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# Using Joinpoint Regression for Drug Utilization Research: Tutorial and Case Study of Prescription Opioid Use in the United States

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| **Abstract:** | Background<br>Drug utilization researchers are often interested in evaluating prescribing and medication use patterns and trends over a specified period of time. Joinpoint regression is a useful methodology to identify any deviations in secular trends without a preconceived notion of where these break points might occur.<br>Objective<br>To provide a step-wise tutorial on the use of joinpoint regression for the analysis of drug utilization data.<br>Methods<br>The tutorial offers an introduction on joinpoint regression followed by a step-by-step application to a case study focusing on national opioid prescribing in the United States. Data was obtained from public files available through the Centers for Disease Control and Prevention from 2006 to 2018. The tutorial provides parameters and sample data needed to replicate the case study and it concludes with general considerations for the reporting of results using joinpoint regression in drug utilization research.<br>Results<br>The case study evaluated the trend of opioid prescribing in the United States from 2006 to 2018 detecting time points of significant variation in 2012 and 2016.<br>Conclusion<br>Joinpoint regression is a helpful methodology for drug utilization to conduct descriptive analyses and corroborate assumptions and parameters for fitting other models such as interrupted time series. Despite being user-friendly, researchers interested in using joinpoint regression should follow best practices for correct measurement of drug utilization. |
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Cover Letter

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November 23, 2020

Shane Desselle, RPh, PhD, FAPhA
Editor-in-Chief
Research in Social and Administrative Pharmacy

Dear Dr. Deselle,

Please find enclosed the manuscript titled "**Using Joinpoint Regression for Drug Utilization Research: Tutorial and Case Study of Prescription Opioid Use in the United States**" for your consideration for the research methods themed issue in *Research in Social and Administrative Pharmacy*.

The purpose of this manuscript is to provide a tutorial for the use of the joinpoint regression methodology applied to drug utilization data. Drug utilization researchers are often interested in evaluating prescribing and medication use patterns and trends over a specified period of time. Joinpoint regression is a useful tool to identify any deviations in secular trends without a preconceived notion of where these break points might occur. While originally created for the analysis of cancer incidence in the United States, the joinpoint regression software can be easily repurposed for pharmacoepidemiology research and can be easily learned by researchers.

I confirm that this report has not been published elsewhere and is not under consideration by another journal. I look forward to receiving feedback from the editorial team on this submission, and I am grateful for the invitation to submit this manuscript to the themed issue.

Sincerely,

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## ABSTRACT

### Background

Drug utilization researchers are often interested in evaluating prescribing and medication use patterns and trends over a specified period of time. Joinpoint regression is a useful methodology to identify any deviations in secular trends without a preconceived notion of where these break points might occur.

### Objective

To provide a step-wise tutorial on the use of joinpoint regression for the analysis of drug utilization data.

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The case study evaluated the trend of opioid prescribing in the United States from 2006 to 2018 detecting time points of significant variation in 2012 and 2016.

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# Using Joinpoint Regression for Drug Utilization Research: Tutorial and Case Study of Prescription Opioid Use in the United States

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To provide a step-wise tutorial on the use of joinpoint regression for the analysis of drug utilization data.

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**Keywords:** Drug utilization; trend analysis; joinpoint regression; segmented regression; tutorial; opioids

## BACKGROUND

Drug utilization researchers are often interested in evaluating prescribing and medication use patterns and trends over a specified period of time.[1–3] While exploratory analyses can be carried out with simple descriptive statistics more often in the form of repeated cross-sectional study designs, some might want to evaluate effects of a policy or other intervention on these secular trends via before and after comparisons with inferential methods.[4] Interrupted time series (ITS) is a strong quasi-experimental study design used in drug utilization research and it allows for the estimation of immediate and trend (i.e. slope) changes over time controlling for pre-existing baseline trends.[5,6] Among several considerations in designing an ITS analysis, the selection of the time point in which the change is modeled (i.e. the interruption) must be determined a priori based on assumptions on the expected time to effect. Joinpoint regression is a useful methodology to identify any deviations in secular trends without a preconceived notion of where these break points might occur.

