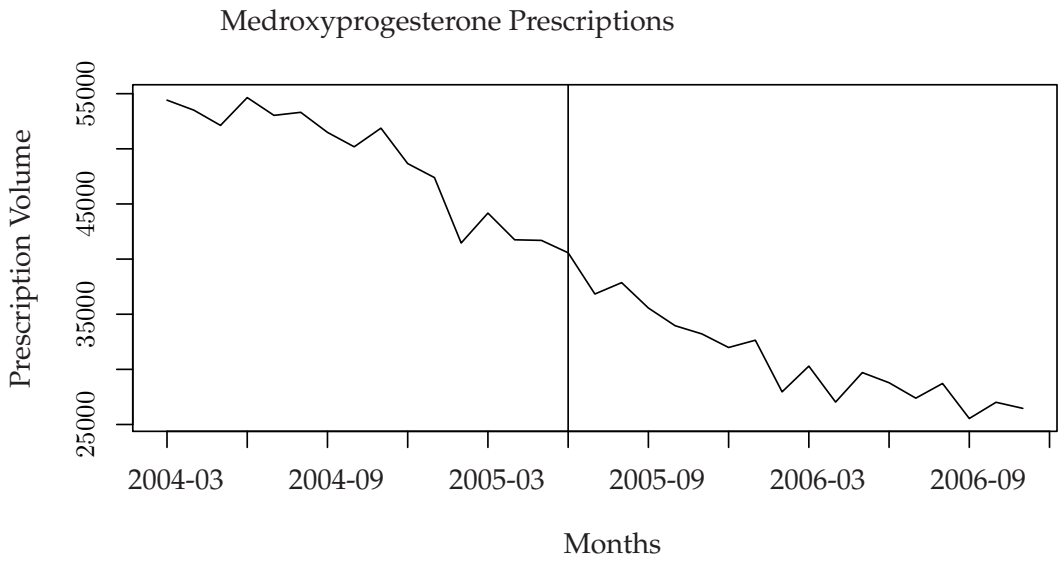

Figure 45: Medroxyprogesterone Prescriptions

This letter describes the findings of a meta-analysis in a peer reviewed journal, which found increased risk of myocardial infarction among patients taking AVANDIA.

On 2007-11-01 Health Canada issued a third DHPL concerning AVANDIA[47]. The letter describes updated to the product monograph related to Health Canada's assessment, reports, and published articles. The changes to the monograph include: that AVANDIA is no longer approved monotherapy of type 2 diabetes unless metformin in contraindicated, AVANDIA is no longer approved for use in combination with sulfonlurea unless metformin is contraindicated or not accepted, and AVANDIA is contraindicated for patients with any stage of heart failure.

	DHPL 1		DHPL 2		DHPL 3	
Statistical Test	*F*-statistic	P-value	*F*-statistic	P-value	*F*-statistic	P-value
Naive *F*	**96.9**	< **0.01**	**94.5**	< **0.01**	**16.9**	< **0.01**
ITSE-Ramsey	**8**	< **0.01**	**15.4**	< **0.01**	1.8	0.18
ITSACORR	**9.4**	< **0.01**	**16.8**	< **0.01**	2.2	0.13

Table 42: Statistical Findings of Structural Break for Rosiglitazone

Prescription volumes (figure 46) appear to hold an increasing trend through the first DHPL. Around the time of the second DHPL, prescription volumes begin to decrease sharply, and continue on their trend through the third DHPL. All of the fixed-point statistical techniques[3] find evidence of structural break for the first two DHPLs. Only the naive-*F* finds evidence of structural break on the third DHPL (42). The sup-*F* statistic occurs on the date 2007-06, and exceeds the critical value (figure 46). This is also the date of issuance of the second DHPL, which would seem to indicate that the change in prescribing behaviour occurred around the date of issuance of the second DHPL.

[3]We now refer to naive-*F*, ITSE-Ramsey, and ITSACORR as fixed point statistical techniques, because they test for break at a fixed point; whereas the sup-*F* test rolls through the sample testing for break at many points.

EXJADE

On 2007-03-09 Health Canada issued a DHPL concerning EXJADE (deferasirox)[41]. The letter informs healthcare professionals of past marketing reports of adverse events. Cases of renal failure were reported among some patients. When surviving patients were taken off of EXJADE, their condition improved. The letter reminded physicians to check serum creatine levels each month for patients taking EXJADE.

On 2008-03-04 Health Canada issued a second DHPL concerning EXJADE[56]. This letter is similar to the previous one. It reports of international cases of hepatic failure among patients, and reports that these cases are most common among patients with the co-morbidities of liver cirrhosis and multi-organ failure. The letter reminds healthcare professionals that patients being treated with EXJADE should have their liver function tested and monitored on a monthly basis. Prescription vol-

	DHPL 1		DHPL 2	
Statistical Test	*F*-statistic	P-value	*F*-statistic	P-value
Naive *F*	0.4	0.66	**8.5**	< **0.01**
ITSE-Ramsey	0.7	0.52	**3.5**	**0.04**
ITSACORR	0.7	0.52	**3.6**	**0.04**

Table 43: Statistical Findings of Structural Break for Deferasirox

umes (figure 47) increase in trend following the first DHPL. Prescription volumes continue to increase through the second DHPL before begining to decline.

None of the fixed-point statistical techniques find evidence of structural break on the first DHPL (2007-03). All three techniques find evidence of a break on the second DHPL (2008-03). The sup-*F* occurs on 2009-03, and exceeds its critical value, indicating the likely presence of a break around 2009-03 (figure 47). The sup-*F* exceeds its critical value almost immediately following the second DHPL, suggesting that a change in prescribing patterns occurred followong the second DHPL.

IRESSA

On 2005-08-26 Health Canada issued a DHPL concerning IRESSA (getfitinib)[9]. The letter informed healthcare professionals that IRESSA has failed a non-inferiority trial against placebo, and that the medication had demonstrated no increased survival or clinical benefit. In addition to this, a change in the product monograph was described. In the change to the product monograph, IRESSA was only to be used as a third line cancer treatment where other options had failed. Also, IRESSA is contraindicated for patients with epidermal growth factor receptor negative tumours.

On 2006-06-05 Health Canada issued a second DHPL letter concerning IRESSA[17]. The letter further restricts the prescribing of IRESSA. The letter informs patients that no new patients should start on IRESSA.

On 2006-12-01 Health Canada issued a third DHPL concerning IRESSA[25]. The letter summarizes some of the outcomes from a study which found no survival benefit of IRESSA, and recommends that patients still taking IRESSA be informed of these findings, and discusses alternative treatment options with their physicians.

On 2007-09-04 Health Canada issued a fourth DHPL concerning IRESSA[43]. The letter reported of a non-inferiority trial that IRESSA failed to Docetaxel, and stated that no Canadian patient should receive IRESSA unless they are on the IRESSA Patient Registry.

	DHPL 1		DHPL 2		DHPL 3		DHPL 4	
Statistical Test	*F*-stat	P-val	*F*-stat	P-val	*F*-stat	P-val	*F*-stat	P-val
Naive *F*	1.2	0.3	**11.7**	< **0.01**	**55.2**	< **0.01**	**10.4**	< **0.01**
ITSE-Ramsey	1.8	0.18	2.8	0.08	**8.8**	< **0.01**	0.8	0.46
ITSACORR	1.8	0.18	3.2	0.06	**9.5**	< **0.01**	1	0.38

Table 44: Statistical Findings of Structural Break for Gefitinib

Prescription volumes (figure 48) are quite low throughout the entire sample window. The series appears to stop increasing and abruptly decrease in the period

of the sample prior to any of the DHPLs. The decreasing trend continues through the 4 DHPLs.

All of the fixed-point statistical techniques find evidence of break associated with the third DHPL. Additionally the naive-*F* finds evidence of break associated with the second and fourth DHPLs (table 44). The sup-*F* at 2005-01, a high point in the series before a long decline, and before any of the DHPLs were issued (figure 48). This seems to suggest that the event that changed prescribing behaviour occurred before any of the DHPLs were issued.

KETEK

On 2006-09-29 Health Canada issued a DHPL concerning KETEK (telithromycin)[26]. The letter informed healthcare professionals of the findings of published case reports, and updates to the product monograph. Instances of liver failure and death have been observed during or following treatments of KETEK.

On 2007-09-30 Health Canada issued a second DHPL concerning KETEK[44]. The letter spoke specifically to the prescribing practices of physicians for KETEK. KETEK is no longer approved for the treatment of bronchitis, sinusitis, or tonsillitis/pharyngitis.

	DHPL 1		DHPL 2	
Statistical Test	*F*-statistic	P-value	*F*-statistic	P-value
Naive *F*	0.7	0.5	**21.5**	< **0.01**
ITSE-Ramsey	0	0.99	1	0.37
ITSACORR	0.1	0.95	2	0.16

Table 45: Statistical Findings of Structural Break for Telithromycin

Prescription volumes (figure 49) oscillate erratically in the sub-sample prior to the first DHPL. Following the first DHPL, prescription volumes level off before beginning their drop to zero. The series is nearly at zero by the time of the second DHPL.

The only evidence of break among the fixed point tests comes from the naive-*F* which finds evidence of break around the second DHPL (table 45). The sup-*F* occurs at 2006-04, and exceeds its critical value(figure 49)– this would seem to imply a break at a point around 5 months before the issuance of the first DHPL.

AVASTIN

On 2007-06-01 Health Canada issued a DHPL concerning AVASTIN (bevacizumab)[20]. AVASTIN is a first line treatment for patients with colon cancer undergoing fluropyrimidine based chemotherapy. The letter was issued to inform healthcare professionals about serious adverse events associated with AVASTIN that have been found in post market and clinical trial reports. The letter directs physicians to discontinue treatment with AVASTIN for patients with tracheo-oesophageal or gastrointestinal fistula, and recommends that physicians find alternative treatments for patients with fistula not in the GI tract.

On 2006-10-24 Health Canada issued a second DHPL concerning AVASTIN[39]. The letter, like the first letter, makes healthcare professionals aware of recent findings in post market and clinical trial reports. The letter advises physicians to permanently discontinue treatment with AVASTIN if hypertensive encephalopathy results. Additionally, reversible posterior lekoencephalopathy syndrome has been associated with AVASTIN, and may be reversible if diagnosed early.

	DHPL 1		DHPL 2	
Statistical Test	*F*-statistic	P-value	*F*-statistic	P-value
Naive *F*	**6.7**	**0.01**	**33.3**	**< 0.01**
ITSE-Ramsey	2.4	0.12	3.1	0.06
ITSACORR	2.7	0.09	**3.8**	**0.03**

Table 46: Statistical Findings of Structural Break for Bevacizumab

Prescription volumes (figure 50) increase modestly up to the first DHPL, after which they begin increasing at a greater rate. Prescription volumes begin an abrupt

decline following the second DHPL.

The naive-*F* finds evidence of break at both DHPLs, whereas the ITSACORR techique only finds evidence of break on the second DHPL (table 13). The sup-*F* occurs at 2007-09, and exceeds it critical value (figure 50). The date of the sup-*F* statistic is only a couple months after the issuance of the second DHPL, and may suggest at the effectiveness of the second DHPL letter.

RITUXAN

On 2006-11-10 Heath Canada issued a DHPL concerning RITUXAN (rituximab)[32]. The letter informed healthcare professionals of recent post market and clinical trial findings. Among the findings were: abdominal pain, bowel obstruction, and bowel perforation sometimes leading to death among patients receiving RITUXAN in combination with chemotherapy for the treatment of Non-Hodgkin's Lymphoma (NHL). The letter clarifies that a causal link between RITUXAN and these outcomes has not been established, and encourages physicians to consider the most appropriate treatment when abdominal pain is reported.

On 2007-08-08 Health Canada issued a second DHPL concerning RITUXAN[46]. The letter informs healthcare professionals of new findings from post marketing and clinical safety reports. Among the findings are: cases of Progressive Multifocal Leukoencephalopathy (PML) following off-label use– there were no reported cases of PML among patients being treated for Rheumatoid Arthritis (RA). Additionally physicians were reminded that the safety and efficacy of RITUXAN for the treatment of anything other than RA has not yet been established.

Prescription volumes (figure 51) appear to increase without much effect coming from either of the DHPLs. It is only six months into the post-DHPLs period of the sample that the series appears to change by *increasing* in slope. None of the fixed point statistical techniques detected break at any of the DHPLs (table 47). The sup-*F* occurred at 2008-08, and exceeded its critical value. The sup-*F* is likely detecting the upward trend is prescription volumes, which is at odds with the information in the DHPLs.

	DHPL 1		DHPL 2	
Statistical Test	*F*-statistic	P-value	*F*-statistic	P-value
Naive *F*	1	0.37	3.2	0.05
ITSE-Ramsey	0.8	0.48	1.8	0.19
ITSACORR	0.8	0.48	1.8	0.19

Table 47: Statistical Findings of Structural Break for Rituximab

TEQUIN

On 2005-12-19 Health Canada issued a DHPL concerning TEQUIN (gatifloxacin)[14]. The letter informs healthcare professionals that cases of hyperglycaemia and hypoglycaemia have been reported with the administration of TEQUIN. Healthcare professionals are encouraged to closely monitor patients on TEQUIN with any of the following conditions: diabetes, >75 and possibly diabetic, age related loss of kidney function, underlying medical problems, and medications related to dysglycaemia.

On 2006-05-12 Health Canada issued a second DHPL concerning TEQUIN[33]. This letter informed healthcare professionals of updated safety information being added to the product monograph. Among the information provided was: TEQUIN is contraindicated for patients with diabetes mellitus, and a warning box has been added to the product monograph to be cautious about the conditions listed in the first DHPL about TEQUIN (above). Prescription volumes (figure 52) appear to be

	DHPL 1		DHPL 2	
Statistical Test	*F*-statistic	P-value	*F*-statistic	P-value
Naive *F*	**7.5**	**< 0.01**	**9.6**	**< 0.01**
ITSE-Ramsey	1.9	0.17	**5.1**	**0.01**
ITSACORR	2	0.15	**5.3**	**0.01**

Table 48: Statistical Findings of Structural Break for Gatifloxacin

quite volatile in the pre-DHPL period of the sample. Between the two DHPLs, prescription volume seems to decrease sharply, after which it seems to level off. All fixed-point statistical techniques detect break around the second DHPL, only the naive-*F* detects break around the first DHPL (table 48). The sup-*F* occurs 8 months prior to the issuance of the first DHPL, but does not exceed it critical value meaning the test does not find evidence of a break (figure 52).

PAXIL

On 2005-09-29 Health Canada issued a DHPL concerning PAXIL (paroxetine)[11]. The letter advises healthcare professionals of the findings from an epidemiological study that found increased risk of cardiovascular malformations among infants of women who were taking PAXIL by comparison with women who were not taking PAXIL. The letter refers physicians to the prescribing guidelines in the product monograph, which advises physicians to consider the totality of benefits and risk to the fetus resulting from a prescribing decision.

