

Developing Medications To Treat SUDs: Pitfalls & Promises

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The Gains In Medications To Treat SUDs Are Incremental

Bloomberg

Titan's Implanted Addiction-Drug Device Works Better Than Placebo in Study

By Nicole Ostrow - Oct 12, 2010

[Titan Pharmaceuticals Inc.](#)'s implanted drug-delivery device helped people fight addiction to heroin and prescription painkillers better than a placebo, a company-funded study found.

The Titan product, shaped like an inch-long match-stick, is implanted under the skin and delivers continuously the drug [buprenorphine](#). Patients implanted with the device showed they were free of illegal opiates in about 40 percent of urine tests in the first 16 weeks, compared with 28 percent of those getting the placebo implant. People on the drug had fewer withdrawal symptoms, according to research published today.

The experimental device, [Probuphine](#), is designed to help addicts who either skip or forget to take doses of buprenorphine, a medicine that reduces craving for opioids and symptoms of withdrawal. The study represents the third of three phases of tests generally required for U.S. Food and Drug Administration approval. Titan plans to seek clearance of Probuphine in the U.S. and Europe.

Why Haven't We Been More Successful At Developing Medications To Treat Addictions ?

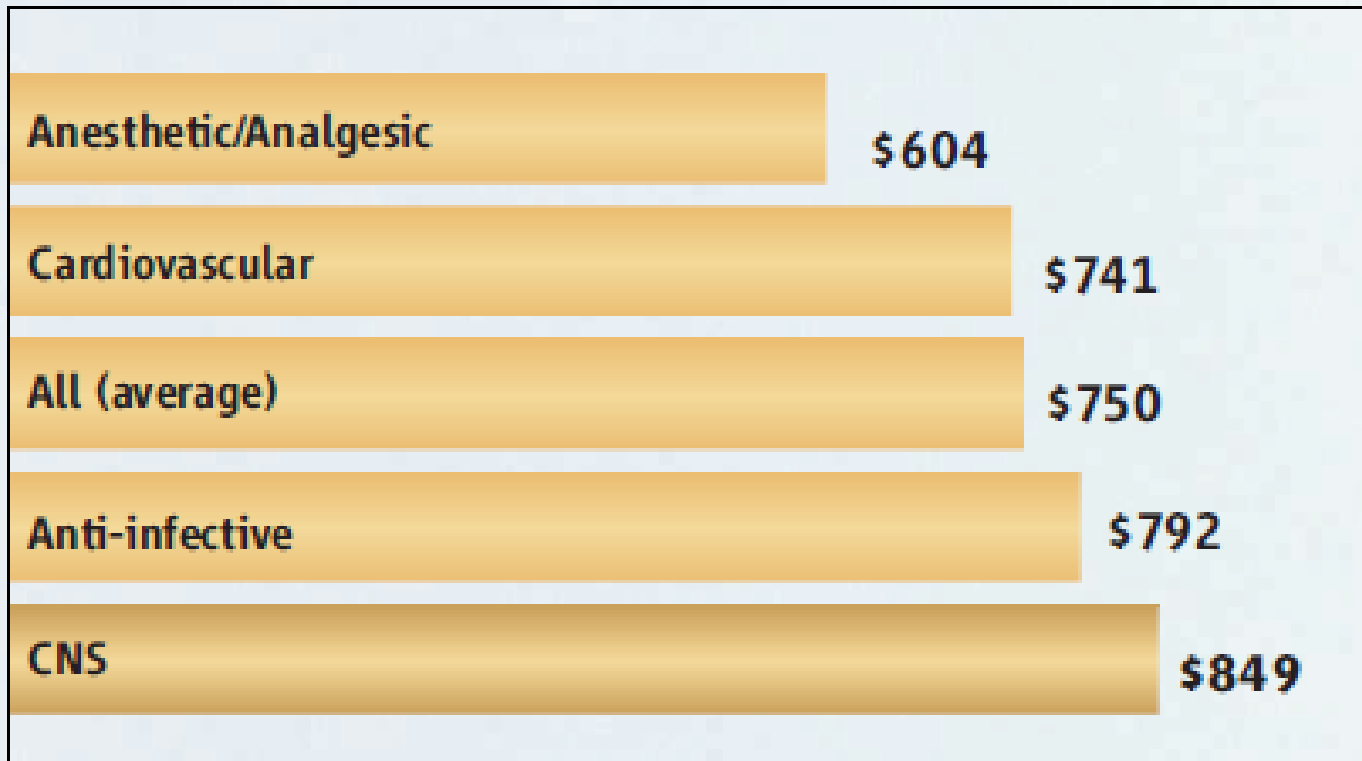
- Historically, big pharma has not embraced developing medications to treat addictions*

(*with the exception of nicotine)

Some of the factors often cited for this indifference:

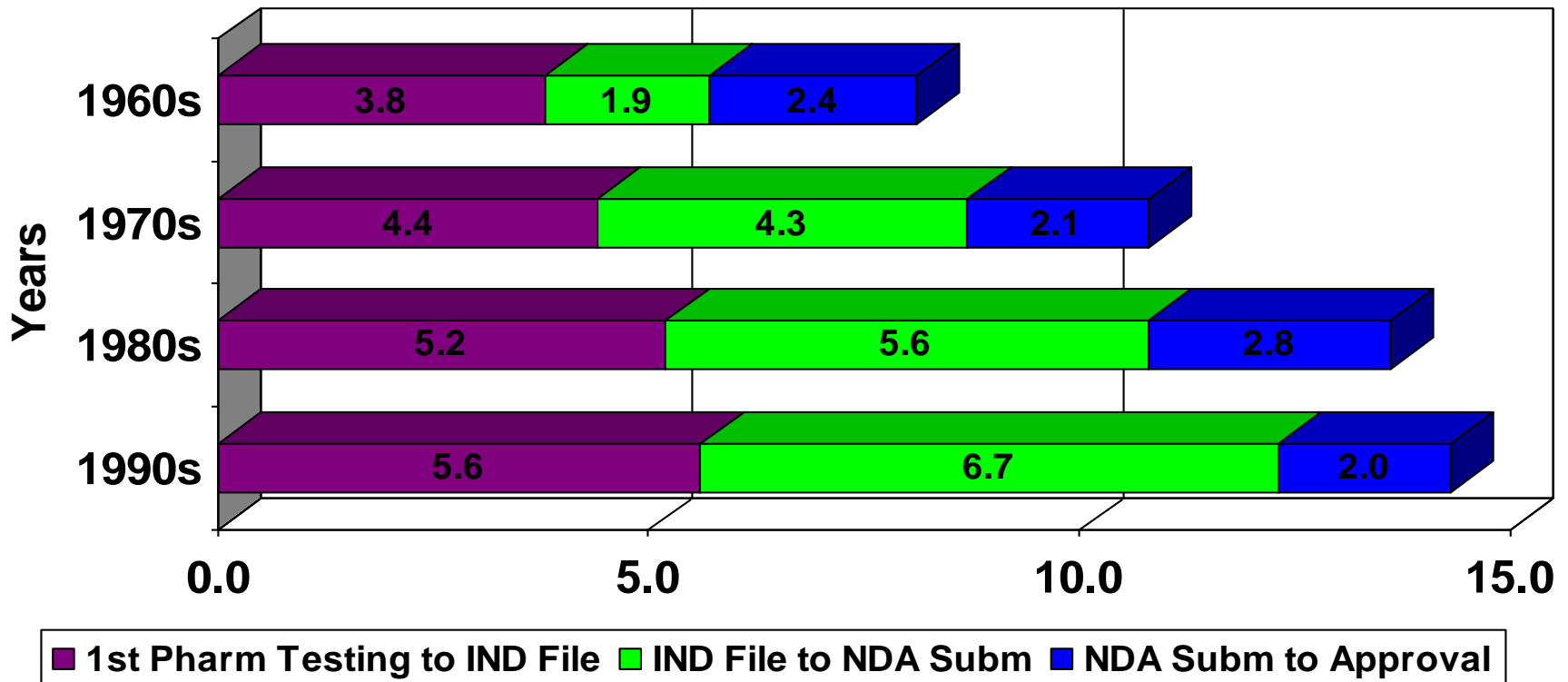
-Cost of developing an NCE (current estimates: a bit south of \$2BB including cost of capital)

High Cost of Developing Drugs To Treat Neuropsychiatric Disorders



The Drug Development Cycle Time Has Increased Dramatically

Time from First Pharmacological Testing to New Drug Approval, 1963 - 1997



Source: Parexel's Pharmaceutical R&D Statistical Sourcebook, 2002/2003.

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- Perceived small market size (translates to return on investment)

2010 Suboxone[®] sales:

> \$1.2 B worldwide (US sales, ~ 1 B)

National Estimates of Drug Use from a Survey of ~ 70,000
Randomly Selected Individuals in the U.S.

	<u>Use During Past Year</u>	<u>Use During Past Month</u>
Cocaine	5.3 Million	1.9 Million
Methamphetamine	850,000	314,000
Heroin	453,000	213,000

Source: U.S. Substance Abuse and Mental Health Services Administration "2008 National Survey on Drug Use & Health"

Estimate of U.S. Market for a First-in-Class Cocaine Addiction Treatment

Assume 1.6 M regular users based on 2009 data

Assume 20% seek treatment each year, market = 320,000
patients/year

Average Tx duration 6 mo at \$700/mo,

ANNUAL SALES IN EXCESS OF \$1.2 BB

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- Difficulties in executing a clinical trial campaign using patients with SUDs (often many comorbid conditions + lifestyle issues)

Article

Randomized, Double-Blind, Placebo-Controlled Trial of Vigabatrin for the Treatment of Cocaine Dependence in Mexican Parolees

Jonathan D. Brodie, M.D., Ph.D.

Brady G. Case, M.D.

Emilia Figueroa, M.D.

Stephen L. Dewey, Ph.D.

James A. Robinson, M.Ed.

Joseph A. Wanderling, M.A.

Eugene M. Laska, Ph.D.

Objective: Cocaine dependence is associated with severe medical, psychiatric, and social morbidity, but no pharmacotherapy is approved for its treatment in the United States. The atypical antiepileptic vigabatrin (γ -vinyl gamma-aminobutyric acid [GABA]) has shown promise in animal studies and open-label trials. The purpose of the present study was to assess the efficacy of vigabatrin for short-term cocaine abstinence in cocaine-dependent individuals.

Method: Participants were treatment seeking parolees who were actively using cocaine and had a history of cocaine dependence. Subjects were randomly assigned to a fixed titration of vigabatrin (N=50) or placebo (N=53) in a 9-week double-blind trial and 4-week follow-up assessment. Cocaine use was determined by directly observed urine toxicology testing twice weekly. The primary endpoint was full abstinence for the last 3 weeks of the trial.

