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RESEARCH NOTE

Segmented regression analysis of interrupted time series studies in medication use research

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SUMMARY

Interrupted time series design is the strongest, quasi-experimental approach for evaluating longitudinal effects of interventions. Segmented regression analysis is a powerful statistical method for estimating intervention effects in interrupted time series studies. In this paper, we show how segmented regression analysis can be used to evaluate policy and educational interventions intended to improve the quality of medication use and/or contain costs.

Keywords: **health policy evaluation, interrupted time series design, longitudinal analysis, medication use research, quasi-experimental design, segmented regression analysis**

INTRODUCTION

Increasingly, educational, administrative and policy interventions are being carried out to improve the quality of medication use and/or contain costs. Such interventions can be implemented at the institutional, regional or national level. For example, a health care organization might conduct education and feedback to its physicians to encourage the use of a preferred histamine-2-receptor antagonist (H2RA) (1). A state might initiate a limit on the number of paid medications per patient per month (2). A federal programme like Medicaid might cease to reimburse for categories of drugs deemed ineffective (3) or a drug with unfavourable side-effects can be withdrawn from the market (4).

Interrupted time series (5, 6) is the strongest, quasi-experimental design to evaluate longitudinal effects of such time-delimited interventions. Segmented regression analysis of interrupted time series data allows us to assess, in statistical terms, how much an intervention changed an outcome of interest, immediately and over time; instantly or with delay; transiently or long-term; and whether factors other than the intervention could explain the change.

Segmented regression analysis is appropriate for studying effects of interventions conducted as part of a randomized trial as well as interventions that constitute a natural experiment. It requires data on continuous or counted outcome measures, summarized at regular, evenly spaced intervals.

The objective of this Research Note is to describe segmented regression analysis in the context of medication use research. Whereas prospective data collection for interrupted time series studies is feasible (7), the present discussion excludes aspects of data collection and focuses on analysis and interpretation of time series data. Our examples consist of studies using existing, computerized databases.

Definitions and parameters of interest

A time series is a sequence of values of a particular measure taken at regularly spaced intervals over time. Segments in a time series are defined when the sequence of measures is divided into two or more portions at change points. Change points are specific points in time where the values of the time series may exhibit a change from the previously established pattern because of an identifiable

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real-world event, a policy change, or an experimental intervention. The choice of the beginning and end of each segment depends on the beginning and end of the intervention, with the possible addition of some pre-specified lag time to allow the intervention to take effect. Segmented regression analysis is a method for statistically modelling the interrupted time series data to draw more formal conclusions about the impact of an intervention or event on the measure of interest.

Two parameters define each segment of a time series: level and trend. The level is the value of the series at the beginning of a given time interval (i.e. the *y*-intercept for the first segment and the value immediately following each change point at which successive segments join). The trend is the rate of change of a measure (in other words, the slope) during a segment. In segmented regression analysis, each segment of the series is allowed to exhibit both a level and a trend. The analyst examines the changes in level and/or trend that follow an intervention. A change in level, e.g. a jump or drop in the outcome after the intervention, constitutes an abrupt intervention effect. A change in trend is defined by an increase or decrease in the slope of the segment after the intervention as compared with the segment preceding the intervention. A change in trend represents a gradual change in the value of the outcome during the segment. Segmented regression analysis (see below) uses statistical models to estimate level and trend in the pre-intervention segment and changes in level and trend after the intervention (or interventions).

Figure 1 shows the time series of mean numbers of dispensed prescriptions per patient per month in a cohort of 860 New Hampshire Medicaid enrolees who received on average three or more drugs per month in the baseline year (2). Beginning in September 1981, New Hampshire's Medicaid programme restricted the number of prescriptions reimbursed to a maximum of three per patient per month to decrease state medication expenditures. Implementation of the three-drug payment limit, or cap, interrupts the time series and creates the two segments of interest. An abrupt level change in the mean number of prescriptions, from about five per patient to fewer than three per patient, followed the cap. There was very little month-to-month change (or trend) in the number of prescriptions before as well as after the cap.

