



First Quarter, 2020

Detection of Drugs with Low Market Penetration in the Survey of Non-Medical Use of Prescription Drugs Program

Key Findings

- Joinpoint regression was used to determine whether a threshold exists in detection of low volume drug substances
- Above 463,000 annual prescriptions dispensed of a drug product, quantitative analysis is appropriate
- The regression model extrapolated to an intercept near zero, and therefore demonstrated internal validity
- Below the threshold 463,000 annual prescriptions dispensed, accurate endorsements likely exist and can be used for qualitative analysis

Introduction

Surveillance of low volume drug targets is a challenging task for any general population survey tool. Due to the broad sampling frame, rare outcomes (e.g., use of a low volume drug) are challenging to detect with suitable sensitivity and precision (i.e., positive predictive value). Only a small number of individuals who take the survey would be expected to endorse rare outcomes, and therefore false positive endorsements of rare outcome bias estimates of prevalence upwards (1). More prevalent outcomes have larger sample sizes, lower uncertainty, and lower magnitude of bias from false positives. Therefore, we hypothesized that a transition exists where, as dispensing volume rises, quantitative analysis of a drug becomes valid. The goal of this technical report is to determine if a threshold exists where prevalence estimates and related statistics can be quantitated in the Survey of Non-Medical Use of Prescription Drugs Program from the Researched Abuse, Diversion and Addiction Related Surveillance (RADARS®) System. Joinpoint analysis (3, 4) was used to determine whether a quantitative relationship exists across the entire range of dispensing or if a threshold exists below which dispensing and estimated number of users are no longer associated.

Methods

Data Sources

The Survey of Non-Medical Use of Prescription Drugs Program deploys repeated, cross-sectional general population drug use surveys to an online panel. Full methodological details are provided elsewhere, and concurrent validity has been demonstrated using national probability surveys (2). Using the 1st quarter 2019 survey (n=29,873), the primary outcome for this technical report was the estimated total number of adults who have used a drug substance in the past year. A total of 38 different active pharmaceutical ingredients were estimated. The predicted number of respondents endorsing rare outcomes was estimated by assuming the prevalence in a simulated sample was the same as in the population. Nationally projected prescriptions dispensed over the same past year period were calculated using the IQVIA™ US-based Longitudinal Patient Database (Danbury, CT). Drug substances included low volume drugs, such as quazepam, and high volume drugs, such as gabapentin. Prescription pain relievers, sedatives, stimulants, and cannabinoids were included.

