Imaging in Analgesic Drug Development (iADD)

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Pain and the Six Conundrums

- Societal Conundrum – an epidemic
- Subjective Measure Conundrum – not objective
- Preventive Conundrum – e.g., postsurgical pain
- Therapeutic Conundrum – 30% efficacy
- Translational Conundrum – no good models
- Drug Development Conundrum – failure rate
Drug Development Conundrum

CNS has traditionally lacked tools for early pharmacologic read-outs

Borsook et al., 2011a; 2011b

60% failed Vs. placebo

11% failed for lack of efficacy differentiation

Elias et al., 2006

iADD in CNS Drug Evaluation

• Define Disease States

• Defining Drug Effects
  • Opioids - Acute Effects
  • Opioids - Chronic Effects

• Choosing Analgesics
  • Buprenorphine/Aprepitant

• pHMRI, PET and Drug Evaluation
  • PETability
  • Drug Dissection

• Enhancing Animal-Human Translational
  • Drugs
  • Pain
  • Disease
Defining Disease States

Objective Measures of Disease State or Drug Effect

Borsook and Becerra 2011
Defining Drug Effects

How well can imaging measure CNS drug effects?
Morphine

**Reward Circuitry**
- Nucleus Accumbens
  - Morphine
  - Saline
- Orbitofrontal Cortex
  - Morphine
  - Saline

**Analgesic Circuitry**
- Periaqueductal Gray

**Autonomic Circuitry**
- Hypothalamus
  - Morphine
  - Saline

**Sedative Circuitry**
- Cortical Regions (LPFC)
  - Thalamus
  - Morphine
  - Saline

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Becerra et al., 2006

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Morphine (agonist) vs. Naloxone (antagonist)

Becerra et al., 2006

Borsook et al., 2010

Borras et al., 2004
Predicting Chronic Drug Effects

Amygdala Volume (Normalized)

- Opioid-Dependent Patients
- Controls

* p < 0.05

Upadhyay et al., 2010
Choosing Effective Analgesics
Predicting Good Drugs

Subjective Ratings

<table>
<thead>
<tr>
<th>Drugs</th>
<th>VAS</th>
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</thead>
<tbody>
<tr>
<td>placebo</td>
<td>Gabapentin</td>
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</table>

fMRI Response

- Imipramine
- Placebo
- Clonazepam

Quantitative Analysis

Percent Volume Change from Placebo

- Imipramine
- Gabapentin
- Topiramate
- Ketorolac
- Clonazepam
- Rofecoxib

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Borsook et al., 2007
phMRI, PET and Drug Evaluation

Can we use functional imaging for CNS Receptor Activation?
CNS Dosing?
Drug Receptor Binding does not equal drug efficacy!
iADD and Chronic Pain

Ketamine
Borsook et al., 2007

Lamotrigine
Scrivani et al. 2009

Duloxetine
Borsook et al., Im sub.

Pregabalin
Becerra et al., Im sub.

Migraine Rx
Borsook et al., Im sub.
Enhancing Animal-Human Translational Processing

A language of translation?
Borsook and Becerra 2010

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Human-Animal Parallels

A. Functional Correlations

B. Morphometric Correlations

C. Analgesic Correlations

Apkarian et al., 2004

Seminowicz et al., 2009

Borsook and Becerra, 2011

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iADD – The Potential in Clinical Trials

- Decreasing the Risk ($)
- Enhancing the Opportunity (# Molecules)
- Evaluating Systems Targets (CNS diseases are Complex)
- Target-Systems Integration (PET/fMRI)
- Rx Domains (Symptoms vs. Disease Modification)
- Responders vs. Non-Responders
- Decreasing the Variance
- CNS Dosing
- Putting it into Action – fNIH/European
Pain

and

Zero Clinical Conundrums