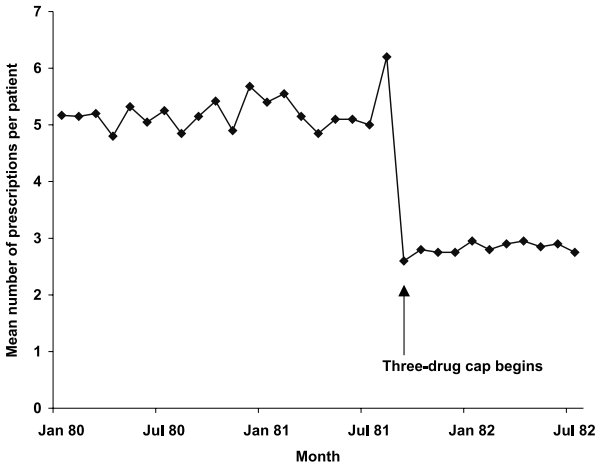

Fig. 1. Average number of constant-size prescriptions per continuously eligible Medicaid patient per month among multiple drug recipients (2).

DATA SOURCES AND MEASURES

Segmented regression analysis requires data collected regularly over time, and organized at equally spaced intervals. Routinely maintained medication use and other health care records, as well as cost data, are commonly used sources of time series data. They include pharmacies' dispensing files, medical records, insurance claims databases that contain pharmacy dispensing, hospital discharge and outpatient clinic records. Birth, death and chronic disease registry records are other routinely collected data. Although these data are not gathered for research purposes, they often provide reliable measures of relevant dependent variables for time series studies of drug use.

Outcome measures for time series studies can include medication use, utilization of other health services or clinical measures. Outcomes can be expressed as averages, proportions or rates. Examples of drug use-related measures are the average number of drugs prescribed per patient, average antibiotic prescription cost, percent of enrolees receiving a particular drug or percent of patients treated according to guidelines. Examples of other service utilization would be average length of hospital stay or monthly rate of admission to nursing homes, whereas clinical measures might include average diastolic blood pressure in a group of patients, or percentage diabetic patients achieving adequate glucose control.

A sufficient number of time points before and after the intervention is needed to conduct segmented regression analysis. A general recommendation is for 12 data points before and 12 data points after the intervention (8), although this number is not based on estimates of power. Rather, with 24 monthly measures, the analyst can adequately evaluate seasonal variation (see below). There also needs to be a sufficient number of observations [a minimum of 100 is desirable (8)] at each data point of the time series to achieve an acceptable level of variability of the estimate at each time point.

STATISTICAL ANALYSIS AND INTERPRETATION

Estimating changes in level and trend through segmented regression

One of the greatest strengths of interrupted time series studies is the intuitive graphical presentation of results, and a visual inspection of the series over time is the first step when analysing time series data. Visually, we compare the time series pattern before the intervention with the pattern after the intervention and assess if, after the intervention, the time series pattern has changed noticeably in relation to the pre-intervention pattern. Looking at the data points in Fig. 1, we would have expected the pre-intervention series to continue at an average of about five prescriptions per patient per month had the prescription cap not occurred. Clearly, after the cap, the mean number of dispensed prescriptions was about half of what would have been expected.

Although we can often detect changes in level and/or trend of the measure of interest by looking at a time series, we cannot easily see whether changes in level and trend could be the result of chance alone or the factors other than intervention. To assess chance and control for other effects, segmented regression analysis is used.

Common segmented regression models fit a least squares regression line to each segment of the independent variable, time, and thus assume a linear relationship between time and the outcome within each segment. We can specify the following linear regression model to estimate the level and trend in mean numbers of prescriptions per patient before the three-drug cap and the changes in level and trend following the cap in New Hampshire:

$$Y_t = \beta_0 + \beta_1{}^*\text{time}_t + \beta_2{}^*\text{intervention}_t + \beta_3{}^*\text{time after intervention}_t + e_t \quad (1)$$

