Nonclinical Assessment of Opioid and Sedative Psychotropic Drug Interactions Exacerbating Respiratory Depression: From the Clinic to the Lab and Back Again

Rodney Rouse
Division of Applied Regulatory Science
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
rodney.rouse@fda.hhs.gov
Disclosure & Disclaimer

• The author has no conflicts of interest to disclose

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News from the Clinic: National Opioid Crisis

• 30% of opioid overdoses involve concomitant use of benzodiazepines\(^1\)

• Patients co-prescribed benzodiazepines and opioids 10-fold higher incidence of overdose death\(^2\)

• Benzodiazepines potentiate opioid-induced respiratory depression, the primary mechanism in fatal opioid overdoses\(^3\)

• 2016 Citizen’s Petition from major city and state health agencies → Black Box Warnings

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1 NIDA (https://www.drugabuse.gov/drugs-abuse/opioids/benzodiazepines-opioids)
3 Horsfall et al. *Basic & Clinical Pharmacology & Toxicology* (2017)
Post-Black Box Warning Concern

• Many Sedative Psychotropic Products:
  – benzodiazepines, TCAs, Z-drugs, barbiturates, etc.
  – Only benzodiazepines contain the boxed warning

• Unintentional Impact:
  – In practice, health providers may shift to non-benzodiazepine sedative psychotropic products
  – Some non-benzodiazepine sedative psychotropic products may be as bad or worse than benzodiazepines----we don’t know
  – Do other sedative psychotropic products need label changes?

Courtesy of Hao Zhu
Laboratory Research Project Proposal

• Research Question: How to assess the potential of enhanced respiratory depression when opioids and sedative psychotropic products are used (especially opioids and sedative psychotropic products that have been on the market for decades)?

Division of Clinical Pharmacology 1
• conducted an initial search through the literature
• proposed an animal study
• initiated a formal consult.

A research group was formed among
• Division of Clinical Pharmacology 1
• Division of Psychiatry Products
• Division of Analgesic and Anesthesia Products
• Division of Applied Regulatory Science

The Division of Applied Regulatory Science took the lead to conduct non-clinical research aimed at identifying the potential for PD interactions.
Nonclinical Research to Inform Labeling

1. Identify sedative psychotropic drugs (SPDs)

2. Literature on what is known about respiratory depression and these drugs

3. Select drugs for assessment

4. Devise an animal model for screening SPDs

5. Use opioid + benzodiazepine as a positive control

Courtesy of Jim Weaver
Drug Identification Strategy

A. List currently marketed drugs that might be classified as ‘sedative psychotropic’ drugs

A total of 74 drugs were identified and grouped into 12 groups (9 drugs ungrouped) by:

- Drug class
- Chemical structural similarity
- Known receptor binding

B. Identify representative drugs within each group for detailed analysis

C. Perform extensive literature search of representative drugs and review human and nonclinical data

D. Locate data gaps, check overall use (enough to be relevant) and adverse event reports to determine candidates for laboratory studies

Courtesy of Jim Weaver
<table>
<thead>
<tr>
<th># in class</th>
<th>Drug Class</th>
<th>Index Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Antihistamine</td>
<td><em>Diphenhydramine</em></td>
</tr>
<tr>
<td>9</td>
<td>Atypical antipsychotic</td>
<td><em>Olanzapine</em></td>
</tr>
<tr>
<td>6</td>
<td>Barbiturate</td>
<td><em>Pentobarbital</em></td>
</tr>
<tr>
<td>9</td>
<td><em>Benzodiazepines</em></td>
<td><em>Diazepam</em></td>
</tr>
<tr>
<td>2</td>
<td>GABA analogue</td>
<td><em>Gabapentin</em></td>
</tr>
<tr>
<td>3</td>
<td>Imidazopyridine</td>
<td><em>Zolpidem</em></td>
</tr>
<tr>
<td>3</td>
<td>MAOI</td>
<td><em>Tranylcypromine</em></td>
</tr>
<tr>
<td>2</td>
<td>SARI</td>
<td><em>Trazodone</em></td>
</tr>
<tr>
<td>4</td>
<td>Skeletal muscle relaxant</td>
<td><em>Baclofen</em></td>
</tr>
<tr>
<td>5</td>
<td>SSRI</td>
<td><em>Paroxetine</em></td>
</tr>
<tr>
<td>9</td>
<td>Tricyclic antidepressant</td>
<td><em>Amitriptyline</em></td>
</tr>
<tr>
<td>10</td>
<td>Typical antipsychotic</td>
<td><em>Haloperidol</em></td>
</tr>
<tr>
<td>9</td>
<td>Ungrouped drugs</td>
<td><em>Meprobamate</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Topiramate</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Suvorexant</em></td>
</tr>
</tbody>
</table>

