

NIDA/Penn International, HIV- Focused Research Collaborations: 1998-2009

**All NIDA funded
All Related to reducing spread of
HIV**

**George E. Woody, MD and Colleagues at
University of Pennsylvania and International Sites**

HIV & Cocaine Dependence in Brazil: First International Study

Flavio Pechansky, M.D., PhD, George E.
Woody, M.D. and Colleagues

Addiction Treatment and Research Center
at the University of Rio Grande do Sul
Porto Alegre, Brazil

Started as result of NIDA/Brazil meeting in
Sao Paulo in 1992

Examined HIV risk in cocaine dependent patients in Porto Alegre over 2 years

5% annual conversion rate

This study + Inciardi/Pechansky data found:

- Stepwise association between type of risk behavior and HIV+
- IDU/gay/bisexual highest proportion HIV+
- Heterosexual, using condoms lowest HIV+

Pechansky, F., Woody, G., Inciardi, J., Surratt, H., et al

Naltrexone treatment and HIV risk reduction for heroin addiction: 10-years Penn-Pavlov experience

George Woody, MD, Edwin Zvartau, MD, PhD, Evgeny Krupitsky, MD, PhD & Colleagues

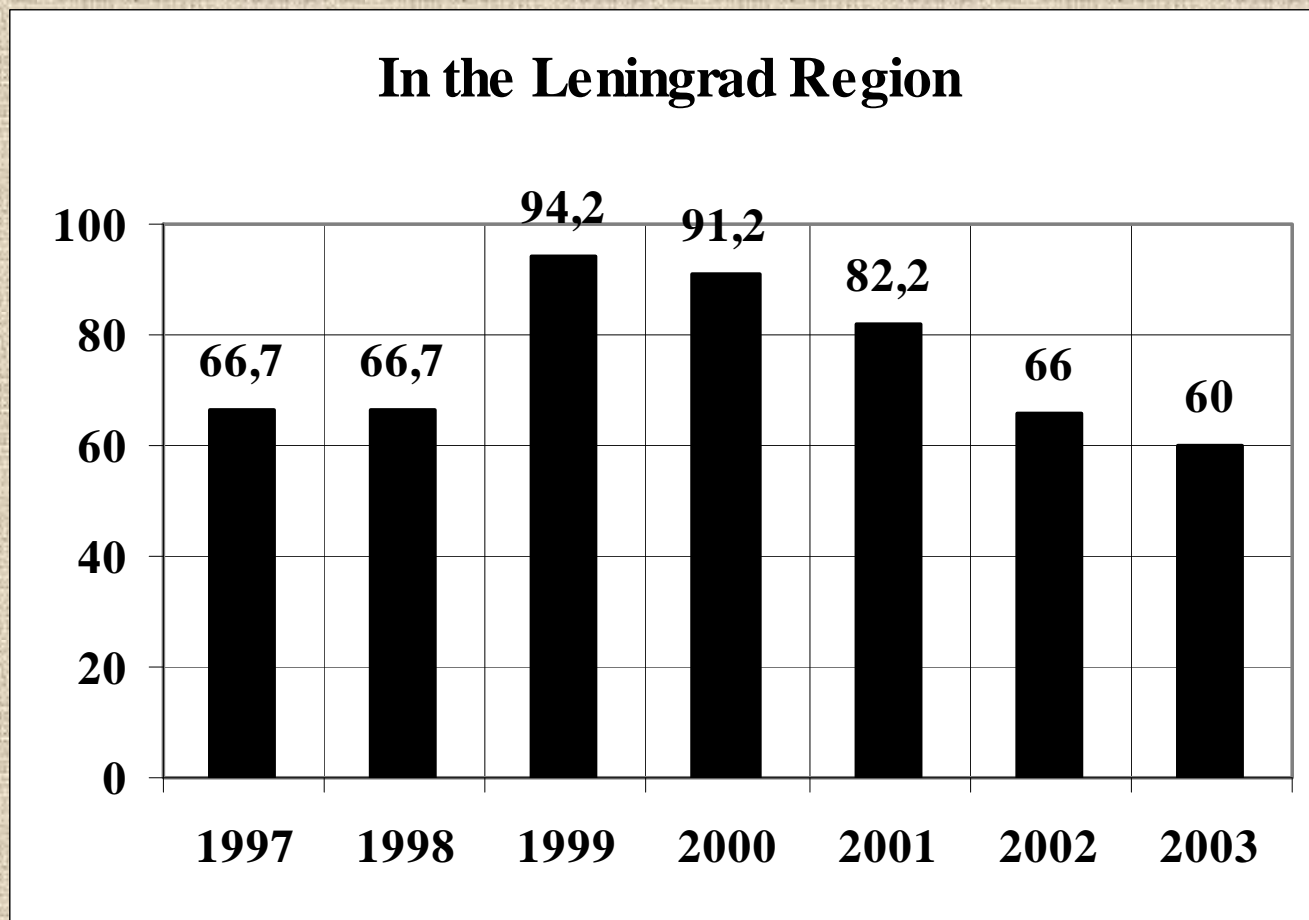
University of Pennsylvania

St. Petersburg Pavlov State Medical University

Leningrad Regional Addiction Treatment & Research Center

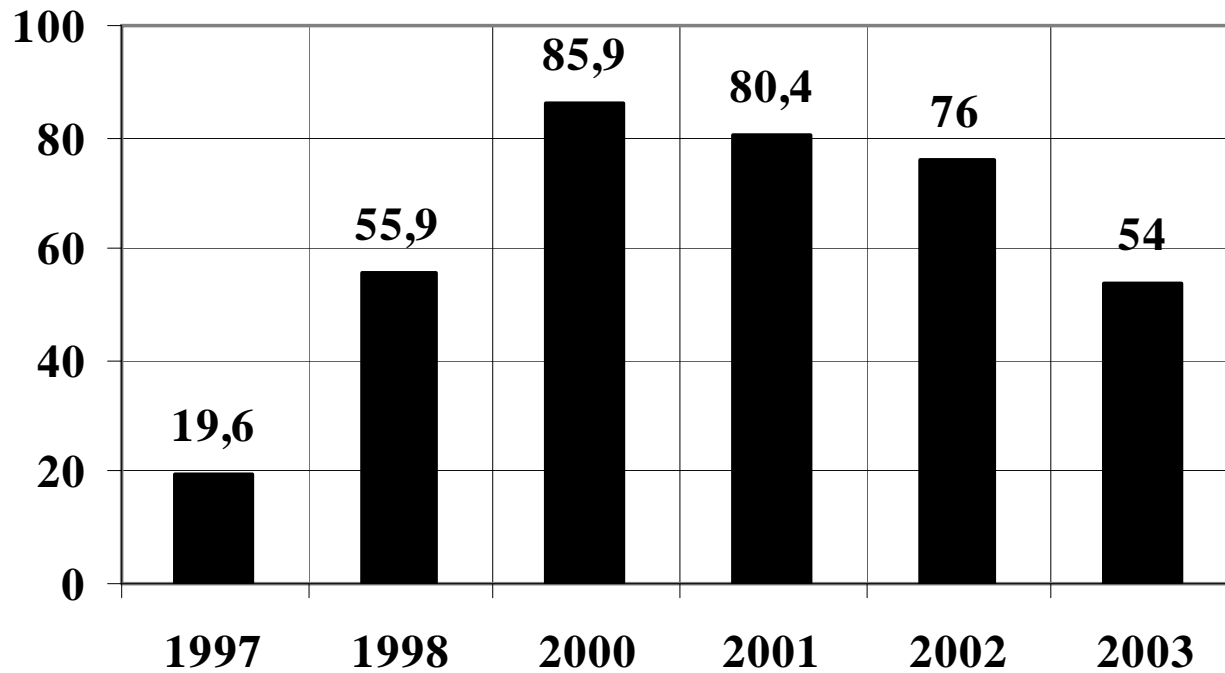