On 2005-12-16 Health Canada issued a second DHPL concerning PAXIL[12]. The letter informs healthcare professionals of the findings of two epidemiological studies (different studies than mentioned in the 2005-09-29 DHPL). Each study found increased risk of cardiovascular malformations among women taking PAXIL by comparison with women who were not taking PAXIL. The letter recommends that physicians inform their patients taking PAXIL that are also currently pregnant of the increased risk of cardiovascular malformations for their fetus, and consider switching treatments (other antidepressants or other therapy types). When a patient is aware of a patient trying to become present, PAXIL should only be considered once other treatment options have been considered. Prescription volumes (figure 53) appear to be decreasing through the sample window. Around the time of the two (close together) DHPLs, the decreasing trend relents, and the series seems to level off.

All of the fixed-point techniques detect break at both of the DHPLs (table 49). The sup-F occurs around 2005-08, and exceeds its critical value (figure 53). All of the *F*-statistics considered for the sup-*F* statistic, a narrow range, exceed the

	DHPL 1		DHPL 2	
Statistical Test	*F*-statistic	P-value	*F*-statistic	P-value
Naive *F*	**4.8**	**0.01**	**3.7**	**0.04**
ITSE-Ramsey	**6.4**	**< 0.01**	**5.7**	**0.01**
ITSACORR	**6.4**	**< 0.01**	**5.7**	**0.01**

Table 49: Statistical Findings of Structural Break for Paroxetine

Andrews' critical value, suggesting that a change is occuring in this region.

