Pharmacodynamics and Pharmacokinetics of Synthetic Cannabinoids

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NMS Labs, Willow Grove, PA
February 21, 2012
Synthetic Cannabinoids

- Chemicals designed to have CB$_1$/CB$_2$ binding properties
- Chemically diverse structure classes
- First synthesized as investigational drugs in the 1980’s
- Adopted by the “Research Chemical” movement in 2000’s
- Sold as “Legal highs”, “Incense blends”, “Potpourri”
What’s in Herbal Incense?

"The stuff that's been put into the incense was originally made in our lab 15 years ago."

*John W. Huffman, ABC News, 3/17/10*
Nomenclature

- Initially synthesized for medicinal research
- JWH compounds are named for John W. Huffman at Clemson University for research on the relationship between the structure of drugs and brain receptor activity
- HU prefaced compounds are named for Hebrew University
- CP 47,497 was initially developed by Pfizer as an analgesic
- AM prefaced compounds are halogenated and named for Northeastern University professor Alexandros Makriyannis
- WIN compounds were developed by Sterling Winthrop
## CB₁ Cannabinoid Receptor
### Central and Peripheral Effects

<table>
<thead>
<tr>
<th>Beneficial Effects</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced nausea/Increased appetite</td>
<td>Increased appetite</td>
</tr>
<tr>
<td>Improved mood, euphoria</td>
<td>High abuse potential, dysphoria</td>
</tr>
<tr>
<td></td>
<td>Vasodilation and tachycardia, increased risk of cardiac events</td>
</tr>
<tr>
<td></td>
<td>Impaired memory and cognition, altered perception</td>
</tr>
<tr>
<td></td>
<td>Impaired coordination and psychomotor performance</td>
</tr>
</tbody>
</table>
CB₁ and Neurotransmission

Presynaptic

GABA or glutamate

Postsynaptic

Endocannabinoid

Pharmacodynamics and Pharmacokinetics of Synthetic Cannabinoids
When marijuana is smoked, its active ingredient, THC, travels throughout the body, including the brain, to produce its many effects. THC attaches to sites called cannabinoid receptors on nerve cells in the brain, affecting the way those cells work. Cannabinoid receptors are abundant in parts of the brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgment, and pleasure.
**CB₂ Cannabinoid Receptor**

**Suggested Peripheral Effects**

<table>
<thead>
<tr>
<th>Beneficial Effects</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced inflammation</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td>Lack of psychoactive effects (?)</td>
<td></td>
</tr>
<tr>
<td>Improved bone strength</td>
<td></td>
</tr>
<tr>
<td>Decreased pain perception</td>
<td></td>
</tr>
</tbody>
</table>
Structure Activity Relationships

Classical CB\textsubscript{1} Binding

Non-Classical CB\textsubscript{1} Binding

\textit{Poso & Huffman, Br J Pharm 153:335-346, 2008.}

Pharmacodynamics and Pharmacokinetics of Synthetic Cannabinoids
<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP47,497 (non-classical)</td>
<td><img src="image1" alt="Molecule" /></td>
</tr>
<tr>
<td>CP 47,497 (C8 analog) – Cannabicyclohexanol (non-classical)</td>
<td><img src="image2" alt="Molecule" /></td>
</tr>
<tr>
<td>HU-210 (and HU-211) (classical, schedule I as THC analog)</td>
<td><img src="image3" alt="Molecule" /></td>
</tr>
<tr>
<td>JWH-018 (non-classical)</td>
<td><img src="image4" alt="Molecule" /></td>
</tr>
<tr>
<td>JWH-073 (non-classical)</td>
<td><img src="image5" alt="Molecule" /></td>
</tr>
<tr>
<td>JWH-200 (non-classical)</td>
<td><img src="image6" alt="Molecule" /></td>
</tr>
</tbody>
</table>
## The Chemical Arms Race