Here, Y_t is the mean number of prescriptions per patient in month t; *time* is a continuous variable indicating time in months at time t from the start of the observation period; *intervention* is an indicator for time t occurring before (intervention = 0) or after (intervention = 1) the cap, which was implemented at month 21 in the series; and *time after intervention* is a continuous variable counting the number of months after the intervention at time t, coded 0 before the cap and (time—20) after the cap. In this model, β_0 estimates the baseline level of the outcome, mean number of prescriptions per patient per month, at time zero; β_1 estimates the change in the mean number of prescriptions per patient that occurs with each month before the intervention (i.e. the baseline trend); β_2 estimates the level change in the mean monthly number of prescriptions per patient immediately after the intervention, that is, from the end of the preceding segment; and β_3 estimates the change in the trend in the mean monthly number of prescriptions per patient after the cap, compared with the monthly trend before the cap. The sum of β_1 and β_3 is the post-intervention slope. Using Model 1 to estimate level and trend changes associated with the intervention, we control for baseline level and trend, a major strength of segmented regression analysis. The error term e_t at time t represents the random variability not explained by the model. It consists of a normally distributed random error and an error term at time t that may be correlated to errors at preceding or subsequent time points (see below). Table 1 contains the parameter estimates from the linear segmented regression model (Model 1) of effects of the New Hampshire three-drug cap on mean monthly number of prescriptions per patient. It should be noted that there was a brief increase in the mean number of prescriptions per patient in the month before the cap, in anticipation of the cap. We excluded this value from the model (see below).

These results indicate that just before the beginning of the observation period, patients received on average five prescriptions per month. Before the cap, there was no significant month-to-month change in the mean number of prescriptions (P-value for baseline trend = 0·6128). Right after the cap, the estimated mean number of

Table 1. Parameter estimates, standard errors and *P*-values from the full and most parsimonious segmented regression models predicting mean monthly numbers of prescriptions per patient in New Hampshire over time

	Coefficient	Standard error	*t*-statistic	*P*-value
a. Full segmented regression model				
Intercept β_0	5·1389	0·0748	68·69	<0·0001
Baseline trend β_1	0·003481	0·006791	0·51	0·6128
Level change after cap β_2	−2·5931	0·1572	−16·49	<0·0001
Trend change after cap β_3	0·0263	0·0193	1·36	0·1849
b. Most parsimonious segmented regression model				
Intercept β_0	5·1677	0·0311	166·38	<0·0001
Level change after cap β_2	−2·3736	0·0563	−42·14	<0·0001

prescriptions dropped abruptly by 2·6 prescriptions per month. There was no significant change in the month-to-month trend in the mean number of prescriptions after the cap (*P*-value for trend change = 0·1849). After stepwise elimination of non-significant terms, the most parsimonious model contained only the intercept and the significant level change in the mean number of prescriptions (Table 1b).

Expressing intervention effects

When expressing the results of segmented regression modelling, we can either report level and trend changes like those in Table 1a or 1b, or we can compare estimated post-intervention values of the outcome to values estimated at that time but based on baseline level and trend only, as if the intervention had not occurred (the counterfactual value). We can express the intervention effect as the absolute difference between the predicted outcome based on the intervention and the counterfactual value, or as the ratio of the predicted to the counterfactual value (usually expressed as a percentage increase or decrease). To estimate the cap effect in New Hampshire, let us express the expected results from regression equation 1 at month 26, which is six months after the three-drug cap was implemented:

$$\hat{Y}_{26(with\ policy)} = \hat{\beta}_0 + \hat{\beta}_1 \times 26 + \hat{\beta}_2 \times 1 + \hat{\beta}_3 \times 6 \qquad (2)$$

Now, let us consider the regression equation 1 at month 26, had the policy not been implemented (i.e. without any post-intervention effects in the model):

$$\hat{Y}_{26(without\ policy)} = \hat{\beta}_0 + \hat{\beta}_1 \times 26 \qquad (3)$$

The difference between equations 2 and 3, $\hat{Y}_{26(with\ policy)} - \hat{Y}_{26(without\ policy)} = \hat{\beta}_2 + \hat{\beta}_3 \times 6$ is the estimate of the absolute policy effect. The relative change in outcome associated with the policy is $(\hat{Y}_{26(with\ policy)} - \hat{Y}_{26(without\ policy)})/\hat{Y}_{26(without\ policy)}$, which can be expressed as a percentage change by multiplying by 100.

Using results in Table 1b, we estimated that in month 26, patients received on average 2·8 prescriptions per month. Had the cap not been introduced, the mean number of prescriptions per patient per month would have been 5·2. Thus, the average number of prescriptions per patient per month decreased by 2·4, or 46% (95% confidence interval −44%, −48%) after the cap was implemented, compared with what it would have been without the cap.