The Joinpoint trend analysis software was developed by IMS, Inc. under contract to the National Cancer Institute (NCI).[7] The program fits the simplest joinpoint model that the trend data allows and identifies significant points where trends change.[8] Joinpoint regression models, composed of continuous linear phases, are also referred to as piecewise regression, segmented regression, and broken line regression. The application of simple segmented regression with user-defined interruptions is well documented in the drug utilization literature.[9,10] While the joinpoint regression software was first created and is more often used to evaluate shifts in trend of cancer incidence over time, the program can be used in any outcome measure assessed over equally distributed time points such as the prevalence of medication use.[11,12] While a comprehensive review of statistics and underlying methodology applied in joinpoint is outside the scope of this introductory tutorial, methods papers can be found in the published literature for a description of the grid search method in segmented regression.[8,13,14] A detailed description of methods used in the joinpoint regression software can be found in the complete user manual published by NCI.[7]

In short, the Joinpoint regression model can be written as:

$$E[y|x] = \beta_0 + \beta_1 x + \delta_1(x - \tau_1)^+ + \ldots + \delta_k(x - \tau_k)^+$$

Where $\tau_k$ are the unknown change points (joinpoints), $\beta_1$ is the regression coefficient prior to first joinpoint, $\delta_k$ is the regression coefficient after joinpoint k, and. The software starts with a user-defined minimum number of joinpoints and tests whether more joinpoints are statistically significant compared to fewer ones using a permutation method with Monte Carlo samples.[8,15] This same process continues until the best-fitting model, with the least number of joinpoints is selected. The overall significance level is maintained using the Bonferroni correction method.

This article is divided in the following sections: First, I will offer an introduction to the steps needed to set up the software correctly to run a trend analysis on drug utilization data. Second, I will apply the same sequence of steps to a case study focusing on national opioid prescribing and I will provide the data and parameters needed for replication. Finally, I will discuss some considerations for reporting of results using joinpoint regression in drug utilization research.

## METHODS: TUTORIAL

Users can download the free desktop version of the Joinpoint Trend Analysis Software from the National Cancer Institute website (Version 4.8.0.1).[7] The Windows-based software application provides a visual interface that allows users to navigate through different screens to set up the parameters for each job. For purposes of this introductory tutorial, I will not cover the command-line version of the joinpoint regression software which can be called by other software programs and requires an Institutional Use Transfer Agreement.

### *Step 1: Data Preparation*

Prior to importing data into the joinpoint software, researchers must first define their research question and determine the unit of analysis for their outcome of interest related to the drug utilization study.[3] Data should be aggregated in equally distributed time intervals ensuring that there are no time points with missing information as this will

result in processing errors. To import data files in comma separated value, text, or excel file formats, users must start a new session in the “File” tab located in the main menu.

### *Step 2: Input File Specification*

The Input File window for the session will display the first 20 observations of the data and is the place where users specify the dependent and independent variables to model. The joinpoint regression software can model counts, proportions, and crude or age-adjusted rates. Each of these types of variables can be either provided in the source data file or calculated by the software. A best practice in drug utilization research is to opt for the use of proportions rather than absolute counts for prescribing and medication use data given the possibility of time-varying exposure at the population level. The latter can occur as a result of seasonal patterns of drug use (e.g. allergy medications) or dynamic changes in the population being studied. The Independent Variable must be a categorical indicator for each time unit (e.g. year) and must be sorted in ascending order. The “By Variable” option in the Input File window is blank by default but must be specified if the user is interested in conducting stratified or advanced analysis like those explained in *step 4*. The log transformation option must be selected if wishing to calculate the percent changes described in *step 6*.

### *Step 3: Selection of Methods and Parameters*

The Methods and Parameters window allows users to specify the minimum and maximum number of joinpoints to test using the Grid Search method.[8,13] In addition, there is an option to require the software to fit an autocorrelated errors model. Unless the researchers have absolute certainty that there is no autocorrelation in the data, it is preferable to allow the software to calculate the autocorrelation parameter. The overall significance level of 0.05 is maintained using the Bonferroni adjustment method for multiple hypothesis testing. The default number of permutations when using the permutation test for model selection is 4,500. A thorough description of BIC methods for model selection as well as the calculation of confidence intervals for the joinpoints through the parametric method or empirical quantiles can be found in the joinpoint software documentation.[7]