Results: Full end-of-trial abstinence was achieved in 14 vigabatrin-treated subjects (28.0%) versus four subjects in the placebo arm (7.5%). Twelve subjects in the vigabatrin group and two subjects in the placebo group maintained abstinence through the follow-up period. The retention rate was 62.0% in the vigabatrin arm versus 41.5% in the placebo arm. Among subjects who reported prestudy alcohol use, vigabatrin, relative to placebo, was associated with superior self-reported full end-of-trial abstinence from alcohol (43.5% versus 6.3%). There were no differences between the two groups in drug craving, depressed mood, anxiety, or Clinical Global Impression scores, and no group differences in adverse effects emerged.

Conclusions: This first randomized, double-blind, placebo-controlled trial supports the safety and efficacy of short-term vigabatrin treatment of cocaine dependence.

After the positive trial in Mexico, Catalyst Pharmaceuticals conducted an 11-site, 180 subject trial in the U.S. that failed to show efficacy of vigabatrin vs. cocaine

Mexico:	3 Grams, 1x/day <u>Observed</u> dosing 2x/week (in-clinic)
U.S.:	1.5 Grams, 2x/day No observed dosing

Noncompliance May Have Spoiled Cocaine Dependence Drug Trial

- SAN FRANCISCO (EGMN) - A trial of the anticonvulsant ***vigabatrin*** to treat cocaine dependence may have failed because the patients weren't taking it and not because the drug didn't work, an analysis of the study results suggests.
- A subsequent analysis of urine samples retained from the study showed that fewer than 40 percent of 53 patients in the vigabatrin arm who completed the 12-week study had urine drug levels that would indicate adherence to the medication regimen. The subsequent urinalyses suggested that at five of the 11 study sites, fewer than half of the patients had taken the medication as prescribed.
- Treatment adherence was rated at 85% using pill counts and patient self-reports to measure treatment adherence.

(headline from HEALTH DAILY NEWS)

Medication Compliance Determined from Urine Vigabatrin Levels (U.S. Trial)

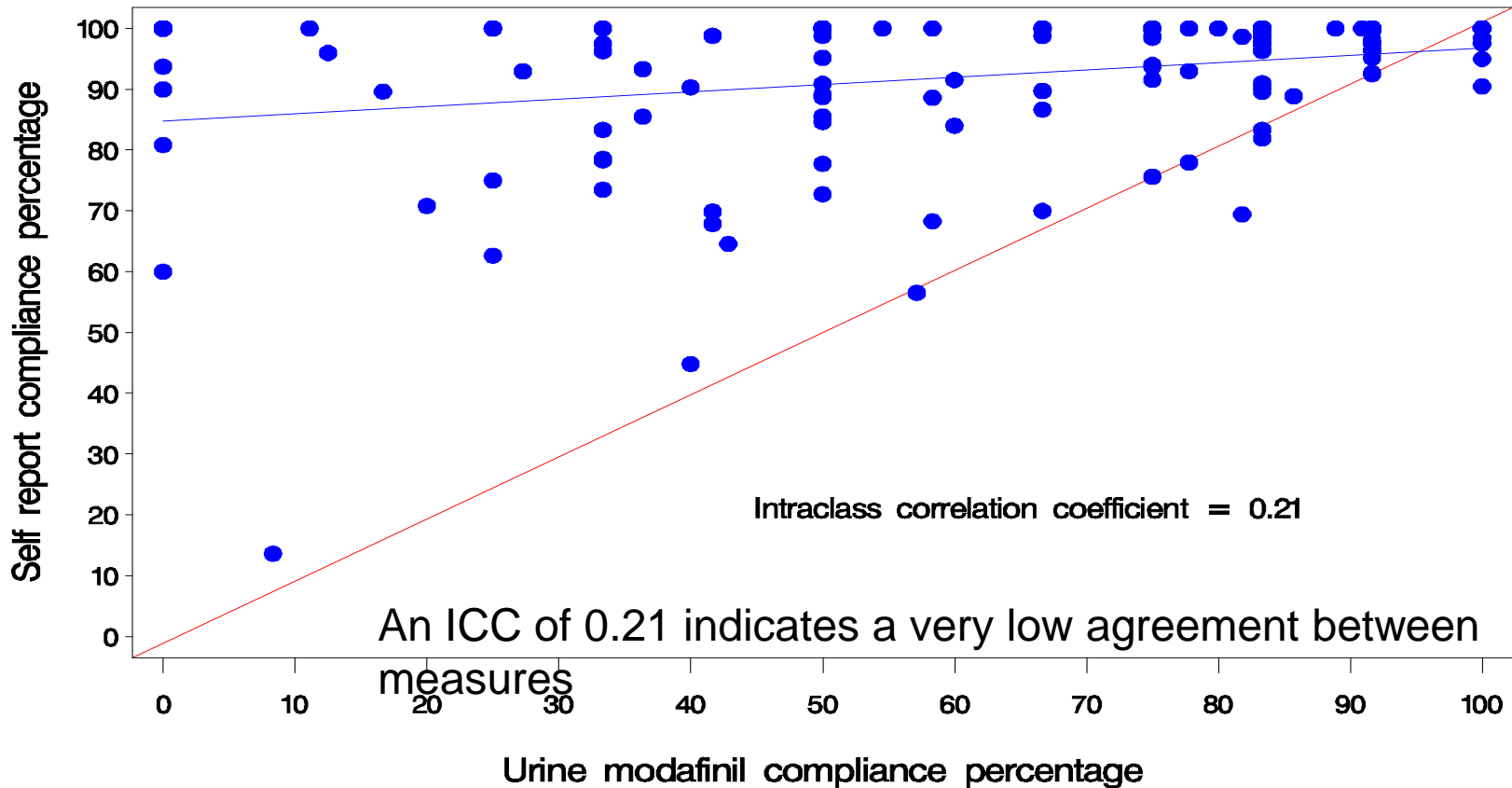
Medication Compliance Status for Completer Population (61/92 in vigabatrin group)		
Compliers ($\geq 630 \mu\text{g/ml}$)	Partial Compliers ($\geq 158 \mu\text{g/ml}$)	Non- Compliers
24 (39.3%)	8 (13.1%)	29 (47.6%)