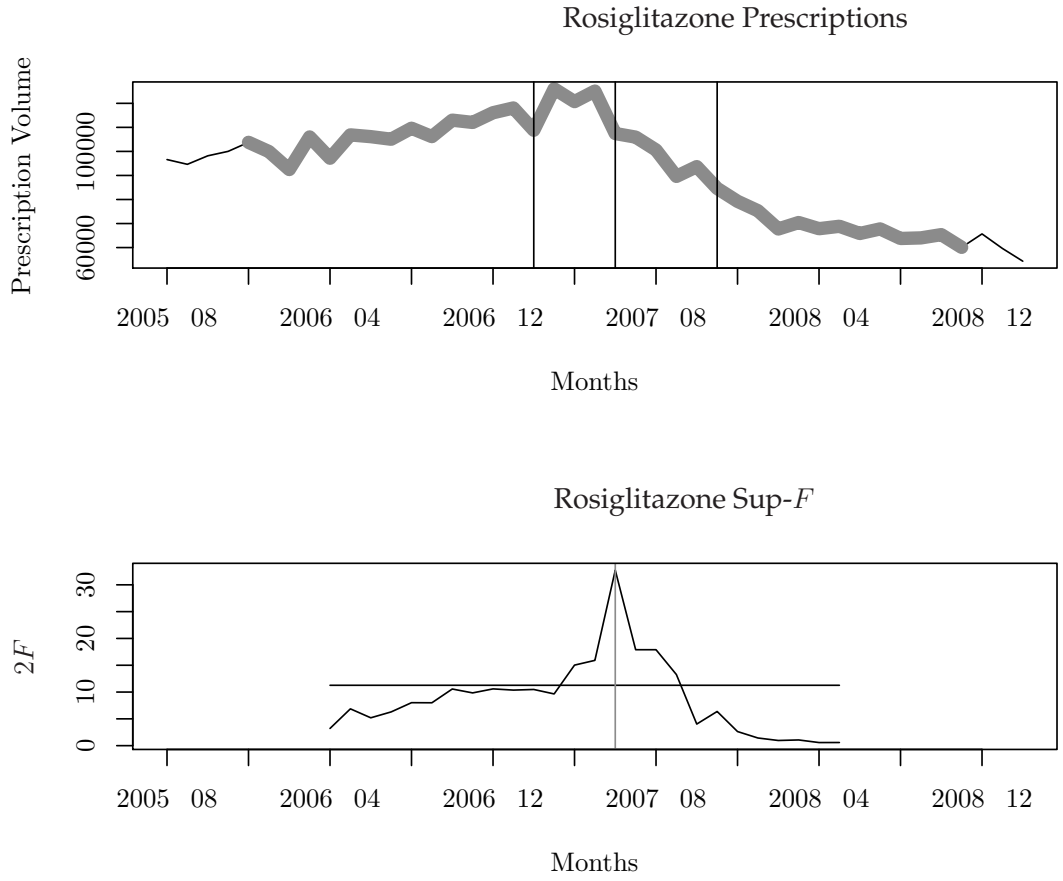

Figure 46: Rosiglitazone Prescriptions and Sup-F Statistic

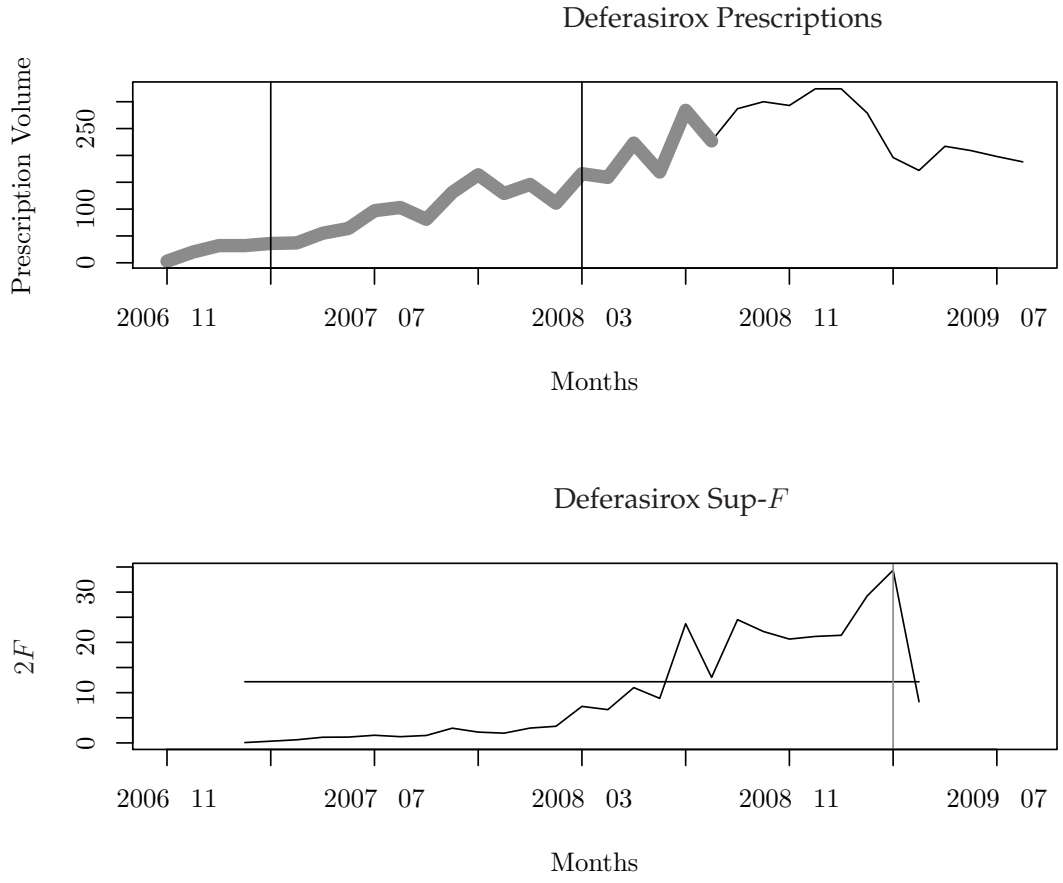

Figure 47: Deferasirox Prescriptions and Sup-*F* Statistic

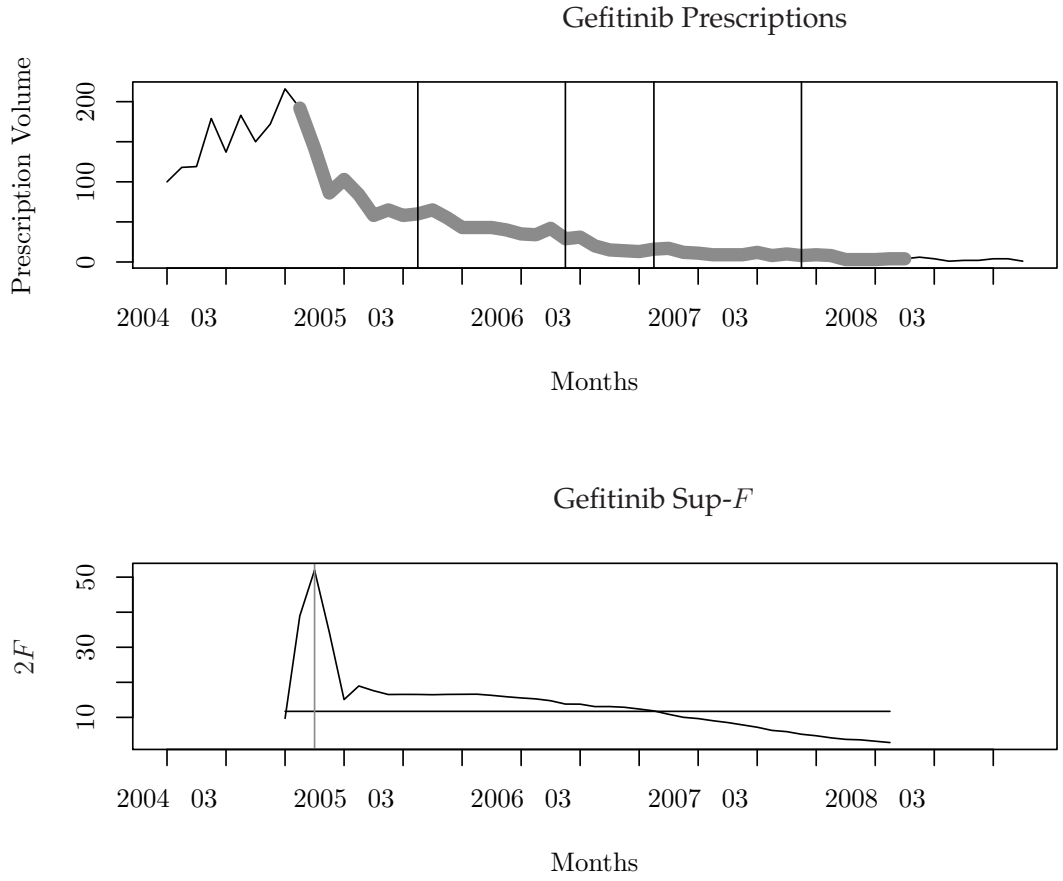

Figure 48: Gefitinib Prescriptions and Sup-*F* Statistic

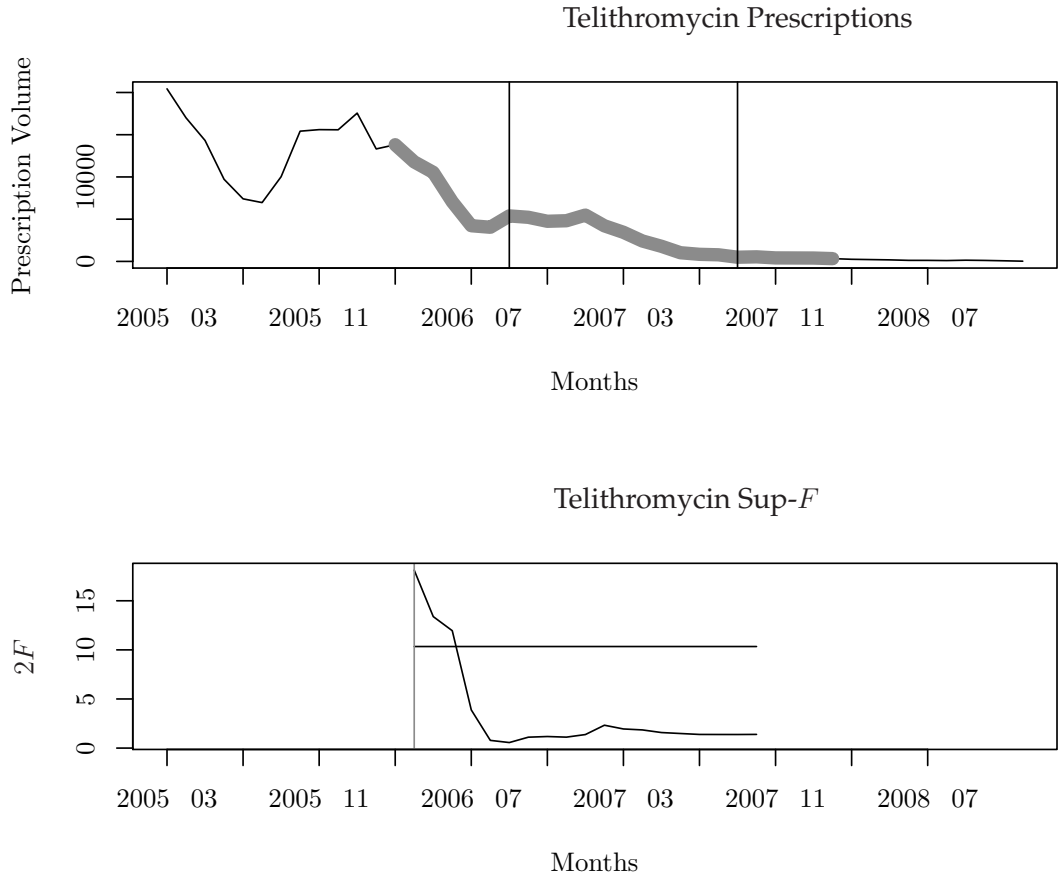

Figure 49: Telithromycin Prescriptions and Sup-*F* Statistic

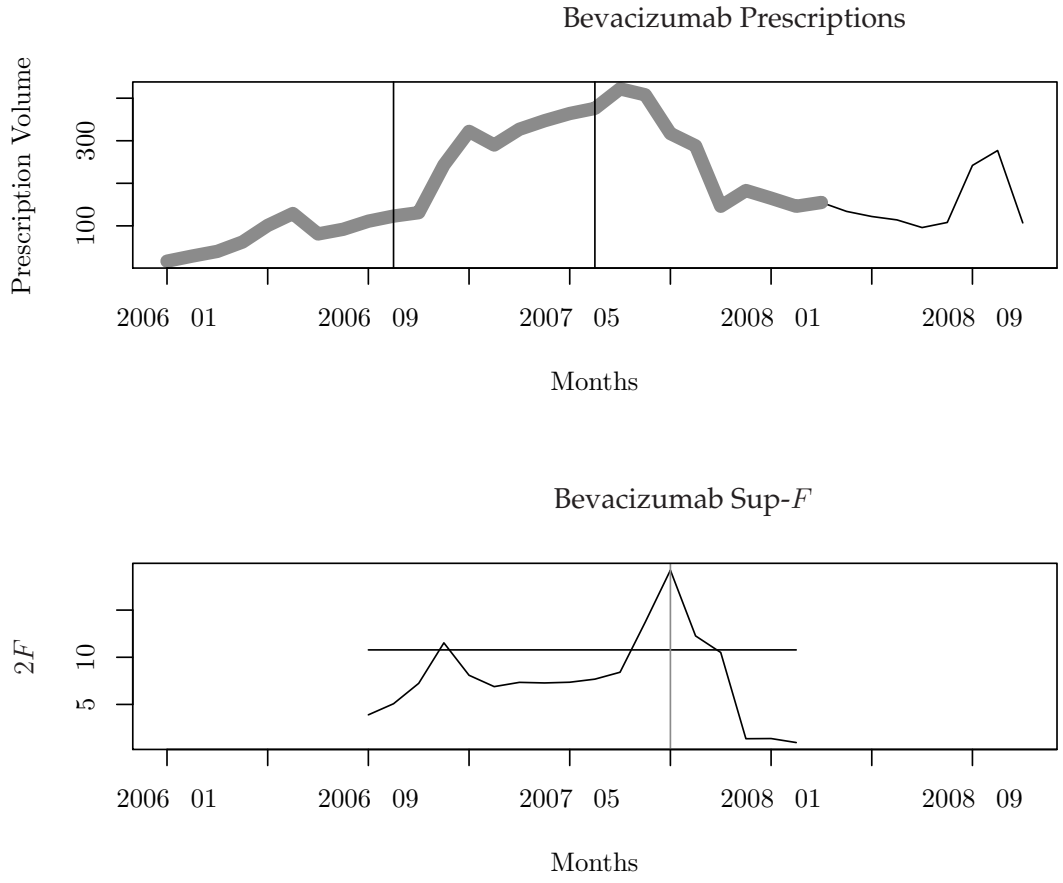

Figure 50: Bevacizumab Prescriptions and Sup-F Statistic

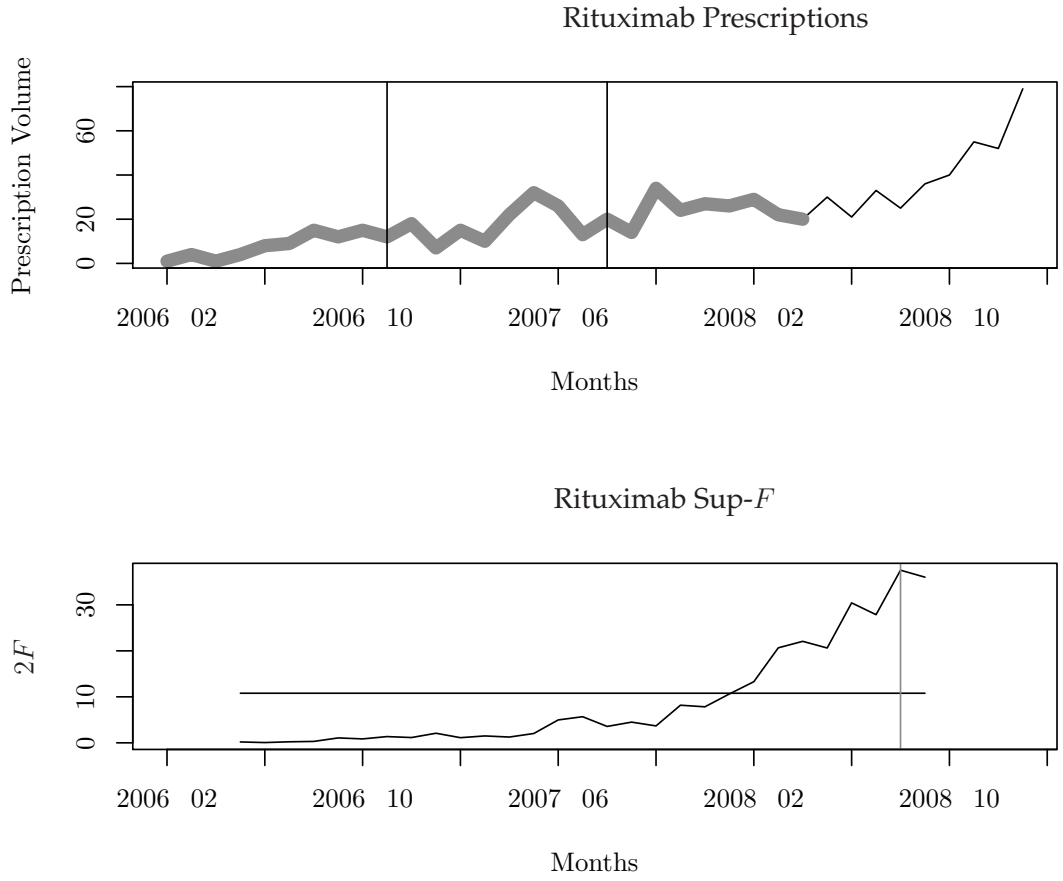

Figure 51: Rituximab Prescriptions and Sup-*F* Statistic

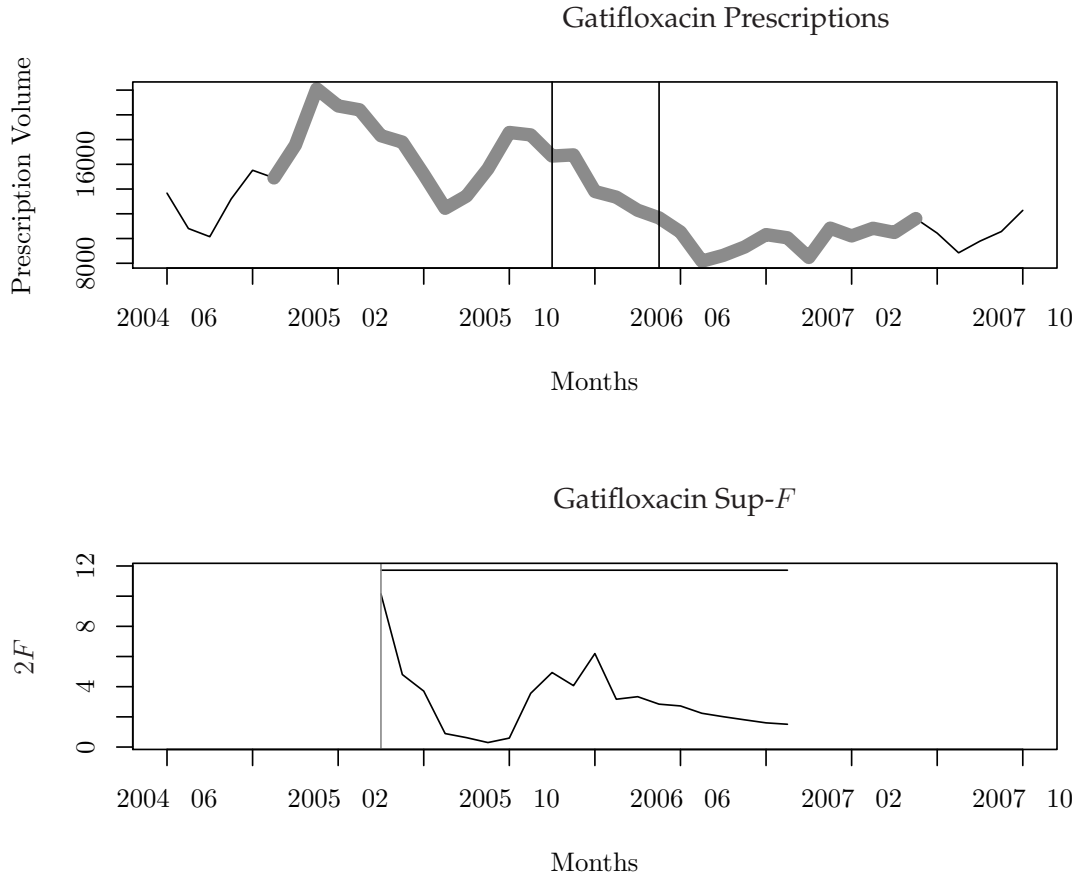

Figure 52: Gatifloxacin Prescriptions and Sup-*F* Statistic

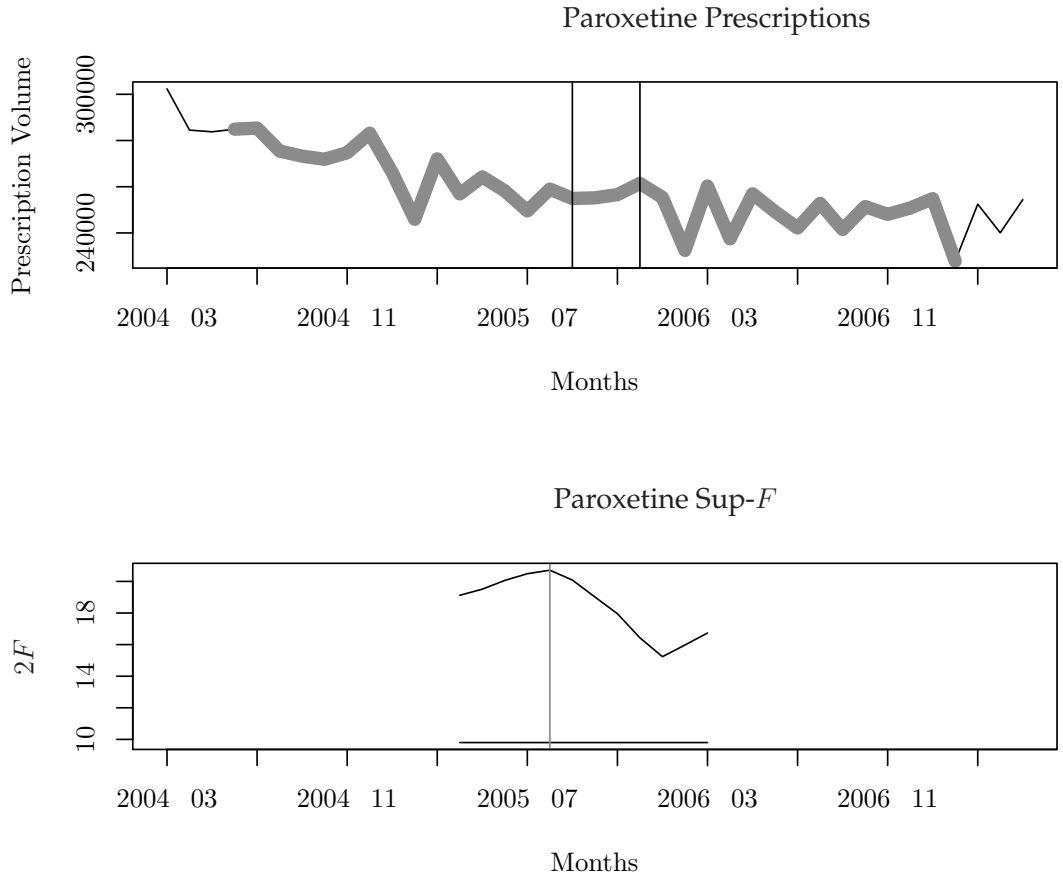

Figure 53: Paroxetine Prescriptions and Sup-*F* Statistic

Chapter 4

Simulation Studies and Correspondence

It is difficult to assess statistical techniques using real collected data. If the process that generated the data was well known, there would be no need for statistical techniques to analyze and understand it. When we do analyze collected data, we must proceed cautiously– we are seeking to understand the data generation process (DGP) from a naive perspective. To assess statistical techniques many statisticians construct data sets with full understanding of the DGP, and evaluate to what extent their statistical techniques are able to capture and summarize the DGP. The techniques considered in this paper, generally, seek to assess if a change in a linear trend occurred at a point in time. It is against this type of DGP that we will evaluate the statistical techniques. The focus of this paper is, primarily, to assess the effectiveness of drug communication systems by evaluating the statistical techniques for detecting structural break at a fixed break point. Because of this, we limit our simulation studies to tests of a fixed break point.

4.1 Size

Size and type I error probability are equivalent notions. Each represents the probability that a statistical test rejects a true null hypothesis. A common way to evaluate

the size of a statistical test is to generate many data sets reflective of the null hypothesis, and perform the statistical test on each one of them. Berger and Casella[64] write that a test statistic, produced from a null DGP (i.e. one in which the null hypothesis is true), will produce p-values that are distributed uniformly over $(0, 1)$. Thus, if N data sets are generated under the null DGP, and our hypothesis rejection criteria is p-values < 0.05 ($\alpha = 0.05$), we should expect to reject $N \times 0.05$ of the test statistics– there should be agreement between the actual size and the nominal size of the test statistic.

Davidson and MacKinnon[69] describe a graphical way to present the correspondence of actual size and nominal size of a test. They consider the empirical distribution function (EDF) of the N p-values produced in a simulation ($p_j,\ j \in 1 \ldots N$).

For any $x_i \in (0, 1)$ the value of the EDF at that point is given by

$$\hat{F}(x_i) \quad = \quad \frac{1}{N} \sum_{j=1}^{N} I(p_j \leq x_i) \,, \tag{32}$$

where p_j is one of the N p-values computed according the testing procedure on the j^{th}DGP, and I is the indicator function that takes on the value 1 when the condition within its brackets is true, and 0 otherwise. This function allows us to plot the correspondence of actual and nominal size over the entire interval. Typically, the most interesting part of the graph is located around the levels that are typically used in hypothesis testing ($\alpha = 0.05$ and $\alpha = 0.10$); for this reason only the lower portions of the graphs are presented ($\alpha \leq 0.2$).

To test for size, we generate samples of the data under our null hypothesis– that there is no change in the slope or intercept parameters resulting from the DHPL. We generate these samples several times to simulate different possible values of the autocorrelation term ρ. We generate, for each of 8 different values of ρ, a variable according to

$$\boldsymbol{y}_t \quad = \quad \beta_1 \boldsymbol{\iota} + \beta_2 \boldsymbol{t} + \rho \boldsymbol{y}_{t-1} + \boldsymbol{\epsilon}_t.$$

Here $\boldsymbol{\epsilon}_t$ is a standard normal variable, β_1 and β_2 are pre-specified and fixed[1], and are simulated 1,000 times for each value of ρ always with a sample size of 40

[1] $\beta_1 = 50$ and $\beta_2 = 0.2$

(20 observations before and after the DHPL date). Simulations and computations are performed using the statistical software R[81]. Generating autocorrelated data series is complicated by the lagged version of the dependent variable. What value should be used for the first value, $y_{t-1} = y_0$. To ensure that y_0 is a well behaved component of the DGP, a number of prior observations are also generated (50 of them). The first of these prior observations is set equal to the constant plus a draw from the standard normal distribution (implicitly using $t = 0$, the initial time period). The following observations are generated by combining the first value of $\boldsymbol{y}_{t-1}$ with the other components as prescribed by the DGP. This ensures y_0 behaves according to the DGP. The prior observations are discarded, and the model is estimated on the remaining records. The EDF for each of our considered statistical techniques are presented in figure 54. The line $y = x$ is presented for convenience to demonstrate where actual size and nominal size are equal.

From the writings of Ramsey and Ramsey[82], Gottman[74], and Crosbie[67], we have some notion about what to expect in the following size simulations. All of the authors consider their tests under multiple sample size scenarios, some more clearly than others. Pre and post-intervention samples of 20 observations are common.

Gottman[74] does size simulations on a more specific hypothesis than the omnibus F-statistic we consider. He considers a test for equality of pre and post-intervention intercept parameters. For pre and post-intervention samples of 20, when $\rho = 0$, he finds actual size of 0.048, just below the 0.05 nominal level of his test. As ρ gets larger, so does the actual size of his test (table 50). This is consistent with the findings for the ITSE-Ramsey test in our simulation (figure 54); that is as ρ gets larger, the actual size of the test increases. Ramsey and Ramsey[82] concentrate their analysis on smaller sample combinations. When results are presented for pre and post-intervention sample size of 20, it is unclear which value of ρ is being considered.