Estimating changes in time series with more than one change point

Segmented regression models can specify more than one change point. For example, one may be interested in the effects of different components of an intervention introduced at different time points, or in the effects of an intervention that was implemented and later withdrawn. One may also want to control for changes in level and slope of the series that are caused by reasons other than the policy. A model with two change points would be:

$$\begin{aligned} Y_t = {} & \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention1_t \\ & + \beta_3 \times time\ after\ intervention1_t \\ & + \beta_4 \times intervention2_t \\ & + \beta_5 \times time\ after\ intervention2_t + e_t \end{aligned} \qquad (4)$$

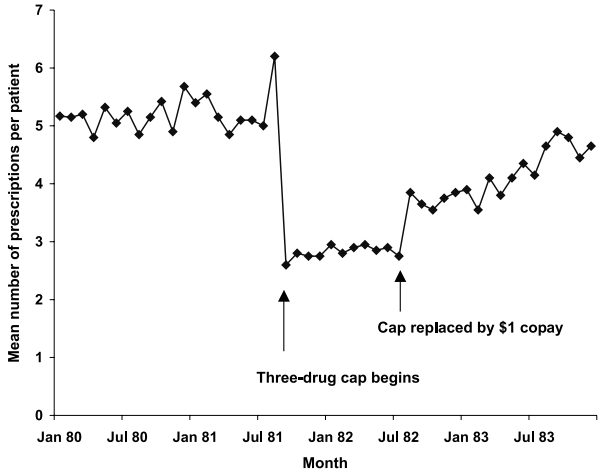

Fig. 2. Average number of constant-size prescriptions per continuously eligible Medicaid patient per month among multiple drug recipients (2).

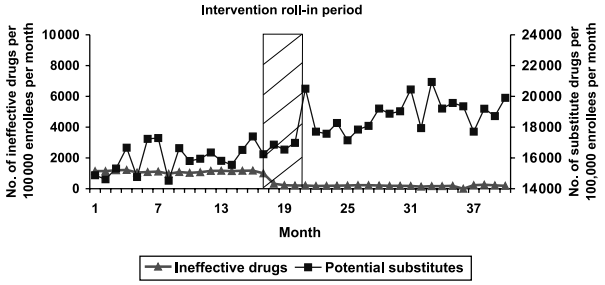

Fig. 3. Dispensings per 100 000 eligible New Jersey Medicaid patients for all ineffective drugs and for potential substitutes before and after implementation of reimbursement limit (3).

Figure 2 contains an example of a time series with two change points of substantive interest, which can be modelled using Model 4. Eleven months after its implementation, New Hampshire's Medicaid office replaced the three-drug cap with a $1 copay, without restriction of the number of drugs per patient per month. Figure 2 shows the time series of the mean number of prescriptions per patient per month, interrupted by the two policy changes. After the $1 copay had replaced the cap, average prescription rates rose again, both in level and slope (to approximately 4·7 prescriptions per patient per month by the end of the observation period) (2).

Additional change points may also serve to control for changes in the series that are not of primary interest but may influence the results. Examples include discontinuities in the series at time points other than that of the intervention because of administrative changes and lagged or multi-period interventions.

Modelling lagged effects and interventions that occur over several periods

Effects of interventions may take time to manifest. Soumerai *et al*. studied the effects of cessation of reimbursement by Medicaid of 141 drugs deemed ineffective on use of substitute medications (3). Not all patients filled a prescription each month. After withdrawal of the ineffective drugs, there was a brief transition period of two to three months until patients were placed on substitute regimens (Fig. 3). That is, there was a two to three months lag in the effect of the intervention. Similarly, intervention effects may occur over several periods, as and when an educational programme is rolled out in a health system. It is important to account for lags and multi-period interventions in the analysis to avoid incorrect specification of intervention effects. To model these effects, one can exclude from the analysis outcome values that occur during the lag or 'during intervention' period. Alternatively, with enough data points, one can model the period as a separate segment.