Only 39% of those in the vigabatrin group who completed the trial had urine levels indicating good medication compliance.

VACSP/NIDA Study # 1026
Phase 2, Double-Blind, Placebo-Controlled Trial of
Modafinil for Methamphetamine Dependence

Placebo	68
Modafinil 200 mg	72
Modafinil 400 mg	70

VA/NIDA Study #1026: Modafinil for Methamphetamine Dependence



Analysis 2: Agreement Analysis of self report compliance with urine modafinil compliance

Doc Path: H:\p1026\reports\docs\Agreement.doc; Prgm Path: H:\p1026\reports\MEDCOMP-v2.sas; Date run: 09/03/2010; Data last updated: 03/10/2010

From: Anderson, et al., 2011

There Are MULLIGANS In Drug Development: Second U.S. Trial of Vigabatrin vs. Cocaine

Targeted enrollment: 200 Subjects

Once daily dosing (3 grams vigabatrin or placebo) x 9 weeks with 1 month follow-up.

Three observed (in-clinic) doses each week.

Three urine samples/week to be assayed for BE (cocaine metabolite)

-Compliance measurement

Primary Outcome Measure:

Percentage of patients abstinent during the last 2 weeks of treatment

-Secondary analysis using the medication compliant population.

Thinking Outside the Pillbox — Medication Adherence as a Priority for Health Care Reform

David M. Cutler, Ph.D., and Wendy Everett, Sc.D.

study showed that even among patients who have health plans with no cost sharing for medications, rates of nonadherence were nearly 40%.³

Noncompliance

- Lack of adherence to medication is an issue in both the conduct of clinical trials AND clinical practice.
- We are, however, focused on this issue of hypothesis testing: Is medication **X** effective in condition **Y**. Hypotheses cannot be adequately tested unless we can ensure patients are medication compliant.

The Conduct Of Clinical Trials Is Unlikely To Change in The Short/Mid Term: How do we tackle the compliance problem?

- Electronic monitoring (e.g. MEMS) [easily gamed]
- Measurement of drug/metabolite in a biological fluid should be incorporated into every SUD trial protocol. Use of “compliant” subjects in statistical evaluation.
- Incorporation of markers, such as riboflavin, into formulations to detect compliance in both placebo and drug groups. Alternatively, the use of “homeopathic” amounts of drug in the placebo, sufficient for detection in blood/urine, prevents subjects from “gaming” the trial.
- **Recognition by regulatory authorities that a “snapshot of compliance” may be the only practical surrogate in a real world setting.**

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- Cost of developing an NCE (current estimates: a bit south of \$2BB including cost of capital)
- Perceived small market size (translates to return on investment)
- Difficulties in executing a clinical trial campaign using patients with SUDs (often many comorbid conditions + lifestyle issues)
- Stigma associated with addiction to illegal substances
- Perception of a high regulatory “hurdle” (abstinence).

Abstinence: The Ideal Outcome

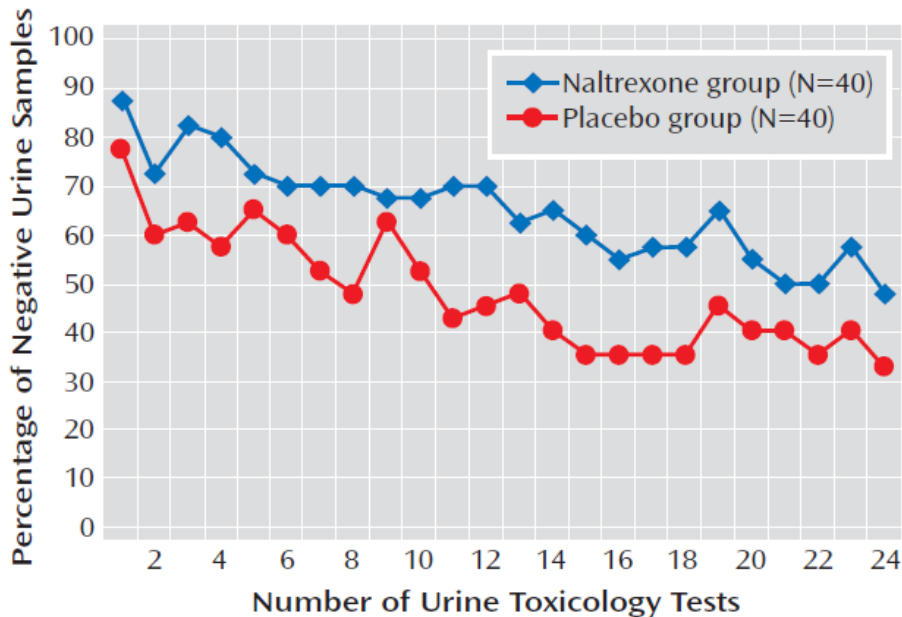
Produced by Medications to Treat SUDs

- Abstinence can be viewed as analogous to remission in other psychiatric disorders.
- Drugs have been approved for (e.g.) schizophrenia and depression if there is a statistically significant improvement in an outcome measure absent remission.
- Is it a realistic expectation that medications (+/- psychotherapy) can produce (sustained) abstinence?

