Critical Review of the Literature
2017-2018

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Outline

1- DDI Publications: What is new in 2017-2018?
   - Publications: updates and trends
   - Most pronounced clinical DDIs
   - Transporter-based clinical DDIs

2- 2017-2018 Highlight: Example of *in vivo* gene-drug-drug-interactions (GDDIs)
   - “Notable Drug-Drug Interaction Between Etizolam and Itraconazole in Poor Metabolizers of Cytochrome P450 2C19.”
Number of Publications Entered in UW DIDB Platform

- Decrease in number of publications in past few years
- However, each publication now includes more studies
Top 10 Journals (2017) contribute ~43% of the published articles

<table>
<thead>
<tr>
<th>Journal</th>
<th>Number of Articles</th>
<th>Overall Percentage</th>
<th>Primary focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Metab Dispos</td>
<td>48</td>
<td>9.1</td>
<td>in vitro</td>
</tr>
<tr>
<td>Xenobiotica</td>
<td>36</td>
<td>6.8</td>
<td>in vitro</td>
</tr>
<tr>
<td>J Pharm Sci</td>
<td>28</td>
<td>5.3</td>
<td>in vitro</td>
</tr>
<tr>
<td>Br J Clin Pharmacol</td>
<td>23</td>
<td>4.4</td>
<td>in vivo</td>
</tr>
<tr>
<td>J Clin Pharmacol</td>
<td>20</td>
<td>3.8</td>
<td>in vivo</td>
</tr>
<tr>
<td>Clin Pharmacol Drug Dev</td>
<td>19</td>
<td>3.6</td>
<td>in vivo</td>
</tr>
<tr>
<td>Antimicrob Agents Chemother</td>
<td>15</td>
<td>2.8</td>
<td>in vivo</td>
</tr>
<tr>
<td>Eur J Drug Metab Pharmacokinet</td>
<td>14</td>
<td>2.6</td>
<td>in vitro / in vivo</td>
</tr>
<tr>
<td>Eur J Clin Pharmacol</td>
<td>12</td>
<td>2.3</td>
<td>in vivo</td>
</tr>
<tr>
<td>Biopharm Drug Dispos</td>
<td>11</td>
<td>2.0</td>
<td>in vitro / in vivo</td>
</tr>
</tbody>
</table>

- Changes in the journals’ scientific coverage in recent years
- DDI publications seem to be distributed more broadly
Types of Articles* (2010-2017)

Number of Publications

Recent decrease in number of publications is observed for all types of citations

*articles can contain both *in vitro* and *in vivo* studies
Types of Articles* (2010-2017)

Number of Studies

Overall amount of information (i.e. number of studies) relatively stable

*articles can contain both *in vitro* and *in vivo* studies
Articles 2017-2018

642* articles

- in vivo: 46% of articles
- in vitro: 58% of articles

Enzymes (53%)
- Metabolism 34%
- Inhibition 51%
- Induction 13%
- Activation 2%

Transporters (47%)
- Substrates 46%
- Inhibition 54%

- There are 25% more in vitro than in vivo articles
- Among in vitro papers, transporter-based DDIs are catching up with metabolism-based DDIs

*23 articles contain both in vivo and in vitro information and are included in each category
Articles 2017-2018

642* articles

in vivo: 46% of articles

Inhibition 50%
Positive: 57%
Negative: 43%

Induction 15%
Positive: 57%
Negative: 43%

Other Mechanisms 6%
Positive: 57%
Negative: 43%

Single drug PK 29%

Organ impairment: 59%
Food-Effect: 41%

in vitro: 58% of articles

*23 articles contain both in vivo and in vitro information and are included in each category
Case Reports of Toxicity (N = 20) victims involved

65% of the victims are NTI drugs

- Immunosuppressant (tacrolimus, everolimus)
- Cancer treatments (busulfan, docetaxel, vinblastine)
- Anticoagulants (rivaroxaban, warfarin)
- Mood stabilizers (lithium)
Case Reports of Toxicity (N = 20) perpetrators involved