<table>
<thead>
<tr>
<th>Compound</th>
<th>Positivity in Blood (%)</th>
<th>CB₁ Ki (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM-2201</td>
<td>61</td>
<td>1.0</td>
</tr>
<tr>
<td>JWH-122</td>
<td>58</td>
<td>0.7</td>
</tr>
<tr>
<td>JWH-210</td>
<td>30</td>
<td>0.5</td>
</tr>
<tr>
<td>JWH-018*</td>
<td>18</td>
<td>9.5</td>
</tr>
<tr>
<td>JWH-250</td>
<td>12</td>
<td>11.0</td>
</tr>
<tr>
<td>JWH-081</td>
<td>11</td>
<td>1.2</td>
</tr>
<tr>
<td>RCS-4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>RCS-8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>JWH-019</td>
<td>2</td>
<td>9.8</td>
</tr>
<tr>
<td>JWH-073*</td>
<td>1</td>
<td>8.9</td>
</tr>
<tr>
<td>AM-694</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>JWH-200*</td>
<td>0</td>
<td>42.0</td>
</tr>
<tr>
<td>D9-THC*</td>
<td>N/A</td>
<td>41.0</td>
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</table>

*Schedule I Controlled Substance, NMS Labs data

Pharmacodynamics and Pharmacokinetics of Synthetic Cannabinoids
NMS Labs Blood Positivity Rates

Pharmacodynamics and Pharmacokinetics of Synthetic Cannabinoids
NMS Labs Blood Positivity Rates

Pharmacodynamics and Pharmacokinetics of Synthetic Cannabinoids
The Next Wave?

Fatty acid amide hydrolase (FAAH) functions at the synapse to breakdown anandamide.

Inhibition is predicted to enhance the effects of endogenous cannabinoids.

In development as a treatment for pain.

Promising FAAH inhibitor moves into clinical trials

Human Studies

- Effects
- Metabolism
- Duration
Marijuana and Driving

**Cognitive and psychomotor effects:**

Relaxation, mild euphoria, laughter, time change effects, possible hallucinations, divided attention impairment.

**Physiological Effects:**

Increased pulse and blood pressure, conjunctival injection, xerostomia/dry mouth, head movements and jerks, blinking, increased appetite.

**Adverse Effects on Driving:**

Increase in Standard Deviation of Lateral Position (weaving), estimation of time to impact, lower arousal, increased sleepiness, increased risk of crash involvement/culpability.
Synthetic Cannabinoid Effects

Urine samples were collected from 3 persons (2 males, 1 female, 22 ± 1 year old) who were seized by police in a condition of drug intoxication. As reported, the behavioral effects were similar to those typical of the administration of the marijuana products, such as the reddening of eyes, tachycardia, anxiety, paranoia and hallucinations accompanied by a short-term memory defects and the impaired sense of time.

Synthetic Cannabinoid Effects

The method was used to examine the blood samples obtained after a self-experiment during which 2 test persons had smoked an incense of the specialty “Smoke”.

The subjects reported sickness, sedation and xerostomia immediately after the smoking. Hot flushes, burning eyes and a subjectively felt thought disruption were also partially experienced. A rise of the pulse rate was observed, while the blood pressure was hardly raised. The pupil reaction was not noticeably affected, the pupil width was at most easily increased. Later, the symptoms went over in a state of light tiredness and exhaustion attenuating 6–12 h post-experiment. The serum samples of both

**Table 4**

Serum concentrations of JWH-018; * exact time 1.33 h, ** half-quantitative value below LOQ, p. = present, qualitative verification in the area of LOD; n.p. = not present.