Crosbie's[67] size results are more difficult to interpret. For a number sample sizes and values of $\rho \in (-0.8, 0.8)$, Crosbie[67] presents the size of tests of:

- The omnibus F-statistic and the alternative intercept parameter both testing

ρ	Actual Size	ρ	Actual Size
-0.90	0.040	0.45	0.062
-0.60	0.044	0.60	0.072
-0.30	0.041	0.70	0.087
0.00	0.048	0.80	0.100
0.30	0.056	0.90	0.158

Table 50: Gottman[74]'s Size Simulation Results: Equality of Intercept Term ($\alpha = 0.05$, $n_1 = n_2 = 20$)

significantly (F+I in the notation of Crosbie); and

- The omnibus F-statistic and the alternative slope parameter both testing significantly (F+S).

For pre and post-intervention sample sizes of 20 each, at the $\alpha = 0.05$ nominal level, for $\rho = 0.8$ Crosbie[67] reports $F+I$ and $F+S$ sizes of 0.02 and 0.03 respectively. This is insufficient to know the actual size of the omnibus test statistic. There may be instances where the omnibus F-statistic is significant and both the alternative slope and intercept term are significant (presumably these would have been double counted for F+I and F+S), and instances where the omnibus F-statistic is significant and neither of the alternative slope and intercept term are significant. Without knowing these intersections and complements we cannot know the actual size of Crosbie's[67] omnibus F-statistic.

For larger values of ρ (≥ 0.5, sub figures (A) and (B) of figure 54), we find that the actual level of the F-statistic is higher than the nominal level of the statistic. For $\rho < 0.5$, the actual size of the ITSACORR statistic tracks quite closely with the nominal size of the statistic.

The naive-F is a test known to be ill suited to the data considered under our null DGP (autocorrelated data). However the naive-F is entirely appropriate when $\rho = 0$, that is when the observations are independent. The naive-F tracks most closely to the line $y = x$ when $\rho = 0$ (as to the other techniques).

Beginning with subfigure (A), $\rho = 0.9$; all of our techniques show greater than actual size. It is worst for the Naive-F, but poor for ITSE-Ramsey and ITSACORR as well. The situation is much the same in panel (B) when $\rho = 0.7$, but the size curves are a little bit closer to the $y = x$ line of symmetry where nominal and actual size are equal. By panel (C), where $\rho = 0.5$, ITSE-Ramsey and ITSACORR begin to have actual sizes that are comparable to their nominal sizes (they actual levels are less than twice the nominal levels). The Naive-F continues to have inflated actual size. By subfigure (D), the actual and nominal size for ITSE-Ramsay and ITSACORR are approximately equal in the < 0.05 region of the figure. When $\rho = 0.1$ and $\rho = 0.0$, subfigures (E) and (F), all techniques have comparable actual and nominal size. When $\rho < 0$, subfigures (G) and (H), ITSE-Ramsey and ITSACORR continue to exhibit actual size approximately equal to nominal size, whereas the Naive-F seriously understates its size relative to the nominal level.

4.2 Power

The power of a statistical test is 1 less the type II error rate of that test. Power is the probability that a statistical test rejects a false hypothesis. Evaluating the power of a statistical test is more involved than evaluating its size. Cohen [66] describes the power of a test being affected by a number of factors. He identifies the significance level, the reliability of the sample, and the effect size. By reliability of the sample Cohen is bringing together notions of precision of the data and sample size, both factors that increase the power of a statistic. By effect size, Cohen means how much different the alternative hypothesis is from the null hypothesis. Cohen presents the ideas differently, but is getting to the same point as Casella and Berger[64] who define power functions of a statistic (and therein make explicit that power changes as a function of distance from the null value of the parameter– effect size). Qualitatively, power functions of good test statistics are near zero when they are very close to the true value of the parameter, and are close to one elsewhere.

To evaluate power, we generate data under the alternative hypothesis of a structural break. For multiple values of ρ, the DGP used to generate data with a

structural break is the following:

$$\boldsymbol{y}_t = \beta_1 \boldsymbol{\iota} \times [I_{t \geq D} \times \theta_{1,i}] + \beta_2 \boldsymbol{t} \times [I_{t \geq D} \times \theta_{2,j}] + \rho \boldsymbol{y}_{t-1} + \boldsymbol{\epsilon}_t, \tag{33}$$

for $\theta_{1,i} \neq 1$ and $\theta_{2,j} \neq 1$, mostly[2]. We choose intercept displacement vector $\boldsymbol{\theta}_1 = [\theta_{1,1}, \theta_{1,2}, \ldots, \theta_{1,k}]$ and slope displacement parameter $\boldsymbol{\theta}_2 = [\theta_{2,1}, \theta_{2,2}, \ldots, \theta_{2,k}]$ such that $(\theta_{p,1}, \theta_{p,k})$ form a symmetric region around 1, and $\theta_{i,j+1} = \theta_{i,j} + \delta_i \; \forall \theta_{i,j} \in \boldsymbol{\theta}_i$ (elements of $\boldsymbol{\theta}_i$ are evenly spaced). From this we can readily produce k^2 different alternative DGPs[3].

We limit our analysis to $\rho \leq 0.5$, as this was the greatest value of ρ for which the atuocorrelation adjusting techniques had actual size $< 2\times$ nominal size. Beyond this value of ρ, the statistical techniques were rejecting null hypotheses twice as often as they should have. We include the Naive-F test for completeness and contrast, not because we believe it to be an appropriate technique.

We evaluate the power at each of the k^2 DGPs, under each of the statistical techniques we are considering, and are able to produce a contour plot of the power for each statistical technique. Following the qualitative recommendation of Casella and Berger[64], these contour plots should be near zero in the middle of the contour plot (where the value of $(\theta_{1,i}, \theta_{2,j})$ is closest to $(1, 1)$, the DGP that does not have a structural break in it), and near one elsewhere. This technique plots power for various alternative hypothesis that are varied by effect size. Throughout we are keeping the level of the test constant ($\alpha = 0.05$) as well as the reliability of the sample by keeping the sample size constant at $n = 40$, and sampling errors from the standard normal distribution. For each of the k^2 possible DGPs, we generate 1,000 samples and apply our techniques to evaluate power. Data generation and simulations were performed using version 6.21 of Ox[71].

To make visually identifying which technique yields more powerful statistics easier, cross-sections of each plot (combinations of $(\theta_{1,i}, 1) \; \forall \theta_{1,i} \in \boldsymbol{\theta}_1$ for the power of the intercept term from equation 35 and $(1, \theta_{2,j}) \; \forall \theta_{2,j} \in \boldsymbol{\theta}_2$ for the power of the

[2]The following definition of $\boldsymbol{\theta}_i$ will make clear the fact that $\theta_{i,p}$ can be equal to one, but of principal interest will the instances where it is not.

[3]We are, here too, using prior 'burn in' observations to generate autocorrelated data that is correlated at even time zero according to the method described in section 4.1.

slope term) are combined with the other techniques–the plot that is greater than all the other identifies the more powerful technique. Figures 55-58 present the power for a number of values of ρ ranging from 0.0 to 0.5.

When $\rho = 0$, all of the statistical test produce similar power profiles (figure 55). This is analogous to figure 54-(F), where all the statistics had approximately equal nominal and actual sizes. As autocorrelation is introduced (figure 56), the Naive-*F* begins pulling away from the autocorrelation adjusting statistics. The power plot of the Naive-*F* is greater than those of the other statistics not because it has better power, but because the test has a higher actual size– power cannot be faily evaluated among tests with different sizes. The autocorrelation adjusting statistical tests perform similarly in terms of power for all considered levels of ρ.

For series with $\rho \leq 0.5$, the autocorrelation adjusting techniques have similar size and power. In the presence of mild autocorrelation, either one of these techniques is appropriate to test for structural break around a fixed time point.

4.3 Correspondence Analysis

The fixed point statistical tests of the previous sections all seek to infer the same information (structural break as evidence of a change in physician prescribing patterns) from identical information sets. We might expect the techniques to perform similarly. In what follows, Cohen's kappa agreement statistic is used to evaluate agreement. We denote finding evidence of structural break at the $\alpha = 0.05$ level as Δ, and not finding evidence of structural break at the $\alpha = 0.05$ level as Δ^{T}. Statistical classifiers may be compared to one another in tables similar to table 51. Intuitively, strong agreement between classifiers should result in many DHPLs being classified along the main diagonal of the table, and few DHPLs off of the main diagonal.

The kappa agreement measure builds upon this intuition, and adjusts for coincident classifications that may have occurred due to chance. More precisely, from among n cases (a DHPL being a case) that are classified into the categories Δ and Δ^{T} (using the notation from table 51) by raters a and b [4], the kappa measure of

[4] A statistical technique is considered a rater, as will be separate physicians later in this analysis.

	Technique 2		
Technique 1	Δ	$\Delta^\intercal$	Total
Δ	$n_{\Delta\Delta}$	$n_{\Delta\Delta^\intercal}$	$n_{\Delta\bullet}$
$\Delta^\intercal$	$n_{\Delta^\intercal\Delta}$	$n_{\Delta^\intercal\Delta^\intercal}$	$n_{\Delta^\intercal\bullet}$
Total	$n_{\bullet\Delta}$	$n_{\bullet\Delta^\intercal}$	n

Table 51: Table of Matched DHPL Pairs According to Statistical Technique

agreement between raters a and b is

$$\hat{\kappa}_{a,b} = \frac{p_a - p_e}{1 - p_e}, \tag{34}$$

where p_a is the probability of coincidental classification, and p_e is the probability of coincident classification due to chance. That is

$$\begin{aligned} p_a &= \frac{n_{\Delta\Delta} + n_{\Delta^\intercal\Delta^\intercal}}{n}, \text{ and} \\ p_e &= \left(\frac{n_{\Delta\bullet}}{n} \times \frac{n_{\bullet\Delta}}{n}\right) + \left(\frac{n_{\Delta^\intercal\bullet}}{n} \times \frac{n_{\bullet\Delta^\intercal}}{n}\right) \end{aligned}$$

A desirable feature of the kappa measure is its interpretability. Values of kappa closer to one (the upper bound of the kappa measure) denote higher agreement between raters. Several authors have published scales about how to interpret levels of agreement. Gwet[76] provides a good overview of the more widely used ones. We try to avoid such scales as they are to some extent arbitrary, and because we will be directly comparing kappa measures to other kappa measures and will not need such scales.

We begin by comparing our two most advanced techniques; the ITSACORR and ITSE-Ramsey techniques. Table 52 shows pretty strong agreement between the two techniques– only 4 cases are classified differently.

a and b, going forward, replace Technique 1 and Technique 2 from table 51.

	ITSE-Ramsey		
ITSACORR	Δ	Δ^T	Total
Δ	20	3	23
Δ^T	1	21	22
Total	21	24	45

Table 52: Concordance of ITSACORR and ITSE-Ramsey Techniques

The kappa statistic admitted from these cases is $\hat{\kappa}_{ITSE,ITSACORR} = 0.82$. The kappa statistics of agreement between ITSE-Ramsey and the naive-F and ITSACORR and the naive-F are $\hat{\kappa}_{ITSE,F} = 0.55$ and $\hat{\kappa}_{ITSACORR,F} = 0.48$. The agreement with the Naive-F technique, for both the autocorrelation adjusting techniques is poorer than the autocorrelation adjusting techniques between each other.

Our principal aim with this correspondence analysis is to compare the statistical techniques against professional opinion. Three physicians[5] assessed many of the DHPLs with a view to assessing their expected impact on prescription volumes[6]. Comparing the findings of physicians with the findings of statistical techniques is interesting; each classifier seeks to infer the same outcome (a change in prescription practices), but uses different information to choose the outcome (a table presenting the classifications of each physician may be found in the appendix, table 57). The statistical techniques know all of the prescription data prior to and after the DHPL, as well as the DHPL issuance date; whereas the physicians know the entire content of the DHPL letter.

The ITSE-Ramsey statistical technique is is the one that will be evaluates against the ratings of each of the physicians[7]. We begin by assessing the extent to which

[5]Don Mattison, Jeremy Grimshaw, and Peter Tugwell

[6]The statistical tests as they were programmed, detected structural break in slope parameters, but did not make inference to direction of the change. The physicians did concern themselves with increases and decreases in prescription volume, but only their expectation for change was used in the analysis.

[7]Because there are differences between the individual classifications of physicians and because there are few physicians (only 3 of them), we treat each physician separately in the analysis.

physician opinion is consistent amongst itself. The following kappa statistics are admitted for all combinations to the three physicians: $\hat{\kappa}_{1,2} = 0.25$, $\hat{\kappa}_{1,3} = 0.45$, and $\hat{\kappa}_{2,3} = 0.51$.

We next consider the extent to which physician sentiment agrees with the statistical technique. Each of the physicians are considered against the statistical techniques and yield the following kappa statistics: $\hat{\kappa}_{S,1} = -0.05$, $\hat{\kappa}_{S,2} = 0.11$, and $\hat{\kappa}_{S,3} = -0.09$.

These values are less than the kappa statistics of agreement between physicians. A common interpretation would be that there is no agreement between any of the physicians and the statistical technique. To be confident, we construct confidence intervals for these kappa statistics following the procedure described by Vierkant[84] for constructing bootstrap confidence intervals for $\hat{\kappa}_{i,j}$. That is, we draw 1000 samples of identical size, with replacement, and compute 1000 values of $\hat{\kappa}_{i,j}$. The 25^{th} and 975^{th}[8] elements of the sorted list of $\hat{\kappa}_{i,j}$s define the 95% bootstrap confidence region. The resulting confidence regions are listed in table 53, and plotted in figure 59.

$\hat{\kappa}$	95% CI	$\hat{\kappa}$	95% CI
$\hat{\kappa}_{1,2}$	(-0.01, 0.51)	$\hat{\kappa}_{s,1}$	(-0.33, 0.24)
$\hat{\kappa}_{1,3}$	(0.16, 0.71)	$\hat{\kappa}_{s,2}$	(-0.17, 0.40)
$\hat{\kappa}_{2,3}$	(0.24, 0.73)	$\hat{\kappa}_{s,3}$	(-0.38, 0.20)

Table 53: Bootstrap Confidence Intervals

All of the confidence intervals that compare statistical techniques to physician opinion include zero– the value that signifies no agreement. None of the within-physician kappa statistics include zero in their confidence regions. There is something that is causing the physicians and the statistical techniques to classify cases differently, we find no agreement between the physicians and the statistical classifiers. We consider possible reasons for this in the conclusion.

[8] 25/1000 + (1-(975/1000)=0.05, the bounds for a 95% confidence region.

