Developing Medications to Treat Addiction: *Implications for Policy and Practice*
Medications Currently Available

**For Nicotine Addiction**
- Nicotine Replacement Therapies (NRT)
- Bupropion
- Varenicline

**For Alcoholism**
- Disulfiram
- Naltrexone
- Acamprosate

**For Opiate Addiction**
- Methadone
- Naltrexone
- Buprenorphine
- Buprenorphine/Naloxone
There is Still Enormous Need For Medications to Treat Addiction

Currently there are no approved medications to treat…

• Cocaine Addiction

• Methamphetamine Addiction

• Marijuana Addiction

…and the efficacy of existing treatments is, on average, only about 30%
Challenges Involved in Developing Medications to Treat Addiction

- STIGMA of addiction
- Lack of pharmaceutical industry involvement
- Prohibitive cost: $2.3 B to bring medication to clinic
- Length of drug discovery process: 7-13 years
- Regulatory issues surrounding controlled substances
ROADBLOCK #1: Lack of Pharmaceutical Industry Interest in Conducting Clinical Trials for Addiction/Alcoholism

170 Pharmacotherapy Trials Smoking Cessation Conducted

440,000 Annual Deaths from Smoking

Current Pharmaceutical Investment in Substance Abuse Treatment

Source: Clinicaltrials.gov, October 2008
In 2002 Buprenorphine and Buprenorphine/Naloxone were approved for prescribing by qualified physicians

Subutex® -- Monotherapy product
Suboxone® -- Buprenorphine/Naloxone

Currently 19,000 physicians are certified to prescribe buprenorphine
(Source: CSAT Buprenorphine Information Center)

- Related to morphine (partial agonist)
- Uses same receptors as morphine but does not produce the same high
- Can be abused, but combining with naloxone decreases abuse potential
- Long-lasting, less likely to cause respiratory depression
Medications to Treat Addiction

Effects of Buprenorphine Maintenance Dose on $\mu$-Opioid Receptor Availability

Naltrexone & Buprenorphine in the Treatment of Cocaine Dependence

Rates (%) of Positive Urines for Cocaine Metabolites

--Naltrexone Alone  --Naltrexone + Buprenorphine

Week 1

Week 2

Week 3

Week 4

Gerra G et al., J Psychopharmacol Online First January 9, 2006.
High Antibody Levels Support Sustained Quit in 5 Injection Regimen

Antibody-Dependent Reduction in Cigarette Consumption in Non-Abstainers

- **Placebo**
- **Bottom 70% in AUC**
- **Top 30% in AUC**

**p-value=0.0014 comparing top Ab responders to placebo in a repeated measures model adjusted for center, week and baseline smoking intensity**

**No compensatory smoking observed in high Ab group**

**p=0.0068 comparing top 30% in AUC to placebo in a Cox model adjusted for center**

NicVAX Subjects: 5 Injection Regimen

- **N=12/30**
- **N=8/71**
- **N=12/100**

Quit for at least 8 weeks continuously and remaining continuously abstinent to study end

**Time to Sustained Abstinence (Weeks)**

**Median Number of Cigarettes per Day by AUC: Subjects Who Did not Abstain in Weeks 19-52**
In 2008 An Estimated 22.2 Million Americans Were Dependent On or Abused Any Illicit Drugs or Alcohol

But...Only 4.0 Million (18%) of These Individuals Had Received Some Type of Treatment In the Past Year

Patients Receiving ORT in US Prisons

- In any given year over 200,000 heroin addicts pass through prison
- An estimated 1,614 - 1,817 prisoners receive methadone in state and federal prisons
- An estimated 57-150 prisoners receive buprenorphine in state and federal prisons
- Most common use: pregnant women, acute opiate withdrawal, chronic pain management

Treatment Linkage & Days Used Heroin
6 Months Post-release

% of the 180 days post-release spent in treatment
% of the 180 days post-release used heroin

C = Counseling Only
C+T = Counseling & Treatment Referral
C+M = Counseling & Methadone Started in Prison

State Prisons Offering Opiate Replacement Tx

ALTERNATIVES TO ORT
Depot Naltrexone

• Can be administered once a month

• Can be used in the prison system and the criminal justice system...ensuring adherence to treatment

• Can be “exported” to countries that have opiate abuse problems but don’t allow agonist therapy--Russia, Egypt

• May help to reduce HIV incidence resulting from i.v. drug abuse
In 1992, the Congress stipulated in the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) Reorganization Act (P.L. 102-321) that DHHS contract with the National Academy of Sciences to establish a committee in the Institute of Medicine (IOM) to examine the current conditions for the development of anti-addiction medications.

Perceived Market Barriers in 1995 IOM Report

- Uncertain market environment
- Limited number of researchers focusing on drug abuse
- Lack of well-characterized animal models of cocaine addiction
- Limited basic science knowledge of addiction, craving and relapse
- DEA regulations
- Complications of concomitant illness and polydrug abuse
- Patient populations perceived as difficult to study
- Efficacy outcomes difficult to define or measure
- Few clinical investigators
- Length of FDA approval process
- State rescheduling
- Varied State/local regulations
- Lack of traditional marketing to physicians
- Pricing clause in DHHS CRADAs
- Small foreign market
- Limited number of narcotic treatment programs
- Stigma of drug abuse
- Bias of some treatment providers against pharmacologic treatments
- Varied State/local treatment regulations and financing mechanisms
- Uncertain treatment financing

IOM Recommendations: Overcome Critical Market Barriers

- Government Funding of New Drug Development
- Expansion and Enhancement of Substance Abuse Treatment System
- Extended Market Exclusivity
Examples of Medications Strategies for Addiction

Non-Addicted Brain

Saliency → Drive → Memory → Control

Interfere with drug’s reinforcing effects

Executive function/Inhibitory control

Strengthen prefrontal-striatal communication

Interfere with conditioned memories (craving)

Teach new memories

Counteract stress responses that lead to relapse

Vaccines

Bupropion

Modafinil

Adenosine A2 antagonists
DA D3 antagonists

N-acetylcysteine

Cycloserine

Orexin antagonists
Varenicline & Bupropion SR Combination Therapy for Smoking Cessation

## Availability of Opiate Replacement Therapy in US Prisons

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<th>NE N (%)</th>
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**Geographic region defined by CDC**

*Nunn et al., Drug and Alcohol Dependence 2009;105:83-88.*
Outpatient Study: Percent of Negative Urines After Depot Naltrexone Administration

Opioid Urine Results for Buprenorphine and Methadone

Adapted from Johnson, et al., 2000
Mean Weekly Cocaine-Free Urine Samples by Medication Condition for Weeks 1 to 20

Martell, BA et al., Arch Gen Psychiatry 2009; 66: 1116-1123.