### *Step 4: Using Advanced Analysis Tools*

The Advanced Analysis Tools window in the session allow users to run more sophisticated models in scenarios when there is need to compare trends in two mutually exclusive groups (pairwise comparisons) or when there is a systematic scale change (e.g. coding practice change) known to the researchers that occurs during the time period studied (jump model or comparability ratio model). For pairwise comparisons such as the test of coincidence (i.e. testing the similarity or two joinpoint regression functions) or the test of parallelism (i.e. testing how parallel are the two regression mean functions), the user must first specify a “By Variable” in the input file window to stratify the data accordingly. To run a jump model or comparability ratio model, users must specify additional parameters such as the time point where the coding change occurs. For more information on these advanced techniques, please refer to the documentation by joinpoint regression.[7]

### *Step 5: Evaluating Output*

Once all parameters have been specified, users can submit the session using the “Execute Current Session” button on the main window menu. The run time for the software will depend on several factors and will generally take longer with a larger number of points in the data, a higher maximum number of joinpoints, a higher number of permutations required, and the selection of any advanced analyses. After the program runs successfully, the Output pop-up window will show the following tabs 1) Graph, 2) Data, 3) Model Estimates, and 4) Model Selection.

1) Graph. The default output window shows the plot of the data points and the fitted joinpoint model selected based on the permutation tests. Users can shift the view to select other joinpoint models tested and can adjust parameters of the graph in the “Output” tab in the main window menu. Customization of the graph output is limited to the title, axes features and labels, legend settings, and a few color and symbol options.

2) Data. This output window shows the observed and modeled dependent variable and the location of the joinpoints if any.

3) Model estimates. This output window shows the results of the selected joinpoint model and includes the model statistics, the estimated joinpoints with corresponding 95% confidence intervals, and the estimated regression coefficients. The general parameterization table shows the slopes between joinpoints and their tests for significance. The model estimates window also contains information on the autocorrelation parameter if specified in the Methods and Parameters.

4) Model Selection. The last output window shows the test for number of joinpoints with the corresponding Bonferroni-corrected critical alpha value.

***Step 6: Reporting Results***

The output window from step 5 can be saved as a .jpo file that can be re-opened in the joinpoint regression software at a later date. In addition, all or individual components of the results can be exported as text or excel files through the “Output” option located on the main window menu. In this export pop-up window, users can customize the formatting of files and figures to a certain extent. While the default graph might be sufficient for the user’s purposes, the exported files can be used in other software to build higher quality figures.

Finally, users might consider log-transformation in the Input File window for a second run of the session to obtain the Annual Percent Change (APC) and the Average Annual Percent Change (AAPC). While called “annual,” this procedure works for any time unit used for the input file (e.g. monthly, quarterly, weekly). These results might be easier to interpret and communicate to broader audiences as they represent a percent change between joinpoints (APC) and the calculated mean percent change between two time points during the study period (AAPC).

**CASE STUDY: National Opioid Prescribing Trends in the United States**

The opioid overdose epidemic in the United States continues to be an important public health issue. In 2017, there were 47,600 drug overdose deaths that involved an opioid in the country.[16] While the majority of these cases were attributed to non-prescription substances (e.g. illicit fentanyl and heroin), prescribing of opioid analgesic medications

continues to be scrutinized by regulatory agencies aiming to decrease their use across health care sectors. The objective of this case study was to identify any significant break points (i.e. joinpoints) in the drug utilization trend for opioid analgesics prescribed in the United States from 2006 to 2018 using joinpoint regression.

***Step 1: Data Preparation***

The data used in this case study was obtained from public files available through the Centers for Disease Control and Prevention (CDC)[17]. Using the IQVIA Xponent 2006–2018 as the source for nationally-representative drug utilization data, the CDC publishes the total number of opioid prescriptions and the prescribing rate per 100 persons in the United States at the national, state, and county-levels from 2006 to 2018. Table 1 shows the case study data containing the estimates of the annual total US population obtained from the US Census.[18] The prescribing rate was calculated by dividing the total number of opioid prescriptions by the total number of the US population for a given year.

***Step 2: Input File Specification***

In the “Dependent Variable” setting, I specified the run type to be calculated from the data file provided using the prescription count as the numerator and the total population variable as the denominator. The “Independent Variable” was the indicator column for each study year. In the first run, I did not specify a log transformation, but as seen in *step 6*, the model was log transformed on a second run to obtain APC and AAPC estimates. The supplementary material provides the sample data in .csv format and eTable 1 lists all the parameters used in the joinpoint regression model in the case study for replication purposes.

