Pharmacology-Guided Dose-Escalation of First-in-Class Drugs

almorexant (ORX1/2-antagonist) and rimonabant (CB1-antagonist)

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Contents:

• causes of failed development
• getting the pharmacology right for highly selective innovative drugs
Failed Clinical Trials in Phase II/III

Phase II

- Efficacy: 51%
- Pharmacokinetics/bioavailability: 1%
- Safety: 29%
- Strategic: 19%

Phase III

- Financial and/or commercial: 7%
- Not disclosed: 6%
- Efficacy: 29%
- Strategic: 21%
- 66%

Determinants of Drug Efficacy

...25 Drugs Withdrawn After Launch...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved</th>
<th>Withdrawn</th>
<th>License</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>amineptine (Survector)</td>
<td>1978</td>
<td>2000</td>
<td>22</td>
<td>abuse, acne</td>
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<tr>
<td>cisapride (Propulsid)</td>
<td>1993</td>
<td>2000</td>
<td>7</td>
<td>cardiac arrhythmia</td>
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<tr>
<td>troglitazone (Rezulin)</td>
<td>1999</td>
<td>2000</td>
<td>1</td>
<td>liver failure</td>
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<tr>
<td>alosetron (Lotronex)</td>
<td>2000</td>
<td>2000</td>
<td>1</td>
<td>ischemic colitis</td>
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<tr>
<td>phenylpropanolamine (Dexatrim)</td>
<td>1970's</td>
<td>2000</td>
<td>30</td>
<td>haemorrhagic stroke</td>
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<tr>
<td>cerivastatin (Lipobay, Baycol)</td>
<td>1997</td>
<td>2001</td>
<td>4</td>
<td>rhabdomyolysis</td>
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<td>rapacuronium (Raplon)</td>
<td>1999</td>
<td>2001</td>
<td>2</td>
<td>bronchospasm</td>
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<tr>
<td>trovafloxacin (Trovan)</td>
<td>1998</td>
<td>2001</td>
<td>3</td>
<td>liver failure</td>
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<tr>
<td>levomethadyl</td>
<td>1993</td>
<td>2003</td>
<td>10</td>
<td>abuse, cardiac arrhythmia</td>
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<tr>
<td>rofecoxib (Vioxx)</td>
<td>1999</td>
<td>2004</td>
<td>5</td>
<td>cardiac risk</td>
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<tr>
<td>pemoline (Cylert)</td>
<td>1975</td>
<td>2005</td>
<td>30</td>
<td>liver failure</td>
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<tr>
<td>valdecoxib (Bextra)</td>
<td>2004</td>
<td>2005</td>
<td>1</td>
<td>cardiac risk</td>
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<tr>
<td>natalizumab (Tysabri)</td>
<td>2004</td>
<td>2005</td>
<td>1</td>
<td>leucoencephalopathy</td>
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<tr>
<td>Tc fanolesomab</td>
<td>2004</td>
<td>2005</td>
<td>1</td>
<td>allergy</td>
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<tr>
<td>hydromorphone (Palladone ER)</td>
<td>2004</td>
<td>2005</td>
<td>1</td>
<td>alcohol interaction</td>
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<tr>
<td>pergolide (Permax)</td>
<td>1988</td>
<td>2007</td>
<td>19</td>
<td>valve regurgitation</td>
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<tr>
<td>tegaserod (Zelnorm)</td>
<td>2004</td>
<td>2007</td>
<td>3</td>
<td>cardiac risk</td>
</tr>
<tr>
<td>lumiracoxib (Prexige)</td>
<td>2006</td>
<td>2008</td>
<td>2</td>
<td>liver failure</td>
</tr>
<tr>
<td>aprotinin (Trasyiol)</td>
<td>1993</td>
<td>2008</td>
<td>15</td>
<td>cardiac risk</td>
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<tr>
<td>rimonabant (Acomplia)</td>
<td>2006</td>
<td>2008</td>
<td>2</td>
<td>depression</td>
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<tr>
<td>efalizumab (Raptiva)</td>
<td>2003</td>
<td>2009</td>
<td>6</td>
<td>leucoencephalopathy</td>
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<tr>
<td>sibutramine</td>
<td>1988</td>
<td>2010</td>
<td>22</td>
<td>cardiac risk</td>
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<tr>
<td>gemtuzumab ozogamicin (Mylotarg)</td>
<td>2000</td>
<td>2010</td>
<td>10</td>
<td>lack of efficacy</td>
</tr>
<tr>
<td>drotrecogin alfa (Xigris)</td>
<td>2001</td>
<td>2011</td>
<td>10</td>
<td>lack of efficacy</td>
</tr>
</tbody>
</table>

pharmacological effect/predictable at time of registration: 27%
pharmacological effect/predictable after time of registration: 9%
drug-class specific rare adverse drug reaction: 36%
rare idiosyncratic/allergic adverse drug reaction: 36%

½ pharmacologic AEs:
- predictable
- dose-related
1980-2000: Dose Reductions After Launch

- 27% of all new FDA-registrations of CNS-active drugs
- 79% safety-related
- three times more often in ’95-’99 than in ’80-’85

Optimizing Drug Action: getting the pharmacology right
Traditional – tolerated dose
Use traditional approach for modern drugs
Pharmacology-Based Phase I
pharmacological effects: essential for therapeutic action

- clinical effect
- type A adverse effects
- therapeutic range
### Which Binding Level Is Required for Therapeutic Activity?