Data organization and layout

Table 2 illustrates the data structure for the analysis of the effects of the New Hampshire Medicaid programme interventions. The aggregated outcome measure, mean number of prescriptions, is calculated at each monthly time point. We specified a pre-intervention trend variable and two level and trend change variables, one each for the three-drug cap and the $1 copay.

Different definitions of the time variable in segmented regression analysis are possible (9). For example, time could be rescaled so that the starting point of the intervention is coded as month 1, with time being measured backward and forward from that point. Alternatively, time at the point of interest, for example six months after the intervention, could be coded as 1, with time counted backward and forward from there. Recoding time in these ways only changes the interpretation of the

Table 2. Structure of data for analysis of the impact of two policy changes on mean number of prescriptions per patient (Fig. 2) (2)

Observation	Mean number of prescriptions per patient	Time (month)	Intervention 1 (three-drug cap)	Time after intervention 1	Intervention 2 ($1 Copay)	Time after intervention 2
1	5·17	1	0	0	0	0
2	5·15	2	0	0	0	0
3	5·2	3	0	0	0	0
4	4·8	4	0	0	0	0
5	5·32	5	0	0	0	0
6	5·05	6	0	0	0	0
7	5·25	7	0	0	0	0
8	4·85	8	0	0	0	0
9	5·15	9	0	0	0	0
10	5·42	10	0	0	0	0
11	4·9	11	0	0	0	0
12	5·68	12	0	0	0	0
13	5·4	13	0	0	0	0
14	5·55	14	0	0	0	0
15	5·15	15	0	0	0	0
16	4·85	16	0	0	0	0
17	5·1	17	0	0	0	0
18	5·1	18	0	0	0	0
19	5	19	0	0	0	0
20	6·2	20	0	0	0	0
21	2·6	21	1	1	0	0
22	2·8	22	1	2	0	0
23	2·75	23	1	3	0	0
24	2·75	24	1	4	0	0
25	2·95	25	1	5	0	0
26	2·8	26	1	6	0	0
27	2·9	27	1	7	0	0
28	2·95	28	1	8	0	0
29	2·85	29	1	9	0	0
30	2·9	30	1	10	0	0
31	2·75	31	1	11	0	0
32	3·85	32	1	12	1	1
33	3·65	33	1	13	1	2
34	3·55	34	1	14	1	3
35	3·75	35	1	15	1	4
36	3·85	36	1	16	1	5
37	3·9	37	1	17	1	6
38	3·55	38	1	18	1	7
39	4·1	39	1	19	1	8
40	3·8	40	1	20	1	9
41	4·1	41	1	21	1	10
42	4·35	42	1	22	1	11
43	4·15	43	1	23	1	12
44	4·65	44	1	24	1	13
45	4·9	45	1	25	1	14
46	4·8	46	1	26	1	15
47	4·45	47	1	27	1	16
48	4·65	48	1	28	1	17

intercept. It does not change the absolute or relative measures of effect.

Correcting for correlation between values of the outcome measure over time

Ordinary least squares regression analysis assumes that error terms associated with each observation (e.g. the differences between the actual outcome value and those predicted from the regression model) are uncorrelated. As time is a predictor in segmented regression analysis, error terms of consecutive observations are often correlated. Prescribing patterns and other health outcomes at two time points that are close to each other may be more similar than outcomes at two time points further apart, resulting in serial autocorrelation of the error terms. Correlation between adjacent data points is termed first-order autocorrelation; correlation between the current point and two months before or after would be second-order autocorrelation and so forth. There may also be seasonal patterns in monthly time series, where prescribing in January of one year is more similar to prescribing in January a year ago than to prescribing in other months. This is an example of higher-order autocorrelation.

Failing to correct for autocorrelation may lead to underestimated standard errors and overestimated significance of the effects of an intervention. Fortunately, one can detect autocorrelation in time series data and available statistical software can control for it. For details on the use of proc autoreg in SAS, please see (10).

To detect autocorrelation, one can visually inspect a plot of residuals against time and conduct statistical tests. Randomly scattered residuals, without a pattern, indicate that there is no autocorrelation (11). Positive autocorrelation exists when consecutive residuals tend to lie on the same side of the regression line; negative autocorrelation exists when consecutive residuals tend to lie on different sides of the regression line (11).