Statistical Analysis

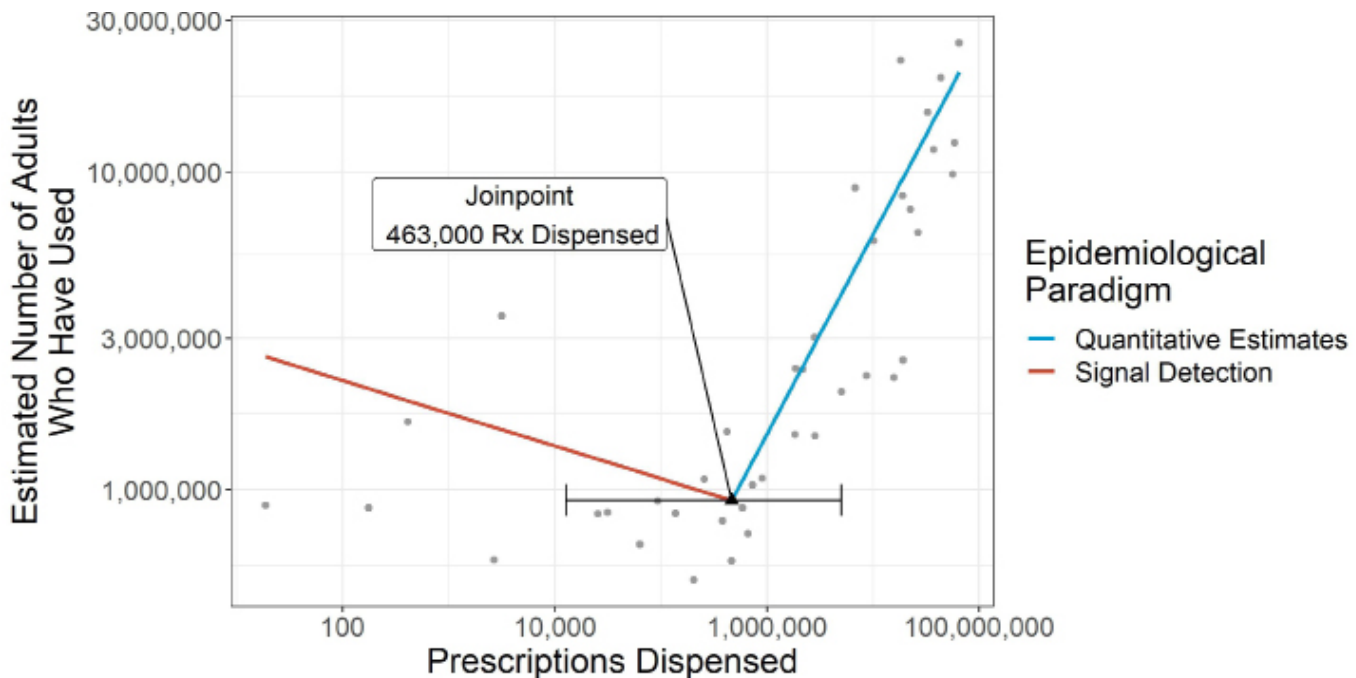
Joinpoint models are disjointed linear regression models where one or more “joinpoints” connect sequential linear trends. This analysis searches a pre-specified grid space and identifies the best fit model; the selection process penalizes more complex models (i.e., more joinpoints). The search grid was specified to include two points on the independent variable between joinpoints and on either end of data. Number of joinpoints searched ranged from zero to four. The BIC3 model selection method was chosen, and resampling (10,000 replicates) were used to calculate confidence interval (CI) of the joinpoint. Student’s t-tests were used to test significance of the slopes. Both number of users (dependent variable) and prescriptions dispensed (independent variable) were log transformed for regression. SAS version 9.4 (Cary, NC) was used to calculate weighted number of users. The joinpoint analysis specified heteroskedastic errors for each dependent observation and utilized the standard error of the sum from the weighted survey estimate for each drug substance.

Results

Two Divergent Linear Relationships Observed

The analysis identified a single joinpoint as the model with the lowest BIC3 score. Figure 1 shows a single distinct shift in the relationship between dispensing and estimated adults who have used. The estimated joinpoint was at approximately 463,000 (95% CI: 12,700 to 5,030,000) prescriptions dispensed. Above this value, the slope was significantly different than zero ($p < 0.001$); below this value, the slope was not significantly different than zero ($p = 0.509$). Two epidemiological paradigms are inferred from these results: a signal detection paradigm and a quantitative estimate paradigm.