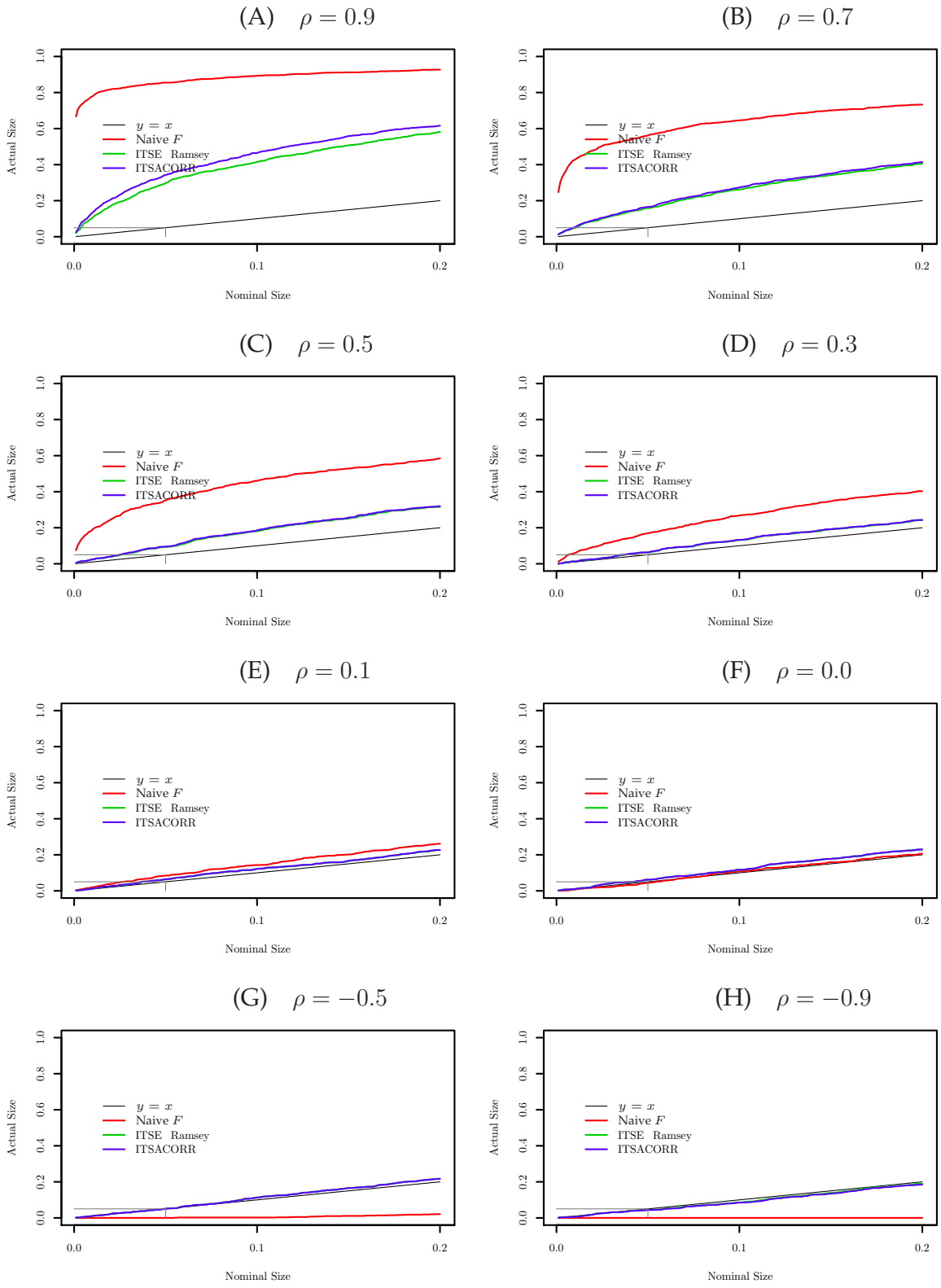

Figure 54: Size Plots and Comparison of ITSACORR, ITSE-Ramsey, and Naive-F for Multiple Values of ρ

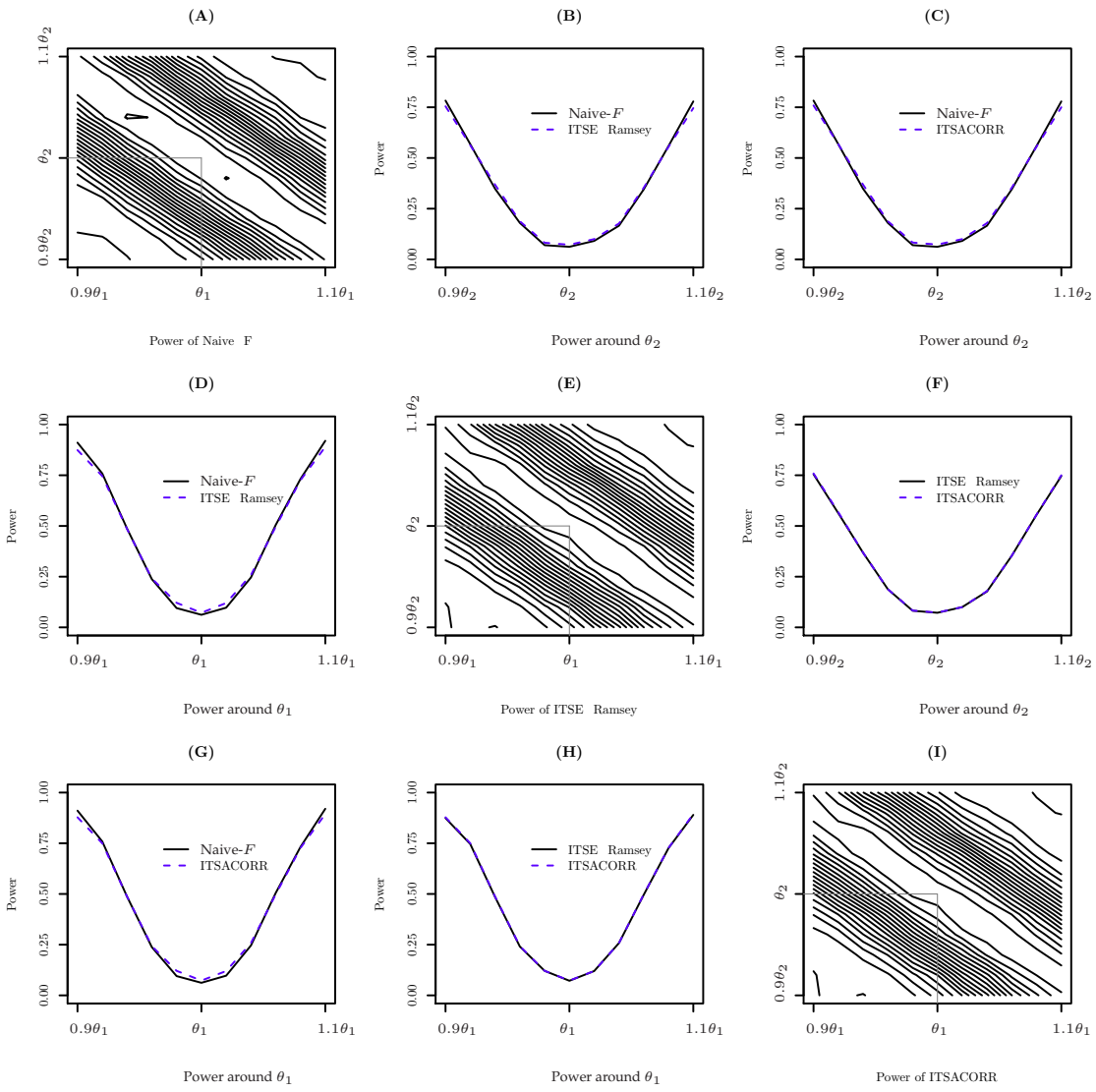

Figure 55: $\rho = 0.0$ – Power Plot and Comparison of ITSACORR, ITSE-Ramsey, and Naive-F Break Detection Techniques

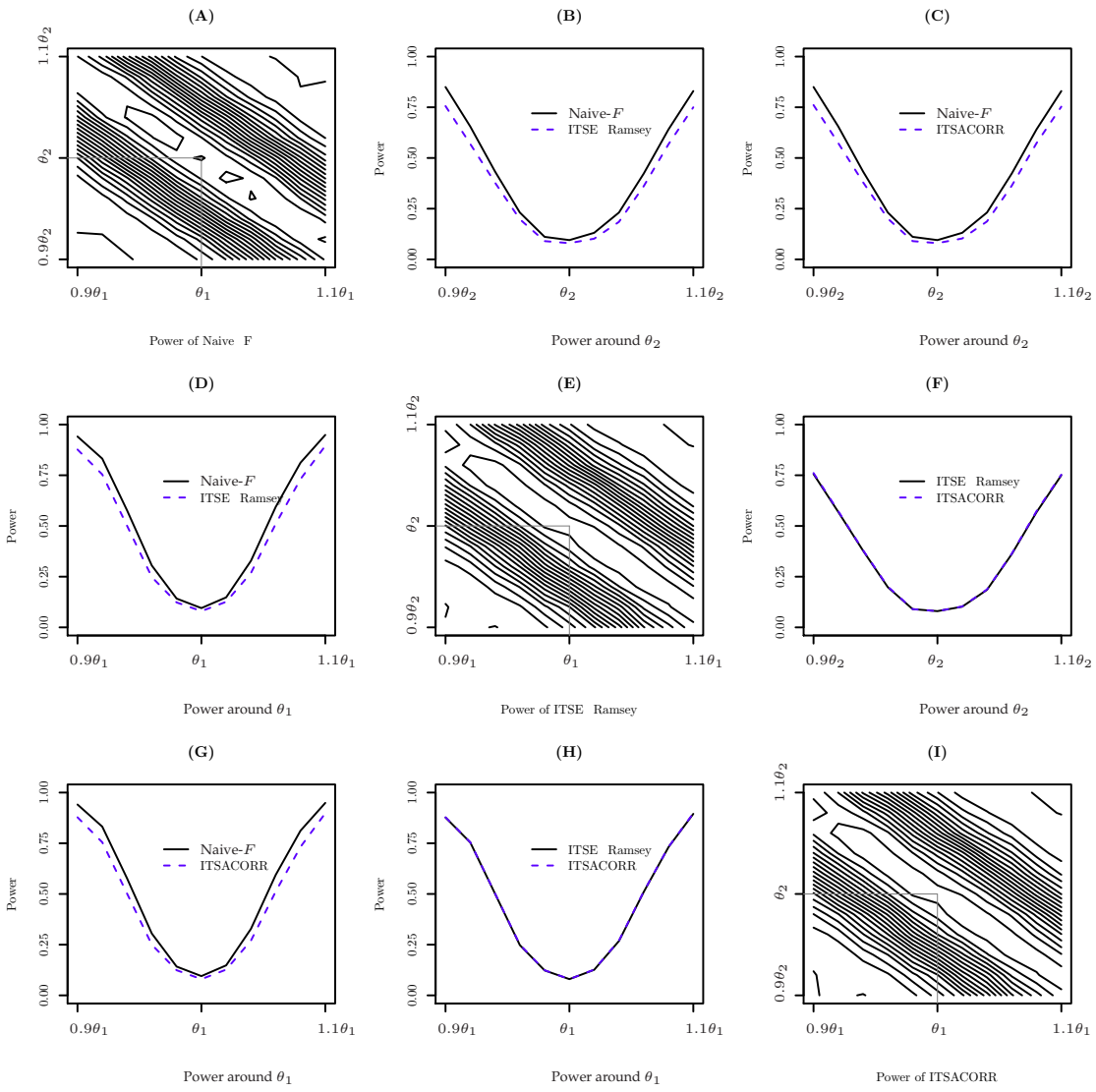

Figure 56: $\rho = 0.1$ – Power Plot and Comparison of ITSACORR, ITSE-Ramsey, and Naive-F Break Detection Techniques

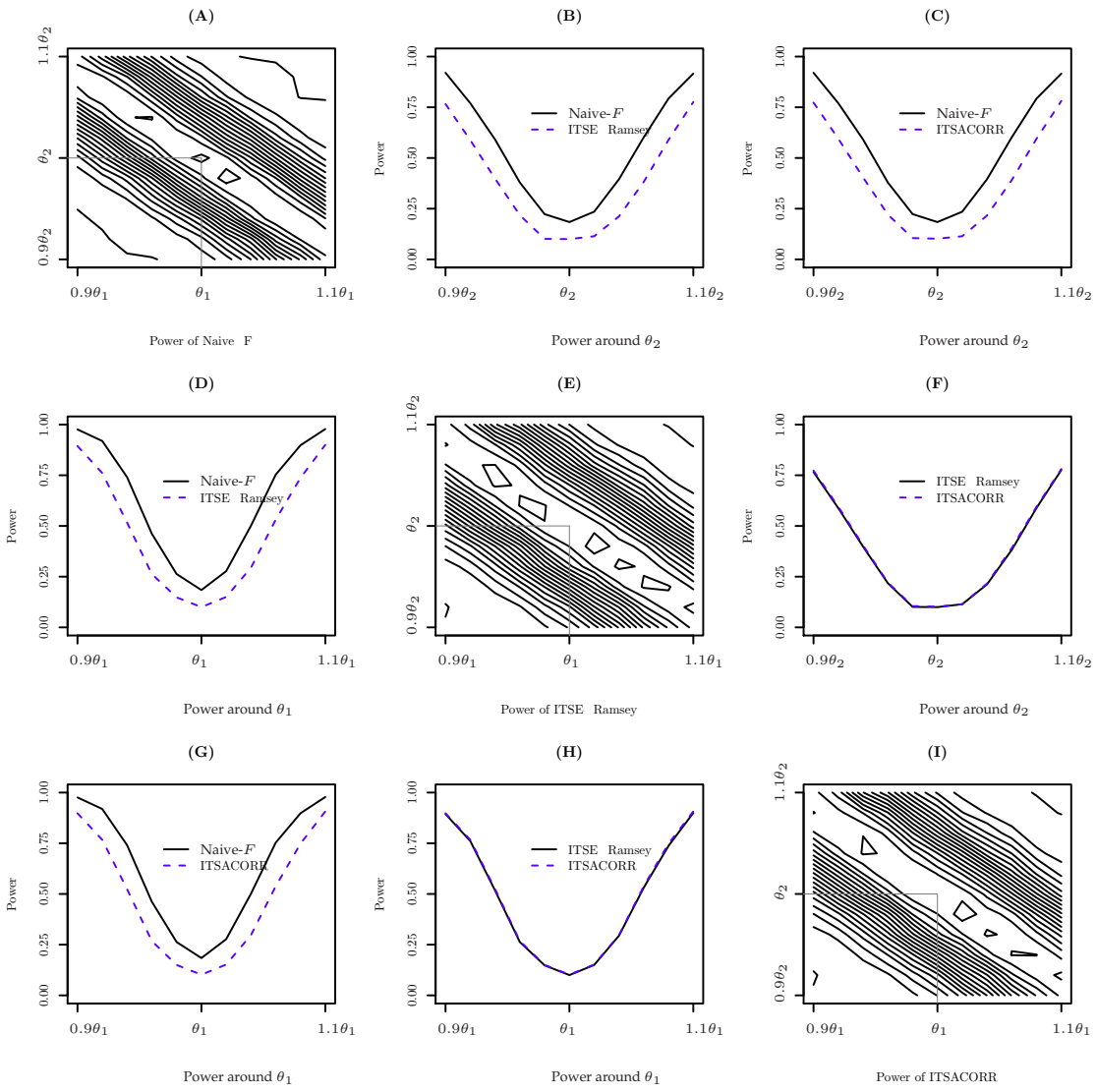

Figure 57: $\rho = 0.3$ – Power Plot and Comparison of ITSACORR, ITSE-Ramsey, and Naive-F Break Detection Techniques