**Integrated Evaluation**

Drugs eliminated because of:

- **Sufficient evidence of no respiratory effect**
  - *Topiramate*
  - *Duloxetine*
- **Sufficient evidence of a respiratory effect**
  - *Baclofen*
  - *Carisoprodol*
- **Insufficient use and no AE reporting of significance**
  - *Amitriptyline*
  - *Imipramine*  

Courtesy of Jim Weaver
Identifying a Practical Preclinical Model

• Measuring respiratory depression
  – Respiratory parameters (rate, tidal volume)
  – Blood gases (pO₂ and pCO₂)

• Animal species
  – Mouse
  – Rat

• Optimal Instrumentation
  – Plethysmograph
  – i-STAT

Illustration by Alan Knapton
Endpoint for Respiratory Depression
Measurable & Relevant

• Arterial pO$_2$ and pCO$_2$
• Accurate reflection of ventilation (clinical use)
• Well defined and relevant change criteria
  – pO$_2$ & pCO$_2$ change in opposite directions (validation)
  – Relevant pCO$_2$ increases (normal 35 to 45)
    • Change from baseline (time zero) > 10%
    • > 45 = clinical hypoventilation
• Relatively easy to measure in cannulated rats
Highpoints of Experimental Design

• Arterial pO$_2$ and pCO$_2$
• i-STAT
• Oral gavage to reflect clinical (prescription) use
• Given first 3 bullets: species selection = rat
  – Gavage volume
  – Serial blood sampling
Pharmacokinetics & Pharmacodynamics

• Dose Selection
  – 3 concentrations
    • Low: Human Equivalent Dose (FDA Guidance-surface area)
    • Medium: Historical Use in Rats
    • High: High Exposure Beneath LD$_{50}$

• Dose Timing to approach simultaneous $C_{\text{max}}$

• Define drug-induced respiratory depression for each drug at selected concentration (exposure-response)
Assessment Criteria

• Respiratory Depression
  – Identify opioid induced increase in pCO₂ (significant & > 10%)
  – Measure additional significant increase in pCO₂ with co-administered drug yielding levels indicative of hypoventilation (> 45)

• Pharmacokinetic Interaction
  – Increased opioid concentrations with co-administration
  – +/- change in co-administered SPD concentrations

• Pharmacodynamic Interaction
  – Larger pCO₂ response with similar blood opioid concentrations when co-administered versus given alone
Opioid Given Alone—Oxycodone (150mg/kg)

- Oxycodone alone PD versus PK
- 0-100 ng/ml oxycodone pCO$_2$ usually less than 55
- Very few points at concentrations greater than 100 ng/ml
- Combined:
  - > concentrations = PK effect
  - greater pCO$_2$ at same concentration = PD effect

n=659 data points
Opioid Given Alone—Oxycodone (150mg/kg)

$pCO_2$ (mean ± standard error)

> 45 = hypoventilation

Simple paired t-test indicates significant mean change from baseline at $p < 0.05$

$n=114$ rats
Oxycodone and Diazepam  PK  
Mean of 3 Experiments

Time -Mean Concentration Profile of Oxycodone in Rats (n=18/group)

Interaction with Diazepam
Alone

Oxycodone exposure by area under the curve evaluation approximately doubled when diazepam was also given

Time -Mean Concentration Profile of Diazepam in Rats

Interaction
Alone

Diazepam exposure by area under the curve evaluation reduced approximately one third when diazepam was given with oxycodone
Oxycodone – Diazepam PD Interaction
Mean of 3 Experiments

Increase in pCO₂ with oxycodone and diazepam co-administration

X = Diazepam dose (30 minutes after Oxycodone)

25% increase in AUC
Co-Administered Oxycodone & Diazepam to Validate the Model

PD effect = increased pCO$_2$ at same administered oxycodone concentration; potentially some PK component
Model Successful in Profiling Opioid Induced Respiratory Depression

• Respiratory Depression
  – Identify opioid induced increase in pCO₂
  – Measure additional increase in pCO₂ with co-administered benzodiazepine indicative of hypoventilation (> 45)

• Pharmacodynamic Interaction
  – Larger pCO₂ response with similar blood opioid concentrations when co-administered versus given alone
Co-administration Effects

n=total data points; oxycodone in ng/ml

Coad-Paroxetine-50

n=36

PD (100%)
PK (400%)

Coad-Paroxetine-5

n=36

PD (35%)
PK (50%)

