How predictive is proof of concept for therapeutic success of a new drug?

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Costs of Drug Development...

$1000,000,000,-
...3/4 Spent On Failures....

Lehman Brothers. Pharma Values
Reducing Attrition in Phase II/II Saves Most

Attrition Rates Are Increasing....

…Registrations Are Decreasing: 275 Launches…. 275 in 2001-2011
### 25 Drugs Withdrawn...

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Withdrawn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

Constipation drug linked to heart attack risk
FDA asks Novartis to stop selling pills used for irritable bowel syndrome

Washington, 3/30/2007

Swiss pharmaceutical maker Novartis AG will stop selling Zelnorm to relieve constipation after it was linked to a higher chance of heart attack and stroke.

Analyses showed 13 of 11,614 patients given Zelnorm had cardiovascular side effects, while just one of the 7,031 patients given dummy pills...

Diabetes drug Rezulin taken off market
Pill linked to 63 liver-poisoning deaths

March 22, 2000
Web posted at: 2:05 p.m. EST (1905 GMT)

From staff and wire reports
WASHINGTON (CNN) -- Rezulin, a once-hailed diabetes drug used by about 750,000 Americans, has been withdrawn from the market after it was linked to at least 63 deaths from liver poisoning.

- odds: 1 in 10 000-100 000
- risk: ‘dozens of victims’

The New York Times
Anticholesterol Drug Pulled After Link With 31 Deaths
By GINA KOLATA and EDMUND L. ANDREWS
Published: August 09, 2001

Bayer A.G., the German pharmaceutical and chemical conglomerate, voluntarily withdrew Baycol, its highly profitable cholesterol-lowering drug, from the world market yesterday. Thirty-one patients have died while taking it, the company reported, because the drug caused an unusual condition in which muscle tissue broke down. Baycol was taken by 700,000 Americans.

Carol Ernst, widow of 59-yo Vioxx-victim Robert Ernst (before or after she heard she was entitled to $253.4 million compensation)
1980-2000: Dose Reductions After Launch

- 22% of all new FDA-registrations
- 79% safety-related
- three times more often in ’95-’99 than in ’80-’85

Failed Clinical Trials in Phase II/III

Phase II

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

Phase III

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

Stroke Cascades

Diagram illustrating the main pathophysiological mechanisms involved in stroke cascades, including arterial occlusion, metabolic reactions, ionic movements, glutamate excitotoxicity, and inflammatory reactions. The diagram also shows processes leading to cell swelling, spreading depressions, cell death, and free radical synthesis.
Late Failures: Adverse Drug Reactions

36% of adverse drug reactions are related to pharmacological mechanisms, of which 36% are avoidable and predictably related to primary pharmacological action, and 36% are unavoidable and unpredictably related to idiosyncratic reactions. The remaining 36% are related to secondary pharmacological actions, with 36% being allergic reactions.
Complexity of Metabolites

Valproic Acid (VPA)

3-keto-VPA
(major)

2-ene-VPA

3-ene-VPA

4-ene-VPA

CYP3A1

CYP2C9

3-Hydroxy-VPA

4-Hydroxy-VPA

5-Hydroxy-VPA

2-propylglutaric acid

2,4-diene-VPA
(toxic metabolite)

4-epoxy-VPA
(toxic metabolite)

cysteine derivative

thiol group

diol

immunogenic
hepatotoxic
teratogenic
mitochondrial toxic
Small Studies Only Detect Frequent Problems

<table>
<thead>
<tr>
<th>n</th>
<th>Incidence (%)</th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>0.1</td>
<td>1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.010</td>
<td>0.096</td>
<td>0.651</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.020</td>
<td>0.182</td>
<td>0.878</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.030</td>
<td>0.260</td>
<td>0.958</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.039</td>
<td>0.331</td>
<td>0.985</td>
<td></td>
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</table>

chance of statistical significance
Large Studies Cannot Rule Out Rare Events

<table>
<thead>
<tr>
<th>frequency in population (1:n)</th>
<th>fold increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>10 000</td>
<td>305 625</td>
</tr>
<tr>
<td>5 000</td>
<td>86 205</td>
</tr>
<tr>
<td>2 500</td>
<td>33 645</td>
</tr>
<tr>
<td>1 250</td>
<td>15 465</td>
</tr>
</tbody>
</table>

number of person–years needed to detect significant risk increase (one-sided exact test) with significance level $\alpha=0.025$ and power $(1-\beta)=0.80$

Variability in Humans
Complexity of Drug Development

Rationale#1: Pathway

Rationale#2: Target

Rationale#3: Drug

Rationale#4: Benefit/Risk

Rationale#5: Effectiveness & Reimbursement

Systems Biology → ‘Right Pathway’

Systems Pharmacology → ‘Right Target’

Translational Sciences → ‘Right Molecule’

‘D-E-R’ → ‘Right Dose’

Optimized Products → ‘Right Patients’

Miiligan PA. Current position and expectation for use of M&S in drug development and regulatory decision making. EMA-EFPIA Modelling and Simulation Workshop. 30/11/2011
Predicting the Unpredictable

Five main ‘proofs-of-concept’

1. Does the drug/active metabolites get to the site of action?
2. Does the compound cause its intended pharmacological/functional effect(s)?
3. Does the compound have beneficial effects on the disease or its clinical pathophysiology?
4. What is the therapeutic window?
5. How does variability in target population affect the product?
Case 1 – Fast Dissociating D2-Antagonist

- JNJ-37822681: D2-antagonist with high specificity and low affinity
- novel concept → which level of occupancy needed for optimal therapeutic window?
- combined phase I approach:
  - binding: PET for receptor binding / brain PK
  - function: CNS-battery for brain PD

![Pie charts showing receptor occupancy for quetiapine, haloperidol, and JNJ-37822681]
$^{11}$C Raclopride PET Binding vs Historic Controls: therapeutic range 20-30 mg? dose interval?