The Durbin–Watson statistic, reported by most least squares regression programs, tests for serial autocorrelation of the error terms in the regression model (11, 12). Values close to 2·00 indicate no serious autocorrelation. Adjustment for autocorrelation involves estimating the autocorrelation parameter and including it in the segmented regression model if necessary. After controlling for autocorrelation, the Durbin–Watson statistic for the final regression model of the New Hampshire cap effects was 2·0822 (*P*-value for hypothesis of positive autocorrelation = 0·5149, *P*-value for hypothesis of negative autocorrelation = 0·4851), indicating no autocorrelation.

Controlling for seasonal changes in series

Time series sometimes exhibit seasonal fluctuations. Use of many drugs varies seasonally because of cyclic variations in the illnesses for which they are prescribed. Detecting seasonality requires baseline series that span enough periods to detect these cyclic patterns. If seasonality exists, it is important to control for it when estimating intervention effects, so that estimated effects are more likely to represent true intervention effects. Including terms to indicate each season in a regression model decreases confounding by seasonality.

When seasonal variation exists, errors for a particular month may be more correlated with errors at the same month one year earlier, than with errors in other months. To estimate this seasonal autocorrelation, the auto-regression model needs to evaluate correlations between error terms separated by multiples of 12 months. Accounting for seasonally correlated errors usually requires at least 24 monthly data points.

Controlling for wild data points

Extreme values that do not seem to fit in the series, referred to as wild data points, may occur in time series. Sometimes these points can be explained. An example might be a sudden peak in drug use a month before a restriction policy is implemented (e.g. 'anticipatory demand'), as occurred in New Hampshire just prior to implementation of the three-drug cap (Figs 1 and 2). At other times, these outliers might be because of measurement error. If the analyst knows the underlying explanation for a wild data point, or is fairly confident that it results from measurement error, the point can be controlled for in the model by entering an indicator variable that has value 1 in that period and 0 in all others. However, if wild data points are likely caused by random variation, they should be treated

as regular data points. Alternatively, one could carry out the analysis with and without the wild data point to evaluate its impact.

Controlling for possible biases

Interrupted time series designs are immune to many of the threats to validity of weaker quasi-experimental and other observational designs. In particular, when segments are properly specified, potential confounding in time series studies is limited to factors that are related to the outcome of interest and that changed at the time of the intervention. Those include effects of simultaneously occurring interventions (known as 'cointerventions'), seasonal changes in the outcome that happen during the time of the intervention, changes in the composition of the study population, or changes in the measurement of the outcome occurring at the time of the intervention. Separating intervention effects from effects that occur at the same time requires use of a control group that is not exposed to the intervention. We discuss below three choices of control groups for interrupted time series studies.

Over the course of a longitudinal study, the composition of the study population may change with respect to characteristics that predict the outcome and could be related to the intervention. For example, a change in the average proportion of elective Cesarean sections could confound the results of a study of the effects on infection rates of continuous quality improvement efforts to prevent surgical site infections after Cesarean section (7). To control for possible confounding, aggregated monthly values of the number of deliveries per site, the percentage of deliveries by Cesarean section, and the percentage of non-elective Cesarean sections were included in the segmented regression models (7).

Changes in the definitions and/or measurement of variables may introduce bias in a time series study. Scrutinizing the consistency of recording is particularly important when using routinely collected, automated data that frequently form the basis for interrupted time series studies.

Control groups in time series studies

At least three types of controls are possible in interrupted time series studies. The control can be a different group of subjects, or be represented by a related but different outcome not expected to change following the intervention, in the same group of subjects. Ideally, a control group that is identical to the study group but does not experience the intervention is followed over the same time period as the intervention group. Comparing the effect in the intervention group with that in the control group then allows separating the intervention effect from others that may have occurred at the same time. Figure 4 shows the effect of New Hampshire's cost-containment policies on a major health outcome, nursing home admissions (13). Because residents tend to stay in nursing homes long-term, the percentage of chronically ill enrolees residing in nursing homes increased over time in the control state, New Jersey, which did not implement either cost-containment strategy. However, the percentage of nursing home residents increased more steeply in New Hampshire than in the control state. Because of either deteriorating health when drugs were discontinued or a desire to shift to an environment exempt from the cap, limiting access to medications was associated with increased admission to nursing homes among low-income, elderly Medicaid patients; and resulting nursing home stays were long-term.

