Pharmacotherapy for Opioid Addiction: Drugs in Development

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Pharmacotherapy for Prescription Opioid Addiction: Implications for Pain Management

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Disclosure

- Walter Ling has received unrestricted education grants from Reckitt/Benckiser and research support from Reckitt/Benckiser and Hythiam Inc.

  He has also served as an occasional consultant to Reckitt/Benckiser, Titan Pharmaceuticals, US World Med, Alkermes, and DemeRx

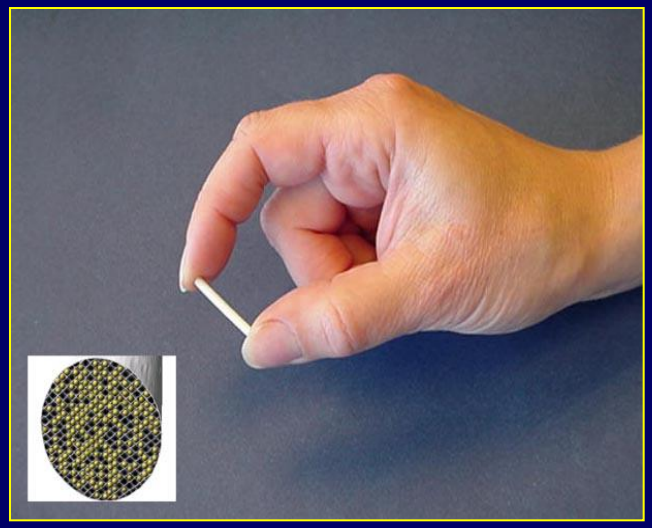
Scope of the Talk

- Probuphine
  - Buprenorphine's success and what follows
- Buprenorphine film
  - Partial fix
- Lofexidine
  - Non-opioid and its role in detoxification
- Vivitrol
  - Way to go? Where to go?
- AV 411(Ibudilast)?

Probuphine® : an Implantable, Six-Month Formulation of Buprenorphine

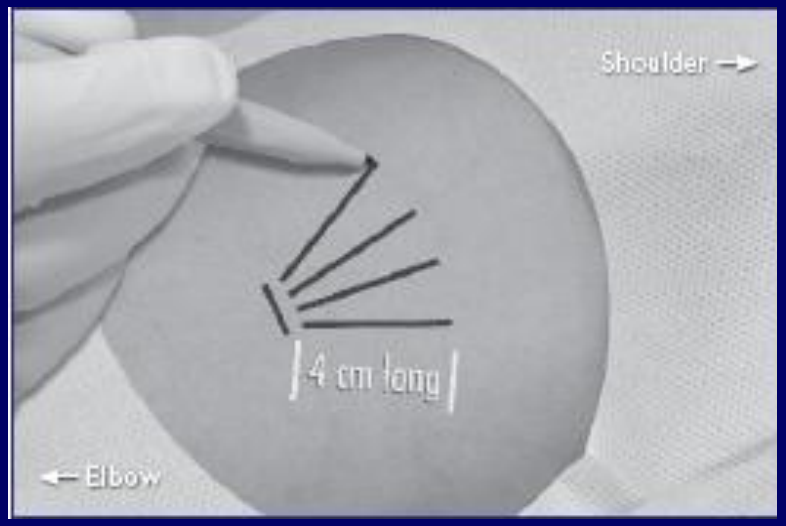
- Subcutaneous implant that delivers low, continuous, steady-state levels of buprenorphine for 6 months

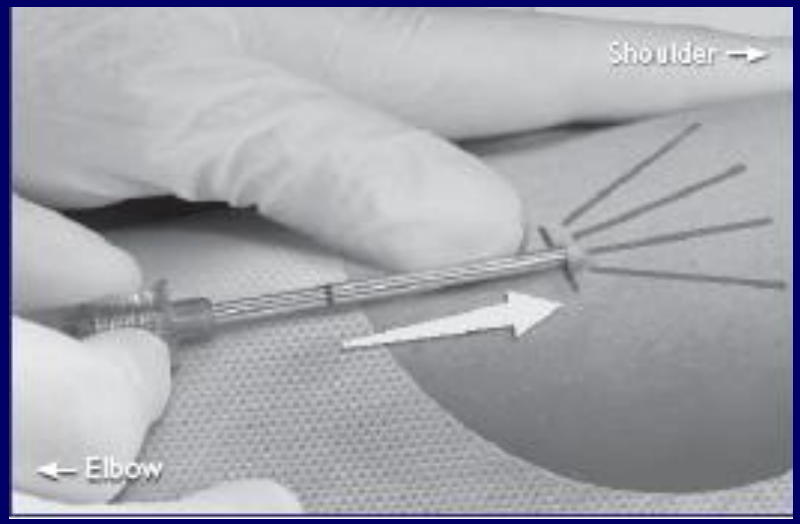
  Ethylene vinyl acetate combined with buprenorphine
  - 26 mm x 2.5 mm, 80 mg buprenorphine