70% due to anti-infective drugs
- ertapenem, flucloxacillin, meropenem, moxifloxacin, nafcillin, rifampin
- HCV and HIV drugs
- fluconazole, voriconazole

20% due to natural products
clementine, turmeric, Ginkgo biloba, garlic
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### Most Pronounced Clinical Inhibitions (Top 10)

<table>
<thead>
<tr>
<th>Victim</th>
<th>Inhibitor</th>
<th>Enzymes / Transporters</th>
<th>Victim AUC ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>trifluridine</td>
<td>tipiracil</td>
<td>thymidine phosphorylase</td>
<td>35.2</td>
<td>Cleary, 2017</td>
</tr>
<tr>
<td>dextromethorphan</td>
<td>GSK1034702</td>
<td>CYP2D6</td>
<td>21.8</td>
<td>Hobbs, 2017</td>
</tr>
<tr>
<td>ivacaftor</td>
<td>ritonavir</td>
<td>CYP3A</td>
<td>19.7</td>
<td>Liddy, 2017</td>
</tr>
<tr>
<td><strong>rosuvastatin</strong></td>
<td>faldaprevir</td>
<td>OATP1B1/1B3</td>
<td><strong>14.7</strong></td>
<td>Huang, 2017</td>
</tr>
<tr>
<td>venetoclax</td>
<td>posaconazole</td>
<td>CYP3A</td>
<td>9.7</td>
<td>Agarwal, 2017</td>
</tr>
<tr>
<td><strong>atorvastatin</strong></td>
<td>faldaprevir</td>
<td>OATP1B1/1B3</td>
<td>9.4</td>
<td>Huang, 2017</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>rifampin SD</td>
<td>OATP1B1/1B3</td>
<td>8.6</td>
<td>Prueksaritanont, 2017</td>
</tr>
<tr>
<td>venetoclax</td>
<td>ketoconazole</td>
<td>CYP3A, (P-gp, BCRP)</td>
<td>7.9</td>
<td>Agarwal, 2017</td>
</tr>
<tr>
<td>pibrentasvir</td>
<td>glecaprevir</td>
<td>P-gp, BCRP</td>
<td>7.5</td>
<td>Lin, 2018</td>
</tr>
<tr>
<td>simeprevir</td>
<td>rifampin SD</td>
<td>OATP1B1/1B3</td>
<td>7.4</td>
<td>Yoshikado, 2017</td>
</tr>
<tr>
<td>midazolam</td>
<td>itraconazole</td>
<td>CYP3A</td>
<td>7.1</td>
<td>Prueksaritanont, 2017</td>
</tr>
</tbody>
</table>

- Transporters (OATP1B1/1B3 inhibition) contribute as much as metabolic enzymes
- Most perpetrators are anti-infective drugs (consistent with role of antibiotics in previous slide)
- All victims are marker or sensitive substrates
**Most Pronounced Clinical Inductions (Top 10)**