St. Petersburg Bekhterev Research Psychoneurological Institute

Prevalence of injection drug users (%) among new HIV positive individuals registered within a year



Prevalence of injection drug users (%) among new HIV positive individuals registered within a year (continued)

In the city of St. Petersburg



Usual Addiction Treatment

- Inpatient detoxification + rehabilitation (3-6 wks)
- Referral to health center after discharge
- Few patients keep appointments
- Relapse high
- Naltrexone approved
- Not widely used due to cost
- Will probably reduce HIV risk if taken as directed
- Not well-studied

Two Formulations Available

- Naltrexone 50 mg tablet - take one/day
 - Low patient interest & high dropout in US
- Implant containing 1000 mg (Prodetoxon)
 - Initially recommended every 2 months
 - Clinical experience shows blocks for 3 months

Four Studies

- Epidemiological study using existing data showing link between heroin addiction and HIV
- Three naltrexone studies

A DOUBLE BLIND PLACEBO CONTROLLED CLINICAL TRIAL OF NALTREXONE FOR HEROIN ADDICTION IN ST. PETERSBURG, RUSSIA

**E. Krupitsky, E. Zvartau, M. Tsoi, V. Egorova, D. Masalov, A. Burakov, T.
Romanova, T. Didenko, E. Verbitskaya,
E. Ivanova, A. Bespalov, N. Neznanov, A. Grinenko, C. O'Brian, G.
Woody,**