Coad-Cyclobenzaprine

n=36

PD (none)
PK (150%)
Co-administration Effects

n=total data points; oxycodone in ng/ml

- **Coad-Quetiapine-250**
  - PD (75%)
  - PK (950%)
  - n=36

- **Coad-Quetiapine-25**
  - PD (none)
  - PK (70%)
  - n=36

- **Coad-Carisoprodol**
  - No Effect
  - n=36

- **Oxycodone-alone**
  - PD (75%)
  - PK (950%)
  - n=36

  - No Effect
  - n=36

  - PD (none)
  - PK (70%)
  - n=36
Co-administration Effects

n=total data points; oxycodone in ng/ml

- **Coad-Suvorexant**
  - n=35
  - No Effect

- **Coad-Duloxetine**
  - n=25
  - PD (none)
  - PK (170%)

- **Coad-Ramelteon**
  - n=36
  - PD (30%)
  - PK (150%)

- **Oxycodone-alone**
  - n=36
No Co-Administration Effect

$n=$total data points; oxycodone in ng/ml

- Coad-Clozapine: n=35
- Coad-Trazadone: n=36
- Coad-Risperidone: n=36
- Oxycodone-alone: n=36

- Oxycodone: 0 to 500
- pCO2: 20 to 80
No Co-Administration Effect

n=total data points; oxycodone in ng/ml
Co-Administration Result Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK</th>
<th>PD</th>
<th>None</th>
<th>?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramelteon</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Suvorexant</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Lower confidence: 
Higher confidence:

Primary PD Effect: Paroxetine
Primary PK Effect: Quetiapine, Carisoprodol, Cyclobenzaprine, Duloxetine
No Effect: Clozapine, Risperidone, Zolpidem, Trazodone, Mirtazapine, Topiramate, Suvorexant
Questionable: Ramelteon
Assessing Clinical Relevance: Approach

Collected mean human Cmax and AUC data from Clinical Pharmacology NDA reviews & literature

Compiled mean rat Cmax and AUC exposure data for each dose administered in rat experiments

Assessed approximate exposure equivalency between rat and human doses

Reviewed clinical dosing recommendations for each drug from product labeling

Estimated whether the rat exposure approximated clinically-relevant human doses

Courtesy of Mike Davis
## Assessing Clinical Relevance: Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Test Dose Rat Exposure</th>
<th>Single Dose Human Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>Relevant</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Relevant to steady state</td>
<td></td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carisoprodol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine 250 mg/kg</td>
<td>Lower</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone (possibly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine 5 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine 25 mg/kg</td>
<td>Higher</td>
<td>Ramelteon</td>
</tr>
<tr>
<td>Clozapine</td>
<td></td>
<td>Zolpidem</td>
</tr>
<tr>
<td>Paroxetine 50 mg/kg</td>
<td>Lower</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Suvorexant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Courtesy of Mike Davis*
# Summary of Interactions and Clinical Relevance

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK</th>
<th>PD</th>
<th>None</th>
<th>?</th>
<th>Clinical Relevance</th>
<th>Repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td>&lt; SS</td>
<td>No</td>
</tr>
<tr>
<td>Quetiapine (250 mg/kg)</td>
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<td>√</td>
<td></td>
<td></td>
<td>SS</td>
<td>No</td>
</tr>
<tr>
<td>Risperidone</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>SS</td>
<td>No</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>&gt; SD</td>
<td>Yes</td>
</tr>
<tr>
<td>Trazodone</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>SD</td>
<td>No</td>
</tr>
<tr>
<td>Carisoprodol</td>
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<td>√</td>
<td></td>
<td></td>
<td>SD</td>
<td>Yes</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td>SD</td>
<td>Yes</td>
</tr>
<tr>
<td>Paroxetine (5 mg/kg)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>SS</td>
<td>No</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>SS</td>
<td>No</td>
</tr>
<tr>
<td>Topiramate</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>SS</td>
<td>No</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td>SS</td>
<td>No</td>
</tr>
<tr>
<td>Ramelteon</td>
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<td>√</td>
<td></td>
<td></td>
<td>&gt; SD</td>
<td>Yes</td>
</tr>
<tr>
<td>Suvorexant</td>
<td></td>
<td>√</td>
<td></td>
<td></td>
<td>&gt; SS</td>
<td>No</td>
</tr>
</tbody>
</table>

SS = steady state  
SD = single dose

Lower confidence  
Higher confidence
Ventilatory Effects of Opioids Can be Easily and Safely Studied in Healthy Subjects

Courtesy of Chris Breder
Back to the Clinic

• Initial studies are proposed with benzodiazepine and 2 other PSDs that showed a signal in rats
  – Determine clinical respiratory depression risk
    • Alone
    • With an opioid
  – Evaluate non-clinical model for clinical predictivity
  – Initiate drug-opioid interaction modeling efforts
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Questions

Division of Applied Regulatory Science