<table>
<thead>
<tr>
<th>Victim</th>
<th>Inducer</th>
<th>Enzymes / Transporters possibly involved</th>
<th>Victim AUC ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>isavuconazole</td>
<td>rifampin</td>
<td>CYP3A</td>
<td>0.12</td>
<td>Townsend, 2017</td>
</tr>
<tr>
<td>doravirine</td>
<td>rifampin</td>
<td>CYP3A</td>
<td>0.13</td>
<td>Yee, 2017</td>
</tr>
<tr>
<td>odanacatib</td>
<td>rifampin</td>
<td>CYP3A, P-gp</td>
<td>0.16</td>
<td>Stoch, 2017</td>
</tr>
<tr>
<td>omeprazole</td>
<td>rifampin</td>
<td>CYP3A, CYP2C19</td>
<td>0.17</td>
<td>Park, 2017</td>
</tr>
<tr>
<td>amenamevir</td>
<td>rifampin</td>
<td>CYP3A</td>
<td>0.17</td>
<td>Kusawake, 2017</td>
</tr>
<tr>
<td>apatinib</td>
<td>rifampin</td>
<td>CYP3A</td>
<td>0.19</td>
<td>Liu, 2018</td>
</tr>
<tr>
<td>istradiesseline</td>
<td>rifampin</td>
<td>CYP3A, CYP2B6, CYP2C8, CYP2C9</td>
<td>0.26</td>
<td>Mukai, 2018</td>
</tr>
<tr>
<td>alectinib</td>
<td>rifampin</td>
<td>CYP3A</td>
<td>0.26</td>
<td>Morcos, 2017</td>
</tr>
<tr>
<td>ixazomib</td>
<td>rifampin</td>
<td>CYP1A2, CYP2B6, other enzymes, P-gp</td>
<td>0.27</td>
<td>Gupta, 2018</td>
</tr>
<tr>
<td>sonidegib</td>
<td>rifampin</td>
<td>CYP3A</td>
<td>0.29</td>
<td>Einolf, 2017</td>
</tr>
</tbody>
</table>

- CYP3A induction is the predominant mechanism
- All most pronounced inductions are due to rifampin
- Victims: mostly cancer treatments and anti-infective drugs
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In vivo Articles Discussing Role of Transporters in DDIs

- P-gp: 25%
- BCRP: 20%
- OATP1B1: 17%
- OATP1B3: 13%
- OATP2B1: 13%
- OCT1: 2%
- OCT2: 2%
- MATE1: 1%
- URAT1: 4%
- OAT3: 1%
- OAT1: 1%

All OATPs: 44% of articles discuss at least one OATP transporter

P-gp and BCRP: significant contributors to clinical DDIs
# P-gp Related Inhibition

<table>
<thead>
<tr>
<th>Victim</th>
<th>Perpetrator</th>
<th>Perpetrator Dose (oral)</th>
<th>Victim AUC ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dabigatran E (µ dose)</td>
<td>itraconazole</td>
<td>200 mg QD [5 days]</td>
<td>6.9</td>
<td>Prueksaritanont, 2017</td>
</tr>
<tr>
<td>dabigatran E (µ dose)</td>
<td>clarithromycin</td>
<td>500 mg BID [5 days]</td>
<td>4.0</td>
<td>Prueksaritanont, 2017</td>
</tr>
<tr>
<td>dabigatran E</td>
<td>cobicistat</td>
<td>150 mg QD [22 days]</td>
<td>2.4</td>
<td>Kumar, 2017</td>
</tr>
<tr>
<td>dabigatran E</td>
<td>rifampin</td>
<td>600 mg SD</td>
<td>2.3</td>
<td>Prueksaritanont, 2017</td>
</tr>
<tr>
<td>dabigatran E</td>
<td>clarithromycin</td>
<td>500 mg BID [5 days]</td>
<td>2.1</td>
<td>Gouin-Thibault, 2017</td>
</tr>
<tr>
<td>digoxin</td>
<td>rolapitant</td>
<td>180 mg SD</td>
<td>1.3</td>
<td>Wang, 2018</td>
</tr>
<tr>
<td>digoxin</td>
<td>mirabegron</td>
<td>100 mg QD [14 days]</td>
<td>1.3</td>
<td>Groen-Wijnberg, 2017</td>
</tr>
<tr>
<td>fexofenadine</td>
<td>piperine</td>
<td>20 mg QD [10 days]</td>
<td>1.7</td>
<td>Bedada, 2017</td>
</tr>
<tr>
<td>fexofenadine</td>
<td>diosmin</td>
<td>150 mg QD [10 days]</td>
<td>1.7</td>
<td>Bedada, 2017</td>
</tr>
<tr>
<td><strong>Co-Meds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>simeprevir*; Y</td>
<td>ledipasvir</td>
<td>90 mg QD [14 days]</td>
<td>3.0</td>
<td>Bourgeois, 2017</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>clarithromycin</td>
<td>500 mg BID [5 days]</td>
<td>2.1</td>
<td>Gouin-Thibault, 2017</td>
</tr>
<tr>
<td>rosvastatin*</td>
<td>itraconazole</td>
<td>200 mg QD [5 days]</td>
<td>1.8</td>
<td>Prueksaritanont, 2017</td>
</tr>
<tr>
<td>glecaprevir*; Y</td>
<td>pibrentasvir</td>
<td>160 mg QD [7 days]</td>
<td>1.8</td>
<td>Lin, 2018</td>
</tr>
<tr>
<td>ledipasvir Y</td>
<td>simeprevir</td>
<td>150 mg QD [14 days]</td>
<td>1.7</td>
<td>Bourgeois, 2017</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>isavuconazole</td>
<td>200 mg TID [8 days]</td>
<td>1.3</td>
<td>Yamazaki, 2017</td>
</tr>
<tr>
<td>peficitinib</td>
<td>verapamil</td>
<td>80 mg TID [10 days]</td>
<td>1.3</td>
<td>Zhu, 2017</td>
</tr>
</tbody>
</table>