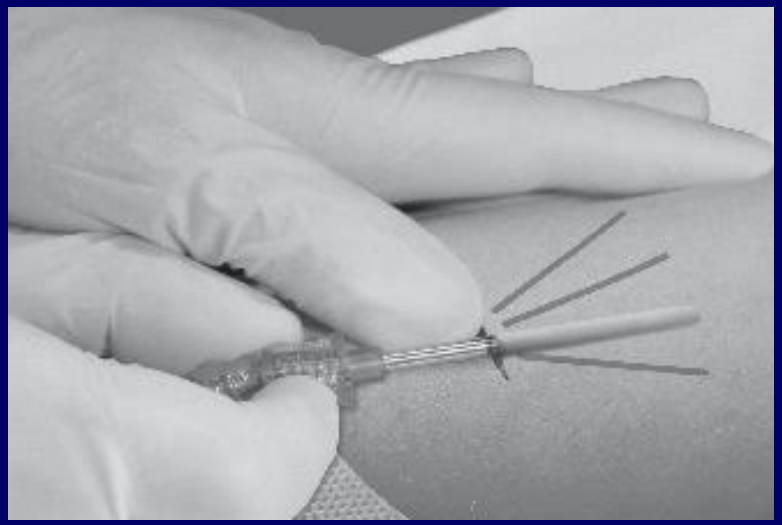


- <u>Potential advantages</u>
  - Reduces risk of diversion
  - Improves compliance
  - Reduces side-effects from fluctuating drug levels
  - Reduces overall drug exposure to the patient