***Step 3: Selection of Method and Parameters***

Having a total of 13 data points in the sample data, the software set a maximum of 2 joinpoints in the Method and Parameters settings page. eTable2 shows the default maximum of joinpoints based on total number of data points in the input file. For the model selection method, I specified the permutation test with a total 4,500 permutations (default), and required the model to be fit with autocorrelated errors based on the data.

### *Step 4: Using Advanced Analysis Tools*

Since pairwise comparisons are of limited use for the specific research question of this case study utilizing national prescribing data, there were no advanced analyses specified. Researchers might consider parallelism or coincidence tests in scenarios for example comparing two different geographic units (e.g. two different states or counties), or two mutually exclusive groups if data allows such stratified analyses (e.g. utilization trends in female versus male patients, or trends in two distinct health programs).

### *Steps 5: Evaluating Output*

Fitting an autocorrelated errors model, Table 2 summarizes the results of the permutation tests obtaining p-values of <0.001 testing the null hypothesis of 0 joinpoints against the alternative of 2 joinpoints, and 0.014 testing 1 joinpoint against 2 joinpoints. Comparing the p-values to the Bonferroni-correct critical alpha value of 0.05/2, the null hypotheses are rejected and the 2-joinpoint model is selected as the final model. Joinpoints occurred in 2012 (95% CI 2008, 2013) and 2016 (95% CI 2011, 2016). (Figure 1) The estimated regression coefficients of the final model in Table 3 show that while there was an initial increase of 1.4 prescriptions/year/100 persons from 2006 to 2012, the slope of the prescribing trend decreased at a rate of 3.9 prescriptions/year/100 persons between 2012 and 2016 and 7.7 prescriptions/year/100 persons between 2016 and 2018.

### *Step 6. Reporting Results*

While the information on the slope between the joinpoints in the trend is helpful information to understand the rate of change per time-unit studied, this information might not be intuitive for some stakeholders. In a second run of the joinpoint model, I required the data to be log-transformed in order to calculate the APC and AAPC values shown in Table 4. Over the entire study period, there was a 3% reduction in the number of opioid prescriptions in the United States. The data points and the coefficients in the final model (Table 3) were exported into R statistical software version 3.6.1 (R Project for Statistical Computing) to generate Figure 1 that includes the fitted lines for all three joinpoint models tested and the APC for each segment in the selected two-joinpoint

model. The supplementary material provides a copy of the joinpoint output file (.jpo) and a copy of the default graph output from the software (eFigure 1).

## DISCUSSION

This article provides an overview of the joinpoint regression software and a step-by-step tutorial on the use of the publicly available software to study drug utilization trends. The case study evaluated the trend of opioid prescribing in the United States from 2006 to 2018 detecting time points of significant variation. Notably, this method was able to detect an inflection point in prescribing in 2012 and a significant rapid decrease in use starting in 2016. These time points are associated with important changes in the medicolegal landscape of opioid use in the United States resulting from a larger number of federal and state level policies intended to mitigate increasing rates of opioid-related overdose deaths.[19–22]

Despite not being used extensively in drug utilization research thus far, joinpoint regression is a useful tool to analyze real-world data to determine breaks in secular drug use trends. The methodology is particularly helpful to plan for inferential analyses like ITS and difference-in-difference (DID) designs where researchers must first determine the time point for the interruption. While strict legally enforced policies could be expected to result in immediate changes from the pre to the post-implementation period, other interruptions might not be quite as clear. Some policies for example might take time to produce an effect resulting in lead or lag times that need to be adjusted for in the model with the use of phase-in periods. There are also scenarios where there might be pre-emptive changes in the trends prior to the interruption or outlier values during the study period. Joinpoint regression can be used as an initial exploratory analysis to ensure assumptions made in the design of ITS and DID hold based on the observed data. There are times when there is no need to model an interruption and joinpoint regression can sufficiently describe the trends. Researchers must ensure that measurement error is minimized in the ascertainment of drug exposure in the database of interest.

When reporting results based on joinpoint regression analysese following a repeated cross-sectional study design, it is important to comply with manuscript reporting guidelines for observational studies such as STROBE[23], reporting guidelines for quality improvement studies like SQUIRE[24], and best practices for reporting of time series[4]. Even though this tutorial focused on drug utilization data, the joinpoint regression software can add to the toolboxes of other fields such as health services research and health policy. Since the software is limited to the estimation of linear trends, future research is warranted in the modeling of generalized linear or non-linear models.