*BCRP also involved; YOATPs also involved

P-gp related inhibition rarely over 2-fold except with dabigatran etexilate
Recent publications evaluate the use of endogenous compounds (coproporphyrin I and III) as potential specific OATP1B markers to study OATP1B-related clinical inhibition.
**Hepatic OATP-Related Inhibition**

<table>
<thead>
<tr>
<th>Victim</th>
<th>Perpetrator</th>
<th>Perpetrator dose (oral)</th>
<th>Victim AUC ratio</th>
<th>Transporter(s) involved</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>simeprevir</td>
<td>rifampin</td>
<td>600 mg SD</td>
<td>7.2</td>
<td>OATP1B</td>
<td>Yoshikado, 2017</td>
</tr>
<tr>
<td>leterminvir</td>
<td>cyclosporine</td>
<td>200 mg SD</td>
<td>3.4</td>
<td>OATP1B P-gp, BCRP</td>
<td>Kropiet, 2018</td>
</tr>
<tr>
<td>bosentan</td>
<td>rifampin</td>
<td>600 mg SD</td>
<td>3.2</td>
<td>OATP1B</td>
<td>Yoshikado, 2017</td>
</tr>
<tr>
<td>selexipag</td>
<td>gemfibrozil</td>
<td>600 mg BID [9 days]</td>
<td>2.0</td>
<td>OATP1B</td>
<td>Bruderer, 2017</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>rifampin</td>
<td>600 mg SD</td>
<td>1.9</td>
<td>OATP1B</td>
<td>Yoshikado, 2017</td>
</tr>
<tr>
<td>glecaprevir</td>
<td>pibrentasvir</td>
<td>160 mg QD [7 days]</td>
<td>1.8</td>
<td>OATP1B P-gp, BCRP</td>
<td>Lin, 2018</td>
</tr>
</tbody>
</table>

Inhibition of hepatic OATPs can lead to significant increases in substrate exposures
### Intestinal OATP2B1-Related Inhibition