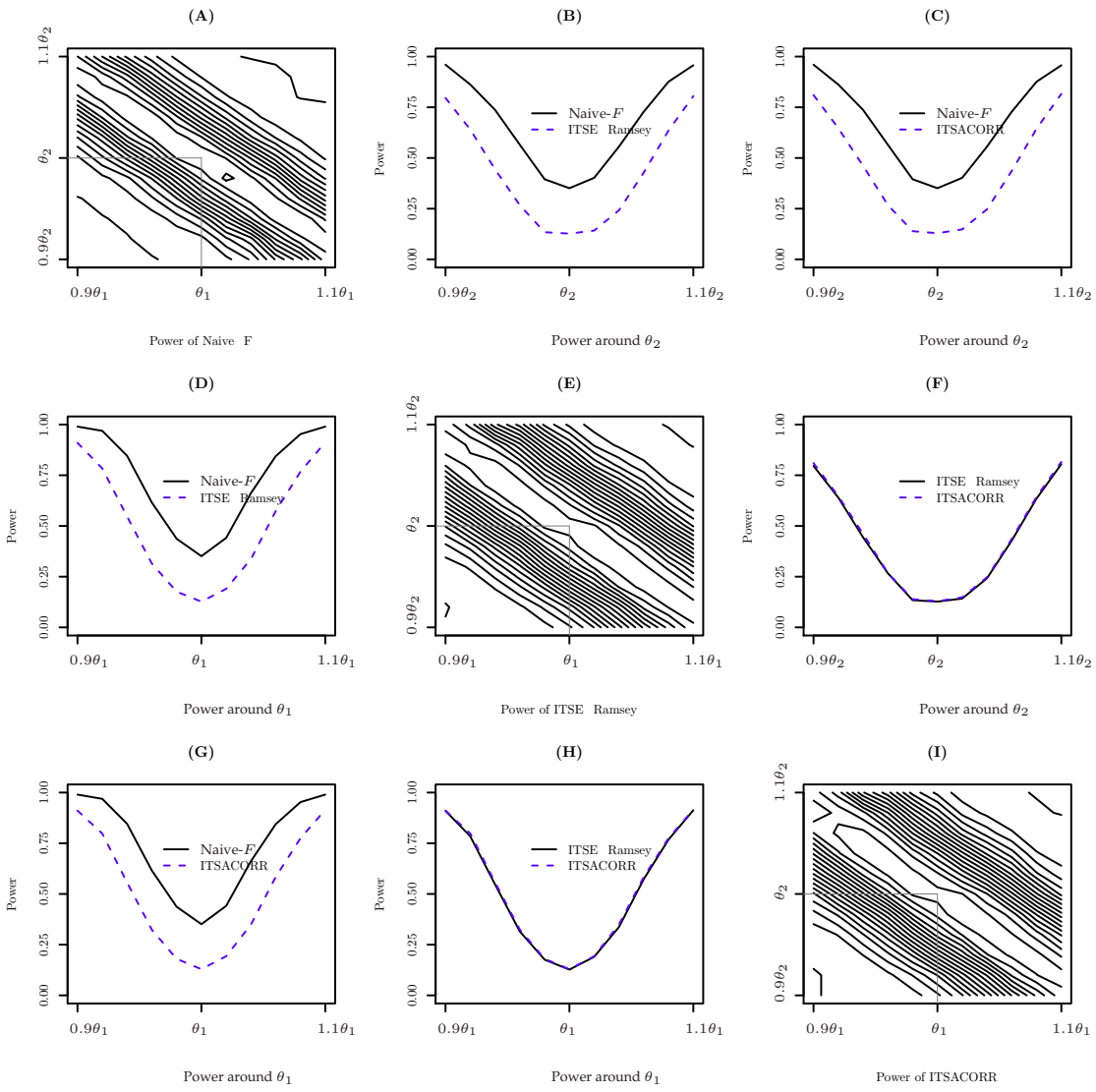

Figure 58: $\rho = 0.5$ – Power Plot and Comparison of ITSACORR, ITSE-Ramsey, and Naive-F Break Detection Techniques

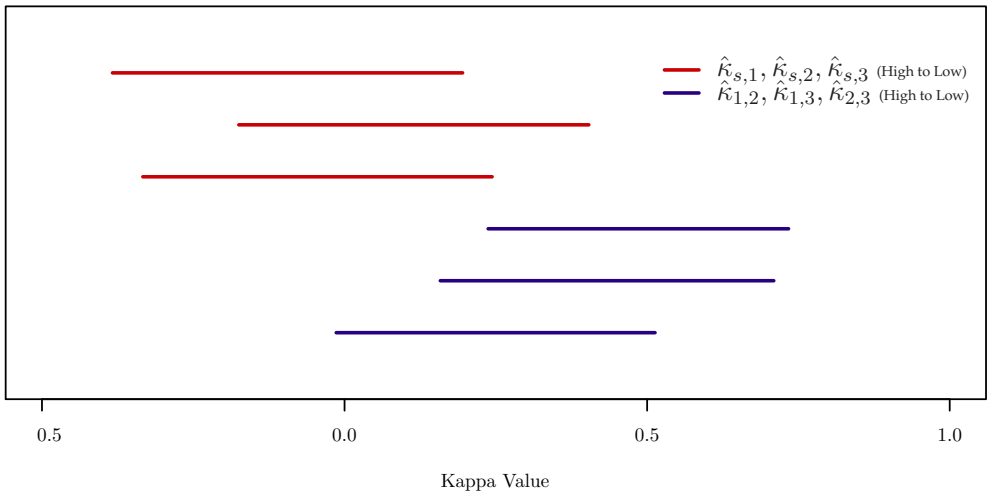

Figure 59: 95% Bootstrap Confidence Intervals of Kappa Statistics Assessing Agreement Between Physician and Statistical Ratings

Chapter 5

Discussion and Conclusion

This thesis sought to use an unconventional data source and a conventional analysis technique to assess the effectiveness of DHPLs sent to physicians. Linear regression is a well suited framework from which to evaluate series that, when plotted, display strong trending patterns. The thesis described an intention to evaluate communication effectiveness of DHPL letters by analyzing prescription volumes centred around a communication date. Although the interrupted time series methodology used in this analysis is well established in other disciplines, two key assumptions were required for its application in the present context. The first is that DHPLs should always precipitate a change in prescription volumes; the second is that physicians would all read and respond in a similar manner to the information and guidance provided in a DHPL.

We know that the first assumption does not always hold– some DHPLs deal with quality control issues that would not be expected to have an impact on physician prescribing practice. Moreover, there are other DHPLs that pertain to market withdrawals, following which the drug is not available in Canada. These letters, too, contribute essentially no information to understanding the effectiveness of DHPLs, as the series all drop suddenly as a result of the medication no longer being available– not because physicians understood or acted upon the information in the letter. We cannot establish the first clause of the second assumption (that

physicians actually read the letters), and so are forced to rely on it without verification. We find middling evidence of similarity of response among physicians in our correspondence analysis, though our sample is very small (mid to low kappa values between physicians (table 53)).

Like many regression based techniques, the methods presented in this thesis rely upon an error term that is identically and independently distributed. We tested the independence assumption in our data and found it lacking, and so shifted our focus to remedial measures to address the autocorrelation present in the data. Including a lagged version of the dependent variable has long been a technique to address first-order autocorrelation. This thesis presented similar techniques that employ this method: the ITSE method was referenced following the work of Gottman[74], as was the technique of Ramsey and Ramsey[82]. It was shown in the text that these techniques are equivalent, and were treated as such through the rest of the thesis.

It is well known that estimating a regression coefficient on a lagged variable by least squares produces a biased estimate of that coefficient. Several authors have explored techniques for reducing this bias. We considered two techniques of bias corrections that approach the challenge from opposite perspectives. The work of McKnight *et al*[77] describe an iterative bootstrapping procedure by which the bias of the autocorrelation term is estimated, and iteratively removed from the estimate until the estimated bias is within an arbitrarily small tolerance. This did not prove to be an effective technique for our data, as many of the estimation routines did not converge. This may be because of the small sample sizes present in our series, relative to the larger sample sized recommended by McKnight *et al*, or the relatively high level of autocorrelation present in our data (figs. 1 and 2). The work of Crosbie stands in contrast to that of McKnight *et al*: whereas McKnight *et al* use iteration and brute force computations to reduce the bias, Crosbie[68, 67] uses a theoretical bias correction. Crosbie's technique is much simpler to implement, and could be implemented on all the data series.

Future work in this area might seek to understand the thresholds in terms of sample size and degree of autocorrelation (recognizing that each may depend on

the other) at which the McKnight *et al* bootstrapping technique ceases to converge. One might also explore the assumption of a time-homogeneous error term. As the process that generates a trend in prescription volumes may change around a communication date, so too may the variation of that process. In finding the homogeneity assumption lacking, one might also consider techniques to correct for heteroskedasticity.

We are grateful to Health Canada for providing us with the data used in our analysis, but acknowledge some limitations. Combining drugs volumes for combination DHPLs, in general, worked very well. The DHPLs concerning the classes of medications related to erectile dysfunction, ADHD, and asthma for which a single DHPL was issued, and for which a series of aggregated values was produced, worked very well. However, in the cases where a combination DHPL mentions different applications of different drugs (for example: ARANESP and EPREX[40]), aggregating the drug volumes prevented us from being able to detect substitution behaviour from one drug in favour of another. In choosing a series length, it is desirable to have many observations in order to achieve high power. It is also desirable to have pertinent data, as determined by temporal closeness to the DHPL issue date. Many of our data series are 36 observations long, and represent 3 years of prescription volumes– this seems to represent a sensible balance between length and pertinence. Subsequent work might explore the availability and quality of the data at a bi-monthly frequency; if the data retains its quality, this could be a way to reduce the window of pertinence around the DHPL while still maintaining a large sample size.

Of the data series considered, 2 of the DHPLs reported quality control issues and 7 reported market withdrawals, and thereby contribute no information to understanding DHPL effectiveness. Nineteen of the data series are confounded by the fact that another DHPL, for the same medication, was issued close to that date. We employed a rolling test for break at an unknown point to interpret these series to address this complication. In some cases, these techniques indicate a sensible region for break point around one or more of the DHPLs. In other cases, however, the break region identified by the rolling test can be either well before or well after

the DHPLs, thereby making interpretation difficult.

If one chooses to accept the statistical findings, instead of the visually intuitive results for those 7 cases identified in the thesis as we have, then there are 36 remaining cases (from 64) on which the primary techniques described in this thesis apply.

In an effort to determine if the findings of the statistical techniques are sensible, we performed a correspondence analysis between the statistical techniques and a group of physicians. We expected some degree of agreement, tempered by the fact that there would likely be some stated/revealed preference bias (with physicians providing the stated preference, and prescription volumes serving as revealed preference); however, we find little agreement of our statistical results with any of the physicians.

Through size and power simulations we were able to demonstrate that the ITSE-Ramsey and ITSACORR techniques are acceptable techniques for testing for break in series with mild ($\rho < 0.5$) autocorrelation. For $\rho > 0.5$, both of the tests have inflated type 1 error rates, and find twice as many significant results as they should. Considering the high level of autocorrelation in our data (figs. 1 and 2), it is entirely plausible that the 7 visually discordant cases identified previously are type I errors.

Applying a structural break methodology to prescription data in order to assess DHPL effectiveness is a novel and informative application of this statistical approach. The methods considered herein do not perform well enough in face of the level of autocorrelation typically present in the data to be considered very useful. In considering other techniques for this kind of research, those techniques should perform well in terms of size at high levels of autocorrelation ($\rho \approx 0.95$) to be considered appropriate.

Chapter 6

Appendix

Series	Drug	Series	Drug
001	Abacavir	033	Telithromycin
002	Carbamazepine	034	Gatifloxacin
003	Darunavir	035	Gefitinib
004	Desmopressin Ddavp	036	Hydroxyurea
005	Metformin	037	Infliximab
006	Natalizumab	038	Lamotrigine
007	Pegvisomant	039	Raloxifene
008	Timolol	040	Sirolimus
009	Varenicline	041	Tipranavir
010	Deferasirox	042	Cialis, Levitra, and Viagra
011	Gefitinib	043	Adhd
012	Lumiracoxib	044	Darbepoetin Alfa
013	Modafinil	045	Estradiol Testosterone Benzoyl-hydrazone
014	Nelfinavir	046	Gatifloxacin
015	Pergolide	047	Octreotide
016	Rosiglitazone	048	Paroxetine
017	Telithromycin	049	Pegaptanib
018	Bevacizumab	050	Enbrel Humira Remicade
019	Cinacalcet	051	Avandia And Avandamet
020	Both Darbe+ Erythro	052	Amphetamine!Dextroamphetamine
021	Pioglitazone	053	Atomoxetine
022	Rituximab	054	Celecoxib
023	Rosiglitazone	055	Fentanyl
024	Sodium	056	Formoterol (Oxeze)
025	Rosiglitazone	057	Gefitinib
026	Bevacizumab	058	Letrozole
027	Deferasirox	059	Medroxyprogesterone
028	Entecavir	060	Paroxetine
029	Norelgestromin and Ethinyl Estradiol	061	Salmeterol
030	Gefitinib	062	Thioridazine
031	Rituximab	063	Zoledronic Acid
032	Tegaserod	064	Formotrerol (Foradil)

Table 54: Drug Series Number Concordance

Series	Naive F		ITSE-Ramsey		ITSACORR	
001	**24.1**	**< 0.01**	**9.6**	**< 0.01**	**14.6**	**< 0.01**
002	0.9	0.43	0.8	0.49	1.2	0.3
003	**7.4**	**< 0.01**	**3.5**	**0.03**	**5.3**	**0.01**
004	1.6	0.21	0.9	0.44	1.4	0.27
005†	**10.6‡**	**< 0.01**	**3.7‡**	**0.01**	0.7	0.49
006†	**12.2‡**	**< 0.01**	**3.3‡**	**0.02**	2.1	0.14
007†	**28.4‡**	**< 0.01**	**5.7‡**	**< 0.01**	**4.4**	**0.02**
008	**84.2**	**< 0.01**	**35**	**< 0.01**	**52.7**	**< 0.01**
009	**157.9**	**< 0.01**	**7.9**	**< 0.01**	**16.1**	**< 0.01**
010	**8.5**	**< 0.01**	2.4	0.09	**3.6**	**0.04**
011	**10.4**	**< 0.01**	0.5	0.66	1	0.38
012	**198**	**< 0.01**	**33.2**	**< 0.01**	**53.3**	**< 0.01**
013	3.3	0.05	1.9	0.16	2.8	0.07
014	**28.4**	**< 0.01**	**10.2**	**< 0.01**	**15.6**	**< 0.01**
015	**26.4**	**< 0.01**	**5.4**	**< 0.01**	**8.6**	**< 0.01**
016	**16.9**	**< 0.01**	1.2	0.33	2.2	0.13
017	**21.5**	**< 0.01**	0.7	0.56	2	0.16
018	**33.3**	**< 0.01**	2.1	0.13	**3.8**	**0.03**
019	**4.5**	**0.02**	1.1	0.35	1.8	0.19
020†	**14.4**	**< 0.01**	**3.6**	**0.02**	**5.6**	**0.01**
021	**5.9**	**0.01**	2.3	0.1	**3.5**	**0.04**
022	3.2	0.05	1.2	0.34	1.8	0.19
023	**94.5**	**< 0.01**	**10.3**	**< 0.01**	**16.8**	**< 0.01**
024	**58.9**	**< 0.01**	**12.6**	**< 0.01**	**19.6**	**< 0.01**
025	**96.9**	**< 0.01**	**5.4**	**< 0.01**	**9.4**	**< 0.01**
026	**6.7**	**0.01**	1.6	0.22	2.7	0.09
027	0.4	0.66	0.5	0.72	0.7	0.52
028	2.6	0.1	0.4	0.73	0.7	0.5
029†	**7.8‡**	**< 0.01**	2.5‡	0.06	1.3	0.28
030	**55.2**	**< 0.01**	**5.9**	**< 0.01**	**9.5**	**< 0.01**
031	1	0.37	0.5	0.69	0.8	0.48
032	**31.3**	**< 0.01**	**5.7**	**< 0.01**	**9**	**< 0.01**

Table 55: ITSA Results- Part 1. A dagger (†) next to the series number indicates that this series had higher orders of the variable time (t) included in their regressions owing to the series' non-linear relationship with time. Double daggers (‡) next to the F-statistic indicate that higher orders of the time variable were retained.