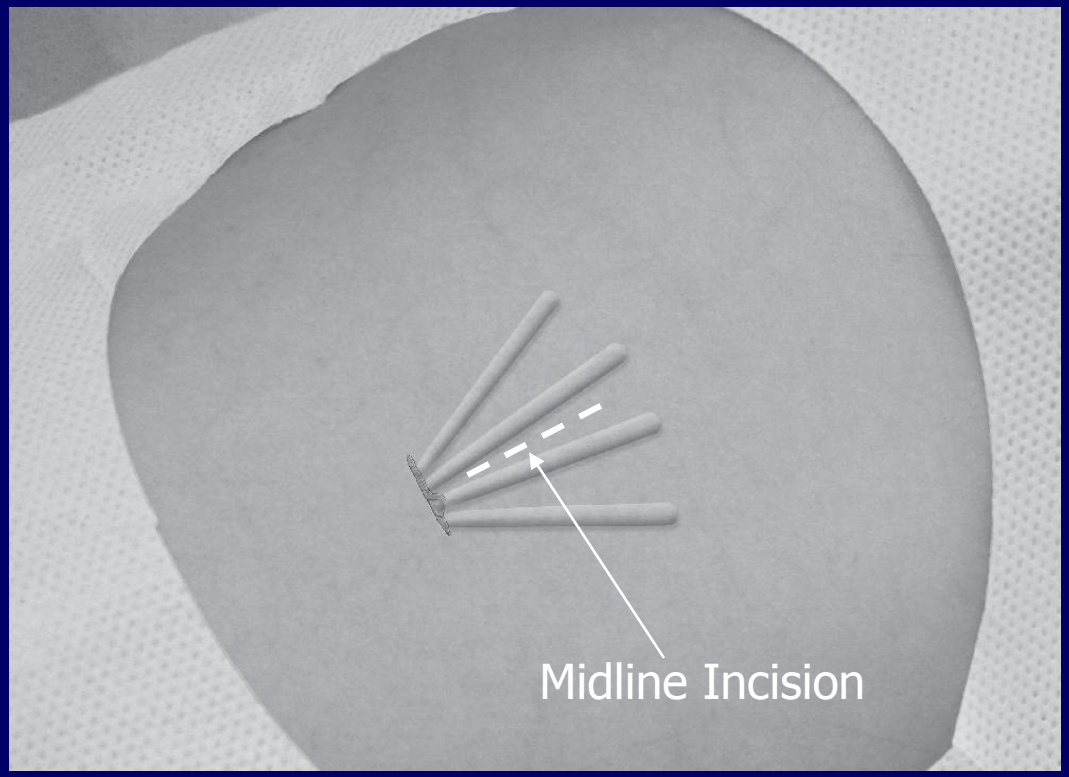
Probuphine Insertion Procedure

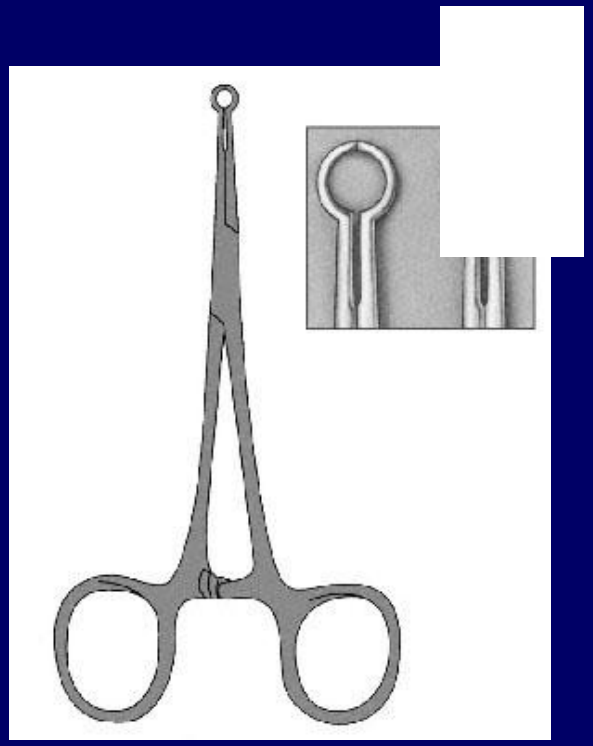






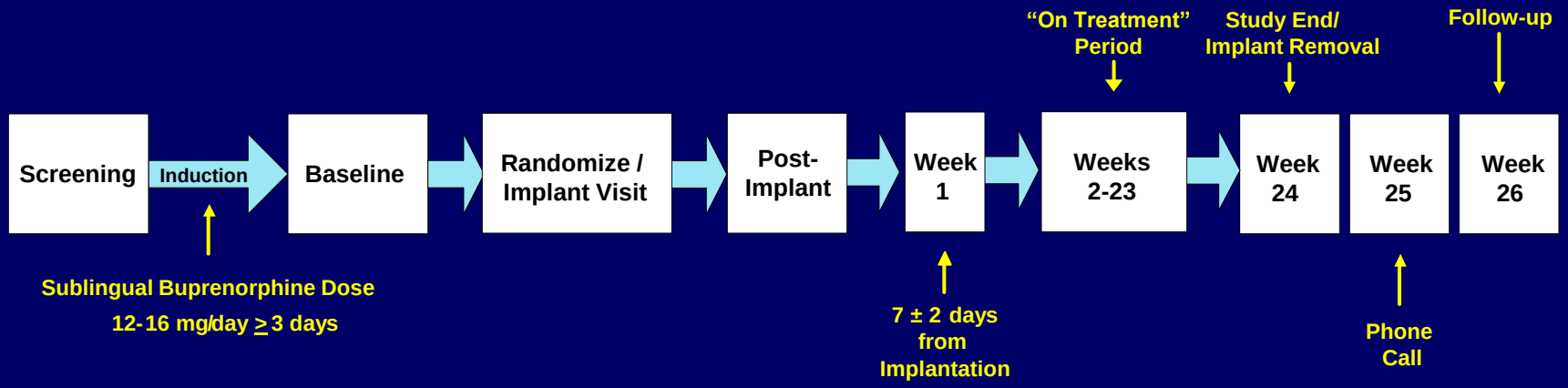
Probuphine Removal Procedure





X-plant clamp

Placebo-Controlled, Randomized, Multicenter Safety and Efficacy Trial



- 18 US sites
- 2:1 randomization (Probuphine implants: placebo implants)
- Patients received 4 initial implants
- One dose increase allowed (5th Probuphine or placebo implant) based on use of sublingual rescue medication
- Intensive study visits: 3x week urine collection + 2x week drug counseling for first 12 weeks, then weekly for weeks 13 - 24