<table>
<thead>
<tr>
<th>Post-smoking time</th>
<th>Volunteer 1 Concentration [ng/ml]</th>
<th>Volunteer 2 Concentration [ng/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>8.1</td>
<td>10.2</td>
</tr>
<tr>
<td>15 min</td>
<td>4.6</td>
<td>6.1</td>
</tr>
<tr>
<td>1 h</td>
<td>1.7*</td>
<td>1.8</td>
</tr>
<tr>
<td>3 h</td>
<td>0.41</td>
<td>0.25</td>
</tr>
<tr>
<td>6 h</td>
<td>0.16**</td>
<td>0.13**</td>
</tr>
<tr>
<td>24 h</td>
<td>p.</td>
<td>p.</td>
</tr>
<tr>
<td>48 h</td>
<td>p.</td>
<td>n.p.</td>
</tr>
</tbody>
</table>

Toxicology

- Limited immunoassay screens
- Not detectable in GCMS screens
- Blood – detect parent compounds
- Urine – Need to look for metabolites
Metabolism

Identification of in vitro metabolites of JWH-015, an aminoalkylindole agonist for the peripheral cannabinoid receptor (CB2) by HPLC-MS/MS.

JWH-015 Metabolic Pathway

Zhang et al. Fig. 9
JWH-018 Studies

Incubation with human liver microsomes
Analysis by LC-MS/MS

Urine from 3 persons known to have smoked JWH-018
Analysis of hydrolyzed urine by GC-MS/MS and LC-MS/MS
JWH-018 Metabolic Pathway

Fig. 2  Proposed metabolic pathway of JWH-018 (according to the metabolic pathway of JWH-015 proposed by Zhang et al. [22]); m/z is given in accordance with the protonated molecules.
JWH-018 Metabolites

Sobolevsky et al, Fig. 6

Pharmacodynamics and Pharmacokinetics of Synthetic Cannabinoids
Missouri K2 Administration Lab

- Spring 2010, UCMO plans DRE training to include K2 smoking Lab
- NMS Labs contacted regarding ability to test urine
- Study expanded to include additional DRE staff, and six subjects
Missouri K2 Administration Study

- IRB approval from University of Central Missouri
- Subjects smoked incense products containing JWH-018, JWH-073
- Subjects performed SFST’s, cognitive tests and DRE Exam
- Blood, urine and oral fluid collected
Missouri K2 Administration Lab

<table>
<thead>
<tr>
<th></th>
<th>K2 Standard</th>
<th>K2 Citron</th>
<th>K2 Summit</th>
<th>Herbal Blend</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-018 (mg/g)</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>JWH-073 (mg/g)</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>CP47,497 (C7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
</tr>
</tbody>
</table>

Free from other known drugs or chemicals
### The Chemical Arms Race

<table>
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<tr>
<th>Compound</th>
<th>Percent of Bloods Submitted</th>
<th>CB₁ Kᵢ (nM)</th>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>JWH-073*</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AM-694</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>JWH-200*</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>D9-THC*</td>
<td>41.0</td>
<td></td>
</tr>
</tbody>
</table>

*Schedule I Controlled Substance, NMS Labs data, n=310, 12/9/11
Missouri K2 Administration Lab

• Onset of subjective effects within 2-3 minutes.

• Subjectively peaking 5-10 minutes.

• Taste tobacco/burning garbage/unpleasant
K2 Standard: Subject Pm

- 39 y.o. Male, 190 lbs, Naive user
- Quiet, cooperative, low key
- Smoked “K2 Standard”, JWH-018, JWH-073 (~1%)
- Excellent baseline performance in DRE/SFST assessment
- 15:02 dosing
  - 1 inhalation of K2 Standard smoked in a small water pipe, 300 mg of material on the screen
K2 Standard: Subject Pm

- **15:05** Effects coming on, head high, buzzed, shaking leg, some anxiety, feels impaired.

- **15:40** SFSTs
  - Marked sway, staggering, loss of balance.
  - Walk and Turn: Lost balance during instructions, trouble placing foot on line, stepped off line, lost balance on turn, marked muscle tremors.
  - One Leg Stand: Lost balance several times, swayed, used arms for balance.
  - Lack of Convergence
K2 Observations

- Subjective Effects:
  - Dry mouth
  - Light headedness/Buzzed
  - Blurred vision
  - Sedation
  - Motor agitation/restlessness
  - Time dilation
  - Mild anxiety/paranoia
  - Post intoxication fatigue
K2 Observations

