Maternal-Fetal PBPK Modeling of Antipsychotic Drugs as Case Study

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Disclaimer

This presentation is the opinion of the author only and does not represent FDA policy and regulation.
Perinatal Health and Regulatory Need

- Need for computational alternatives to support the evaluation of safety and efficacy of therapeutic agents for patients in perinatal life-stages who are frequently excluded from clinical trials

- Utilize life-stage PBPK models as tools to evaluate and optimize treatments specifically in the perinatal life-stages

- The confidence in the use of such tools in regulatory decision-making and pose challenges in conducting timely and thorough review of submissions
Project Goal and Purpose

- To develop a PBPK model for different perinatal life stages (fetuses, neonates, infants, young children, pregnant and lactating women)

- To serve as an in-house tool allowing for flexibility to conduct any investigative analysis, and to better inform dosing for antipsychotics and COVID-19 treatments in these data-sparse populations
Strategy for Model Development

Curate data: Gather available information (existing databases, body of literature, and FDA in-house data) for parameterization of perinatal life-stage PBPK models

Design model:
- Maternal Component
- Fetal Component
- Population Modeling
- Other Perinatal Life-stages including Pediatrics

Code model component: Code the model using an open-source language based on the determined model structure and parameters. Conduct sensitivity analysis to confirm model dimensionality

Test model component: Verify the model’s predictive capability using case studies

Document model and scope gap/needs: Document model code including assumptions and decisions. Identify gaps in data and modeling needs to guide future research to facilitate regulatory application of PBPK modeling tools in perinatal periods
## Repository for Physiological Changes

### Equations for Maternal Fetal Physiological Changes

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Body Fat (kg)</strong></td>
<td>17.14 + 0.1305<em>GA + 0.0008</em>GA^2 (Eq 9)</td>
<td>20.2+0.125*FA (Eq 15)</td>
<td>17.067+0.14937*GA (Eq 3)</td>
</tr>
<tr>
<td><strong>Cardiac Output (L/h)</strong></td>
<td>301+5.916<em>GA-0.088</em>GA^2 (Eq 14)</td>
<td>6.09exp(-exp(-0.352logFA + 1.36)) + 5.14 (Eq 19 L/min)</td>
<td>301.78+3.2512<em>GA+0.15947</em>GA^2-0.0047059*GA^3 (Eq 13)</td>
</tr>
<tr>
<td><strong>Plasma Volume (L)</strong></td>
<td>2.50-0.0223<em>GA+0.0042</em>GA^2-0.00007*GA^3 (Eq 15)</td>
<td>2.36+0.0000841<em>FA+0.00395</em>FA^2-0.0000817*FA^3 (Eq 29)</td>
<td>2.4958+1.2406/(1+exp(-0.31338*(GA-17.813))) (Eq 5)</td>
</tr>
<tr>
<td><strong>Hematocrit (%)</strong></td>
<td>39.1-0.0544<em>GA-0.0021</em>GA^2 (Eq 17)</td>
<td>40.1+0.0299<em>FA-0.0180</em>FA^2+0.000401*FA^3 (Eq 21)</td>
<td>39.192-0.10562<em>GA-(7.1045</em> 10^-4)*GA^2 (Eq 24)</td>
</tr>
<tr>
<td><strong>Albumin (g/L)</strong></td>
<td>45.8-0.1775<em>GA-0.0033</em>GA^2 (Eq 19)</td>
<td>14.7<em>exp(-0.0454</em>FA)+31.7 (Eq 9)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Alpha-1-Acid Glycoprotein AAG (g/L)</strong></td>
<td>0.74-0.0088<em>GA+0.0001</em>GA^2 (Eq 20)</td>
<td>0.0000768<em>FA^2-0.00573</em>FA+0.701 (Eq 11)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Glomerular Filtration Rate</strong></td>
<td>114+3.2367<em>GA-0.0572</em>GA^2 (mL/min, Eq 27)</td>
<td>0.113+8.73<em>FA-0.716</em>FA^2+0.0245<em>FA^3-0.000294</em>FA*^4 (FA&lt;=14)</td>
<td>(17+(12.5-17)/40*GA)/100 (unitless, Eq 16)</td>
</tr>
<tr>
<td><strong>Placenta Volume</strong></td>
<td>0.716<em>GA+0.9149</em>GA^2-0.0122*GA^3 (mL, Eq 43)</td>
<td>0.937<em>exp(-6.10</em>exp(-0.0813*FA))-0.00211 (L, Eq 48)</td>
<td>0.15 (FA&gt;14) (L/min, Eq 27)</td>
</tr>
<tr>
<td><strong>Amniotic Fluid Volume</strong></td>
<td>1.9648<em>GA-1.2056</em>GA^2+0.2064<em>GA^3-0.0061</em>GA^4-0.00005*GA^5 (mL, Eq 44)</td>
<td>exp(-10+1.22<em>GA-0.0653</em>GA^2+0.00169<em>GA^3-0.0000169</em>GA^4) (L, Eq 33)</td>
<td>822.34/(1+exp(-0.26988*(GA-20.150))) (mL, Eq 9)</td>
</tr>
<tr>
<td><strong>Fetal Tissue Volume</strong></td>
<td>0.01<em>exp((0.955/0.0702)</em>(1-exp(-0.0702*GA))) (mL, Eq 42)</td>
<td>5.90/(1+exp(-4.45*logFA + 15.8)) (L, Eq 39)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abduljalil et al. 2012 (PMID: 22515555); Abduljalil et al. 2019 (PMID: 29987449); Dallmann et al. 2017 (PMID: 28401479); Kapraun et al. 2019 (PMID: 31048866); Zhang et al. 2017 (PMID: 28588050)
Code the Pregnancy PBPK Model in R