Protocol Design Highlights

- **Rescue with sublingual buprenorphine (Suboxone®)**
  - Sublingual buprenorphine ≥ 3 days/week for 2 consecutive weeks or ≥ 8 days for 4 consecutive weeks = mandatory implant dose increase
  - Treatment Failure = continued need for sublingual rescue medication (as above) after 5th implant

Efficacy Measures

- Primary efficacy analysis
  - Cumulative distribution function (CDF) of the % negative urine samples at weeks 1-16
- Key secondary efficacy analysis
  - Cumulative distribution function (CDF) of the % negative urine samples at weeks 17-24
- Other secondary variables
  - Mean % urines negative for illicit opioids
  - Retention: proportion (%) of study completers
  - Mean total score on the subjective opioid withdrawal scale (SOWS)
  - Mean total score on the clinical opiate withdrawal scale (COWS)
  - Mean subjective opioid craving assessment (VAS)
  - Clinician and patient rated CGI

Patient Demographics (N = 163)

Gender: 69% male

Average age: 37 years

Race: 75% (white)

Primary opioid: 63% (heroin)

37% (prescription)

Patient Disposition

	Probuphine		Placebo	
	n	%	n	%
Patients	108	100	55	100
Completers (Retention)	71	66	17	31
Treatment Failures	0	0	17	31
Protocol Non-Compliance	12	11	7	13
Lost to Follow-up	10	9	4	7
Adverse Events	4	4	0	0
Other	11	10	10	18

Main Efficacy Results: Drug Use

- Primary efficacy endpoint: CDF of % negative urines, weeks 1-16
  - **Probuphine > Placebo, *P* = .0361**

