Assessment of prior opioid tolerance among new users of fentanyl transdermal system in FDA’s Sentinel System

Noelle Cocoros, Marc Larochelle, Jennifer Popovic, Andrew Petrone, Cynthia Kornegay, Jing Ju, Judith Racoosin

ICPE, Montreal
August 28, 2017
Disclosure statement

- This work was funded by FDA contract HHSF223200910006I.
- The authors have no relationships to disclose.
Background

- Some extended-release and long-acting (ER/LA) opioid analgesic formulations and dosages are intended only for patients with prior opioid tolerance
  - Extended-release hydromorphone – all doses
  - Extended-release oxycodone (single dose >40 mg or daily dose >80 mg)
  - Fentanyl transdermal system (FTS) – all doses
REMS for ER/LA opioid analgesics

- FDA approved a Risk Evaluation & Mitigation Strategy (REMS) for ER/LA opioid analgesics in July 2012
- Requires ER/LA opioid analgesic sponsors to fund provider education on safe prescribing
- “Blueprint” developed by FDA includes
  - Assessing patients for treatment
  - Initiating, modifying, and discontinuing therapy
  - Monitoring ongoing therapy
  - Counseling patients about safe use
  - Being familiar with product-specific drug information
Evaluating REMS Impact

Candidate metrics for monitoring ER/LA opioid analgesic REMS impact have been proposed

- A metric to identify opioid tolerance in patients prescribed select ER/LA opioid analgesics was developed and applied to the US Medicare population (Willy et al 2014)
Objective

- To identify the proportion of new FTS users <65 years who had evidence of prior opioid tolerance, stratified by product strength and tolerance definition
Sentinel Initiative

- Launched in 2008 by FDA to leverage electronic data sources (largely claims) for medical product safety surveillance

- Sentinel utilizes a distributed database with data partners throughout the US
  - Currently 17 Data Partners - primarily commercial insurers
  - >200 million unique members
Methods

- 13 Data Partners
- Retrospective cohort
- Jan 1, 2009 - Dec 31, 2013
- Inclusion criteria:
  - <65 years of age
  - First incident dispensing of FTS / user, 183 day washout
  - Medical and pharmacy enrollment during washout period
- Exclusion criteria:
  - Medical claim for opioid poisoning during washout period
  - Inpatient stay 30 days prior to dispensing
## Tolerance definitions

<table>
<thead>
<tr>
<th>≥ 30 mg oxycodone equivalents</th>
<th>Primary Definition</th>
<th>Secondary Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 0 mg oxycodone equivalents</td>
<td>Tertiary Definition</td>
<td>Quaternary Definition</td>
</tr>
</tbody>
</table>

Per day for 7 consecutive days immediately prior to new opioid-tolerant-only dose index date

Per day for **any** 7 days in 30 days prior to new opioid-tolerant-only dose index date

≥ 30 mg oxycodone equivalents

> 0 mg oxycodone equivalents

© 2017 Sentinel Operations Center. All Rights Reserved.
Analysis

- Stratified by tolerance definition, sex, age category, year, and strength
  - 12, 25, 75, 100 mcg/hr + non-manufacturer strengths (multiple dispensings occurring on the same day were summed)
## Number of fentanyl patch episodes by strength, 2009-2013

<table>
<thead>
<tr>
<th></th>
<th>12 mcg/hr</th>
<th>25 mcg/hr</th>
<th>50 mcg/hr</th>
<th>75 mcg/hr</th>
<th>100 mcg/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Episodes</strong></td>
<td>16,379</td>
<td>44,450</td>
<td>18,527</td>
<td>5,118</td>
<td>3,507</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 11</td>
<td>32</td>
<td>23</td>
<td>7</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>12 - 17</td>
<td>75</td>
<td>79</td>
<td>32</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>18 - 24</td>
<td>375</td>
<td>827</td>
<td>380</td>
<td>99</td>
<td>77</td>
</tr>
<tr>
<td>25 - 34</td>
<td>1,464</td>
<td>3,731</td>
<td>1,614</td>
<td>523</td>
<td>290</td>
</tr>
<tr>
<td>35 - 44</td>
<td>2,841</td>
<td>7,954</td>
<td>3,502</td>
<td>1,011</td>
<td>686</td>
</tr>
<tr>
<td>45 - 54</td>
<td>5,214</td>
<td>14,785</td>
<td>6,358</td>
<td>1,785</td>
<td>12,76</td>
</tr>
<tr>
<td>55 - 64</td>
<td>6,378</td>
<td>17,051</td>
<td>6,634</td>
<td>1,687</td>
<td>11,66</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5,124</td>
<td>18,327</td>
<td>8,727</td>
<td>2,510</td>
<td>1,839</td>
</tr>
<tr>
<td>Female</td>
<td>11,255</td>
<td>26,123</td>
<td>9,800</td>
<td>2,608</td>
<td>1,668</td>
</tr>
</tbody>
</table>
Number of fentanyl patch episodes by strength and age, 2009-2013

Members <18 yrs have age had <100 episodes per strength
Number of fentanyl patch episodes by strength and year, 2009-2013
Fentanyl patch episodes with evidence of prior tolerance by strength & tolerance definition, 2009-2013

**Primary** ≥30 mg / d in prior 7 consecutive days
**Secondary** ≥30 mg / d for 7 d in 30 d prior
**Tertiary** >0 mg / d in prior 7 consecutive days
**Quaternary** >0 mg / d for 7 d in 30 d prior
Fentanyl patch episodes with evidence of prior tolerance by strength & age, primary definition, 2009-2013

Primary def: ≥30 mg / d in prior 7 consecutive days
Fentanyl patch episodes with evidence of prior tolerance by strength & time, **primary definition**, 2009-2013

Primary def: ≥30 mg / d in prior 7 consecutive days
Large proportion of FTS episodes lack evidence of tolerance

- Proportion with prior tolerance especially low among patients receiving lower strength fentanyl patches
- Nearly half (43%) of those with highest strength product do not have evidence of tolerance by the primary definition
- REMS-affiliated provider training started March 2013; thus, these data do not provide sufficient opportunity to evaluate the impact of training on safe prescribing practices
Strengths and limitations

- Size of Sentinel distributed data network

- Limitations:
  - Algorithm for determining opioid tolerance has not been validated
  - Predominantly commercially insured
  - Opioid dispensings incomplete if members bypass insurance and pay out-of-pocket
  - Prior opioids may have been provided in setting not captured in data (e.g. rehab)
Acknowledgments

- **FDA**
  - Aaron Niman
  - Judy Racoosin
  - Cynthia Kornegay
  - Mary Willy
  - Judy Staffa
  - Melissa Robb
  - Jing (Julia) Ju

- **Sentinel SOC**
  - Marc Larochelle
  - Elizabeth Cavagnaro
  - Sandra Feibelmann
  - Andrew Petrone
  - Jennifer Popovic
  - Ryan Saliga
  - Yury Vilk

Many thanks are due to Data Partners who provided data used in the analysis.
Questions?

Noelle_Cocoros@harvardpilgrim.org