**Physiological Parameters**

**Perinatal Life-Stage PBPK Shell Model**

**Chemical-Specific Parameters**

**Model Analysis**

**Dosing Regimen**

**Model Transparency:**
open-source R language ("mrgsolve")

---

Shell Model (generic base model)

```r
# Read Shell Model + Source the Equations
library(cubano)
library(tidyr)
library(mrgsolve)
setwd("/path/to/model""); source("/path/to/chemical-parameters.R")
darwin_oral_600 <- read_excel("/path/to/darwin_oral_600.xlsx") %>% as.data.frame()
mod <- srcId(cache("darwin"))
par(mex)

# Generate Physiological Parameters

# Set the Dosing Regimen + Run the Simulation

1. Read Shell Model + Source the Equations

2. Generate Physiological Parameters

3. Set the Dosing Regimen + Run the Simulation
```
Pregnancy PBPK Model

Abduljalil et al. 2012

\[
BW = 61.1 + 0.2409 \times GA + 0.0038 \times GA^2 \\
CO = 301 + 5.916 \times GA - 0.088 \times GA^2
\]

Dallmann et al. 2017

\[
CO = 6.09 \times \exp(-0.352 \times \log(FA) + 1.36)) + 5.14 \\
HCT = 40.1 + 0.0299 \times FA - 0.0180 \times FA^2 + 0.000401 \times FA^3
\]

Customized Equations

\[
BW = 61.03 - 0.010614 \times GA + 0.029161 \times GA^2 - (5.0203 \times 10^{-4}) \times GA^3 \\
CO = 301.78 + 3.2512 \times GA + 0.15947 \times GA^2 - 0.0047059 \times GA^3
\]

BW: body weight; CO: cardiac output; HCT: hematocrit; GA: gestational age; FA: fertilization age
Application of the Model to Antipsychotic Drugs

- Antipsychotics are widely used during pregnancy and sometimes for the pre-existing condition
- Antipsychotics are often off-label use for pregnant women
- Antipsychotics are being prescribed increasingly during pregnancy and the postpartum period
- The dose-dependent drug effects and toxicity of antipsychotics on fetuses are still lacking
- Concerns and debates for birth defects using of antipsychotics during the first trimester