Key secondary endpoint: CDF of % negative urines, weeks 17-24

  - **Probuphine > Placebo, *P* = .0004**

Other secondary endpoint: CDF of % negative urines, weeks 1-24

  - **Probuphine > Placebo, *P* = .0117**

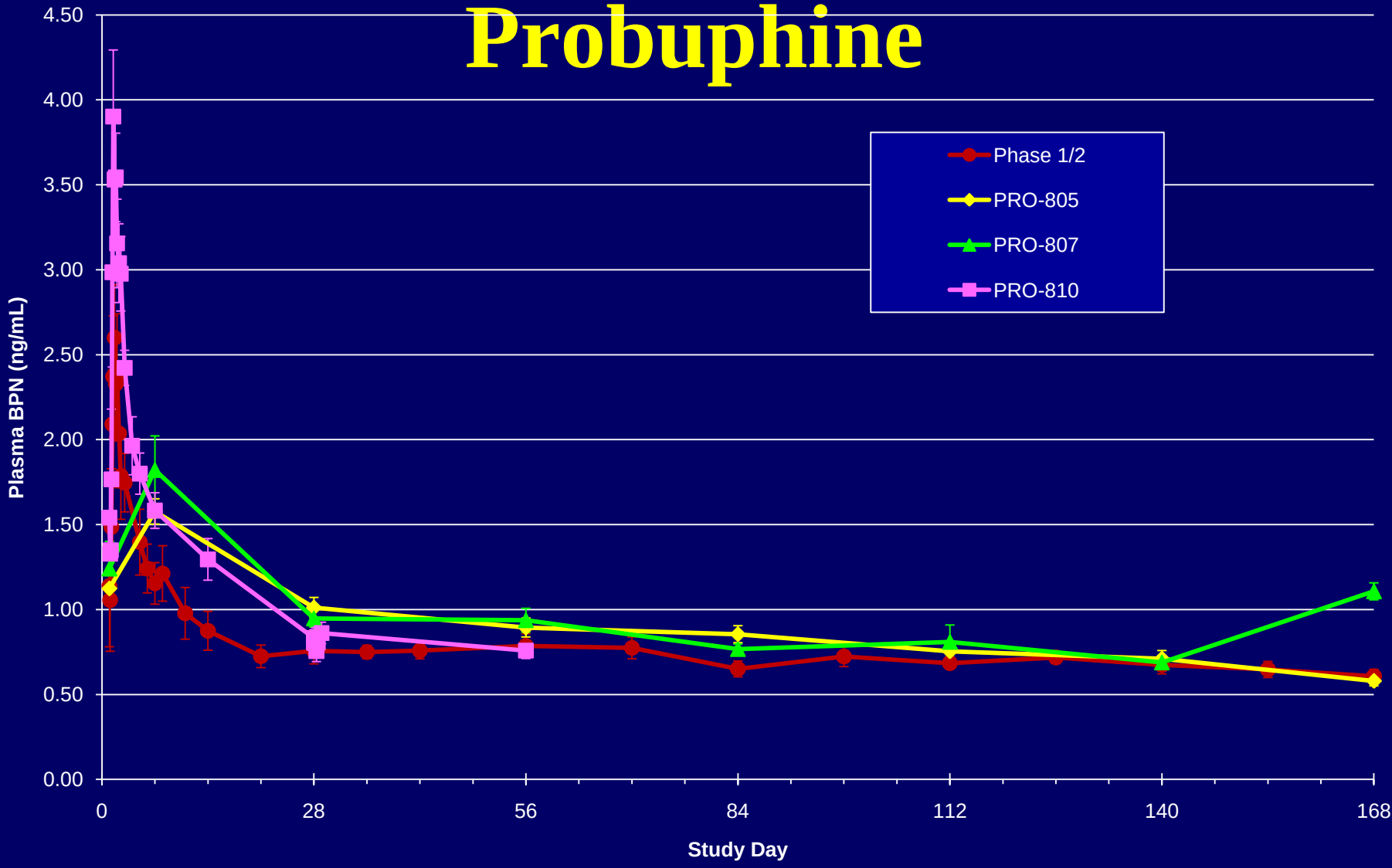
Other Secondary Efficacy Results

Outcome Measure (24 weeks)	Probuphine > Placebo
Treatment Retention	$p < .0001$
Patient-Rated Opioid Withdrawal	$p = .0039$
Clinician-rated Opioid Withdrawal	$p = .0004$
Global Improvement of Opioid Addiction (Clinician-Rated)*	$p < .0001$
Global Severity of Opioid Addiction (Clinician-Rated)*	$p = .0004$
Opioid Craving Visual Analog Scale (VAS)	$p = .0009$

Serious Adverse Events

	Probuphine n = 108			Placebo n = 55		
System Organ Class	**Events**	**n**	**%**	**Events**	**n**	**%**
All serious adverse events	5	2	1.9	5	5	9.1
Implant site serious adverse events						
Cellulitis	0	0	0.0	1	1	1.8
Other serious adverse events						
Pneumonia	0	0	0.0	1	1	1.8
Burn	1	1	0.9	0	0	0.0
Drug dependence	0	0	0.0	1	1	1.8
Suicidal ideation	0	0	0.0	1	1	1.8
Chronic obstructive pulmonary disease	2	1	0.9	0	0	0.0
Pulmonary embolism	2	1	0.9	0	0	0.0
Respiratory failure	0	0	0.0	1	1	1.8

Clinical Pharmacokinetics of Probuphine



Probuphine Summary

- Under the conditions of the study, Probuphine was better than placebo in the treatment of opioid-addicted patients as measured by: illicit opioid use, retention, symptoms of withdrawal, craving and global impression of improvement.
- The number and profile of adverse events and serious adverse events were low, mild to moderate, and similar to placebo.
- The implant procedure was generally well tolerated and there was no evidence of implant diversion or misuse.
- Probuphine delivers a low level of plasma buprenorphine continuously for six months; it was thus associated with lower overall drug exposure relative to sublingual buprenorphine, hence fewer side effects?