**St.Petersburg Pavlov State Medical University
University of Pennsylvania, Department of Psychiatry**

Supported by NIDA grant # 3 P60 DA05186-13S1

METHODS

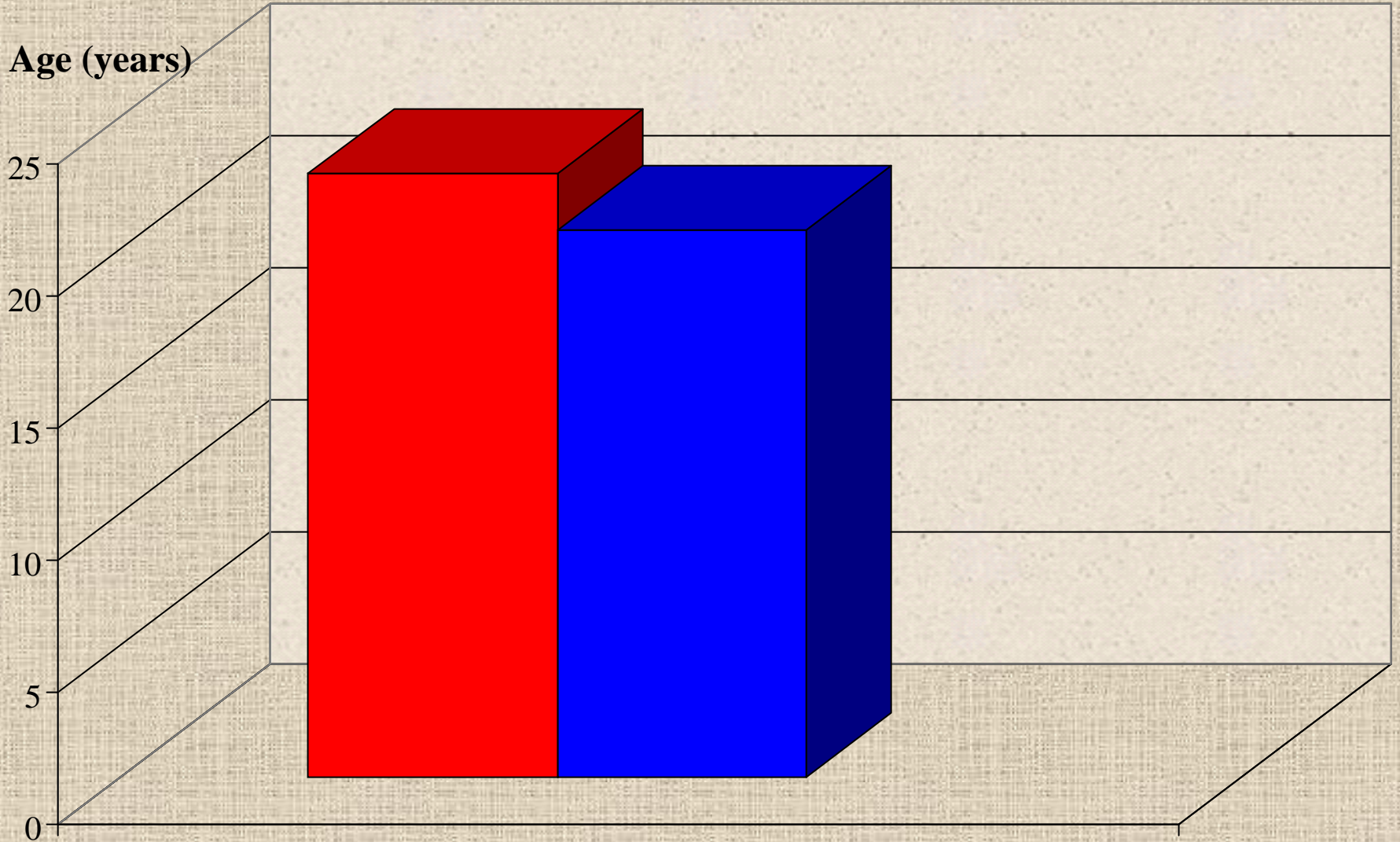
- **52** male and female heroin addicts after detoxification, giving informed consent and passing a narcan challenge had been randomly assigned to one of **two treatment groups**:

Two cell study design:

- 1. Naltrexone (50mg/day) (27 patients)**
 - 2. Placebo (25 patients)**
- All patients offered biweekly clinical management / compliance enhancement counseling.
 - Treatment lasted 6 months.
 - All patients had at least one family member who is able to supervise medication compliance.