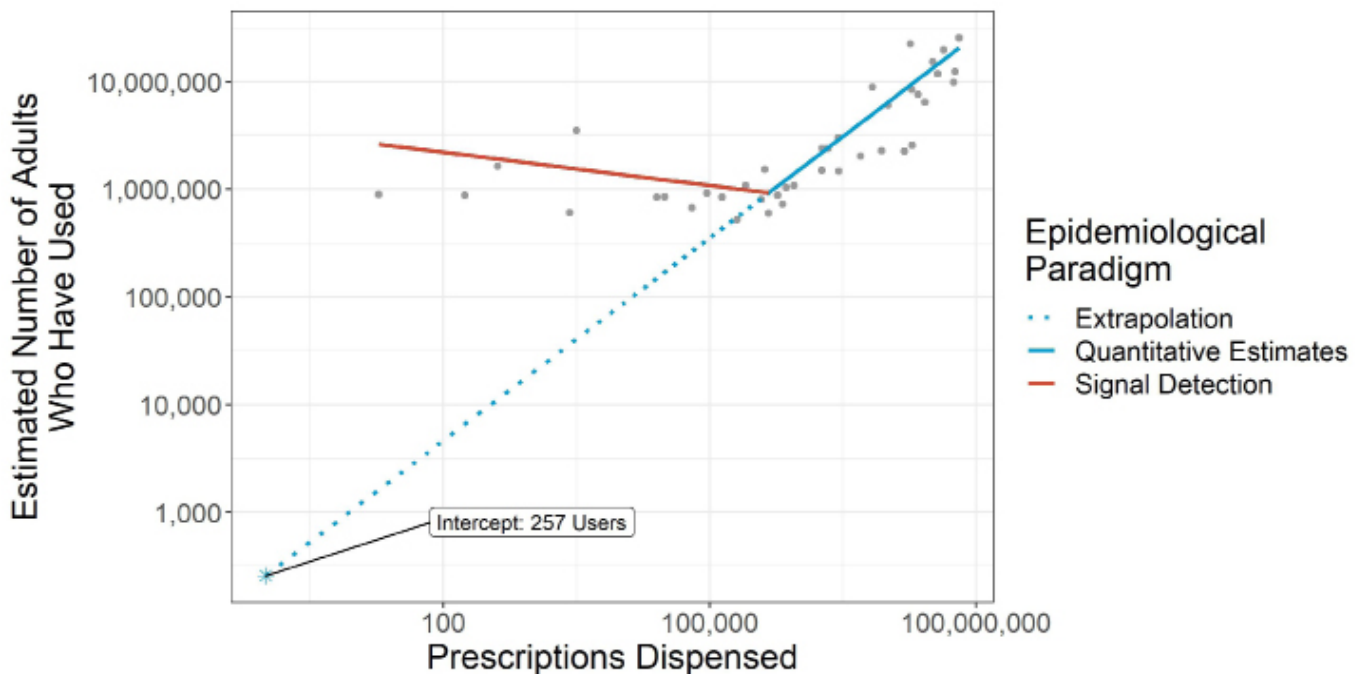
Figure 1: A Single Joinpoint Identifies a Threshold in Detection. Each point is a different drug substance. Two epidemiological paradigms are inferred from the results. Results are presented on log-log scale.



Internal Validity of the Model

If the quantitative estimate paradigm is valid, then the extrapolation of the log transformed linear trend should intercept the y-axis near one estimated user. Figure 2 demonstrates that when extrapolated, the linear trend in the quantitative estimates paradigm intercepts at 257 adults who have used (which is near zero relative to the scale of this analysis as this makes up less than 1% of the sample population). This provides evidence for the internal validity of this trend, and deviation from this trend is deviation away from a quantitative paradigm. A likely source of the deviation observed among low volume drugs within the signal detection paradigm is poor precision in detecting the behavior; low volume drugs have a greater number of false positive endorsements relative to true positive endorsements. In comparison, false positive endorsements of higher volume drugs are a lower proportion of total endorsements.

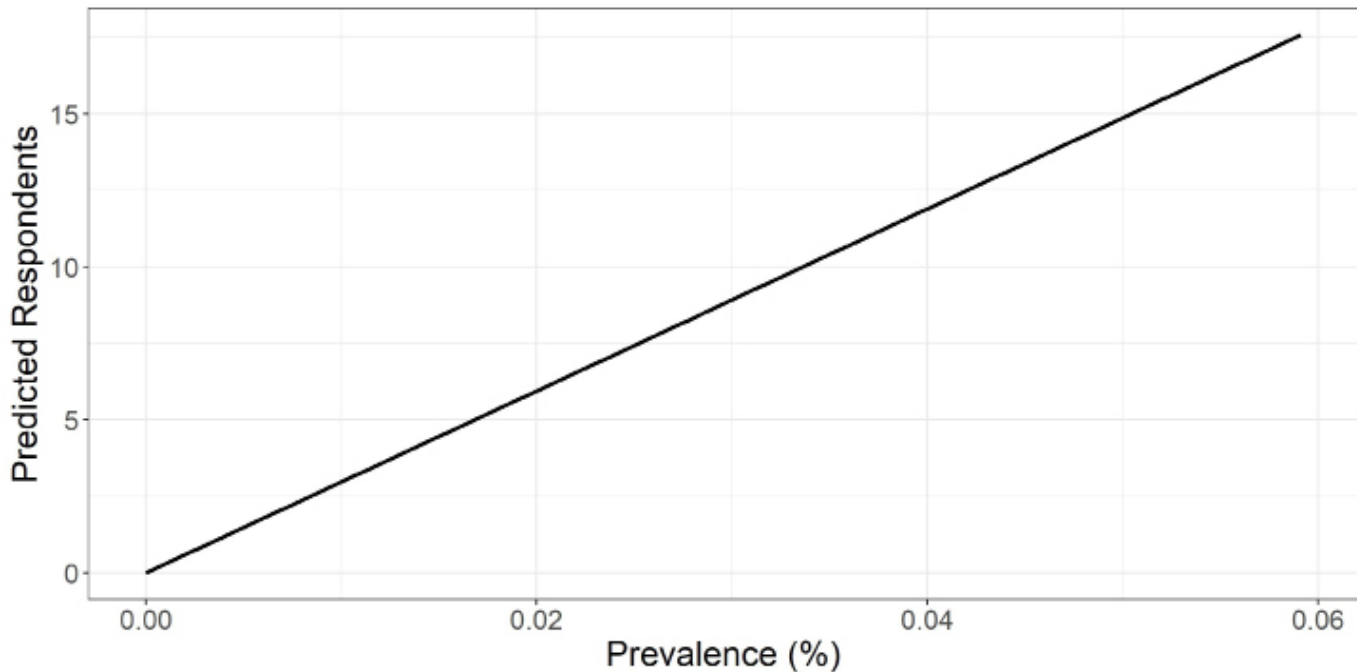
Figure 2: Extrapolation to the Y-Intercept Demonstrates Internal Validity. Each point is a different drug substance. The quantitative estimate paradigm is extrapolated to the y-intercept. Results are presented on log-log scale.