## CONCLUSION

Joinpoint regression is a helpful methodology for drug utilization research to conduct descriptive analyses and corroborate assumptions and parameters for fitting other models such as interrupted time series. Despite being user-friendly, researchers interested in using joinpoint regression should follow best practices for correct measurement of drug utilization.

## ACKNOWLEDGMENTS

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## TABLES

**Table 1. Total number and prevalence of opioid prescriptions dispensed per year in the United States, 2006-2018**

| Year | Total Number of Opioid Prescriptions [a] | Total US Population [b] | Prescribing Rate per 100 Persons [c] |
|---|---|---|---|
| 2006 | 215,917,663 | 298,379,912 | 72.4 |
| 2007 | 228,543,773 | 301,231,207 | 75.9 |
| 2008 | 237,860,213 | 304,093,966 | 78.2 |
| 2009 | 243,738,090 | 306,771,529 | 79.5 |
| 2010 | 251,088,904 | 309,321,666 | 81.2 |
| 2011 | 252,167,963 | 311,556,874 | 80.9 |
| 2012 | 255,207,954 | 313,830,990 | 81.3 |
| 2013 | 247,090,443 | 315,993,715 | 78.1 |
| 2014 | 240,993,021 | 318,301,008 | 75.6 |
| 2015 | 226,819,924 | 320,635,163 | 70.6 |
| 2016 | 214,881,622 | 322,941,311 | 66.5 |
| 2017 | 191,909,384 | 324,985,539 | 59.0 |
| 2018 | 168,158,611 | 326,687,501 | 51.4 |

a. Source Centers for Disease Control and Prevention [17]
b. Source US Census Data[18]
c. (Total Number of Opioid Prescriptions / Total US Population) * 100

**Table 2. Permutation Test for Number of Joinpoints**

| Test Number [a] | Null Hypothesis | Alternate Hypothesis | P-Value | Significance Level [b] |
|---|---|---|---|---|
| 1 | 0 Joinpoint(s) | 2 Joinpoint(s) [c] | 0.0002222 | 0.025 |
| 2 | 1 Joinpoint(s) | 2 Joinpoint(s) [c] | 0.0135556 | 0.05 |

a. 4,500 permutations per test
b. Significance level for individual test (alpha = 0.05)
c. Final model selected

**Table 3. Estimated Regression Coefficients from Joinpoint Regression, US Opioid Prescribing [a]**

| Parameter | Parameter Estimate | Standard Error | Test Statistic (t) | Prob > \|t\| |
|---|---|---|---|---|
| Intercept 1 | 0.728 | 0.013 | 54.004 | <0.001 |
| Intercept 2 | 1.103 | 0.076 | 14.537 | <0.001 |
| Intercept 3 | 1.516 | 0.218 | 6.955 | <0.001 |
| Slope 1 | 0.014 | 0.003 | 4.368 | 0.007 |
| Slope 2 | -0.039 | 0.008 | -4.668 | 0.005 |
| Slope 3 | -0.077 | 0.017 | -4.414 | 0.007 |

a. See supplementary material for complete list of model specifications.

**Table 4. Estimated Annual Percent Changes (APC), US Opioid Prescribing**

| Segment | Lower Endpoint | Upper Endpoint | APC | 95% CI | Test Statistic (t) | Prob > \|t\| |
|---|---|---|---|---|---|---|
| 1 | 2006 | 2012 | -1.8 | 0.7, 2.9 | 4.2 | <0.001 |
| 2 | 2012 | 2016 | -5.1 | -7.9, -2.1 | -4.4 | <0.001 |
| 3 | 2016 | 2018 | -12.4 | -19.7, -4.4 | -3.9 | <0.001 |