  - **Aripiprazole**: High Protein Binding; Multiple Metabolic Enzymes (with more than one metabolites)
  - **Risperidone**: High Protein Binding; Multiple Metabolic Enzymes
  - **Clozapine**: High Protein Binding; Multiple Metabolic Enzymes
# Application of the Model to Antipsychotic Drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Human fup</th>
<th>logP</th>
<th>MW</th>
<th>pKa</th>
<th>Kp</th>
<th>Metabolism</th>
<th>BDDCS</th>
<th>ECCS</th>
<th>Available PBPK</th>
<th>Available pregnancy PBPK</th>
<th>Available pregnancy PK data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>0.01</td>
<td>5.21</td>
<td>448.4</td>
<td>7.6</td>
<td>All Tissue to Plasma Partition Coefficients were Calculated using Rodgers and Rowland Method in Simcyp</td>
<td>CYP3A4 CYP2D6</td>
<td>2</td>
<td>2</td>
<td>Yes (Vieira et al. 2014)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.1</td>
<td>4.07</td>
<td>410.5</td>
<td>8.2</td>
<td>CYP2D6 (major) CYP3A4 (minor)</td>
<td>1</td>
<td>2</td>
<td>Yes (Kneller et al. 2020)</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>0.05</td>
<td>3.21</td>
<td>326.8</td>
<td>7.5</td>
<td>CYP1A2 CYP2D6 CYP3A4</td>
<td>2</td>
<td>2</td>
<td>Yes (Wong et al. 2019)</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

**Data Available for Non-Pregnancy Model**
- **Available adult PBPK models**
  - Aripiprazole: Vieira et al. 2014 (PMID: 24556783)
  - Risperidone: Kneller et al. 2020 (PMID: 31359271)
  - Clozapine: Wong et al. 2019 (PMID: 30676661)

**Data Available for Pregnancy Model**
- **Available PK data for non-pregnant adults and pregnancy**
  - Aripiprazole: Boulton et al. 2018 (PMID: 18563956); Westin et al. 2018 (PMID: 28643331)
  - Risperidone: Novalbos et al. 2010 (PMID: 20814331); Westin et al. 2018 (PMID: 28643331)
  - Clozapine: Hägg et al. 1999 (PMID: 10379638); Westin et al. 2018 (PMID: 28643331)

Values of physicochemical parameters are from DrugBank and PubChem

BDDCS: Biopharmaceutics Drug Disposition Classification System; ECCS: Extended Clearance Classification System
**in vitro to in vivo Extrapolation (IVIVE)**

Recombinant CYPs

![In vitro system](image)

**In Vitro CL_{int}**

\[
\text{Rate} = \frac{\text{Vmax}}{K_m} \cdot \frac{[X]}{\text{pmol/pmol CYP enzyme}}
\]

\[\text{CL}_{int, \text{in vivo}} = (\text{CL}_{int, \text{in vitro}}/\text{FU}_{mic}) \times \text{ISEF} \times \text{MPPGL} \times \text{Abundance} \times \text{liver weight}\]

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Metabolic Enzyme Isoforms</th>
<th>Metabolic Pathways</th>
<th>Vmax</th>
<th>Km</th>
<th>CL_{int} (in vitro)</th>
<th>fumic: fraction unbound in microsomal systems (if available)</th>
<th>ISEF: Intersystem Extrapolation Factor (if recombinant enzymes used)</th>
<th>MPPGL: Microsomal Protein Per Gram of Liver (life-stage specific)</th>
<th>Total CL_{int} (in vivo, per of kg liver)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>CYP2D6</td>
<td>DM-1451</td>
<td>0.42</td>
<td>15.7</td>
<td>0.027</td>
<td>0.435</td>
<td>1.069</td>
<td>40</td>
<td>26.68</td>
<td>FDA Review (2001)</td>
</tr>
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<td></td>
<td></td>
<td>DM-1452</td>
<td>3.92</td>
<td>27.9</td>
<td>0.141</td>
<td>0.435</td>
<td>1.069</td>
<td>40</td>
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<tr>
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<td>OPC-14857</td>
<td>2.81</td>
<td>26.2</td>
<td>0.107</td>
<td>0.435</td>
<td>1.069</td>
<td>40</td>
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<tr>
<td></td>
<td></td>
<td>DM-1451</td>
<td>12.5</td>
<td>514</td>
<td>0.024</td>
<td>0.435</td>
<td>0.226</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DM-1452</td>
<td>19.6</td>
<td>757</td>
<td>0.026</td>
<td>0.435</td>
<td>0.226</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OPC-14857</td>
<td>6.21</td>
<td>298</td>
<td>0.021</td>
<td>0.435</td>
<td>0.226</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>7.550</td>
<td>1</td>
<td>1</td>
<td>40</td>
<td>211.92</td>
<td>Vieira et al. 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP3A4</td>
<td>NA</td>
<td>NA</td>
<td>0.180</td>
<td>1</td>
<td>1</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>CYP1A2</td>
<td>NA</td>
<td>13.1</td>
<td>14.2</td>
<td>0.923</td>
<td>1</td>
<td>0.571</td>
<td>40</td>
<td>81.12</td>
<td>Ghoneim et al. 2020</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP2D5</td>
<td>4.5</td>
<td>19.5</td>
<td>0.231</td>
<td>1</td>
<td>1.069</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CYP3A4</td>
<td>NA</td>
<td>11.6</td>
<td>0.127</td>
<td>1</td>
<td>0.226</td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proctor et al. 2004; Song et al. 2017
Model Simulation