What does the FDA want?

A success/failure analysis is required (no group means).

FIGURE 2. Percentage of Negative Urine Samples in the Naltrexone and Placebo Groups During the 12-Week Trial (Intention-to-Treat Analysis)



Lindstrom, et al., 2008

What does the FDA want?

- A success/failure analysis is required (no group means).

“Success” must be clinically significant.

Preferably, success will be defined by a period of abstinence that lasts through the end of treatment.

(note: a grace period is allowed for onset of action)

Celia Winchell, M.D.

Medical Team Leader for Addiction Drug Products

FDA Division of Anesthesia, Analgesia, and Rheumatology Products.

Abstinence: The Ideal Outcome

Produced by Medications to Treat SUDs

- Current regulatory view: no amount of illegal drug use is the only acceptable outcome.
- In alcohol abuse, a positive outcome is a (significant) reduction in the number of heavy drinking days (this reduction is associated with positive health benefits for the patient)
- Challenge: How to link a (e.g.) 30% reduction in mean cocaine use to a quantifiable benefit to the patient.

Bupropion for the Treatment of Methamphetamine Dependence

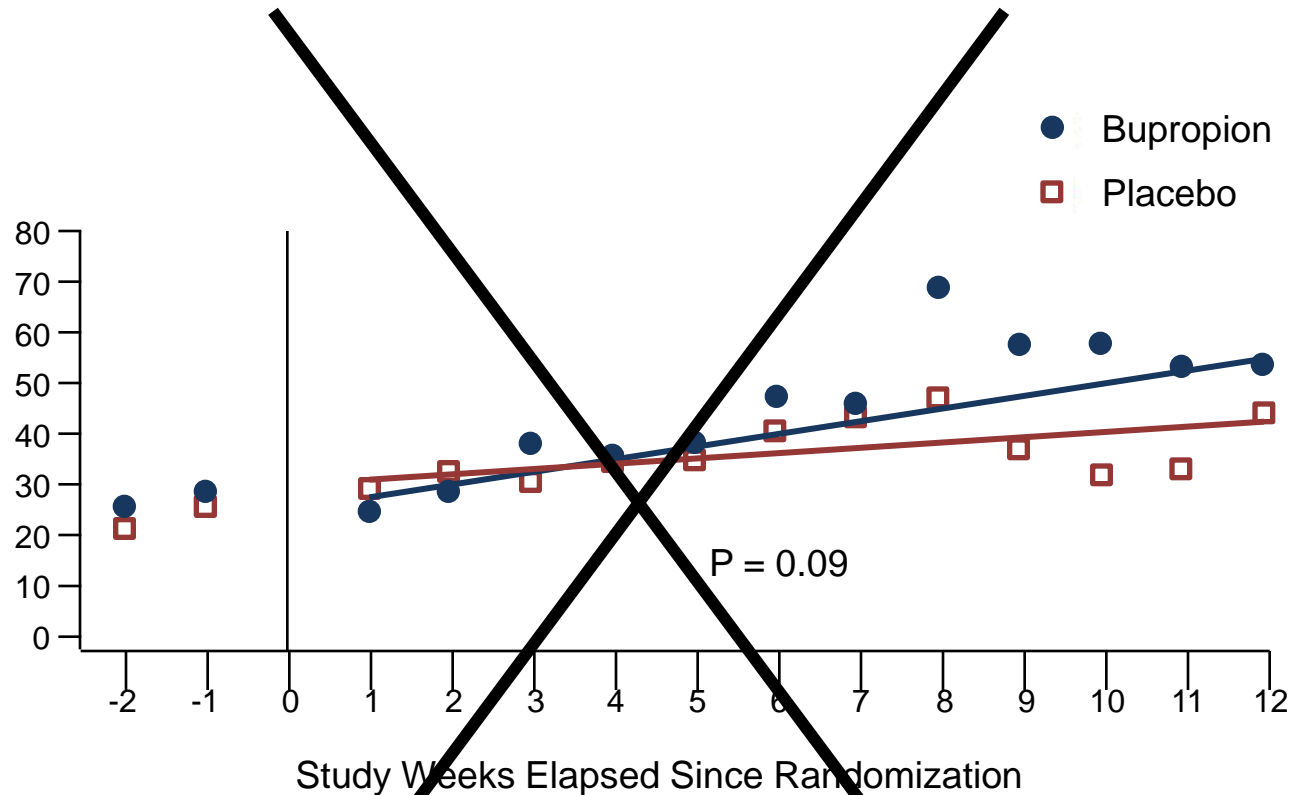
Ahmed M Elkashf^{1*}, Richard A Rawson², Ann L Anderson¹, Shou-Hua Li¹, Tyson Holmes³, Edwina V Smith¹, Nora Chiang¹, Roberta Kahn¹, Frank Vocci¹, Walter Ling², Valerie J Pearce², Michael McCann⁴, Jan Campbell⁵, Charles Gorodetzky⁶, William Haning⁷, Barry Carlton⁷, Joseph Mawhinney⁸ and Dennis Weis⁹