<table>
<thead>
<tr>
<th>Victim</th>
<th>Perpetrator</th>
<th>Perpetrator Dose (oral)</th>
<th>Victim AUC ratio</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>glibenclamide</td>
<td>grapefruit juice</td>
<td>200 mL TID [3 days]</td>
<td>0.5</td>
<td>Kashihara, 2017</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>ronacaleret</td>
<td>400 mg QD [10 days]</td>
<td>0.5</td>
<td>Johnson, 2017</td>
</tr>
<tr>
<td>celiprolol</td>
<td>grapefruit juice</td>
<td>200 mL TID [3 days]</td>
<td>0.6</td>
<td>Kashihara, 2017</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>grapefruit juice</td>
<td>200 mL TID [3 days]</td>
<td>0.7</td>
<td>Kashihara, 2017</td>
</tr>
<tr>
<td>sulfasalazine</td>
<td>grapefruit juice</td>
<td>200 mL TID [3 days]</td>
<td>0.7</td>
<td>Kashihara, 2017</td>
</tr>
<tr>
<td>sumatriptan</td>
<td>grapefruit juice</td>
<td>200 mL TID [3 days]</td>
<td>0.7</td>
<td>Kashihara, 2017</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>epigallocatechin gallate</td>
<td>300 mg SD</td>
<td>0.8</td>
<td>Kim, 2017</td>
</tr>
</tbody>
</table>

Ronacaleret: investigational drug candidate for treatment of osteoporosis (now terminated)
Glibenclamide, rosuvastatin and sulfasalazine are dual substrates for OATP2B1 and BCRP

Inhibitors of intestinal OATP2B1 are mostly natural products
**DDI Publications 2017-2018: Conclusions**

- **Literature**
  Overall, same amount of information available despite a decrease in number in published articles
  More *in vitro* transport data becoming available

- **Most pronounced clinical interactions**
  Inhibition: significant contribution of hepatic OATPs
  Induction: rifampin used as a multi-CYP inducer

- **Transporter-based DDIs**
  Investigation of new potential endogenous markers for OAPT1B-based DDIs
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Example of Gene-Drug-Drug-Drug-Interactions (GDDIs)

Case Study

Notable Drug-Drug Interaction Between Etizolam and Itraconazole in Poor Metabolizers of Cytochrome P450 2C19.


DDI Between Etizolam and Itraconazole in CYP2C19 Poor Metabolizers

Victim: etizolam
- Thienodiazepine
- Anxiety disorder with depression, panic disorder and insomnia
- Relatively safe - low abuse potential
- Marketed in Italy, South Korea and Japan
- One of the most prescribed benzodiazepines in Japan
- Metabolism*: CYP2C19 and CYP3A

Perpetrator: itraconazole
- Antifungal
- Strong CYP3A inhibitor

CYP2C19 polymorphisms
- Japanese: ~20% are poor Metabolizers

*Ref: In vitro: Niwa, 2005
In vivo: Araki, 2004; Suzuki, 2004; Kondo, 2005; Fukasama, 2005
DDI Between Etizolam and Itraconazole in CYP2C19 Poor Metabolizers

*in vitro* experiments: estimation of etizolam $f_{m_{CYP3A}}$

**Experiments**
- Human liver microsomes prepared from CYP2C19 PM donors
- Etizolam: 0.2 or 1.0 μM
- Itraconazole: 0, 0.0015, 0.56, 1.4, 3.5, or 8.7 μM

**Results: fraction metabolized by CYP3A**
- $f_{m_{CYP3A}}$ etizolam: 0.60 ± 0.06
- $K_{i_{, itraconazole}}$: 0.73 ± 0.28 μM

Based on the estimated $f_{m}$ value, the magnitude of increase in $AUC_\infty$ was estimated 2.5-fold *in vivo.*
DDI Between Etizolam and Itraconazole in CYP2C19 Poor Metabolizers

*in vivo study*

**Subjects and study design:**
16 healthy male Japanese volunteers: CYP2C19 EMs (N = 8) CYP2C19 PMs (N = 8)

**Fixed-sequence**

**Etizolam administration**
0.25 mg single dose (9:00 am) alone on Day 1 and with itraconazole on Day 5

**Itraconazole administration**
200 mg twice daily (9:00 am and 9:00 pm) on Days 2-5
DDI Between Etizolam and Itraconazole in CYP2C19 Poor Metabolizers

Results

Predicted magnitude of AUC increase in PMs (2.5-fold) consistent with the observed increase in vivo.