Model Calibration with Non-pregnant Adults

- Adult Aripiprazole 2 mg iv
- Adult Aripiprazole 5 mg oral
- Adult Risperidone 1 mg oral
- Adult Clozapine 12.5 mg oral

Model Evaluation with Daily Dose through Pregnancy

- Aripiprazole oral 15 mg daily
- Risperidone oral 5 mg daily
- Clozapine oral 300 mg daily

95 percentile
5 percentile
Mean
Pregnant Women Population

Based on National Health and Nutrition Examination Survey (NHANES)

**Age**

Age ratios of pregnant women change throughout years

**Ethnicity & BMI**

IOM Report, 2009

Figure 3. Birth rates, by age of mother: United States, 1990–2018

NOTE: Rates are plotted on a logarithmic scale.

CDC NVSS Report
## Population Pregnancy Model

### Hierarchical Workflow (2 Steps)

1. **HTTK Population Generation**
   - **Age Groups**
     - 30-34
     - 25-29
     - 20-24
     - 35-39
     - 15-19
     - 40-44

2. **Monte Carlo Simulation**
   - Time dependent changes
   - Dynamic Variability

### Ethnicity
- African American
- Other Hispanic
- Mexican American
- Caucasian
- Other

### BMI
- Underweight
- Normal
- Overweight
- Obese

---

Abduljalil et al. 2012; Dallmann et al. 2017; Kapraun et al. 2019
Pharmacokinetic Profiling

- By applying the population model based on different ethnic, BMI, and age groups, the subgroups can be separated to view the PK profile individually.
Model Assumptions:

1. The placenta considered as a permeability-limited compartment.

2. The passive diffusion of drugs is proportional to the placenta villous surface area.

3. The drug exchange between amniotic sac and maternal circulation considered negligible.

4. The drug concentrations in fetal venous plasma equals to drug concentrations in umbilical cord plasma.
### Observed data from previous reports

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Mean (ng/mL)</th>
<th>SD</th>
<th>Dose (mg/day)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>3</td>
<td>44.33</td>
<td>7.76</td>
<td>10 mg/day</td>
<td>Windhager et al. 2014</td>
</tr>
<tr>
<td>Risperidone</td>
<td>6</td>
<td>1.6</td>
<td>1.05</td>
<td>3 mg/day</td>
<td>Newport et al. 2007</td>
</tr>
<tr>
<td>Clozapine</td>
<td>5</td>
<td>70.4</td>
<td>27.4</td>
<td>200 mg/day</td>
<td>Imaz et al. 2018</td>
</tr>
</tbody>
</table>

### Umbilical Cord Plasma Concentrations of Antipsychotics

- **Aripiprazole oral 10 mg daily**: Concentrations peak around 30 weeks of gestation, with a 95th percentile of approximately 150 ng/mL and a 5th percentile of around 40 ng/mL.
- **Risperidone oral 3 mg daily**: Concentrations peak around 30 weeks of gestation, with a 95th percentile of approximately 2.0 ng/mL and a 5th percentile of around 1.0 ng/mL.
- **Clozapine oral 200 mg daily**: Concentrations peak around 30 weeks of gestation, with a 95th percentile of approximately 200 ng/mL and a 5th percentile of around 50 ng/mL.
Flexible to Keep up with Current Research

Abduljalil et al. 2012 (PMID: 22515555); Abduljalil et al. 2020 (PMID: 32840724); Ke et al. 2019 (PMID: 30924921)
Conclusions

• Pregnancy and maternal-fetal PBPK is a useful tool to predict the intra-uterine exposure

• The population model based on the demographics of real population can help advance the variability assessment in these susceptible populations

• Maternal-fetal PBPK model can help determine the safety and efficacy of therapeutic agents and can also be adapted for chemical risk assessment as necessary
Acknowledgements

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