When a separate control group is not available, evaluating a related but different outcome within the intervention group that should not be influenced by the intervention can identify changes that would have occurred independently of the intervention. For example, in the study of reimbursement changes for ineffective drugs (3),

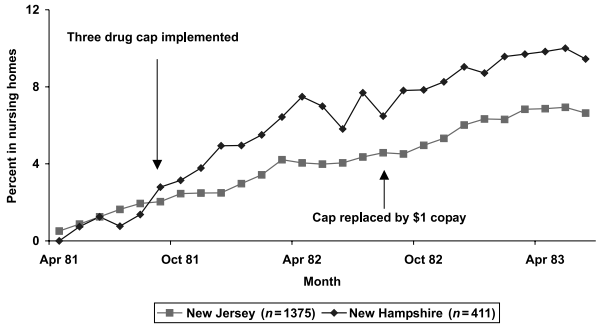

Fig. 4. Monthly percentages of study patients residing in nursing homes (13).

investigators compared use of ineffective drugs over time with use of drugs that were neither ineffective drugs nor plausible substitutes for the withdrawn drugs (insulin, digoxin and eye ointments) (3). Other policy or measurement changes that may have confounded the policy's effect on the use of ineffective drugs and their substitutes would have appeared as changes in the use of these control medications. Use of the control drugs was stable and suggested that the observed changes in the study drugs were in fact the result of the cessation of reimbursement, rather than some other factor that affected drug use in Medicaid (3).

Ross-Degnan *et al*. (4) used a somewhat different approach to defining a control group in the study of the effects on prescribing of other analgesics of market entry and withdrawal of zomepirac, a non-steroidal analgesic (NSAID). Even without zomepirac's market entry and withdrawal, the outcome, prescribing of other analgesics, could have changed over time. Market entry and exit of zomepirac, however, occurred nation-wide; theoretically leaving no control group that was not exposed to the interventions. When it entered the market, zomepirac prescribing rose within two months to 11% of total analgesic prescribing among certain physicians and remained remarkably constant at that level until it was withdrawn 28 months later. Other physicians never prescribed zomepirac at all. These physicians who never prescribed zomepirac could be considered unaffected by the market changes and the authors used them as a control group to examine changes in prescribing of non-zomepirac analgesics.

During the time zomepirac was on the market, use of other NSAIDs increased among physicians who never prescribed zomepirac, likely because of increased marketing efforts (Fig. 5). Controlling for this change in NSAID prescribing, the authors estimated that entry of zomepirac decreased the market share of other NSAIDs among physicians who prescribed it by 8·1% and that its withdrawal increased other NSAID use by 6·8% (4).

Analysis of the outcome of interest in the study group only is less desirable because it does not allow control for other events that may have influenced the outcome and that may have occurred at the same time as the intervention. However, because level and trend of the pre-intervention

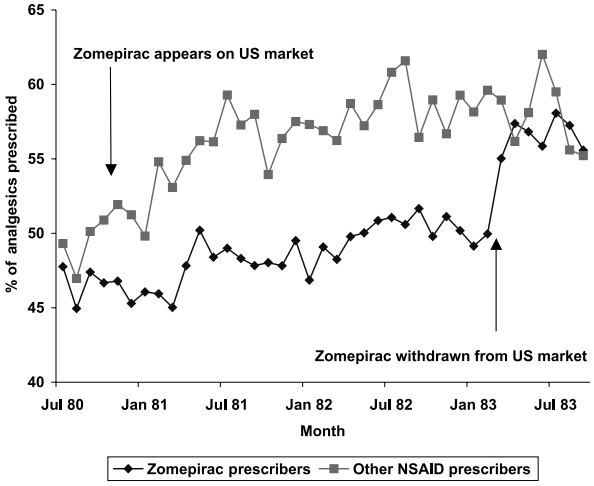

Fig. 5. Market share of other non-steroidal anti-inflammatory drugs prescribed by primary care physicians (4). Copyright © 1993. American Medical Association.

segment serve as control for the post-intervention segment, single group time series still address important threats to internal validity and represent a methodologically acceptable design for studying intervention effects (5, 14).