Buprenorphine Film

- Improvement over tablet formulation:
  - Child resistant: reduces accidental exposure
  - Quicker dissolution and better taste
  - “Interchangeability” with tablets

Lofexidine

- Alpha 2-adrenergic receptor agonist; related to clonidine
- Acts centrally, binding specifically to subtype 2A alpha-2-adrenergic receptor—less hypotensive effect.
- Suppresses acute withdrawal symptoms: chills, cramps, sweating, muscle aches and pain, tearing and rhinorrhea.
- Non-opioid agent for opioid detoxification
- Marketed in UK since 1992: 2.4 mg/d

Lofexidine: Placebo-Controlled Multicenter Study

Background: Open label study (N=54) after 8 days of morphine stabilization. From 1.6 mg—4.0 mg for up to 7 days; tapered over 3 days, showed dose dependent decrease in objective signs of opiate withdrawal; optimal dose: 3.2 mg/d

- Three days of 100 mg. morphine stabilization, 4 days (4-7) of 3.2 mg Lofexidine or placebo; 1.6 mg drug or placebo on day 8. All received placebo days 9 and 10.
- Primary outcome MHOWS score on day 5—day 2 of 3.2 mg drug or placebo.
- Significant effect during first 5 days of abstinence.
- Study stopped because of significant effect of lofexidine over placebo.

Lofexidine: Potential Advantages

- Little abuse potential
- Not requiring special regulatory control
- Accessibility to physicians and patients
- May attract new and different patient population: free from stigmatization
- Fewer side effects than clonidine

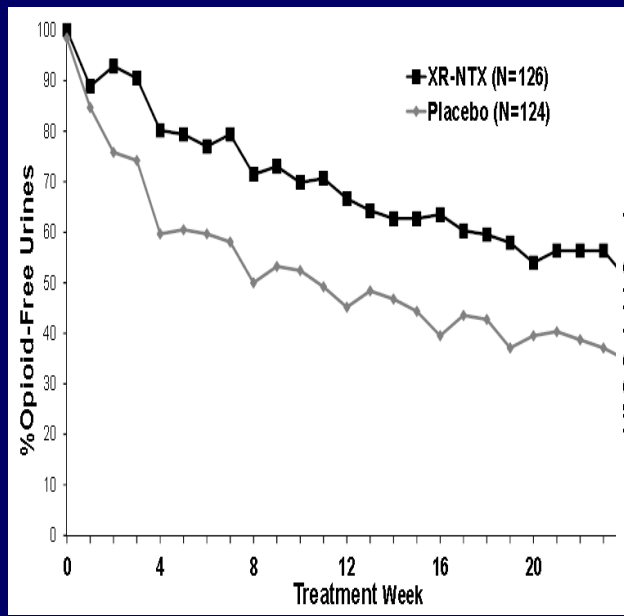
Vivitrol for Opioid Addiction

- Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomized trial

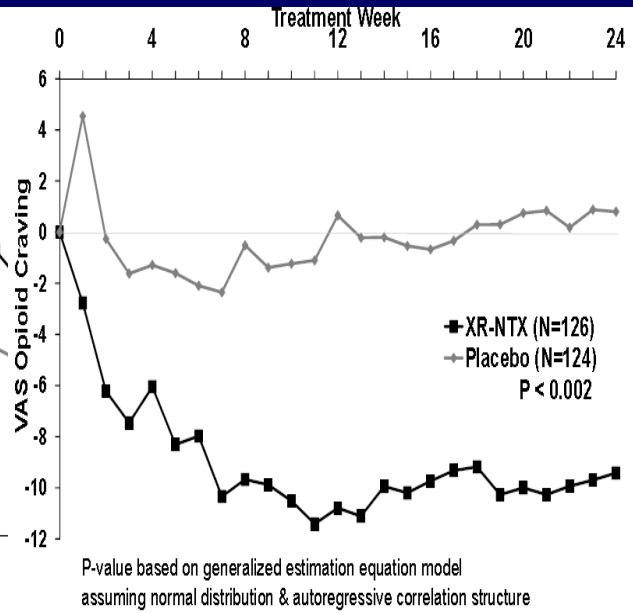
- *Evgeny Krupitsky, Edward V Nunes, Walter Ling, Ari Illeperuma, David R Gastfriend, Bernard L Silverman*
  - *Lancet 2011; 377: 1506-13*