Series	Naive F		ITSE-Ramsey		ITSACORR	
033	0.7	0.5	0	1	0.1	0.95
034	**9.6**	**< 0.01**	**3.4**	**0.03**	**5.3**	**0.01**
035	**11.7**	**< 0.01**	1.8	0.16	3.2	0.06
036	0.4	0.65	0.8	0.49	1.2	0.31
037	**5.1**	**0.01**	**7.6**	**< 0.01**	**11.3**	**< 0.01**
038	1.3	0.29	**3**	**0.04**	**4.5**	**0.02**
039	1.1	0.36	0.5	0.7	0.7	0.5
040	**3.5**	**0.04**	2.1	0.12	3.2	0.05
041	**9.4**	**< 0.01**	**4.1**	**0.02**	**6.4**	**0.01**
042	**4.2**	**0.02**	1	0.39	1.6	0.22
043	0.1	0.86	0.1	0.97	0.1	0.87
044	**8.6**	**< 0.01**	**4.1**	**0.01**	**6.3**	**0.01**
045	**21**	**< 0.01**	**5.3**	**< 0.01**	**8.4**	**< 0.01**
046	**7.5**	**< 0.01**	1.2	0.31	2	0.15
047†	**3.3‡**	**0.04**	0.6	0.6	1	0.39
048	**3.7**	**0.04**	**3.8**	**0.02**	**5.7**	**0.01**
049†	1.8‡	0.2	0.3	0.86	0.4	0.67
050	**8.2**	**< 0.01**	**4**	**0.02**	**6.1**	**0.01**
051	2.4	0.11	1.9	0.15	2.9	0.07
052	**10.8**	**< 0.01**	3	0.05	**4.9**	**0.01**
053	**52.6**	**< 0.01**	1.5	0.25	3.5	0.05
054†	**9.5**	**< 0.01**	1.2	0.32	2	0.15
055	2.1	0.15	1.4	0.25	2.2	0.13
056†	2.3	0.11	0.8	0.51	1.2	0.31
057	1.2	0.3	1.2	0.32	1.8	0.18
058	**8.5**	**< 0.01**	**3.2**	**0.04**	**4.8**	**0.02**
059	**6.7**	**< 0.01**	2.5	0.08	**3.8**	**0.03**
060	**4.8**	**0.01**	**4.3**	**0.01**	**6.4**	**< 0.01**
061	3	0.06	1.4	0.26	2.1	0.14
062†	**34.2‡**	**< 0.01**	**3.6‡**	**0.02**	2.8	0.08
063	**108.6**	**< 0.01**	**7.3**	**< 0.01**	**12.8**	**< 0.01**
064	0.4	0.7	0.2	0.89	0.3	0.73

Table 56: ITSA Results- Part 2. A dagger (†) next to the series number indicates that this series had higher orders of the variable time (t) included in their regressions owing to the series' non-linear relationship with time. Double daggers (‡) next to the F-statistic indicate that higher orders of the time variable were retained.

Series	Phys. 1	Phys. 2	Phys. 3	Series	Phys. 1	Phys. 2	Phys. 3
001	NC	NC	-	036	C	NC	NC
021	C	C	C	038	NC	NC	NC
043	NC	C	C	049	NC	NC	NC
043	NC	NC	C	047	C	C	NC
013	C	C	C	064	C	NC	NC
050	NC	NC	NC	015	C	C	C
041	NC	NC	NC	003	C	NC	NC
044	C	C	C	012	C	C	C
020	C	NC	NC	040	C	NC	NC
023	C	NC	NC	005	NC	NC	NC
028	NC	NC	NC	037	NC	C	NC
054	C	C	C	019	C	NC	C
009	C	C	C	061	C	NC	C
042	NC	NC	NC	007	NC	NC	C
045	C	C	C	053	C	NC	C
059	C	NC	C	002	NC	NC	NC
004	C	NC	C	062	C	C	C
055	NC	C	C	008	NC	C	NC
039	NC	C	C	006	NC	NC	NC
029	C	C	C	014	C	C	C
058	C	NC	C	032	C	C	C
024	C	C	C	063	NC	NC	NC
056	C	NC	NC				

Table 57: Classification of DHPL letters (by Series number)– 'NC' for no change, 'C' for change, and '-' for unknown.

Series	Obs	Obs≥DHPL	Obs<DHPL	Series	Obs	Obs≥DHPL	Obs<DHPL
001	36	16	20	033	36	16	20
002	36	16	20	034	36	16	20
003	36	16	20	035	36	16	20
004	36	16	20	036	36	16	20
005	36	16	20	037	36	16	20
006	35	16	19	038	36	16	20
007	36	16	20	039	36	16	20
008	36	16	20	040	36	16	20
009	33	16	17	041	23	16	7
010	34	16	18	042	36	16	20
011	34	14	20	043	36	16	20
012	27	14	13	044	36	16	20
013	34	14	20	045	36	16	20
014	34	14	20	046	36	16	20
015	34	14	20	047	34	16	18
016	34	14	20	048	36	16	20
017	34	14	20	049	22	16	6
018	35	16	19	050	36	16	20
019	36	16	20	051	36	16	20
020	36	16	20	052	35	16	19
021	36	17	19	053	25	16	9
022	36	16	20	054	36	16	20
023	36	16	20	055	36	16	20
024	36	16	20	056	36	16	20
025	36	16	20	057	35	16	19
026	27	16	11	058	36	16	20
027	22	16	6	059	33	16	17
028	22	16	6	060	36	16	20
029	36	16	20	061	36	16	20
030	36	16	20	062	35	16	19
031	27	16	11	063	35	16	19
032	36	16	20	064	36	16	20

Table 58: Observation Counts Before and After DHPL

Series	Start	Series Values – Part 1									
001	2006-12	5,293	5,288	4,846	5,572	5,294	5,885	5,711	5,841	6,199	5,493
002	2006-09	82,418	87,188	85,392	86,335	89,364	80,519	88,838	84,998	91,351	88,828
003	2006-11	16	30	41	42	111	148	273	285	325	384
004	2007-01	1,035	919	1,070	980	1,093	1,032	1,061	1,033	896	1,001
004	2007-01	1,035	919	1,070	980	1,093	1,032	1,061	1,033	896	1,001
005	2007-01	110,871	90,784	98,929	98,722	109,807	109,321	113,516	114,099	108,720	120,251
006	2007-01	2	2	8	19	36	33	19	29	12	14
007	2006-12	-	1	1	1	-	1	5	8	5	5
008	2007-01	3,983	3,551	3,745	3,533	3,658	3,482	3,562	3,577	3,375	3,528
009	2007-03	1	850	7,141	12,283	17,783	22,519	29,121	44,642	58,520	65,818
010	2006-11	3	20	32	32	36	37	55	64	97	103
011	2006-04	34	42	29	31	20	15	14	13	16	17
012	2006-11	182	1,904	6,662	12,956	20,885	25,243	31,070	33,710	36,262	35,894
013	2006-06	4,224	4,063	4,322	4,110	4,355	4,394	4,276	4,317	3,890	4,400
014	2006-03	818	711	780	800	803	806	695	717	699	662
015	2006-02	1,353	1,521	1,363	1,570	1,376	1,475	1,547	1,379	1,513	1,395
016	2006-05	106,868	106,137	105,074	109,641	106,156	112,998	112,055	116,087	118,064	108,794
017	2006-03	13,817	11,784	10,539	7,057	4,226	4,046	5,387	5,222	4,754	4,815
018	2006-01	17	29	40	62	101	129	81	92	111	123
019	2005-12	204	182	191	240	197	321	290	335	367	387
020	2005-10	12,187	12,198	12,496	11,932	10,890	12,465	11,405	13,673	13,337	13,885
021	2005-11	39,511	41,912	41,151	38,068	43,973	40,726	45,388	45,279	44,386	46,841

Table 59: Data Series 001–021, Part 1 (See Drug Series-concordance, table 54)

Series	Start	Series Values – Part 2									
001	2006-12	6,201	6,084	6,130	6,062	5,932	6,064	6,211	6,460	6,097	**6341**
002	2006-09	91,395	92,627	85,163	92,204	89,586	90,398	91,762	88,022	91,584	**91609**
003	2006-11	341	432	433	463	531	572	614	705	741	**734**
004	2007-01	942	943	864	870	906	910	928	906	973	**895**
004	2007-01	942	943	864	870	906	910	928	906	973	**895**
005	2007-01	120,097	125,339	125,656	118,086	126,004	140,614	150,232	148,843	155,976	**146633**
006	2007-01	21	23	146	130	167	184	204	230	**260**	259
007	2006-12	10	7	5	16	13	20	31	25	27	**30**
008	2007-01	3,446	3,296	3,323	3,001	3,144	3,122	3,253	3,126	1,925	**268**
009	2007-03	102,498	109,093	116,929	122,122	116,152	101,763	**88092**	76,935	83,477	88,104
010	2006-11	81	131	164	129	146	111	166	**159**	223	169
011	2006-04	12	11	9	9	9	12	8	10	8	**9**
012	2006-11	32,840	4,480	**49**	27	7	6	2	2	1	1
013	2006-06	4,282	4,802	4,716	4,675	4,736	4,562	4,935	4,840	4,744	**4587**
014	2006-03	673	592	638	644	689	671	643	654	500	**414**
015	2006-02	1,385	1,436	1,325	1,381	1,320	1,304	1,188	1,188	1,169	**600**
016	2006-05	126,027	120,708	125,091	107,438	105,940	100,592	89,611	93,672	84,623	**79235**
017	2006-03	5,483	4,215	3,446	2,417	1,790	1,027	841	782	498	**542**
018	2006-01	131	243	322	290	327	347	364	376	**422**	408
019	2005-12	410	437	466	475	429	497	511	548	534	**626**
020	2005-10	14,715	13,409	14,559	14,303	13,976	14,667	12,959	14,376	13,784	**14631**
021	2005-11	44,962	48,208	49,307	51,301	51,469	47,501	54,189	51,923	**58071**	59,020

Table 60: Data Series 001–021, Part 2 (See Drug Series-concordance, table 54)

Series	Start	Series Values – Part 3									
001	2006-12	6,070	6,127	6,270	5,971	6,526	5,916	5,610	5,996	5,862	5,711
002	2006-09	93,319	92,202	95,468	90,280	91,329	95,033	88,400	97,126	91,917	85,474
003	2006-11	786	757	775	875	819	939	1,021	914	1,030	1,020
004	2007-01	788	863	780	891	773	726	816	839	791	850
004	2007-01	788	863	780	891	773	726	816	839	791	850
005	2007-01	150,474	162,364	155,386	177,349	155,992	127,333	139,485	138,386	140,523	147,704
006	2007-01	290	292	282	341	321	263	368	419	355	424
007	2006-12	33	36	33	37	39	39	41	45	43	40
008	2007-01	193	158	111	95	75	70	53	41	43	35
009	2007-03	81,593	76,255	87,118	79,820	84,577	79,137	75,152	71,532	65,450	62,370
010	2006-11	284	227	287	300	293	324	324	279	196	172
011	2006-04	8	3	3	3	4	4	6	4	1	2
012	2006-11	-	2	1	2	1	1	1	-	-	-
013	2006-06	4,258	4,319	4,631	4,722	4,944	4,949	4,615	4,753	4,991	4,864
014	2006-03	340	325	253	255	251	273	238	212	221	216
015	2006-02	350	255	168	57	21	7	2	6	3	4
016	2006-05	75,324	67,632	70,411	67,859	68,855	65,860	67,760	63,790	64,024	65,377
017	2006-03	415	408	400	330	252	218	182	125	122	102
018	2006-01	317	288	146	183	165	146	155	134	122	114
019	2005-12	569	573	624	599	581	617	657	715	772	820
020	2005-10	13,485	13,894	13,972	12,678	13,857	13,279	13,071	12,304	11,931	12,410
021	2005-11	61,727	63,440	60,455	67,005	66,517	67,794	65,946	63,177	67,187	66,911

Table 61: Data Series 001–021, Part 3 (See Drug Series-concordance, table 54)

Series	Start	Series Values – Part 4					
001	2006-12	5,820	5,923	5,644	5,850	5,848	5,775
002	2006-09	95,040	93,543	92,677	95,705	95,365	94,136
003	2006-11	1,012	1,088	1,128	1,150	1,195	1,277
004	2007-01	839	836	825	797	779	868
004	2007-01	839	836	825	797	779	868
005	2007-01	152,716	171,452	180,402	196,490	184,988	222,250
006	2007-01	415	363	399	377	393	-
007	2006-12	38	46	40	32	34	30
008	2007-01	41	28	36	26	21	19
009	2007-03	69,153	74,347	69,195	-	-	-
010	2006-11	217	209	198	188	-	-
011	2006-04	2	4	4	1	-	-
012	2006-11	-	-	-	-	-	-
013	2006-06	5,139	4,913	4,544	5,289	-	-
014	2006-03	205	212	210	200	-	-
015	2006-02	2	-	-	-	-	-
016	2006-05	60,094	65,685	59,646	54,344	-	-
017	2006-03	143	117	74	28	-	-
018	2006-01	96	108	242	277	107	-
019	2005-12	817	869	925	934	994	891
020	2005-10	12,600	12,960	12,998	13,830	12,814	12,946
021	2005-11	70,922	68,904	71,708	67,440	68,244	71,207

Table 62: Data Series 001–021, Part 4 (See Drug Series-concordance, table 54)