¹Clinical Medical Branch, Division of Pharmacotherapies and Medical Consequences, National Institutes of Health, National Institute on Drug Abuse, Bethesda, MD, USA; ²Department of Psychiatry, Integrated Substance Abuse Programs, University of California, Los Angeles, Los Angeles, CA, USA; ³Division of Biostatistics, Department of Health Research and Policy, School of Medicine, Stanford University, Stanford, CA, USA; ⁴Department of Psychiatry, Matrix Institute on Addictions, Costa Mesa, CA, USA; ⁵Department of Psychiatry, University of Missouri, Kansas City, MO, USA; ⁶Department of Psychiatry, Quintiles Inc., Kansas City, MO, USA; ⁷John A. Burns School of Medicine, Department of Psychiatry, University of Hawaii, Honolulu, HI, USA; ⁸South Bay Treatment Center, San Diego, CA, USA; ⁹Department of Addiction Medicine, Lutheran Hospital, Powell Addiction Research Center, Des Moines, IA, USA

Bupropion was tested for efficacy in increasing weeks of abstinence in methamphetamine-dependent patients, compared to placebo. This was a double-blind placebo-controlled study, with 12 weeks of treatment and a 30-day follow-up. Five outpatient substance abuse treatment clinics located west of the Mississippi participated in the study. One hundred and fifty-one treatment-seekers with DSM-IV diagnosis of methamphetamine dependence were consented and enrolled. Seventy-two participants were randomized to placebo and 79 to sustained-release bupropion 150 mg twice daily. Patients were asked to come to the clinic three times per week for assessments, urine drug screens, and 90-min group psychotherapy. The primary outcome was the change in proportion of participants having a methamphetamine-free week. Secondary outcomes included: urine for quantitative methamphetamine, self-report of methamphetamine use, subgroup analyses of balancing factors and comorbid conditions, addiction severity, craving, risk behaviors for HIV, and use of other substances. The generalized estimating equation regression analysis showed that, overall, the difference between bupropion and placebo groups in the probability of a non-use week over the 12-week treatment period was not statistically significant ($p = 0.09$). Mixed model

Bupropion vs. Methamphetamine (all study participants)

Percentage of Patients
with a Week of
Methamphetamine-Free
Urines



Bupropion vs. Methamphetamine Reanalysis (all study participants)

Abstinence During
 Last 2 Weeks

	Failures	Successes	← At least 2 urines/week with 100% clean
Placebo	67 (93.1%)	5 (6.9%)	← 2.9 x
Bupropion	63 (79.8%)	16 (20.3%)	

$p = 0.020$ (two-tailed Fisher's exact test)

What does the FDA want?

A success/failure analysis is required (no group means).

“Success” must be clinically significant.

Preferably, success will be defined by a period of abstinence that lasts through the end of treatment.

(note: a grace period is allowed for onset of action)

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Why 2 weeks?

1 Week vs. 2 Weeks

During the week immediately prior to randomization, 15% of study participants did not test positive for methamphetamine.

