

# HowOften: Large Scale Incidence Rate Calculation of Every Side Effect for Every Drug

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## Background

Adverse drug reactions (ADRs) are a common cause for emergency department visits, hospitalizations and ambulatory visits and cost healthcare systems billions of dollars, yet there is still little known about the real-world incidence of possible side effects following initiation of a drug.<sup>1</sup> Current strategies to identify ADRs, such as randomized control trials, observational studies and adverse event reporting systems,<sup>2</sup> identify some side effects for some drugs, but the majority of potential drug-side effect pairs remain untested.

While not causal, incidence rates still have clinical value as seen in prior work with OHDSI, which for example calculated incidence rates of clinical conditions that can occur after COVID-19 vaccination. The results helped inform the European Medicines Agency (EMA) decision to reinstate the AstraZeneca COVID-19 vaccine despite reports of clotting.<sup>3,4</sup> In this study, we used real world data to calculate the incidence of every clinical condition following initiation of every drug and prepared the results for publication to a website to aid clinicians in decision-making.

## Methods

This study is an observational cohort study using eleven databases which had been converted to the OMOP CDM. Analysis was done on electronic health record (EHR) data from Columbia University Irving Medical Center (both inpatient and outpatient) and the Premier Hospitalization database, as well as administrative claims data from IBM MarketScan Commercial Claims and Encounters (CCA), Medicare Supplemental Beneficiaries (MDCR), Multi-state Medicaid (MDCD), Japan Medical Data Center (JMDC), Optum, and IMS Australia, Germany, and France which has both EHR and claims data. SNOMED CT condition codes were used to define clinical conditions and RxNorm terms for marketed drug ingredients were used to define instances of drug exposure.

Analysis was run in October 2017 and cohorts were based on the first exposure of a drug. Patients required at least one year of data prior to the drug initiation and could not have had prior codes for that drug. The incidence proportion for a clinical condition was defined as the number of patients who have a new occurrence of the condition during the time at risk, which was 1-year post exposure, divided by the number of patients in the cohort. Patients previously diagnosed with the condition prior to drug initiation were excluded. Given patients may not have had data captured during the entire time at risk, we calculated the incidence proportion using only patients who had data entries throughout the entire at-risk period as well as using all patients regardless of how long they were observed post-exposure.

We pre-selected 10 known and studied drug-side effect pairs: 1) lisinopril and angioedema, 2) lisinopril and cough, 3) sertraline and suicidal ideation, 4) sertraline and sexual dysfunction, 5) lamotrigine and stevens-johnson syndrome 6) atorvastatin and muscle pains, 7) levofloxacin and tendon rupture, 8) canagliflozin and urinary tract infection, 9) prednisone and deep venous thrombosis, 10) warfarin and bleeding. We compared the calculated incidences to incidences identified in the literature.

## Results

We evaluated 13,005,797 unique drug-outcome pairs from 2,072 drug concepts and 21,433 outcome concepts. Results were displayed on an internal site that allowed users to select a drug and a condition to calculate an incidence rate (Figure 1). If no condition is selected, ADRs extracted from the Food and Drug Administration (FDA) drug label are listed with their corresponding calculated incidences.

**OHDSI**  
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**How Often...**

How often do patients get a condition after starting a drug?

Which drug are you interested in?

Enter generic drug name

Which condition are you interested in?

Leave blank for conditions on product label

**What this does**

Use this tool to look up the proportion of people taking a drug who are newly diagnosed with a condition within 1 year of starting the drug. You can search for a specific drug-condition incidence by entering your drug and condition of interest in the fields above. Or, you can browse a list of conditions of potential interest by leaving the condition field blank, and you'll be shown conditions listed on the drug's product label.

**What this does not do**

This tool **does not** demonstrate that a drug causes a condition (i.e., that the condition is a side effect of the drug). Instead, for example, the condition may be part of the reason you are taking the drug, or the condition may just be common in the population.

This tool provides the overall observed risk in a population, but does not provide the attributable risk due to drug exposure. The results provided are raw unadjusted numbers for each diagnosis. The data made available through this site are for informational purposes only and are not a substitute for professional medical advice or services. You should not use this information for comparing drugs or making decisions related to diagnosing or treating a medical or health condition; instead, please consult a physician or healthcare professional in all matters related to your health.

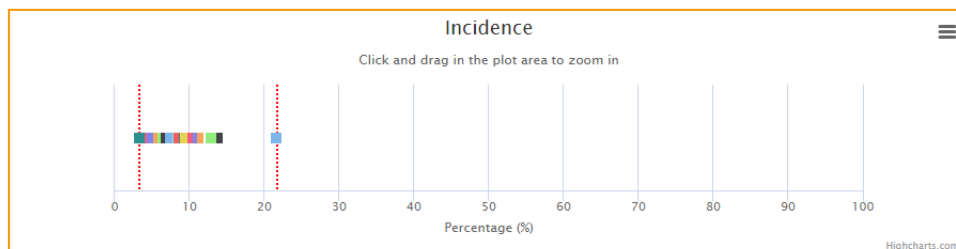
**Figure 1. Entry Screen for the prototype.**

Upon searching for a drug-condition pair, a range of incidences is provided with the specific proportions listed for each database that had patients with a new incidence of the condition after drug initiation. Two incidences were calculated for each database; one using only patients who were observed for the entire at-risk period and another using all patients with the drug exposure. Both were included in our target-pair comparisons.

The results for one particular database, Premier Hospitalization Database, which only included data on hospitalized patients, was often significantly higher than the rest of the databases when only using patients who had data for the entire time-at-risk (Figure 2). For our target-pair comparisons, we excluded the Premier results as patients with hospitalizations for the entire 1 year at-risk period likely represent a biased population.

## Risk of cough with Lisinopril

Amongst patients taking Lisinopril, onset of cough occurs in 3.33% to 21.67% of patients during the 1 year after starting the drug



Source	Country	Condition	Incidence (%)	Patients at Risk	Requires Full Time at Risk ⓘ
Premier	US	Cough	21.67	2,598	Yes
MDCCD	US	Cough	13.83	154,437	Yes
MDCCR	US	Cough	12.89	472,728	Yes
Optum Extended SES	US	Cough	11.24	1,165,871	Yes

**Figure 2. Sample drug-condition pair with incidence proportions for each included database.** For each database that contained patients with the drug exposure, two incidence rates were calculated - using either only patients with data for the full 1 year time at risk or using all patients. Each color correlates to a different calculated incidence rate.

For some adverse outcomes, there were only studies evaluating the entire drug class, such as serotonin reuptake inhibitors (SSRI) instead of sertraline or angiotensin-converting enzyme (ACE) inhibitors for lisinopril. We also did not discriminate based on medication indication, dose, or frequency as our analysis included all patients with the drug exposure.

We found that for our ten target pairs, nine of the calculated incidence ranges overlapped with rates found in the literature (Table 1), which included meta-analyses, systematic reviews, individual randomized control trials and observational studies, and UpToDate. For five pairs, the calculated ranges almost fully subsumed all results found in literature and four pairs had some overlap between the calculated range and range identified through literature. One pair, sertraline and sexual dysfunction did not have any overlap with our calculation significantly underestimating the incidence rate. This may be due to an underrepresentation in billing codes of certain clinical conditions that may be considered sensitive.

**Table 1. Comparison of incidence rates calculated in HowOften project with rates reported in literature and UpToDate.**

Drug	Condition	Number of Patients in Cohort	HowOften Calculated Incidences (%)	Comparison Sources Incidences (%)
Lisinopril	Angioedema	6,693,344	0.12 - 0.77	0.1 - 0.7 <sup>5,6</sup> 0.2 <sup>7</sup> 0.49 <sup>8</sup>
Lisinopril	Cough	5,514,370	3.33 - 13.83	5 - 20 <sup>9</sup> 2.7 - 12.3 <sup>10</sup> 3.9 - 35 <sup>11</sup>
Sertraline	Suicidal Thoughts	3,420,513	0.26 - 3.67	0.39 - 1.82 <sup>12</sup>
Sertraline	Sexual Dysfunction	3,604,138	0.04 - 1.17	15 - 80 <sup>13</sup>

				56 - 62.9 <sup>14</sup>
Lamotrigine	Steven-Johnson Syndrome	666,468	0.02 - 0.08	0.02 - 0.07 <sup>15</sup>
Atorvastatin	Muscle Pain	4,933,241	0.63 - 4.42	25 - 27.1 <sup>16</sup> 1.6 <sup>17</sup> 9.4 <sup>18</sup>
Levofloxacin	Tendon Rupture	9,857,172	0.01 - 0.19	0.01-0.1 <sup>19</sup> 0.01 <sup>20</sup>
Canagliflozin	Urinary Tract Infection	165,590	0.76 - 8.30	4.3-5.9 <sup>21</sup> 8.1-8.2 <sup>22</sup>
Prednisone	Deep Venous Thrombosis	926,859	0.17-2.36	0.23 <sup>23</sup> 0.38 <sup>24</sup> 3.6 <sup>25</sup>
Warfarin	Bleeding	1,594,115	1.80 - 20.38	10 - 16 <sup>26</sup> 3.8 <sup>27</sup>

## Conclusion

The calculated incidence proportions for known adverse effects for drugs were largely well-aligned with previous knowledge and suggests that large-scale incidence rate calculations may allow for evaluation of every possible ADR without manual curation. Although not causal, which should be communicated clearly to users, incidence rates, especially low ones, can be clinically relevant in whether the potential effect influences a clinical decision. The clinical condition that was not consistent with literature suggests sensitive conditions may be underrepresented in coding data and additional work should be done to characterize these conditions. There is ongoing work to better define outcome cohorts using both diagnosis codes and phenotyping work by OHDSI workgroups, calculating incidence proportions using different time-at-risks and stratifying by patient characteristics and data source.

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