Prolactin Release: Functional D2-Biomarker

Effective Dose in Clinical Trial: therapeutically effective dose 10 BID

Anghelescu I, Janssens L, Kent J, De Boer P, Van Osselaer N, Tritsmans L, Daly EJ, Van Nueten L, Schmidt ME. Sustained treatment response in schizophrenia to JNJ-37822681 can be predicted within three days. Euro Neuropsychopharmacol 2011;21(suppl3):S490–S491
**Case 2 – Partial GABA-A α2,3-Agonist**

<table>
<thead>
<tr>
<th></th>
<th>α1</th>
<th>α2</th>
<th>α3</th>
<th>α5</th>
</tr>
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<tbody>
<tr>
<td>TPA023</td>
<td>0</td>
<td>11</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>MK-0343</td>
<td>18</td>
<td>23</td>
<td>45</td>
<td>18</td>
</tr>
<tr>
<td>SL65.1498</td>
<td>45</td>
<td>115</td>
<td>83</td>
<td>48</td>
</tr>
</tbody>
</table>

The table above demonstrates the *in vitro* efficacies relative to full agonist activity. The efficacies are indicated by the numbers in the table, with higher numbers generally representing greater efficacy. The substances tested include TPA023, MK-0343, and SL65.1498, and the effects measured are sedation, postural instability, anxiolysis, and memory disturbance.
11C Flumazanil PET: full vs subtype GABA-A-agonist: which dose?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline</th>
<th>2 h</th>
<th>6.5 h</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>~0%</td>
<td>~15%</td>
<td></td>
</tr>
<tr>
<td>Lorazepam, Subject #1</td>
<td>~5%</td>
<td>~6%</td>
<td></td>
</tr>
<tr>
<td>Lorazepam, Subject #2</td>
<td>~5%</td>
<td>~9%</td>
<td></td>
</tr>
<tr>
<td>TPA023, Subject #1</td>
<td></td>
<td></td>
<td>63%</td>
</tr>
<tr>
<td>TPA023, Subject #2</td>
<td></td>
<td></td>
<td>47%</td>
</tr>
<tr>
<td>TPA023, Subject #3</td>
<td></td>
<td></td>
<td>64%</td>
</tr>
</tbody>
</table>

lorazepam 2 mg

TPA023 2 mg

Saccadic Peak Velocity, Binding Affinity and Anxiolytic Dose

Kd at benzodiazepine binding site (nM)

SPV dose equivalence (10 mg Temazepam)

Dose Temazepam (mg)

Change in SPV (deg/sec)
Slope SPV/VAS: Clear α2 Selectivity

![Graph showing VAS Alertness: change from baseline compared to SPV: change from baseline. The graph includes two treatments: lorazepam 2 mg (filled circles) and TPA023 1.5 mg (open squares). The y-axis represents VAS Alertness change from baseline, ranging from -40 to 10, while the x-axis represents SPV change from baseline, ranging from -120 to 20. The graph highlights a clear α2 selectivity with lorazepam showing a steeper decline compared to TPA023.]
$\alpha_1/\alpha_2$-ratio vs SPV/VAS-slope

$R^2 = 0.86$
$p = 0.004$
Effective TPA023 Dose in Clinical Trials: 1.5-4.5 mg twice daily

Case 3 – Cannabinoid antagonists

- CB1-antagonist has no measurable effects in healthy subjects
- Phase 0: development of reliable CB1-agonist model (THC)
- Phase I: measure/model suppression of THC-effects by CB1-antagonist
Cannabinoid Challenge: ‘classical’ Dutch mode of administration
Cannabinoid Challenge: development of novel mode of administration

- GMP-compliant THC-production
- Intrapulmonary administration
  - Vaporizer
  - Paced puffing protocol
- Dose Finding
  - 2 – 4 – 6 – 8 mg
  - 90 min intervals
Cannabinoid Challenge: effects and PK/PD-relationships

VAS alertness

BodySway

VAS 'high'

HeartRate
Surinabant: no effects of 60 mg alone, but clear suppression of THC-effects at 5-20 mg

Surinabrant reduction rate:

![Graph showing the relationship between dose (mg) and the percentage of reduction rate (P(VAS_feeling high)>14)].

- 2mg: Reduction rate
- 5mg: Reduction rate
- 20mg: Reduction rate
- 60mg: Reduction rate
Effective Surinabant Dose in Clinical Trials: weight change during smoking cessation

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 Jan 4. [Epub ahead of print].

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
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%).
Rimonabant reduction rate: unnecessarily high?
Conclusions

- Clinical pharmacology cannot prevent all late phase drug failures:
  - poorly understood diseases
  - rare/unpredictable SAEs
  - benefit/risk considerations
  - strategic/financial

- Good clinical pharmacology can prevent *unnecessary* late stage failures:
  - poor action site penetration
  - suboptimal pharmacological activity
  - underestimated pharmacological (predictable) SAEs
  - incorrect dose estimates
  - drug-disease/-drug interactions

- But only if we integrate all available knowledge intelligently and learn from experience
The Role of the Clinical Pharmacologist

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