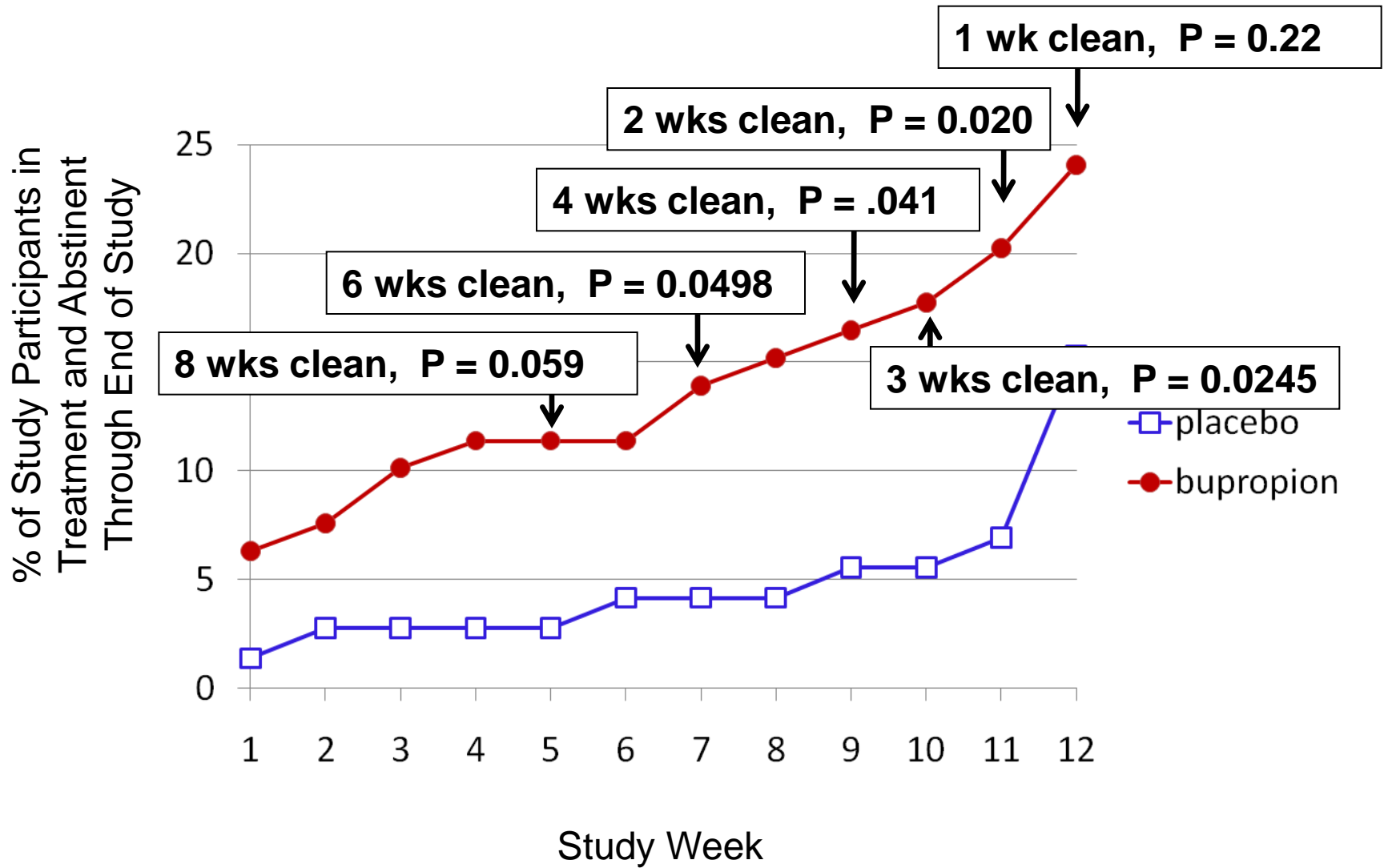
During the two weeks immediately prior to randomization, 6% of study participants did not test positive for methamphetamine.

Bupropion vs. Methamphetamine Reanalysis (all study participants)

	Abstinence During Last Week		← At least 2 urines with 100% clean
	Failures	Successes	
Placebo	61 (84.7%)	11 (15.3%)	
Bupropion	60 (75.9%)	19 (24.1%)	

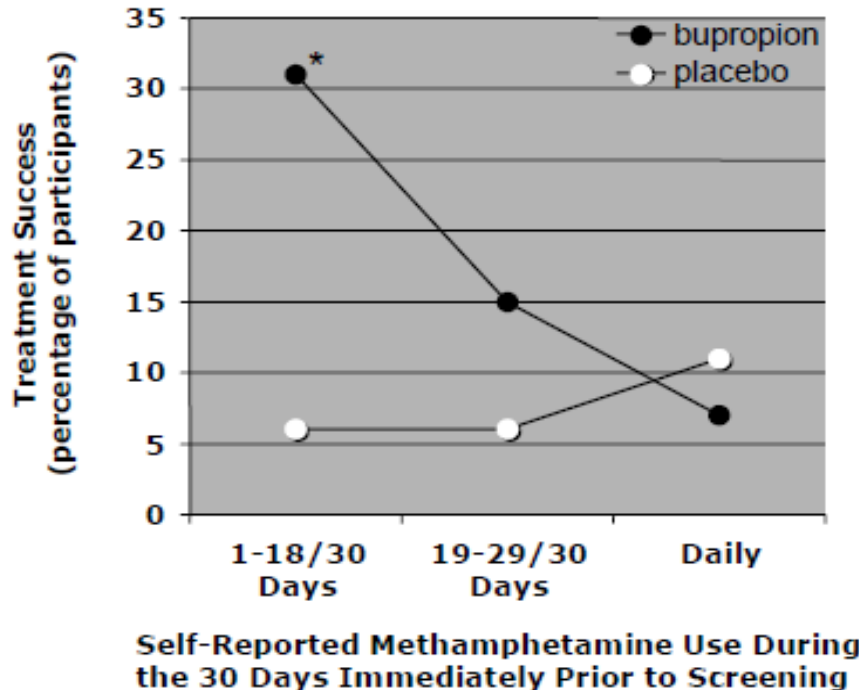
$p = 0.22$

What about > 2 weeks abstinence?



(Gave at least 2 urines/week with 100% clean until end of study)

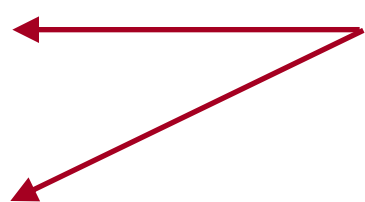
Bupropion Is Most Effective In Producing Abstinence In “Light-to-Moderate” Methamphetamine Users (success defined as ≥ 2 weeks of methamphetamine free urine lasting through the end of study)



No measure of medication compliance was included in this study. Based on compliance data in other studies, these data may underestimate the efficacy of bupropion in producing ≥ 2 weeks of EOSA

Bupropion vs. Methamphetamine “Low” Baseline Use (≤ 18 days)

Abstinence During Last 3 Weeks

	<u>Failures</u>	<u>Successes</u>	
Placebo	34 (97.1%)	1 (2.86%)	 8.7 x
Bupropion	27 (75.0%)	9 (25.0%)	

P = 0.007 (Chi-square test)

Reanalysis of data from Elkasheff, et al., 2008

Based on this reanalysis, a second study was initiated.
Top line data should be available 4Q'11

What Can We Do?