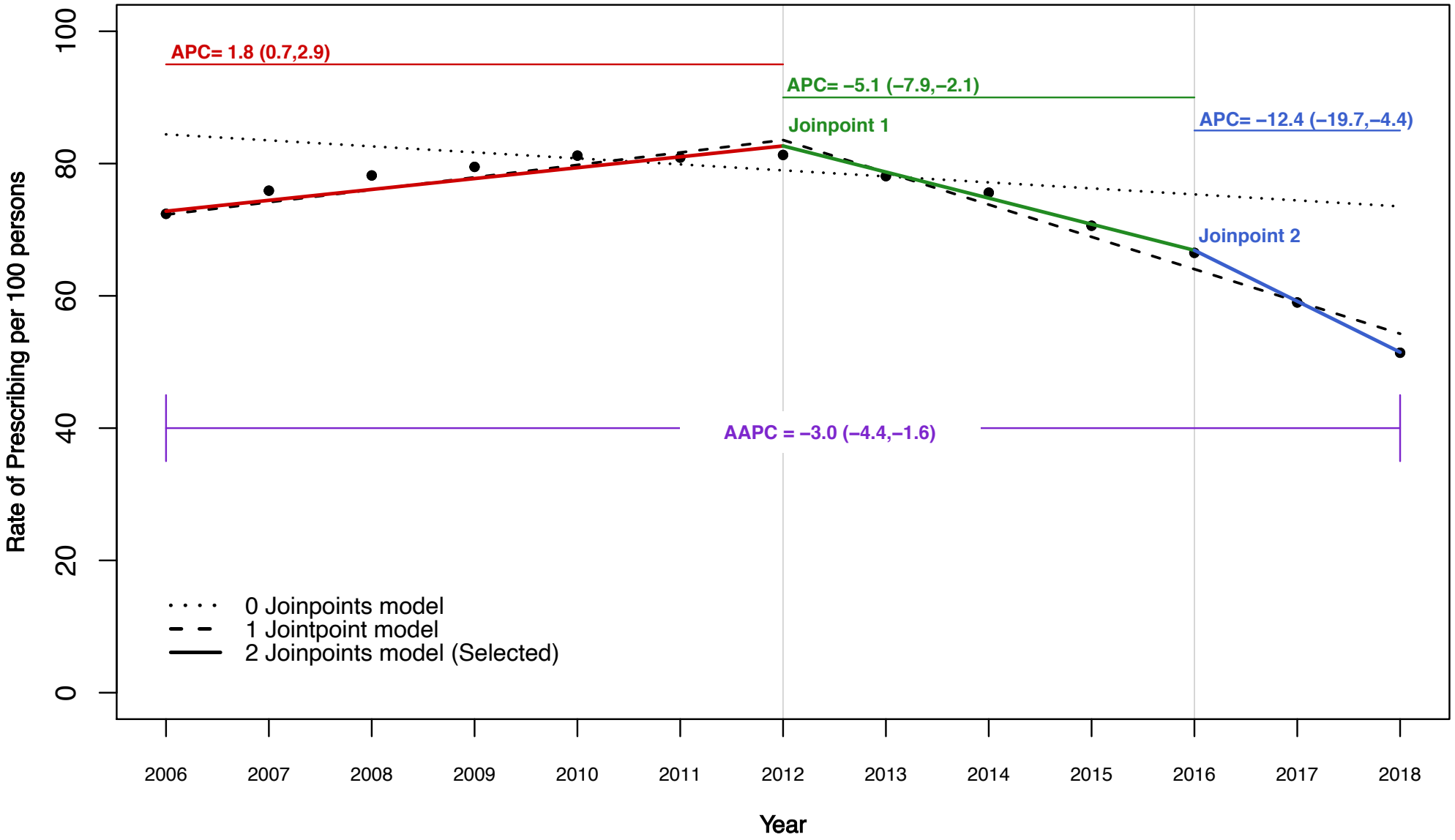
Average Annual Percent Change (AAPC) = -3.0 (95%CI -4.4, -1.6)

## FIGURES

**Figure 1. Joinpoints and Annual Percent Changes in Trend Analysis of Opioid Prescribing, United States (2006-2018)**

**Footnote:** APC: Average Annual Percent Change. AAPC: Average Annual Percent Change. (95% Confidence Interval)

Figure 1


APC= 1.8 (0.7,2.9)
APC= –5.1 (–7.9,–2.1)
Joinpoint 1
APC= –12.4 (–19.7,–4.4)
Joinpoint 2
AAPC = –3.0 (–4.4,–1.6)
0 Joinpoints model
1 Jointpoint model
2 Joinpoints model (Selected)
Rate of Prescribing per 100 persons
0
20
40
60
80
100
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
Year

Supplementary Material (Sample Data)

Click here to access/download

**Supplementary Material**

USA.csv

Supplementary Material (Joinpoint Session)