Addiction Vaccines: Promises vs. Reality

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Classical Medications for Drug Users

- Typically small molecule therapeutic drugs.
- They act in the brain.
- Therapeutic drugs are multifunctional and can have significant problematic side effects.
- Vaccines don’t have these brain-based side effects, but could have other side effects.
Vaccination as a Treatment for Drug Addiction

Potential Advantages

- Targets the drug in the serum rather than the brain.
- Vaccines are proven safe and effective without drug-like side effects.
- Improved compliance (not everyday admin).

Potential for relapse prevention because antibodies remain in the serum for a long time.

Combine vaccines with classical treatments
Cocaine Vaccine: What is it?

- Active immunisation
- Hapten: Cocaine derivative
- Carrier protein: Cholera toxin B (rCTB)
  - Drug molecules by themselves do not produce antibodies.
- Aluminium hydroxide adjuvant
Cocaine bound to Cholera toxin
B lymphocytes make ABs
Antibodies keep drugs out of the brain
Antibodies keep drug out of brain
Effects of cocaine vaccine in animals

- Vaccine generated antibodies can bind injected cocaine.
- NO animal toxicity. Even at several times a clinically relevant dose.
- Vaccine decreased cocaine self administration (SA) in rodents.
Antibodies are specific binders

- Antibodies can be very, very specific for a given molecular structure.
- One study showed a 100,000 fold higher binding affinity for cocaine (left) vs benzoylcegonine, using serum from mice.
Rodents Self-Administering Cocaine

Cocaine continued each day [yellow], substitute saline for cocaine (red), vaccine + cocaine (green)

- Infusions per hour
- Day

- Baseline
- Day 1
- Day 2
- Day 3
- Day 4
- Day 5
AB Response Varies (human data)
**Figure 3:** Nicotine-specific IgG antibody responses in human volunteers after vaccination with the Immunodrug™ candidate CYT002-NicQb to treat nicotine addiction. Vaccination was performed twice with CYT002-NicQb plus Alum as adjuvant. The graph shows geometric mean nicotine-specific antibody titers of 8 participants per dose regimen as measured by ELISA.
Human Laboratory Study
Meg Haney – Columbia University

- Determine direct relationship between plasma antibody levels and cocaine’s subjective and cardiovascular effects

- Administer smoked cocaine (0, 25, 50 mg) to non-treatment seeking, cocaine-dependent research volunteers pre-vaccine and at 12 weeks post-vaccine
Plasma Antibody (n=10)

### Titer

**High Antibody**

**Low Antibody**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Titers (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>300</td>
</tr>
<tr>
<td>26</td>
<td>600</td>
</tr>
<tr>
<td>39</td>
<td>900</td>
</tr>
<tr>
<td>52</td>
<td>1200</td>
</tr>
</tbody>
</table>

- Four shots
Good Drug Effect

High AB

Low AB

Smoked Cocaine Dose (mg)

Ratings (mm)

max = 100

Week 3
Week 13
Outpatient cocaine vaccine RCT (randomized clinical trials) Efficacy Studies
Fewer cocaine urines at higher Vaccine Dose
Vaccination makes antibodies by Week 4 (n=11)

Z = -3.17, p = 0.0015
Less relapse to cocaine use with high vs low dose vaccination
(Percent of patients relapsing in each dosage group)
Antibody response to Cocaine-CTB conjugate vaccine in humans

IgG anti-cocaine (µg/ml)

0 4 8 12 16 weeks
Cocaine-free urines for 20 week trial:
Placebo vs. patients with Hi vs. Lo Anti-cocaine antibodies
Cocaine urines fall as Antibody levels rise

Weeks 1, 4, 8, 12, 16, 20; p<0.0001 (Z= -4.0)
Conclusions from Vaccine RCT

- Cocaine vaccine better than placebo
- Cocaine-free urines increase as AB levels increase
- 75% of patients had effective antibody response
- Vaccine is medically safe, even with 10 times more cocaine use than during baseline
- Better vaccine needed.
Companies Working on Nicotine Vaccines

- Celtic Pharma (TA-NIC)
- Nabi Biopharmaceuticals (NicVAX)
- Cytos Biotechnology (NIC002)