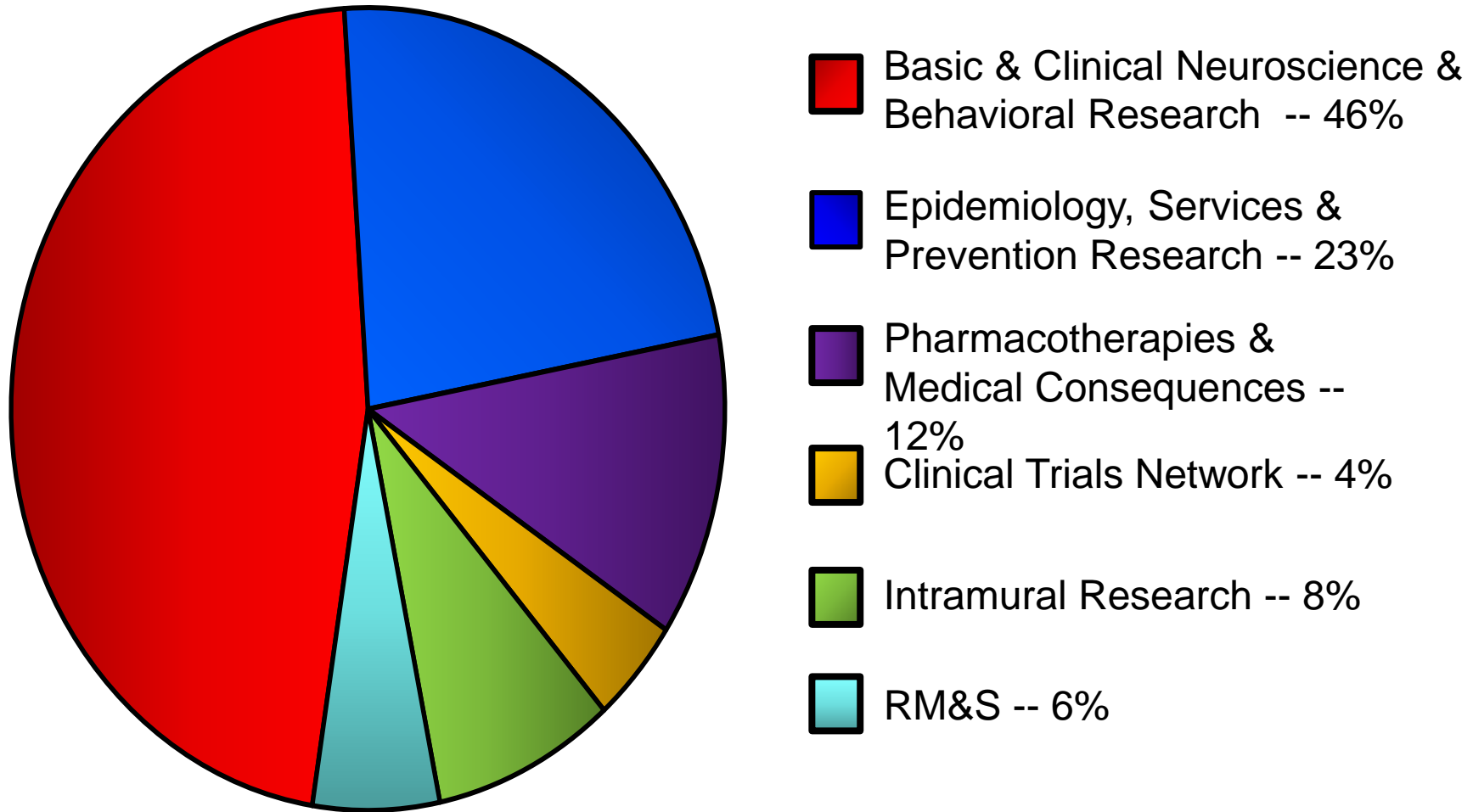
Problem: A General Lack of Interest By Pharma/Biotech In Developing Therapeutics for SUDs.

Solution 1: Government funding (grants and contracts) to academia and pharma/biotech.

- Advances in our understanding of the neurochemistry of addiction provide a basis for the hypothesis-driven testing of repurposed compounds (e.g. lorcaserin, fenobam) that either have been or are currently in development.

-However, given the cost and time commitment required to bring a compound to “market”, how much of a government investment is appropriate/warranted?

National Institute on Drug Abuse Portfolio FY 2010 Actual



What Can We Do?

Solution 2: Incentivize pharma/biotech to invest in SUDs

How?

- By promulgating the view that SUDs are neglected disorders and offering economic incentives (market exclusivity, patent extension) for investment in R&D.
- By educating the pharma/biotech/investment community that treatment of SUDs has the potential for profitability. Based on data generated in 2006, 1.2% of the population abuse stimulants (amphetamine +methamphetamine) other than cocaine (~2.4% of the population) [SAMSHA Publication 07-4293, 2008]. By comparison, schizophrenia affects ~1% of the population.

What Can We Do?

Profit is the strongest, if not sole driver of capital. In our economic current model, medications to treat SUDs must be viewed as profitable as other indications to attract investment.

A continued lack of private investment in SUDs (given the societal burden) favors stronger investment in a public (or PPP) model.