Series	Start	Series Values – Part 1									
022	2006-02	1	4	1	4	8	9	15	12	15	12
023	2005-12	103,778	99,942	92,467	106,021	97,165	106,868	106,137	105,074	109,641	106,156
024	2005-12	114	120	118	125	108	118	120	110	118	96
025	2005-08	96,609	94,632	98,171	100,017	103,778	99,942	92,467	106,021	97,165	106,868
026	2006-01	17	29	40	62	101	129	81	92	111	123
027	2006-11	3	20	32	32	36	**37**	55	64	97	103
028	2006-10	5	18	36	42	56	**88**	85	95	103	121
029	2005-05	26,726	27,279	28,525	30,035	30,329	32,836	29,855	30,185	30,632	27,449
030	2005-06	65	58	60	65	55	43	43	43	40	35
031	2006-02	1	4	1	4	8	9	15	12	15	12
032	2005-09	5,861	5,977	5,931	6,113	6,027	5,723	6,781	6,333	7,001	6,799
033	2005-03	20,433	17,000	14,321	9,724	7,410	6,964	10,027	15,420	15,602	15,583
034	2004-11	14,902	17,553	22,103	20,720	20,408	18,315	17,795	15,185	12,444	13,434
035	2004-12	192	142	86	103	84	58	65	58	60	65
036	2004-09	3,890	3,963	4,042	4,232	4,009	3,842	4,280	4,015	4,338	4,357
037	2005-01	2,091	1,890	2,292	2,098	2,348	2,285	2,240	2,505	2,363	2,311
038	2005-02	28,080	31,826	30,540	32,294	32,090	31,707	33,705	33,306	34,800	35,007
039	2004-11	29,363	30,206	27,745	25,149	27,575	27,072	27,828	27,298	26,131	27,328
040	2005-02	667	710	682	781	768	729	769	753	728	788
041	2006-01	1	6	11	22	42	46	**56**	59	53	63
042	2004-12	127,501	110,533	105,663	111,537	110,127	112,281	110,307	110,362	107,985	109,558
043	2004-11	160,175	145,703	158,075	156,746	161,860	163,437	172,122	147,798	115,945	130,457

Table 63: Data Series 022–043, Part 1 (See Drug Series-concordance, table 54)

Series	Start	Series Values – Part 2									
022	2006-02	18	7	15	10	22	32	26	13	20	**14**
023	2005-12	112,998	112,055	116,087	118,064	108,794	126,027	120,708	125,091	107,438	**105940**
024	2005-12	116	109	129	139	97	107	103	100	65	**16**
025	2005-08	106,137	105,074	109,641	106,156	112,998	112,055	116,087	118,064	108,794	**126027**
026	2006-01	**131**	243	322	290	327	347	364	376	422	408
027	2006-11	81	131	164	129	146	111	166	159	223	169
028	2006-10	120	143	179	187	211	245	249	246	284	294
029	2005-05	30,380	29,568	30,931	30,182	29,728	29,505	27,756	28,406	27,581	**28357**
030	2005-06	34	42	29	31	20	15	14	13	16	**17**
031	2006-02	**18**	7	15	10	22	32	26	13	20	14
032	2005-09	6,506	6,896	6,696	7,045	7,047	7,095	7,122	6,521	7,139	**316**
033	2005-03	17,558	13,317	13,817	11,784	10,539	7,057	4,226	4,046	5,387	**5222**
034	2004-11	15,635	18,576	18,379	16,667	16,763	13,801	13,347	12,287	11,671	**10526**
035	2004-12	55	43	43	43	40	35	34	42	29	**31**
036	2004-09	4,138	4,496	4,492	4,453	4,629	4,757	4,594	4,283	4,757	**4348**
037	2005-01	2,661	2,758	2,828	2,346	2,911	2,641	3,007	3,030	2,919	**3021**
038	2005-02	36,244	36,103	33,679	37,678	35,234	38,620	38,806	38,750	41,275	**38850**
039	2004-11	26,361	27,289	26,402	26,643	25,938	23,006	25,560	24,348	26,271	**24786**
040	2005-02	857	792	709	837	769	890	906	931	952	**870**
041	2006-01	60	93	59	70	95	75	101	90	85	90
042	2004-12	112,982	114,386	126,256	113,688	106,102	118,166	112,364	121,165	125,246	**124620**
043	2004-11	165,712	170,340	176,466	165,776	174,405	164,242	181,034	170,942	188,463	**165561**

Table 64: Data Series 022–043, Part 2 (See Drug Series-concordance, table 54)

Series	Start	Series Values – Part 3									
022	2006-02	34	24	27	26	29	22	20	30	21	33
023	2005-12	100,592	89,611	93,672	84,623	79,235	75,324	67,732	70,411	67,859	68,855
024	2005-12	13	3	6	4	1	-	1	-	-	-
025	2005-08	120,708	125,091	107,438	105,940	100,592	89,611	93,672	84,623	79,235	75,324
026	2006-01	317	288	146	183	165	146	155			
027	2006-11	284	227								
028	2006-10	315	335								
029	2005-05	28,169	25,385	27,714	26,726	26,908	26,575	26,787	26,590	24,850	26,179
030	2005-06	12	11	9	9	9	12	8	10	8	9
031	2006-02	34	24	27	26	29	22	20			
032	2005-09	31	19	17	10	11	5	8	8	12	2
033	2005-03	4,754	4,815	5,483	4,215	3,446	2,417	1,790	1,027	841	782
034	2004-11	8,168	8,638	9,315	10,318	10,059	8,471	10,840	10,209	10,828	10,488
035	2004-12	20	15	14	13	16	17	12	11	9	9
036	2004-09	4,891	4,673	4,525	4,721	4,633	4,930	4,913	4,964	5,033	4,500
037	2005-01	3,185	3,382	3,343	3,355	3,769	3,386	3,965	3,646	4,158	4,032
038	2005-02	41,751	41,520	42,473	43,878	40,273	45,003	43,974	47,562	46,443	47,859
039	2004-11	24,204	24,558	23,413	24,778	23,730	23,947	23,871	21,237	23,040	22,325
040	2005-02	924	941	948	930	878	993	940	1,039	966	1,003
041	2006-01	93	91	84							
042	2004-12	126,310	124,064	126,656	127,706	140,402	128,252	118,238	131,263	125,260	134,220
043	2004-11	133,823	151,832	175,525	189,602	192,187	179,567	192,184	180,484	194,915	194,307

Table 65: Data Series 022–043, Part 3 (See Drug Series-concordance, table 54)

Series	Start	Series Values – Part 4					
022	2006-02	25	36	40	55	52	79
023	2005-12	65,860	67,760	63,790	64,024	65,377	60,094
024	2005-12	1	-	-	-	-	2
025	2005-08	67,632	70,411	67,859	68,855	65,860	67,760
026	2006-01						
027	2006-11						
028	2006-10						
029	2005-05	25,844	26,593	26,593	25,001	26,478	25,930
030	2005-06	8	3	3	3	4	4
031	2006-02						
032	2005-09	3	9	18	-	1	5
033	2005-03	498	542	415	408	400	330
034	2004-11	11,614	10,435	8,844	9,790	10,566	12,276
035	2004-12	9	12	8	10	8	9
036	2004-09	5,055	4,649	5,227	4,959	5,248	5,314
037	2005-01	4,167	4,251	4,023	4,565	4,434	4,273
038	2005-02	48,752	45,801	49,719	48,915	49,970	51,528
039	2004-11	23,973	22,969	23,259	23,284	21,780	23,994
040	2005-02	1,001	952	1,023	962	1,003	949
041	2006-01						
042	2004-12	139,057	139,896	143,283	131,917	143,085	141,639
043	2004-11	207,073	183,146	157,635	171,211	191,508	211,749

Table 66: Data Series 022–043, Part 4 (See Drug Series-concordance, table 54)

Series	Start		Series Values – Part 1								
044	2004-05	4,118	4,452	4,743	4,508	4,617	4,462	4,717	4,956	4,606	4,343
045	2004-05	1,804	1,861	1,722	1,792	1,593	1,645	1,811	1,631	1,590	1,482
046	2004-06	13,669	10,809	10,148	13,199	15,519	14,902	17,553	22,103	20,720	20,408
047	2004-09	3	7	5	5	-	6	3	1	-	15
048	2004-06	284,898	285,380	275,448	273,219	271,880	274,723	283,164	266,162	245,900	272,053
049	2005-09	13	2	18	15	12	**3**	16	7	47	46
050	2004-07	9,312	8,826	8,991	9,355	10,409	11,691	9,182	8,834	10,154	9,689
051	2004-06	81,873	84,648	82,692	83,135	85,120	86,844	92,268	84,203	79,920	90,409
052	2004-03	2,047	3,619	5,249	4,930	4,547	5,287	7,431	9,442	10,795	10,294
053	2005-02	8	1,452	3,055	5,415	6,378	7,045	8,262	9,371	**9667**	10,114
054	2004-03	242,947	235,533	238,506	249,385	247,872	243,221	249,887	348,441	283,214	241,888
055	2004-03	40,142	38,836	39,885	42,338	42,881	41,064	42,986	42,683	43,928	44,344
056	2004-03	16,762	16,318	16,026	16,135	16,147	14,944	15,398	16,284	15,765	17,411
057	2004-03	100	118	119	179	137	183	150	172	216	192
058	2004-05	5,582	5,935	6,107	5,695	6,190	6,459	6,586	6,692	6,625	6,226
059	2004-03	54,413	53,511	52,123	54,646	53,033	53,311	51,491	50,184	51,874	48,659
060	2004-03	302,361	284,508	283,757	284,898	285,380	275,448	273,219	271,880	274,723	283,164
061	2004-03	31,959	30,801	30,151	30,705	31,089	28,916	30,237	31,083	31,889	33,400
062	2004-03	6,896	6,649	6,375	6,583	6,634	6,224	6,064	6,084	6,328	6,292
063	2004-03	1,122	1,117	1,092	1,118	1,100	992	942	879	935	922
064	2004-03	913	909	872	877	972	846	967	851	951	974

Table 67: Data Series 044–064, Part 1 (See Drug Series-concordance, table 54)

Series	Start	Series Values – Part 2									
044	2004-05	4,887	4,393	4,650	4,837	4,843	5,240	5,107	5,073	5,227	**5438**
045	2004-05	1,666	1,620	1,760	1,547	1,493	1,610	1,628	1,533	1,520	**1083**
046	2004-06	18,315	17,795	15,185	12,444	13,434	15,635	18,576	18,379	16,667	**16763**
047	2004-09	14	17	10	5	8	23	12	**20**	15	4
048	2004-06	256,901	264,265	258,181	249,534	258,963	254,909	255,195	256,588	261,425	**255342**
049	2005-09	53	69	55	77	31	34	18	17	13	16
050	2004-07	10,534	10,854	10,573	11,639	11,149	11,594	11,793	12,308	12,236	**10996**
051	2004-06	87,784	92,212	93,145	91,134	96,609	94,632	98,171	100,017	103,778	**99942**
052	2004-03	12,039	4,291	98	4	17	1	-	96	**3037**	4,856
053	2005-02	10,429	10,436	10,390	11,749	11,345	12,436	12,373	11,433	12,635	13,314
054	2004-03	161,623	145,211	163,900	156,760	163,241	163,558	161,281	172,195	168,220	**166911**
055	2004-03	39,667	38,233	43,196	40,507	43,676	43,704	41,720	44,270	43,076	**42256**
056	2004-03	15,728	14,713	16,066	15,079	15,535	14,940	14,254	14,481	14,603	**15163**
057	2004-03	142	86	103	84	58	65	58	60	**65**	55
058	2004-05	7,132	6,718	7,346	7,573	7,111	7,661	7,855	7,991	7,941	**7428**
059	2004-03	47,392	41,458	44,173	41,749	41,696	40,571	**36833**	37,863	35,564	33,956
060	2004-03	266,162	245,900	272,053	256,901	264,265	258,181	249,534	258,963	254,909	**255195**
061	2004-03	29,064	26,939	29,570	27,959	28,875	28,376	27,194	27,867	27,848	**28525**
062	2004-03	5,281	4,943	5,499	5,096	5,152	5,222	5,063	5,385	**5176**	3,417
063	2004-03	674	568	606	502	514	472	455	556	**451**	464
064	2004-03	799	789	876	800	784	833	725	780	736	**785**

Table 68: Data Series 044–064, Part 2 (See Drug Series-concordance, table 54)

Series	Start	Series Values – Part 3									
044	2004-05	5,203	4,772	5,558	5,103	5,825	5,843	6,114	6,424	6,036	6,603
045	2004-05	726	401	347	280	257	146	170	155	140	121
046	2004-06	13,801	13,347	12,287	11,671	10,526	8,168	8,638	9,315	10,318	10,059
047	2004-09	11	15	15	15	14	10	3	4	8	2
048	2004-06	232,446	260,288	237,449	256,923	249,221	242,144	252,810	241,494	251,401	248,039
049	2005-09	9	18								
050	2004-07	12,793	11,914	13,976	13,583	13,774	14,338	14,145	14,988	14,997	15,433
051	2004-06	92,467	106,021	97,165	106,685	106,127	105,050	109,605	106,124	112,959	112,024
052	2004-03	6,727	7,111	7,812	8,186	9,644	9,606	11,072	10,040	8,229	9,501
053	2005-02	14,673	15,104	15,396	16,154	15,270					
054	2004-03	167,760	169,726	164,998	154,358	177,681	167,384	187,522	185,017	175,819	183,806
055	2004-03	42,608	43,348	42,503	39,374	44,868	41,212	45,652	44,519	42,946	45,819
056	2004-03	14,833	15,603	14,634	13,314	14,589	13,638	14,692	14,005	14,079	14,219
057	2004-03	43	43	43	40	35	34	42	29	31	20
058	2004-05	7,111	6,366	7,245	6,676	7,628	7,761	7,601	8,093	7,864	8,560
059	2004-03	33,215	31,982	32,643	27,960	30,293	27,032	29,706	28,787	27,388	28,720
060	2004-03	256,588	261,425	255,342	232,446	260,288	237,449	256,923	249,221	242,144	252,810
061	2004-03	28,378	30,347	28,405	25,873	29,086	26,479	28,486	27,180	24,231	23,985
062	2004-03	2,414	1,940	1,588	1,157	1,090	840	822	720	657	603
063	2004-03	493	484	486	487	551	476	565	517	545	548
064	2004-03	777	762	711	625	659	637	642	711	631	672

Table 69: Data Series 044–064, Part 3 (See Drug Series-concordance, table 54)

Series	Start	Series Values – Part 4					
044	2004-05	6,514	6,614	6,846	6,169	6,869	6,683
045	2004-05	88	82	65	55	67	24
046	2004-06	8,471	10,840	10,209	10,828	10,488	11,614
047	2004-09	6	9	23	25		
048	2004-06	250,783	254,827	227,782	252,437	240,073	254,401
049	2005-09						
050	2004-07	16,286	14,740	16,704	16,458	17,910	17,492
051	2004-06	116,028	118,010	108,743	125,948	120,642	125,037
052	2004-03	11,622	13,170	14,239	13,431	14,292	
053	2005-02						
054	2004-03	178,314	191,344	194,892	196,287	195,017	173,439
055	2004-03	43,831	46,877	46,147	46,486	49,953	44,571
056	2004-03	14,494	15,004	14,884	15,362	15,129	13,563
057	2004-03	15	14	13	16	17	
058	2004-05	8,253	8,436	8,684	7,873	8,979	8,743
059	2004-03	25,543	27,015	26,463			
060	2004-03	241,494	251,401	248,039	250,783	254,827	227,782
061	2004-03	23,406	24,929	24,114	25,311	24,696	21,898
062	2004-03	483	405	358	307	256	
063	2004-03	549	535	567	531	559	
064	2004-03	620	684	684	670	616	552

Table 70: Data Series 044–064, Part 4 (See Drug Series-concordance, table 54)

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