• Psychomotor Effects

• Highly variable response

• DRE Exam
  • Increased pulse and blood pressure
  • Lack of convergence
  • No HGN, or VGN
  • Pupils normal, muscle tone normal
K2 Observations

• Standard Field Sobriety Tests
  • 3-4 inches of sway, leg body tremors
  • Loss of balance
  • Loss of motor coordination
# K2 Effects

<table>
<thead>
<tr>
<th></th>
<th>Sobolevsky et al, 2010</th>
<th>Teske et al, 2010</th>
<th>Auwater et al, 2009</th>
<th>Elsohly, 2008</th>
<th>This Study - subject number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 DUls, positive for JWH-018</td>
<td>2 subjects smoked JWH-018</td>
<td>2 subjects Cannabicyclohexanol + JWH-018</td>
<td>THC K2 Standard</td>
<td>1</td>
</tr>
<tr>
<td><strong>Red eyes / bloodshot</strong></td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Burning of the eyes</strong></td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
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<tr>
<td><strong>Xerostomia (dry mouth)</strong></td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Increased pupil diameter</strong></td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>Equiv</td>
</tr>
<tr>
<td><strong>Tachycardia</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hallucinations</strong></td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
</tr>
<tr>
<td><strong>Paranoia</strong></td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sickness</strong></td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
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<tr>
<td><strong>Sedation</strong></td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Changes in perception/mood</strong></td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Loss of concentration</strong></td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Impaired sense of time</strong></td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Tiredness</strong></td>
<td>-</td>
<td>6-12 hours</td>
<td>6-24 hours</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Self assessed impairment</strong></td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Missouri K2 Administration Study

Smoked “K2 Citron”
10 mg/g JWH-018/073
0.3 g in water pipe
3 inhalations over 30 minutes
K2 Conclusions

- Blood concentrations of the parent drug were typically less than 1 ng/mL within 2 hours of smoking.
- Urine was positive within 1 hour of administration, for mono- and di-hydroxy metabolites.
K2 Administration Phase II

- IRB approval from University of Central Missouri
- Subjects smoked one of 6 herbal incense products
- Subjects performed SFST’s, cognitive tests and DRE Exam
- Blood, urine and oral fluid collected
### K2 Administration Phase II

<table>
<thead>
<tr>
<th></th>
<th>Legal Eagle</th>
<th>8-Ball</th>
<th>UK Blend I</th>
<th>Freedom</th>
<th>C4</th>
<th>SOHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-019</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JWH-081</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JWH-122</td>
<td></td>
<td></td>
<td>+</td>
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<tr>
<td>JWH-210</td>
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<td>+</td>
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<tr>
<td>JWH-250</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
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<tr>
<td>RCS-4</td>
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<td></td>
<td>+</td>
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<tr>
<td>RCS-8</td>
<td>+</td>
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<tr>
<td>AM-2201</td>
<td></td>
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<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Pharmacodynamics and Pharmacokinetics of Synthetic Cannabinoids
Legal Eagle: Subject Cm

- Male, Previous Marijuana/K2 Smoker, 150lbs
- Outgoing, loud, laughing, joking
- Smoked “Legal Eagle” containing JWH-250, JWH-019, JWH-081, RCS-4 (~1%)
- Good baseline performance in DRE/SFST assessment
- 12:19 dosing
  - 4 inhalations of Legal Eagle smoked in a small water pipe, 300 mg of material on the screen
Pharmacodynamics and Pharmacokinetics of Synthetic Cannabinoids
Legal Eagle: Subject Cm

- 12:19  Inhaled, held 6 seconds
- 12:20  Inhaled, held 12 seconds
- 12:20  “Pretty stoned”, Feels the high coming on. “This stuff is pretty potent”.
- 12:24  Inhaled ~20 seconds, held 3 seconds
- 12:24  Some unease, paranoia, feels “Chill, relaxed”
- 12:30  Inhaled, held 2 seconds
- 12:30  Euphoria is subsiding, eyes glassy/bloodshot
Legal Eagle: Subject Cm