AGE OF HEROIN ADDICTS

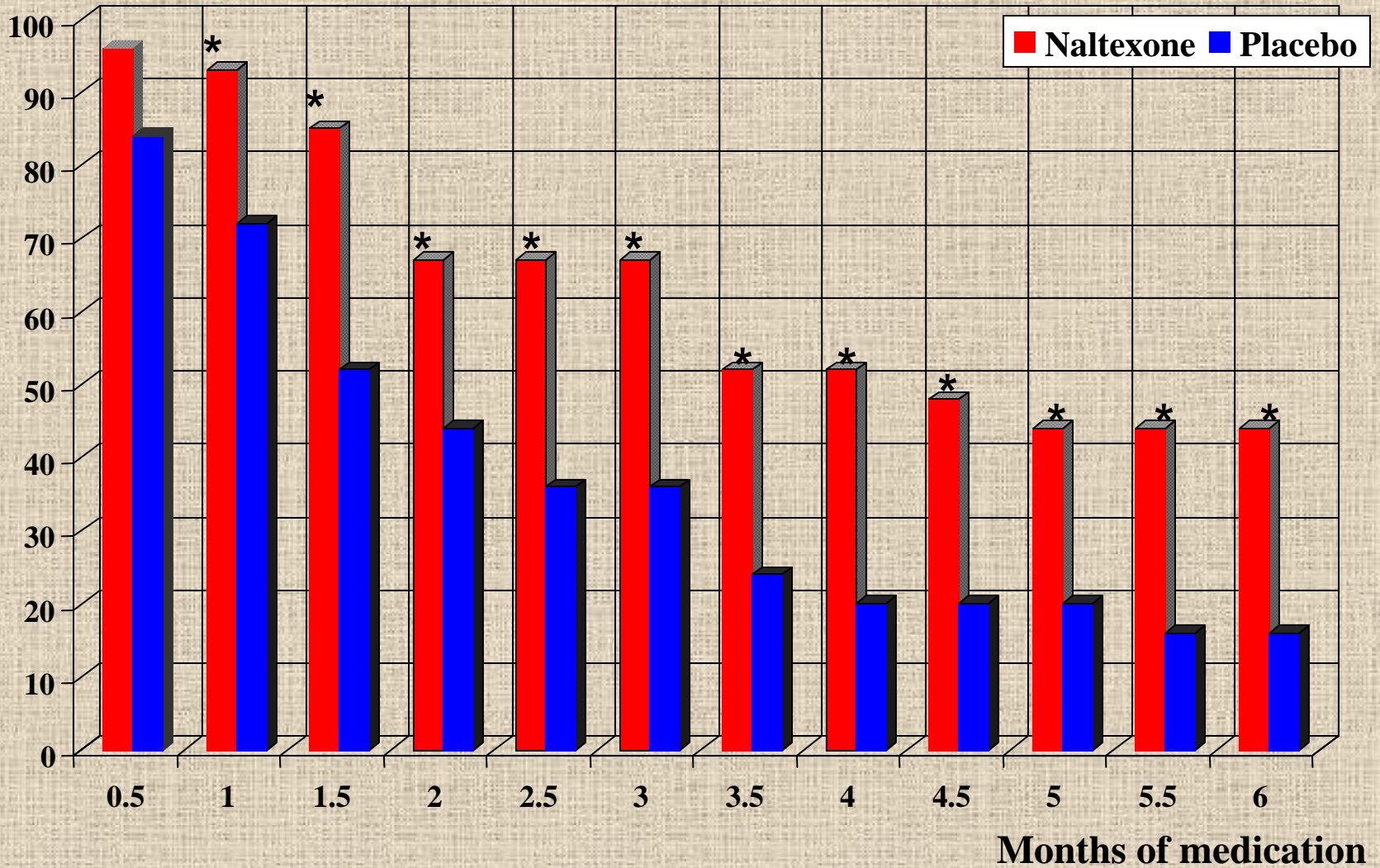
■ Naltrexone ■ Placebo



Rate of Abstinence: Relapse Free Proportion

Abstinent subjects (%)

* - $p < 0.05$



How can we improve naltrexone treatment?



**A DOUBLE BLIND PLACEBO CONTROLLED CLINICAL
TRIAL OF NALTREXONE AND FLUOXETINE FOR HEROIN
ADDICTION IN ST. PETERSBURG, RUSSIA**

**E. Krupitsky, E. Zvartau, M. Tsoi, V. Egorova, D. Masalov,
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HYPOTHESIS

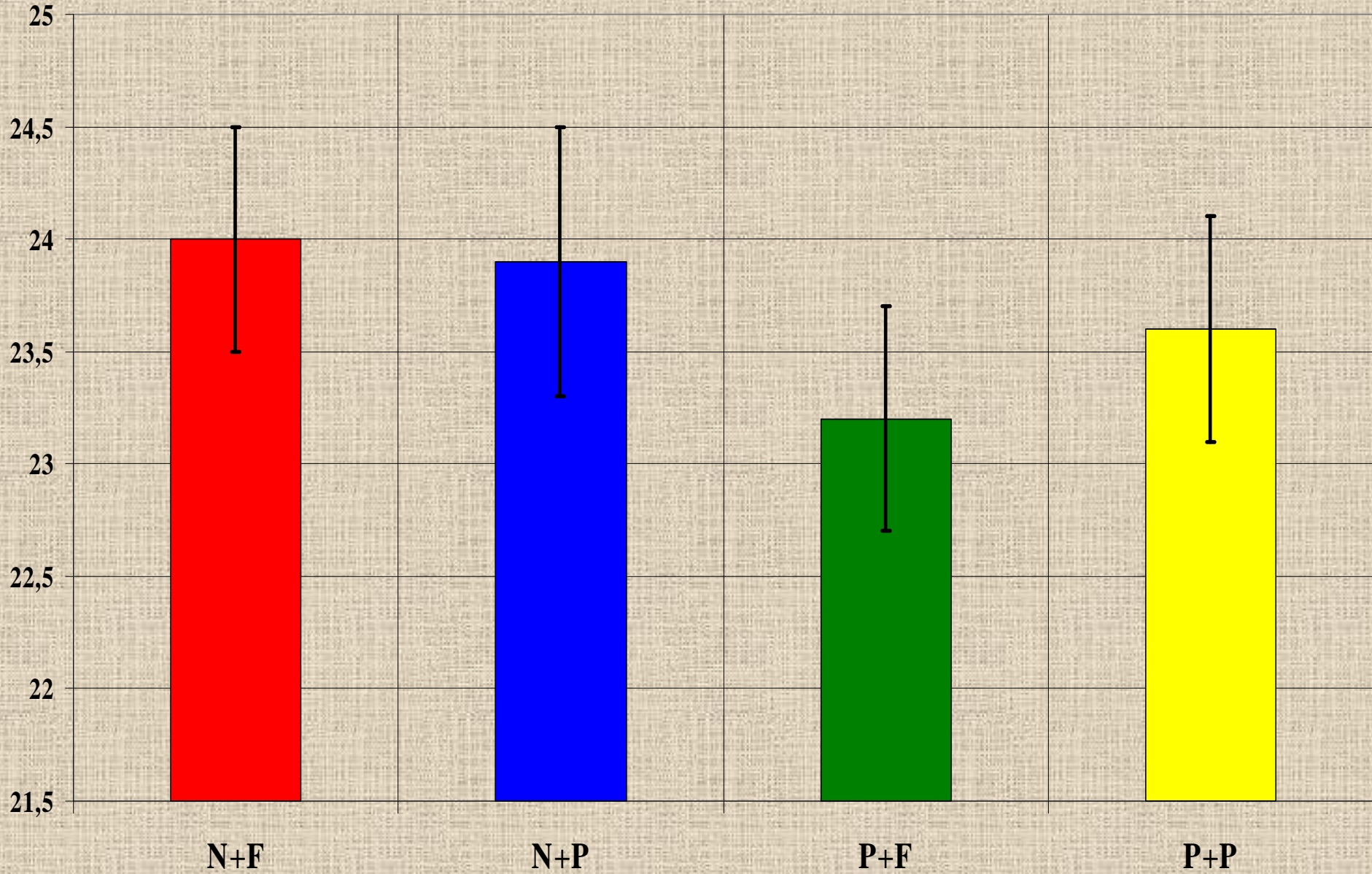
- Antidepressant might reduce protracted withdrawal
- If combined with naltrexone, might improve outcome

