Exposure to N-nitrosodimethylamine
/N-nitrosodiethylamine-contaminated Angiotensin-II Receptor Blockers
Products in the United States

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Background

• In 2018, N-nitrosodiethylamine (NDMA) and N-nitrosodimethylamine (NDEA) were discovered in several valsartan (an angiotensin receptor blocker (ARB)-containing products. NDMA and NDEA are mutagenic carcinogens in several animal species.

• NDMA and NDEA were generated as a by-product when the chemical manufacturing process was changed.1

• FDA coordinated a voluntary recall of these products (recalled products) and began retesting all valsartan products, including both recalled products and those currently marketed in the United States, for NDMA and NDEA.2

• Ongoing characterization of valsartan-containing products is crucial for future pharmacopoeidemiologic safety assessments.

• We sought to examine the extent of exposure, duration of use and switching patterns from NDMA/NDEA-contaminated valsartan products to other angiotensin-receptor blockers (non-valsartan ARBs) or other antihypertensives – angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs) of these products.

Methods

• Between January, 2010 to most recent available data (1/31/2019), we identified patients 18 years and older from 15 data partners in the Sentinel Distributed Database (SDD).

• Using NDAs, valsartan products were categorized as probably contaminated (NDMA/NDEA-positive, NDMA-positive, NDEA-positive based on FDA’s testing of finished drug products (FDPs) and manufactured recalled products lots) possibly contaminated (recalled products but not tested), and non-contaminated (non-recalled and NDMA/NDEA-negative) products.

• Exposure episode lengths were defined using days supplied, allowing a gap of 15 days or less between dispensions to create continuous treatment.

• Follow-up began on the dispensing date of the respective valsartan category until the first occurrence of: discontinuation, end of data, end of the exposure episode or death.

• Annual trends of prevalence of each valsartan product category and duration to discontinuation or switch from probably-contaminated valsartan products to another valsartan product or antihypertensive were calculated.

Results

Descriptive Data

• We identified 1.6, 11.7, 7.3 and 5.3 million users of valsartan, ACEI, CCB and non-valsartan ARB users during the study period respectively.

• Non-recalled valsartan dispensings made up 58.1% of all valsartan dispensings, while losartan (61.2%), amldipine (75.5%) and losartan (74.5%) were most frequently dispensed for ACEI, CCB and non-valsartan ARBs, respectively.

• Similar demographic and clinical characteristics for valsartan, CCB and non-valsartan ARBs were observed (Table 1).

• ACEI users were likely male with a lower proportion of users having a hypertension diagnosis at baseline (Table 1).

Table 1. Baseline Characteristics for Exposure Cohorts (Treatment Episodes)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Valsartan</th>
<th>ACEI</th>
<th>CCB</th>
<th>Non-valsartan ARBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-44, %</td>
<td>31.4</td>
<td>16.4</td>
<td>13.1</td>
<td>12.3</td>
</tr>
<tr>
<td>Age 45-64, %</td>
<td>39.2</td>
<td>28.5</td>
<td>28.7</td>
<td>31.9</td>
</tr>
<tr>
<td>Age 65+, %</td>
<td>35.5</td>
<td>55.1</td>
<td>55.9</td>
<td>45.8</td>
</tr>
<tr>
<td>Male, %</td>
<td>49.0</td>
<td>54.9</td>
<td>54.3</td>
<td>48.6</td>
</tr>
<tr>
<td>Reconsidered History among New Users Only (30 day washout period)</td>
<td>7.2</td>
<td>7.2</td>
<td>7.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>5.5</td>
<td>7.7</td>
<td>6.7</td>
<td>7.9</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>30.6</td>
<td>25.2</td>
<td>25.1</td>
<td>31.5</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>87.1</td>
<td>87.1</td>
<td>87.1</td>
<td>87.1</td>
</tr>
<tr>
<td>Renal disorders, %</td>
<td>29.5</td>
<td>29.5</td>
<td>29.5</td>
<td>29.5</td>
</tr>
</tbody>
</table>

Download a comma-separated CSV file containing these data: https://github.com/FDA-EMI/rdm-valsartan

Discussion

• Probably-contaminated valsartan dispensings increased steadily and were the most frequently dispensed valsartan product in 2018 and 2017.

• In 2018, probably- and possibly-contaminated valsartan dispensings declined with most patients switched to non-valsartan ARBs. Switching trends to ACEI or CCB were consistent over time, suggesting that these intended medical switches rather than in response to the recall.

• Shorter time to switching from probably-contaminated to non-valsartan ARBs in 2018 ensured patients their continued treatment after discontinuation of contaminated product.

• Exposure misclassification is possible since we rely on dispensed data to ascertain trends.

Conclusion

• Though valsartan dispensings were already on the decline prior to contamination, we observed further decline in dispensings likely due to the recall notice.

• Patients were more likely to switch to another ARB rather than another antihypertensive medication within 1-3 months.

• Future analyses will be updated as data is accrued to examine whether the observed trends continue.

• Additional analyses will also examine time to discontinuation and switching to non-recalled valsartan products.

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