• ~12:45 Subject thought he could drive OK, but, “wouldn’t want to take the risk of a DUI.”
  • Feels relaxed, content, chill, head-high
  • Paranoia was transient, during smoking
  • Talkative, “ranting”, short attention span
Legal Eagle: Subject Cm

- 12:45 ~30 minutes post dose SFST
  - Euphoric, talkative
  - Lack of convergence
  - Reddened bloodshot eyes
  - Pulse 102 vs 78 pre dose
  - Minimal sway on SFST, some leg tremors, generally good performance, good balance.
Legal Eagle: Subject Cm

Pharmacodynamics and Pharmacokinetics of Synthetic Cannabinoids
8 Ball: Subject Am

- 24y.o., Male, Previous Marijuana Smoker, 153 lbs
- Quiet, calm, relaxed, passive.
- Smoked “8 Ball” containing JWH-081, JWH-250 (~1%)
- Good baseline performance in DRE/SFST assessment
- 10:54 dosing
  - 3 inhalations of UK Blend smoked in a small water pipe, 300 mg of material on the screen
8 Ball: Subject Am

Blood Concentrations

Concentration (ng/mL) vs. Elapsed time (hours)

Oral Fluid

- JWH-081
- JWH-250

Pharmacodynamics and Pharmacokinetics of Synthetic Cannabinoids
8 Ball: Subject Am

- 10:54 Inhaled, held 8 seconds
- 10:55 Inhaled, held 10 seconds
- 10:56 A little light headed, “heart is speeding up”
- 10:57 Inhaled deeply, held 23 seconds
- 10:59 “..more focused...vision is delayed”. Smiling, fixed gaze
- 11:01 “Wow, its hitting me now... like I blacked out”
- 11:02 Subject becomes uncomfortable, folds arms, becomes tense, not relaxed
8 Ball: Subject Am

• 11:03 Feeling dizzy, scared, emotional, depressed, claustrophobic, doesn’t understand why people smoke K2, feels like he’s not in control of his emotions. Says he’s angry for losing control.

• 11:06 Tense, eyes closed, holding his head, crossing arms, apprehensive, breathing faster.

• 11:07 Expected alcohol buzz, but feels “oppressed”

• 11:11 “I’m getting good, more coherent”
“I can’t believe it caused claustrophobia”
“Objects are moving left and uphill”
Nursing staff are making him nervous
8 Ball: Subject Am

- 11:41 Getting more clarity, "shaking", 7 on distress scale compared to 1 at the peak of effect. Stated if he drove now he would crash into a tree.
- 11:57 More relaxed, laughing, difficulty focusing.
- 13:23 Still residual negative mood, dazed, confused, irritable.
8 Ball: Subject Am

- SFST Performance – 70 minutes post dose
  - Extreme Leg and Body Tremors, Hard to stand
  - Terminated Romberg test
  - Walk and Turn: missed numbers, tremors, stepped off the line, used arms for balance – Impaired.
- One Leg Stand: Numerous errors in counting, very poor balance.
- Problems focusing on the tests, fixated on distractions, poor attitude, became uncomfortable in the dark room.
8 Ball: Subject Am

- Evaluations stopped at 16:00 hrs, five hours post dose.
- Some residual effects
8 Ball: Subject Am

Urine Concentrations

Concentration (ng/mL)

Elapsed time (hours)

0 0:25 2:25 3:14 23:10

4-OH JWH-250
Phase II Conclusions

• Effects were qualitatively similar to marijuana with some additional anxiety/paranoia
• Subjects reported a noticeable hangover effect
• Short time to peak effects after smoking
Synthetic Cannabinoids

- Potential to cause physiological and psychomotor effects consistent with DRE cannabis category
- Effects include Lack of Convergence, reddened conjunctivae, intoxication, time dilation effects, laughter, agitation, anxiety and paranoia
- Blood concentrations below 1 ng/mL within an hour or two after smoking
- Detectable in oral fluid
- Urine concentrations may be detectable for 24 hours
Acknowledgements

- Sherri Kacinko, Ph.D.