Stratification in time series studies

An intervention's effects may vary across different groups. When this is the case, intervention effects can be studied separately in each group. For example, Brufsky *et al*. (1) expected that effects of interventions to encourage prescribing of less costly cimetidine rather than other H2RA in a large health maintenance organization (HMO) would differ according to physicians' incentives to change prescribing patterns, which depended on their contractual arrangements with the HMO. The authors stratified the analysis and examined intervention effects among 'staff model' and 'group model' HMO physicians separately. They confirmed that effects of the interventions differed by contractual arrangement between the HMO and its physicians (1).

Specifying the final segmented regression model

Several different approaches exist for deciding which variables to include in a final model. Frequently, analysts begin by specifying the full regression model (Table 1a), including the baseline

trend, and all level and trend changes. This full model contains the largest number of covariates and may have the least power to detect significant predictors of the outcome. Therefore, non-significant variables are often removed. Through stepwise backward elimination (15), for example, one may select the most parsimonious model, that is, the one that only includes statistically significant predictors (at a predetermined significance level) (Table 1b). The full and most parsimonious models will not correctly estimate the effect of the intervention if confounders exist. Therefore, important measured confounders should be added to the model, regardless of statistical significance. For theoretical reasons, one may also include important non-significant predictors that may control for threats to validity, such as history or maturation (5). For example, the baseline trend is often added to the model, assuming that it is generally an important control variable for secular trends, regardless of statistical significance.

To assess the fit of the final model, we examine residuals around the predicted regression lines. Residuals that are normally distributed and that follow no observable pattern over time indicate that the assumptions underlying the linear model are met (15).

STRENGTHS OF SEGMENTED REGRESSION ANALYSIS

Randomized controlled trials are rarely possible to assess the impact of policy changes. Time series designs are the strongest, quasi-experimental designs to estimate intervention effects in non-randomized settings. In contrast to cross-sectional observational studies, segmented regression analysis of interrupted time series data allows analysts to control for prior trends in the outcome and to study the dynamics of change in response to an intervention.

Even without a control group, segmented regression analysis addresses important threats to internal validity (such as history and maturation) by making multiple assessments of the outcome variable both before and after the intervention. In contrast, cross-sectional analyses compare the outcome between groups at one point after the intervention and pre–post studies compare two points, one before and one after the intervention. Both approaches may easily lead to invalid results because of the failure to control for pre-existing trends.

Interrupted time series also visually display the dynamics of response of a population to an intervention by showing whether an effect is immediate or delayed, abrupt or gradual, and whether or not an effect persists or is temporary. Segmented regression analysis can estimate the size of the effect at different time points, as well as changes in the trend of the effect over time.

LIMITATIONS OF SEGMENTED REGRESSION ANALYSIS

As with other analyses, there are limitations. The models we discussed assume a linear trend in the outcome within each segment. The assumption of linearity often may hold only over short intervals. Changes may follow non-linear patterns. For example, intervention effects may diffuse across a population with an increasing or decreasing curvilinear trend. Some effects can be accommodated in linear models by use of geometrically increasing or decreasing trend terms, but some non-linear trends may require other types of mathematical models such as Box-Jenkins models (16). Although these models are widely used for predicting future trends, they are of less use in examining changes in trend that occur at defined time points. In addition, medication use research frequently lacks the required minimum of 50 time points for employing these models.

Segmented regression typically aggregates individual-level data by time point. For example, in the study of the New Hampshire cost containment interventions, the investigators calculated mean monthly numbers of prescriptions per patient. The unit of analysis in the segmented regression model was the monthly mean prescription number, rather than each individual's number of prescriptions per month. Contrary to cross-sectional analysis methods, such as logistic regression, segmented regression analysis of time series data does not allow control for individual-level covariates. Individual-level characteristics, however, would only confound the time series results if they predicted the outcome and changed in relationship to the time of the intervention.

SUMMARY

In summary, segmented regression analysis of interrupted time series data is a robust modelling technique that allows the analyst to estimate dynamic changes in various processes and outcomes following interventions intended to change medication use, while controlling for secular changes that may have occurred in the absence of the intervention.

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