METHODS

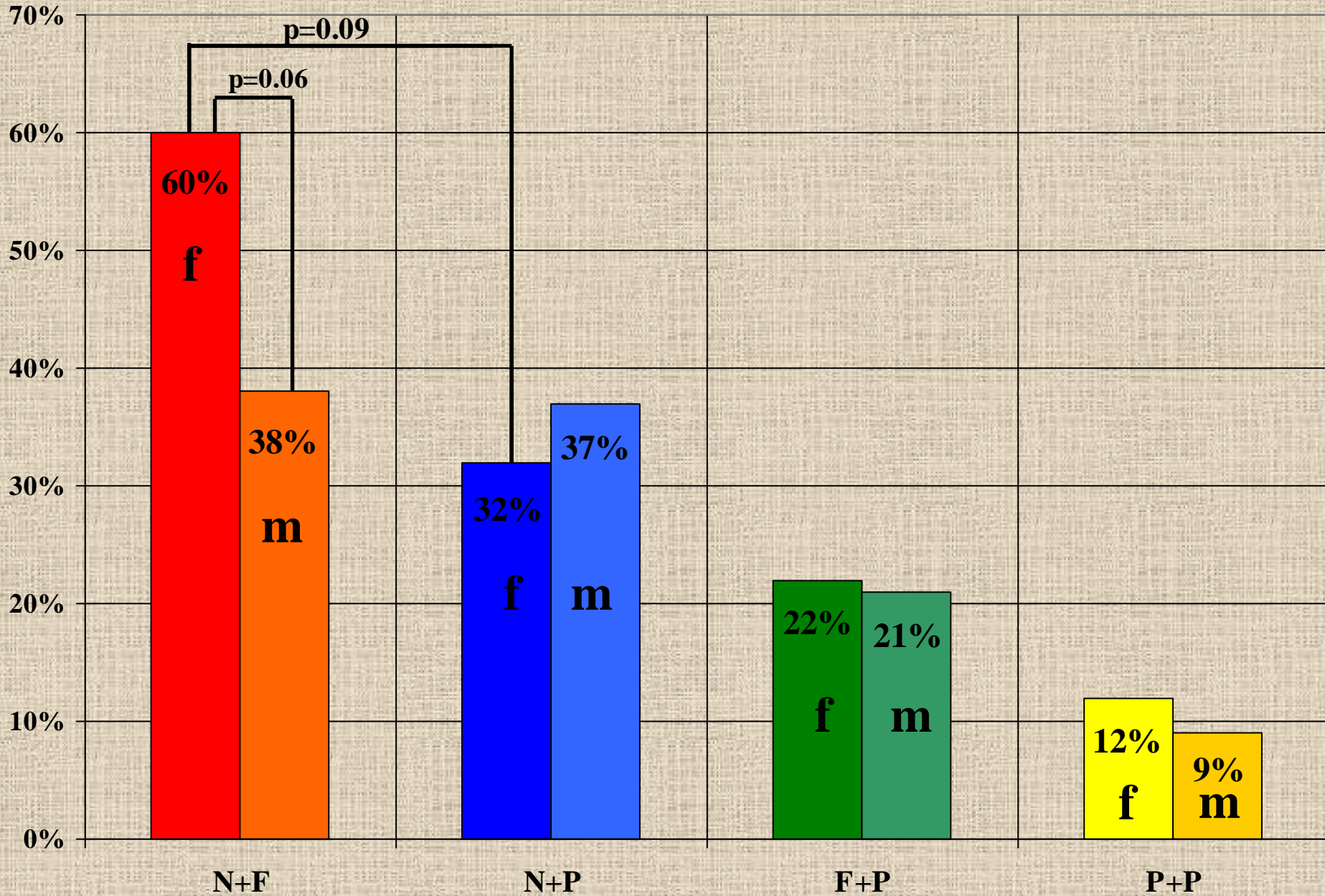
- **280** male and female heroin addicts randomized to one of **four treatment groups (70/group)**:
 - 1. Naltrexone (50mg/day) + Fluoxetine (20mg/day) (N+F)**
 - 2. Naltrexone (50mg/day) + Placebo (N+P)**
 - 3. Placebo + Fluoxetine (20mg/day) (P+F)**
 - 4. Placebo + Placebo (P+P)**
- All offered biweekly clinical management/compliance enhancement counseling.
- Treatment lasted 6 months.
- All had at least one family member able to supervise medication compliance.

