Comment:
Using Trend-in-Trend to Evaluate Drug Abuse

Rose Radin, PhD, MPH
Division of Epidemiology II
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
May 16, 2019
Presentation outline

1. Evaluating opioid analgesics with abuse-deterrent (AD) labeling
   – Category 4 labeling and postmarketing requirements
   – Goals for accurate evaluation

2. Comments on applying trend-in-trend
   – Exploratory method for evaluating AD opioids
   – Advantages, disadvantages, remaining questions

3. Future directions
EVALUATING OPIOID ANALGESICS WITH ABUSE-DETERRENT (AD) LABELING
Opioid analgesics with AD labeling

- Are not abuse-proof
- Are not designed to prevent addiction
- Have properties expected to deter abuse through specific routes (e.g., nasal, injection), as demonstrated in premarket assessments
Opioid analgesics with AD labeling

- 10 products labeled as “expected to deter abuse” by specific routes
- Based on Category 1-3 (premarket) studies

<table>
<thead>
<tr>
<th>Product</th>
<th>AD Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin</td>
<td>Arymo ER*</td>
</tr>
<tr>
<td>Embeda</td>
<td>Roxybond* (first IR)</td>
</tr>
<tr>
<td>Hysingla ER</td>
<td>Troxyca ER</td>
</tr>
<tr>
<td>MorphaBond</td>
<td>Targiniq ER</td>
</tr>
<tr>
<td>Xtampza ER</td>
<td>Vantrela ER</td>
</tr>
</tbody>
</table>

- All have postmarket requirements (PMRs) to study the impact of AD properties on abuse and related outcomes
- **None with Category 4 (postmarket) AD labeling**

*Not currently marketed
Evaluating AD opioid analgesics: Category 4 labeling supplement application

• 2015 Final Guidance¹
  – “When postmarketing data become available that demonstrate a meaningful reduction in abuse by one or more routes of administration, these data should be added to the product labeling.”
  – Should not demonstrate a shift in routes of abuse that represents a greater risk (e.g., oral/nasal to injecting)

• “...flexible, adaptive approach...”

¹ Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry, Department of Health and Human Services, Food and Drug Administration, April 2015
Evaluating AD opioids to inform regulatory decisions

- Results in meaningful reduction in abuse and its consequences
- People do not shift to riskier routes of abuse
- We have not settled on the definitive methods
- Ecologic designs, Trend-in-Trend, retrospective cohort studies are possible methods
  - Multiple data sources, study designs
  - Use active comparators
Goals for evaluating AD opioids

• Valid, precise estimates for causal inference
• Sampling that allows inferences to defined target population
• Data are accurate and complete
  – Opioid analgesic products
  – Outcomes
• Design and analysis minimize confounding, bias
• Consistent results across multiple data sources, study designs, and sensitivity analyses
Challenges for each goal

• Make inferences to defined target population
  – Finding exposed people and outcomes to study
  – Abuse is a covert behavior
  – AD opioid analgesics are low-volume

• Complete and accurate data
  – Research participants may misreport product names

• Design and analysis minimize confounding, bias
  – Ecologic time-series, retrospective cohort designs are vulnerable to confounding
CONSIDERATIONS FOR APPLYING TREND-IN-TREND TO REGULATORY QUESTIONS
Interesting descriptive findings from Dasgupta et al.¹

- Each product had substantial spatial and temporal variation in utilization
  - Each profile was unique
- Few ZIP-quarters had any abuse cases
  - ZIP-quarters with any abuse often had only one case
  - Abuse was more likely in ZIP-quarters with any dispensing
- Association between dispensing and abuse was non-linear for many low-volume products

Trend-in-Trend Advantages

• Adjusts for important sources of confounding
  – Other interventions, secular trends
  – Geographic differences (probably, though no direct evidence of this in Dasgupta et al.)
  – Patient characteristics (possibly, though not examined by Dasgupta et al.)

• Uses a logistic regression model that appears to be more appropriate to the reality of the data distribution
Disadvantage:
Interpreting the odds ratio for Product X

<table>
<thead>
<tr>
<th></th>
<th>Any Abuse</th>
<th>No Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Dispensing</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>No Dispensing</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

• OR = (A/B) / (C/D)

• **All Cells:** What other products were dispensed in that ZIP-quarter?

• **Cell C:** The outcome is product-specific, so, how did someone get exposed to Product X in that ZIP-quarter?
Trend-in-Trend Disadvantages

• The interpretation is complicated, and the reference group is not clear

• Desirable to use active comparators, but that would not be feasible for many products

• Certain drugs cannot be studied with Trend-in-Trend if utilization is either high or very low
  – Very narrow application
  – Comparators?
Trend-in-Trend does not address these challenges

<table>
<thead>
<tr>
<th>Goals</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferences to defined target population</td>
<td>Abuse is a covert behavior; AD opioid analgesic products are “low volume”</td>
</tr>
<tr>
<td>Data are accurate and complete</td>
<td>Product names may be misreported – bias aggravated by low volume products</td>
</tr>
</tbody>
</table>

Address these challenges through careful study design:
- Study population definition
- Data collection and validation
FDA’s selected questions about Dasgupta et al.

- Used composite outcome from OTP/SKIP and PC
  - Differential coverage of ZIP-quarters
  - Are the odds ratios consistent across data sources?
- We would like to learn more about calculating the precision around the reported estimates from Trend-in-Trend model
FUTURE DIRECTIONS
Possible to study related outcomes?

• Route of abuse: intranasal, intravenous routes
  – Self-reported data

• Overdose from any opioid
  – Individual-level claims data linked to cause-of-death data
Conclusions

• FDA currently considers Trend-in-Trend an exploratory method for evaluating AD opioid analgesics
  – Trend-in-Trend has distinct advantages and disadvantages
  – May hold promise for studying abuse, overdose, and related outcomes in selected situations
• For evaluating AD opioid analgesics, exposure and outcome ascertainment continue to be fundamental considerations