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Pharmacological Activity</th>
<th>Receptor Occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic</td>
<td>DA2 competitive antagonist</td>
<td>- 60-80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 17-67% for clozapine</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>GABA-A positive allosteric modulator</td>
<td>- 5-30% for benzodiazepines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- &gt;60 for new partial subtype selective compounds</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>5HT transporter inhibitor</td>
<td>- 50-&gt;80%</td>
</tr>
<tr>
<td>CNS stimulants</td>
<td>DA transporter inhibitor</td>
<td>- 50-80%</td>
</tr>
<tr>
<td>New compound</td>
<td><em>New mechanism</em></td>
<td>- <em>often no available tracer</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- <em>usually unknown occupancy</em></td>
</tr>
</tbody>
</table>

Optimizing Drug Action: pharmacology-guided dose selection for first-in-class CNS-active drugs

Case 1: dual-orexin antagonist
    almorexant

Case 2: cannabinoid CB1 antagonists
    surinabant and rimonabant
Pharmacology-Guided Dose Selection - Case 1: Almorexant – first Dual ORX1/2-Antagonist (DORA)

- first-in-class with theoretical narcolepsy-like AEs:
  - sleep attacks
  - cataplexy
  - hypnagogic hallucinations
  - sleep paralysis

- SAD: extensive CNS-profiling
  - alertness
  - motor control
  - psychomimetic effects
  - sleep EEG

- benchmarking with zolpidem 10mg
  - (adverse) effect profile
  - indications of sleep promotion

Case 1: PK/PD-based dose selection of almorexant
Case 1: confirmation of safe effective low dose

- sleep-promotion
- low pharmacological activity
- no harmful narcolepsy-like effects

Hoever P et al. Orexin receptor antagonism, a new sleep-enabling paradigm: a proof-of-concept clinical trial. CPT 2012;91:975-85
First-in-class insomnia drug on the brink of approval nod

Merck’s dual orexin receptor antagonist suvorexant is approaching the regulatory finish line, 15 years after orexins were discovered.

and co-commercialise other orexin receptor antagonists

Actelion will receive an upfront payment of CHF 150 million (approximately £66 million) and will be eligible for additional potential milestone payments of up to CHF 415 million in regards to the successful development and approval of almorexant in primary insomnia.
Rimonabant: obituary for a wonder drug

S Matthijs Boekholdt, Ron J G Peters

www.thelancet.com Vol 376 August 14, 2010 489

Rimonabant 20 mg (n=9351) or matching placebo (n=9314)

There were four suicides in the rimonabant group (0.07%) and one in the placebo group (0.02%).
Pharmacology-Guided Dose Selection – Case 2: rational development of CB1-antagonists

- no PD-effects in healthy subjects
- develop THC-challenge model
- determine peripheral/central pharmacological activity using PK/PD
- determine relevant inhibition levels in clinical trials

isolation of THC for inhalation

development of THC challenge and PK/PD-model

Pharmacologically active doses of surinabant: peripheral effects up to 40% peripheral suppression

dose-dependent suppression of THC-effects
PK/PD-analysis

Ferrona G, Klumpers L, Van Gerven J, Roy C. PK and PK/PD modeling of CB1 blocker antagonism of THC induced CNS and Heart Rate effects. PAGE Poster 2010
Pharmacologically active doses of surinabant: central effects


Phase IIa clinical trial: weight gain during smoking cessation

weight change during smoking cessation (kg)

CB1-inhibition 10%↓ 20%↓ 40%↓

Tonstad S, Aubin HJ. Efficacy of a dose range of surinabant, a cannabinoid receptor blocker, for smoking cessation: a randomized controlled clinical trial. J Psychopharmacol 2012;26:1003-9

Rigotti NA, Gonzales D, Dale LC, Lawrence D, Chang Y; CIRRUS Study Group. A randomized controlled trial of adding the nicotine patch to rimonabant for smoking cessation: efficacy, safety and weight gain. Addiction 2009;104:266-76
CB1-inhibition of clinically active rimonabant dose: central (60%) > peripheral (40%) suppression rates

- 60mg SD ≅ 20mg MD
- 5mg SD ≅ 5mg MD

weight reduction? < psychiatric adverse effects?
Peripherally restrictive CB1-antagonists: improved therapeutic window?

- **Drinabant**: 40% peripheral $\rightarrow$ 30% central suppression
- **TM38837**: 40% peripheral $\rightarrow$ 15% central suppression

Weight reduction? $\gg$ Psychiatric adverse effects?
Conclusions

- For selective drugs, pharmacodynamically active concentrations in healthy subjects are often closely related to therapeutic levels
- Pharmacokinetic-pharmacodynamic relationships are an important aspect of ‘proof-of-pharmacology’
- Pharmacology-guided dose escalation
  - allows maximization of therapeutic window
  - may avoid adverse events associated with unnecessarily high doses
  - increases confidence in dose optimization
Clinical Pharmacology in Clinical Trial Design

“I think you should be more explicit here in this phase.”