Trend-in-trend method to analyze abuse of new and low volume opioids in the community setting

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Background

New opioids with properties intended to deter abuse need to be evaluated by FDA to determine if they have lower abuse in routine practice. Competing interventions to curb opioid prescribing and reduce prescription drug abuse are threats to validity in time-series analyses. Trend-in-trend is a hybrid model form that stratifies by cumulative probability of exposure while treating calendar time as an instrumental variable.

Methods

Unit of Analysis

The unit of analysis was 3-digit zone improvement plan (ZIP) code and calendar quarter, referred to as ZIP-quarter. Analysis was limited to areas covered by surveillance systems providing outcome data, comprising 873 (94%) out of 929 3-digit ZIP codes in the US.

Exposure Data

From July 2009 to December 2016 there were 3.75 billion outpatient units dispensed among 22 new or low volume opioids. National outpatient pharmacy dispensing data were obtained from the National Prescription Audit Plus (IQVIA, Research Triangle Park, NC, USA). Data are generated in outpatient pharmacies for every dispensing of a prescription medication; approximately 90% of all retail pharmacies are included and extrapolated nationally. “Units dispensed” refers to the number of individual tablets, patches, lozenges, etc.

Outcome Data

Over 30 calendar quarters, a total of 56,571 product-specific abuse cases were reported. The RADARS Poison Center Program comprises 50 poison centers from 48 states. Poison centers provide toxicology management advice; callers are caregivers, patients, and healthcare providers. Nurses and pharmacists assist in individual patient care, documenting each case, including specific product exposures identified by the caller, intent and route of exposure, and medical outcome. Records are uploaded to a central database, reconciliation between structured fields and free text call notes. The RADARS System Opioid Treatment Program (OTP) and Survey of Key Informants’ Patients (SKIP) use a common questionnaire allowing data to be combined, collectively generating 3,900 completed surveys annually. Each newly admitted patient is offered the opportunity to complete a validated questionnaire. In the second calendar quarter of 2016, 59 methadone programs in 30 states provided data to OTP; 98 clinics in 42 states sent data to SKIP, many of which were office-based addiction treatment (e.g., buprenorphine) providers. The final composite outcome definition for logistic models combined data from the three RADARS programs. The outcome can be interpreted as any product-specific abuse reported at entry into drug treatment or intoxication resulting in a call to a poison center.

Statistical Models

Product-specific odds ratios compared places without dispensing to places with any dispensing. The causal contrast represents the odds of product-specific abuse in the community given exposure. Logistic regression was first used to generate unadjusted odds ratios (ORs) for each opioid separately. Two adjusted estimates were generated, stratifying by tertiles of cumulative exposure probability (adjusted for population). We summarized stratum-specific ORs for each drug using Mantel-Haenszel ORs. Trend-in-trend models were run using the same tertiles of cumulative exposure probability.

Precision

Standard deviations were calculated using bootstrapping of the trend-in-trend estimates. Once the overall estimate was obtained for a specific drug, 1000 samples were generated from the data by applying a random index across time allowing for replacement. This sampling index was applied identically across strata for a given permutation to retain the relationship between strata. From the 1000 permutations, the 2.5th and 97.5th percentiles were obtained and converted to 95% confidence intervals.

Effect Measure

Key Findings & Limitations

- Dispensing tiers and concurrent interventions are threats to validity.
- Dispensing of new and low volume opioids is idiosyncratic. Early adopter physicians may be different from the general population of prescribers.
- Current methods are insufficient, but T-in-T addresses many limitations. But, it may be best suited for rare events.
- Opioids with abuse-deterrent labeling may have lower abuse than traditional formulations, both on absolute and relative scales.
- There is no established benchmark for choice of comparators for new and low volume opioids.

Suggested Readings

- Ertefaie A et al. Statistical Power for Trend-in-trend Design. PMID: 29337845
- Ji X et al. The Trend-in-trend Research Design for Causal Inference.. PMID: 27775954
- Dart RC et al. Do abuse deterrent opioid formulations work? PMID: 29308584

Results

Among 22 opioid products, three analgesics had FDA-approved labeling describing properties intended to deter abuse based on benchtop manipulation, pharmacokinetic, and human abuse liability studies. These three were Drugs 18, 20 and 21, which ranked near the lowest in both absolute (population-adjusted rates: 1.7, 0.9, and 8.2 per million people per quarter, respectively) and relative measures (trend-in-trend ORs: 1.96, 1.79, 1.69, respectively).

Opioid Dispensing Patterns Over Time and Place

Time Course Sparklines and Linearized US Maps

Drug Dispensing Rates and by 3-Digit ZIP Code

Average Units Discharged per Calendar Quarter 60,000,000

<table>
<thead>
<tr>
<th>Drug</th>
<th>Top Per Capita Dispensing Rates</th>
<th>Per Capita Dispensing Rate, by 3-Digit ZIP Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxypropone immediate-release</td>
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<td>900</td>
</tr>
<tr>
<td>Generic fentanyl patch</td>
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<td>Commonplace immediate-release</td>
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<td>Oxycodone single-entity tablets</td>
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<td>Naproxen</td>
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<td>100</td>
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<tr>
<td>OxyContin</td>
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</tbody>
</table>

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