Itraconazole exposure similar between EM and PM
Etizolam intestinal availability similar between EM and PM

Authors’ Conclusion

➢ Magnitude of DDI between etizolam and itraconazole is dependent upon CYP2C19 genotype

➢ Prediction of the extent of DDI expected in PMs may be determined via *in vitro* measurements of $f_m$ using HLM (or cryopreserved human hepatocytes) from PM donors

➢ PGx testing of patients may be useful to manage these genotype-dependent DDIs.
Inhibition of Secondary Clearance Pathway

**CYP2C19 EM**
- etizolam → CYP2C19 → 8-ethylhydroxy etizolam → α-hydroxy etizolam
- itraconazole inhibits CYP3A

AUC increase in etizolam: 1.66-fold

**CYP2C19 PM**
- etizolam → CYP2C19 → 8-ethylhydroxy etizolam → α-hydroxy etizolam
- itraconazole inhibits CYP3A

AUC increase in etizolam: 2.34-fold

Maximum increase in etizolam exposure: 6.18-fold
(exetizolam administered after the introduction of itraconazole)
Scenarios Where PGx Critically Affects the Extent of DDIs

Inhibition of Primary Clearance Pathway

CYP2D6 EM

- CYP2C19
- CYP3A

venlafaxine

CYP2D6 PM

- CYP2C19
- CYP3A

venlafaxine

quinidine

N-desmethyl venlafaxine

O-desmethyl venlafaxine (active metabolite)

N-desmethyl venlafaxine

O-desmethyl Venlafaxine (active metabolite)

AUC increase in venlafaxine exposure:
(R)-VEN: 12.2-fold; (S)-VEN: 3.8-fold

No effect on venlafaxine AUC
(R)-VEN: 0.99-fold; (S)-VEN: 1.15-fold

Maximum increase in venlafaxine exposure:
(R)-VEN: 12.2-fold; (S)-VEN: 3.8-fold

(VEN administered after the introduction of quinidine)

Genotype affects Concentrations of Perpetrator Tacrolimus

CYP2C19 EM

\[ \text{tacrolimus} \xrightarrow{\text{CYP3A}} M_{\text{Tac}} \xrightarrow{\text{CYP3A}} \text{4-hydroxy voriconazole} \]

voriconazole

AUC increase in tacrolimus: 4.4-fold

CYP2C19 PM

\[ \text{tacrolimus} \xrightarrow{\text{CYP3A}} M_{\text{Tac}} \xrightarrow{\text{CYP3A}} \text{4-hydroxy voriconazole} \]

voriconazole

AUC increase in tacrolimus: 6.0-fold

Maximum increase in tacrolimus exposure: 6.5-fold
(tacrolimus administered after the introduction of voriconazole)

Scenarios Where PGx Critically Affects the Extent of DDIs
PGx affects Elimination of Active Metabolite

CYP2C19 EM

- clobazam
  - CYP3A
  - CYP2C19
  - N-desmethylclobazam (active metabolite)
  - 4-hydroxy-N-desmethylclobazam

  **AUC increase in NDCBZ:** 4.5-fold

 CYP2C19 PM

- clobazam
  - CYP3A
  - CYP2C19
  - N-desmethylclobazam (active metabolite)
  - 4-hydroxy-N-desmethylclobazam

  **No effect:** 1.04-fold increase in NDCBZ

**Maximum increase in N-desmethylclobazam exposure:** 15.5-fold
(clobazam administered after the introduction of stiripentol)
Example of Gene-Drug-Drug-Drug-Interactions (GDDIs)

Conclusions

- Clinical trials evaluating the interplay of gene-drug together with drug-drug interaction are difficult to implement.
- GDDIs are often identified via case reports of toxicity.
- Both EM and/or PM subjects might be affected by DDI depending on the underlying mechanism.
- Extent of the GDDI depends on the timing of the victim first administration relative to the perpetrator.
- *In vitro*-based predictions represent a useful tool to evaluate these often complex clinical situations.
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Thank you!

Questions?