Responses in the Signal Detection Paradigm

Endorsements for rare outcomes could still yield useful information. Figure 3 shows the predicted number of respondents in the 1st quarter 2019 survey based on the prevalence of the behavior in the population. Even when prevalence is low, a small number of responses are expected to be accurate. When approximately 10,000 adults in the US engage in a rare behavior, one of these adults is estimated to be in the survey. For example, a drug with 50,000 unique patients in a year would be expected to have 10 patients enter the survey as respondents across both semiannual launches. If more than 10 endorse use, then follow-up surveys could be used to confirm the endorsements and seek qualitative information about behavior. Some potential topics could be how the respondent transitioned to use (e.g., via medical advice, introduction via peers), whether the drug is effective, what side effects the respondent experiences, or if the respondent is seeking further substance use (e.g., for high-seeking purposes, for unmet medical need). Though estimates of how many individuals were crudely calculated, this illustrates the potential value of respondents even when dispensing is below the quantitative threshold.

Figure 3: Predicted Respondents for Rare Outcomes. Estimated number of true positive endorsements of a rare outcome from the assumption that prevalence is the same in the sample as in the population. This range represents the low end of the signal detection paradigm.



Conclusions

Joinpoint analysis of estimated number of adults who have used from the Survey of Non-Medical Use of Prescription Drugs Program and prescriptions dispensed revealed a single joinpoint. We interpret this threshold as demarcating two distinct epidemiological paradigms. Above the threshold, in the quantitative estimate paradigm, there is a statistically significant association of the estimated number of users with dispensing. Quantitative prevalence estimates and related statistics likely represent behavior in the general adult population, emphasizing the utility of a national survey of drug use behaviors. The joinpoint model selected is internally valid against the expected intercept. Below the threshold, the association is no longer significant, and endorsements are likely biased with poor precision. Data collected in this paradigm likely still contain some accurate endorsements, but require additional follow-up to confirm endorsements. Qualitative analysis of these data is appropriate for a signal detection paradigm of epidemiology.

Suggested Citation

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References

- ¹Brenner H, Gefeller O. "Variation of Sensitivity, Specificity, likelihood ratios, and predictive values with disease prevalence." *Statistics in Medicine* 1997; 16(9): 981-991
- ²Black JC, Rockhill K, Forber A, Amioka E, May KP, Haynes CM, Dasgupta N, Dart RC. "An Online Survey for Pharmacoepidemiological Investigation (Survey of Non-Medical Use of Prescription Drugs Program): ValidationStudy." *J Med Internet Res* 2019; 21(10):e15830
- ³Kim HJ, Fay MP, Feuer EJ, Midthune DN. "Permutation tests for joinpoint regression with applications to cancer rates." *Statistics in Medicine* 2000; 19:335-351: (correction: 2001;20:655)
- ⁴Joinpoint Regression Program, Version 4.6.0.0 - April 2018; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute