



Estimating the incidence of idiosyncratic drug-induced liver injury

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Introduction

- Idiosyncratic drug-induced liver injury (DILI) is the leading reason for post-marketing drug withdrawal.
- While idiosyncratic DILI is estimated to occur at a rate of 1:100 to 1:1,000,000 exposed individuals, the incidence of idiosyncratic DILI from most medications is not known.

Aim Estimate the incidence of idiosyncratic DILI for commonly-prescribed drugs.

Methods We used two databases in this study:

1. The DILI Network (DILIN) Prospective study has enrolled cases of suspected DILI at 6-8 medical centers in the US since 2004. Cases were adjudicated for causality by at least three experts as previously described. We included **high-likelihood DILI cases from DILIN** (probable or higher) between 2005-2019.

2. The Medical Expenditure Panel Survey (MEPS) Household Component is a set of surveys designed to estimate nationally-representative use of medications. It allows one to extrapolate **total number of annual prescriptions for each prescription medication in the US**. We estimated the number of **unique individuals receiving a new prescription of each medication in each year from 2005-2019**.

- For each medication, we estimated the estimated incidence (EI) of DILI based on the number of cases of DILI in DILIN relative to that of **amoxicillin-clavulanate**, since a **population-based estimate of DILI incidence in Iceland** has been reported at 42 cases per 100,000 prescriptions (PMID 23419359).

- EI was estimated as follows:

$$EI(\text{Drug } A) = EI(A/C) * \frac{\# \text{ DILIN cases of drug } A}{\# \text{ DILIN cases of } A/C} * \frac{\# \text{ annual new prescriptions of } A/C}{\# \text{ annual new prescriptions of drug } A}$$

- 95% confidence intervals (CI) in EI were estimated based on uncertainty in the following:

- # DILIN cases of Drug A: 95% CI of number of cases of drug A in DILIN was estimated by a Poisson distribution using the total number of DILIN cases as the parameter.
- EI(A/C): 95% CI derived from the Björnsson et al study: 42 [95% CI 24-70] per 100,000 prescriptions.

- We determined the lower (and upper) limits of the 95% CI of EI by multiplying the lower (and upper) limits of the 95% CIs of EI(A/C) and # DILIN cases of drug A.

- We report incidence as **EI** or **rate of DILI**, i.e. cases per 100,000 new prescriptions.

DILI incidence for major culprit drugs			
DILI rate	Drug		
Cases : new prescriptions	Antibiotics	Other drugs	
1 : <1,000		Phenytoin Carbamazepine	Sulfasalazine Leflunomide
1 : 1,000-5,000	Minocycline Amox-clav Nitrofurantoin Terbinafine TMP-SMX	Lamotrigine Valproate Diclofenac Methimazole	Allopurinol Hydralazine Amiodarone
1 : 5,000-25,000	Levofloxacin Ciprofloxacin	Atorvastatin Rosuvastatin Pravastatin	Fenofibrate Duloxetine Montelukast
1 : 25,000-100,000	Doxycycline Azithromycin Clindamycin	Simvastatin	
1 : >100,000	Amoxicillin		

Table 1: Implicated drugs in DILIN and numbers of new users used to calculate DILI estimated incidence (EI). EI was calculated as in Methods (95% confidence interval have been added); a higher EI indicates lower incidence of DILI. Only drugs with ≥5 cases in DILIN 2005-2019 and prescription data in MEPS for ≥10 of 15 years are shown.

Medication	2005-2019 DILIN cases	2005-2019 new users (millions)	Incidence of DILI Cases per 100,000 new prescriptions (95% CI)
Phenytoin	13	0.7	226 (67-629)
Leflunomide	5	0.4	158 (29-599)
Sulfasalazine	11	1.1	123 (34-358)
Carbamazepine	11	1.3	106 (30-309)
Minocycline	44	5.7	95 (38-207)
Methimazole	7	1.4	61 (14-205)
Valproate	9	2.3	48 (12-149)
Lamotrigine	17	4.8	43 (14-113)
Amoxicillin/clavulanate	191	54.3	43 (24-70) - ASSUMED
Nitrofurantoin	53	15.3	42 (18-90)
Amiodarone	9	2.8	40 (10-123)
Terbinafine	20	6.3	39 (13-97)
Hydralazine	10	3.2	38 (10-114)
Allopurinol	12	6	24 (7-70)
TMP/SMX	77	44.6	21 (9-43)
Diclofenac	23	13.4	21 (7-51)
Fenofibrate	8	6.6	15 (4-47)
Duloxetine	10	10.6	11 (3-34)
Atorvastatin	31	38.2	10 (4-23)
Levofloxacin	17	30.1	7 (2-18)
Rosuvastatin	7	13.5	6 (1-21)
Pravastatin	5	12.2	5 (0.9-19)
Ciprofloxacin	23	60.2	5 (2-11)
Montelukast	5	23.5	3 (0.5-10)
Clindamycin	5	23.9	3 (0.5-10)
Doxycycline	6	35.9	2 (0.4-7)
Simvastatin	5	31.3	2 (0.4-7)
Azithromycin	27	204.9	2 (0.6-4)
Amoxicillin	16	307.0	0.6 (0.2-2)

Limitations

- DILI incidence may be different in Iceland and the US.
- Detection of DILI and rate of referral for enrollment in DILIN may differ across medications and time.
- Using number of new patients (not all patients) receiving a prescription may overestimate DILI incidence in drugs used chronically or if DILI arises >1 year after initiation.
- MEPS does not provide data on parenteral drugs and uncommonly-prescribed medications (e.g. INH).

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