Age (M±SE)

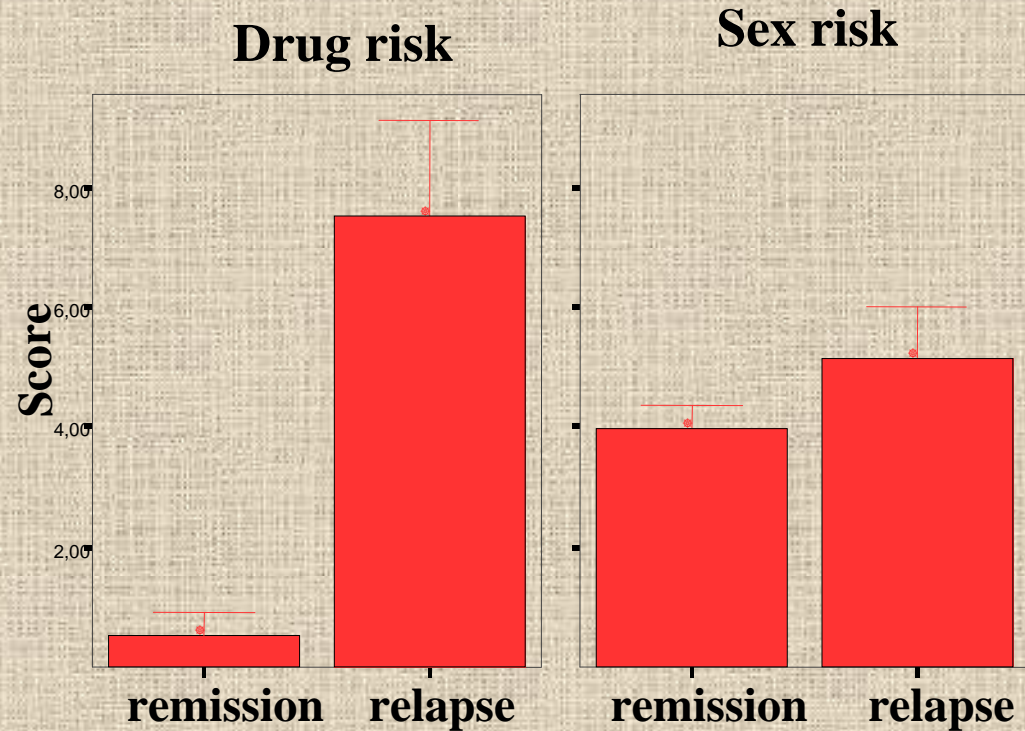
years



Gender differences in the 6 months retention rate



HIV Risk Assessment Battery



Conclusion (continued)

- ❖ HIV drug risk reduced in addicts who did not relapse
 - ❖ (regardless of treatment condition)
 - ❖ Treatment reduced depression, anxiety, and improved overall function in those who did not relapse
 - ❖ (regardless of treatment condition)
- *Number who did not relapse was much higher in naltrexone patients**

Is there another way to improve naltrexone therapy ?



**The major problem with Naltrexone is compliance...
So may be long acting sustained release formulation is the
way to improve naltrexone therapy ?**

**DOUBLE BLIND RANDOMIZED PLACEBO
CONTROLLED STUDY OF EFFECTIVENESS
OF IMPLANTABLE NALTREXONE
(PRODETOXONE) FOR TREATMENT OF
HEROIN ADDICTION (Interim analysis)**

E. Krupitsky, E. Zvartau, V. Egorova, D.
Masalov, A. Burakov, M. Tsoy, N.
Bushara, T. Romanova, E. Verbitskaya,
Ch. O'Brian, G. Woody