Follow progress on their web sites
Synthesis of NicVAX

3 amino nicotinic acid

Conjugation using a succinic acid linker

Carrier protein
Effect of Nicotine Vaccine on Serum Nicotine Concentration in Rats

(Satoskar et al, 2003)
Nicotine Vaccine and Maintenance of Self-Administration
NicVAX™ is intended to be used:

- As either an aid or stand-alone therapy for smoking cessation (maintenance and relapse)
- As either an aid or stand-alone therapy for smoking reduction (reduced maintenance)
- For the prevention of tobacco/nicotine dependence (acquisition and maintenance)
Clinical Trials with NicVAX™

• Phase I safety study, n = 20 non-smokers. Well tolerated, no SAEs

• Phase I/II trial in the Netherlands to assess the safety of multiple doses and collect data on ab titer, and evaluate abstinence and relapse rate, in 21 smokers and 9 exsmokers

• Multi-site Phase II trial (U.S.) in 63 smokers, to assess immunogenicity and safety in smokers - data analysis showed a 33% quit rate

• New Phase II study underway in the Netherlands in 30 smokers to provide additional data on optimal dose and dosing schedule

• Larger Phase II multi-site efficacy study (n=200) funded through a NIDA grant
Cytos Nicotine Vaccine - Results from their Web Site

**CYT002-NicQb Phase II Results**

Continuous Abstinence from Smoking (per Protocol)

<table>
<thead>
<tr>
<th></th>
<th>6 month*</th>
<th>12 month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>high responder</td>
<td>57% (30 / 53)</td>
<td>42% (22 / 53)</td>
</tr>
<tr>
<td>medium responder</td>
<td>32% (17 / 53)</td>
<td>21% (11 / 53)</td>
</tr>
<tr>
<td>low responder</td>
<td>32% (17 / 53)</td>
<td>26% (14 / 53)</td>
</tr>
<tr>
<td>Placebo</td>
<td>31% (25 / 80)</td>
<td>21% (17 / 80)</td>
</tr>
</tbody>
</table>

*p in parenthesis: number of continuously abstinent subjects / total number of subjects in group.*
Primary Endpoint: Eight-week Continuous Abstinence

**Antibody Level vs. Quit Rate**

*Eight-Week Continuous Abstinence*

<table>
<thead>
<tr>
<th>Antibody Response</th>
<th>N</th>
<th>% of Drug Treated Patients</th>
<th>Quit Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>61</td>
<td>30%</td>
<td>24.6% 13/61 (p=0.04)</td>
</tr>
<tr>
<td>Low</td>
<td>140</td>
<td>70%</td>
<td>10% 14/140</td>
</tr>
<tr>
<td>Placebo</td>
<td>100</td>
<td></td>
<td>13% 13/100</td>
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*Weeks 19-26 after first vaccination*
Can Someone Smoke Enough to Overcome the Vaccine Titer? Evidence suggest not.
Conclusions

- Vaccines against nicotine can be safe and well tolerated.
- There is a relationship between high antibody titers and continued abstinence.
- Further trials ongoing.
- FDA approval needed.
Monoclonal Antibodies

- Under development in several labs.
- Instantly useful; not a vaccine!
- Not at the same level of development as the vaccines.
- Targets such as PCP and cocaine that can be a problem in overdose.
- Catalytic ABs have been made.
Ethical Issues

Use in Children: Informed consent is a problem, and does the benefit (utility) outweigh the risks?

- Legal coercion.

- Prevention? Use of vaccines before a problem exists?

- Not easy for patient to change his/her mind about Tx after vaccination.

- We can’t ignore other proven Txs for drug use and perhaps need to find best combinations of Txs.
Other issues

- Most drug users are multi-drug users. Is the use of multiple vaccines for multiple drugs at the same time acceptable? Probably yes.

- Ethical issues and other issues can be dealt with better as we learn more and gain experience with such vaccines.
Overall Conclusions

- Vaccines have advantages over classical medications.
- Usefulness depends on AB response and quality. Currently, variable responses. Improve vaccines, adjuvants and schedules.
- Ethical issues with forced vaccination and underage individuals.
- Vaccines not yet ready for major use and are unlikely to be the final and only answer.
There is a need to produce better vaccines that produce higher antibody levels that last longer than 3-4 months. Thus, we need improved vaccines, adjuvants, boosters and schedules of inoculation.
Acknowledgements

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