Vivitrol: The Russian study
Key Efficacy Outcomes

3A. % Opioid-Free Urines by Week

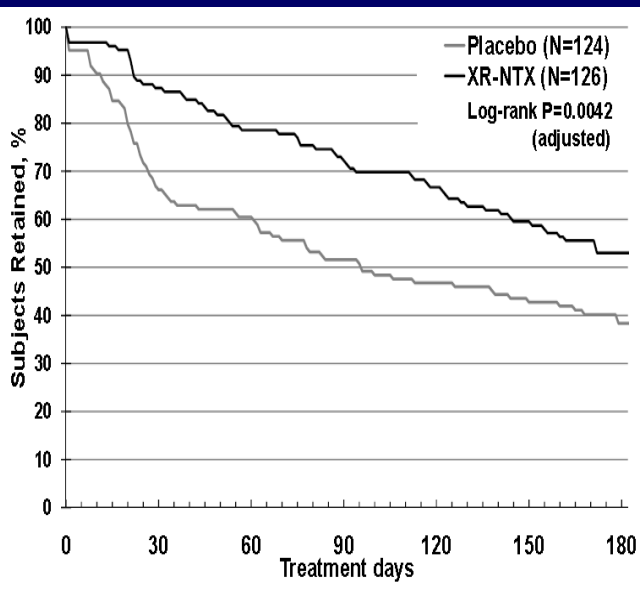


3B. Mean Change From Baseline in Craving



P-value based on generalized estimation equation model assuming normal distribution & autoregressive correlation structure

3C. Time-to-Discontinuation (Kaplan-Meier)



AV 411 (Ibudilast)

- Glial cell regulator: attenuates glial cell activation
- Marketed for treatment of asthma
- Enhance morphine analgesia
- Decreases opioid tolerance
- Suppresses opioid withdrawal
- In early development—too early to tell

Probuphine: Criticisms and Comments

- Probuphine: Implanting is a hassle (mostly an inconvenience)

  But of course buprenorphine beats placebo.

  Need to compare to Subutex and Suboxone.

  Well, yes and no. At some point a comparison makes sense but not necessarily in this study designed as part of medication development.

  Probuphine's advantage lies somewhere else: fixing problems with compliance, diversion and accidental poisoning-- all obvious and don't need to be shown here.

  Some unexpected advantages: pts like not having to think of and deal with medications daily. Even those lost to follow up had a good reason—implant still worked.

Buprenorphine Film: Small Improvement

- Partial fix for unintentional pediatric exposure
  - Ninety-five percent happened at home
  - Parental behavior—lack education, complacency, no use of preventive measures (locked boxes)

- Mixed results on patient preference
- Does little for compliance and diversion
- Vigorous promotion creates backlash from clinician advocates of Subutex and Suboxone

Lofexidine: Reality Check

- What does detox do?
  - " Detoxification may be good for a lot of things; staying off drugs isn't one of them"
- " Who needs lofexidine when you have buprenorphine"?
  - "They--the buprenorphine patients wanting to get off buprenorphine—do".
- Needs one more study for FDA approval
- Time will tell after that

Vivitrol

- Approved in October 13, 2010
- Criticisms: directed at FDA
  - Single study in Russia
  - Not “made in USA” but “made AS in USA”?
  - Ethical considerations
  - No “ post treatment” safety data
  - Compared to other treatment—buprenorphine

Conclusion: What Does It all Mean?

- Probuphine development is testimony to buprenorphine's success and the problems it creates: compliance, diversion, and accidental poisoning, especially in children.
- Probuphine appears to be the best candidate so far in fixing these problems.
- R/B's own attempt—film--seemed at best a modest partial fix, and vigorous promotion of the film may have created its own problem.
- Lofexidine probably has a niche market but that remains to be seen and it needs more work
- Vivitrol should also have a niche market but only time can tell

No Crystal Ball
But Time and Chance

Those who live by the crystal ball end up eating glass

"I returned, and saw under the sun, that the race is not to the swift, nor the battle to the strong, neither yet bread to the wise, nor yet riches to men of understanding, nor yet favor to men of skill; but time and chance happeneth to them all". Ecclesiastes 9: 11

Thank you, thank you, and thank you.