St.-Petersburg Pavlov State Medical
University,
University of Pennsylvania

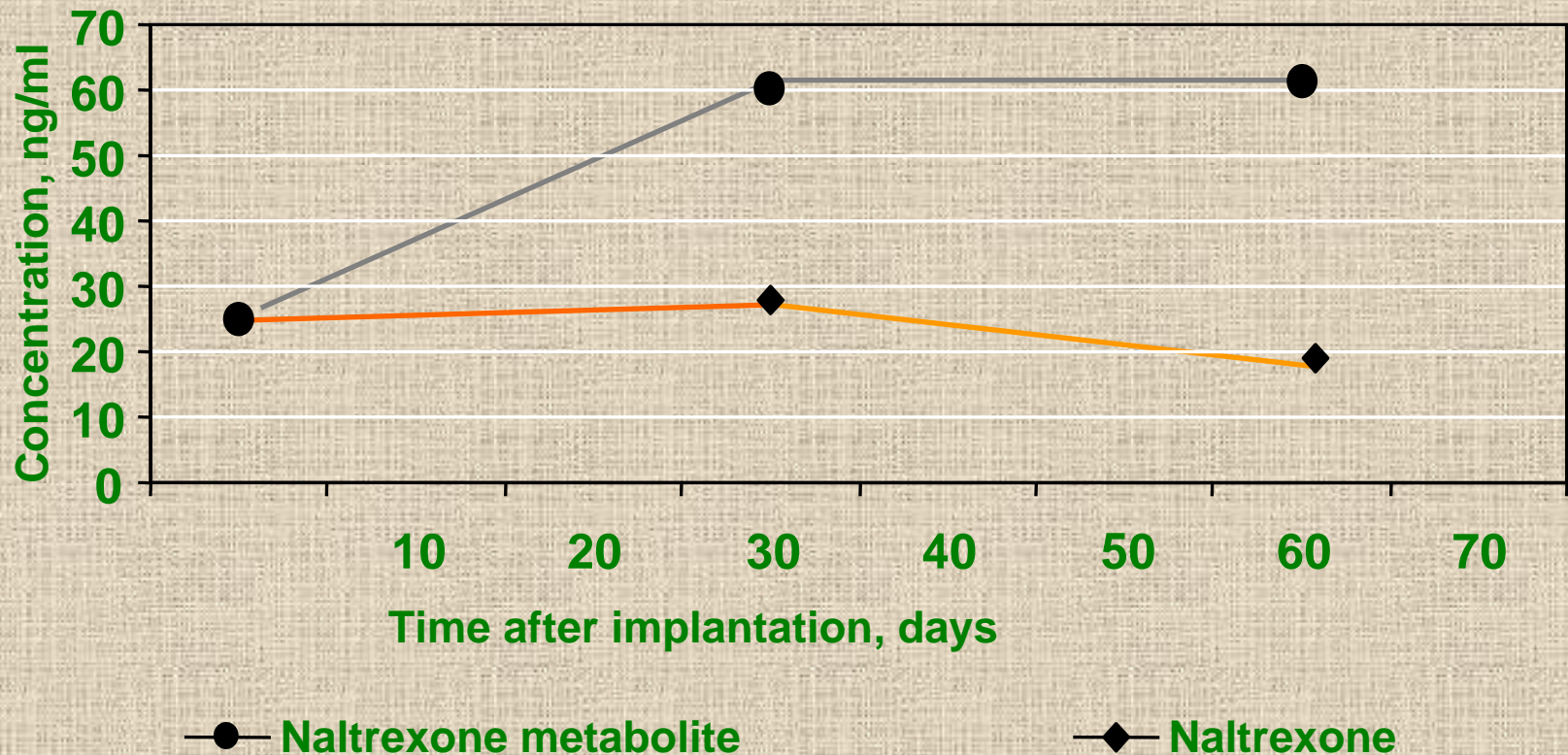
Supported by NIDA Grant R01-DA-017317

Prodetoxone: Route and Dosage

PRODETOXONE[®], tablets for implantation
1000 mg of naltrexone



Pharmacokinetics of Prodetoxone



Blood samples were collected in one week, one and two months after implantation

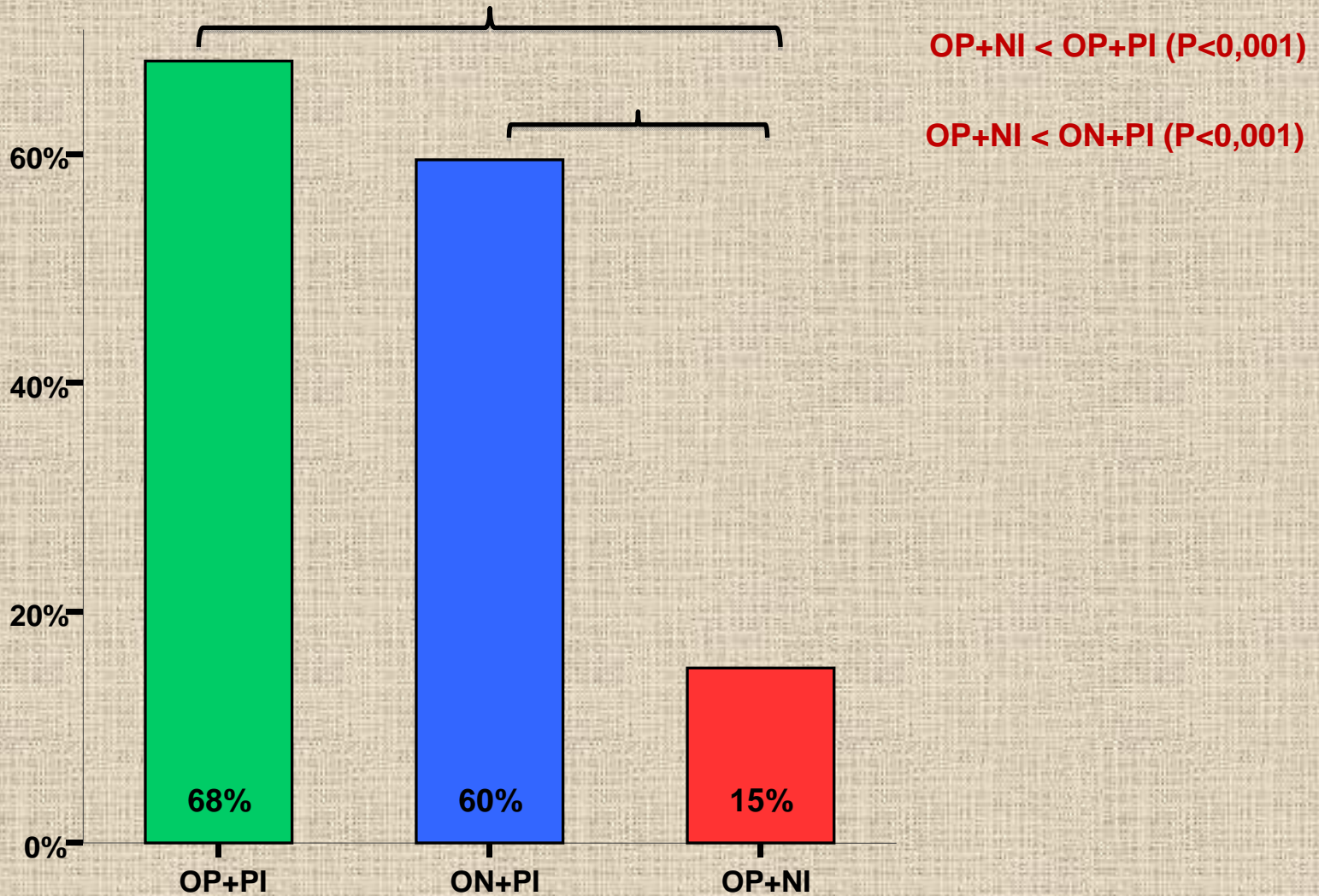
METHODS

- **190** male and female heroin addicts after detoxification, giving informed consent and passing a Naloxone challenge randomly assigned to one of **three treatment groups**:
 - 1. Naltrexone Implant (1000 mg) (3 times, every 2 months) + Oral Placebo (OP+NI). 66 patients.**
 - 2. Oral Naltrexone (50mg/day) + Implant Placebo (3 times, every 2 months) (ON+PI). 62 patients.**
 - 3. Implant Placebo (3 times, every 2 months) + Oral Placebo (OP+PI). 62 patients.**
- All offered biweekly counseling.
- Treatment lasted 6 months.
- All had at least one family member who was able to supervise medication compliance.
- Targeted study sample – 306 patients

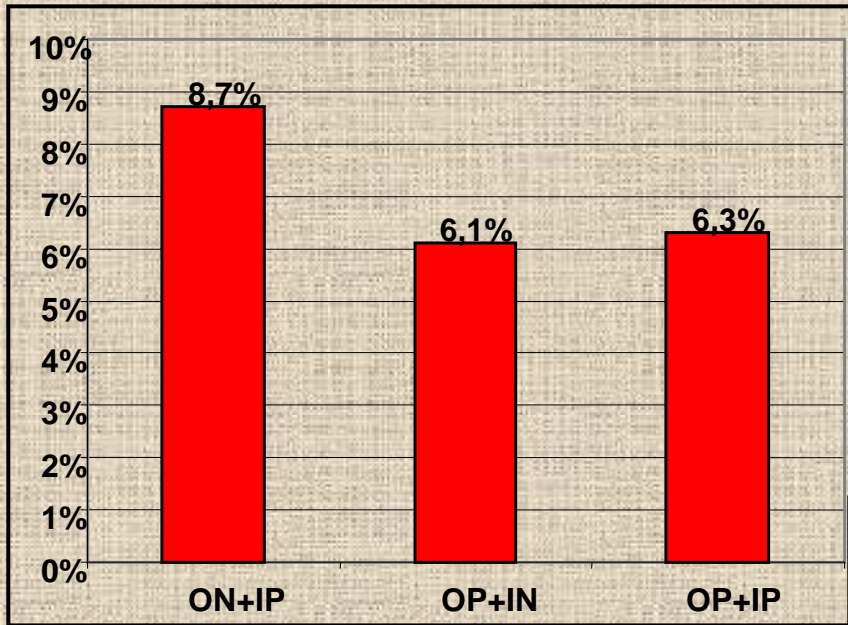
Demographics and Clinical Characteristics

	Group		
	OP+PI	ON+PI	OP+NI
N	62	62	66
Gender (female)	25,0%	24,8%	22,6%
Age (M±SEM)	28,4±0,57	27,4±0,53	28,4±0,57
Duration of heroin dependence (M±SEM)	8,9±0,53	8,8±1,08	8,4±0,37
Number of previous treatments (M±SEM)	4,4±0,45	3,6±0,36	5,3±0,43

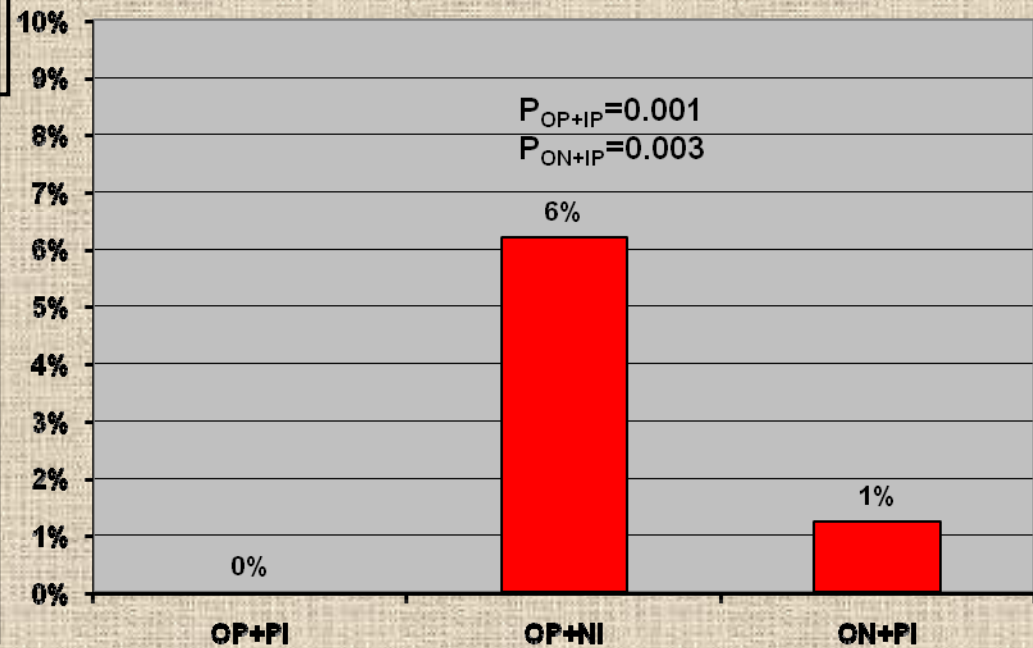
6 Month Relapse Rate (end of treatment)



Adverse events (non surgical)



Adverse events (surgical, % of implantations)



Next Study (submitted to NIDA)

- Addiction interferes with adherence to antiretroviral therapy (ART) for HIV treatment
- Relapse a problem in AIDS Centers
- Propose to randomize detoxified addicts starting ART to oral naltrexone or Prodetoxon
- Primary outcome will be response to ART over next 12 months
- Should know if will be funded in next 6 months

Methadone Maintenance and HIV Risk in Ukraine

Anatoliy M. Viyevskiy, M.D., Ph.D.

Sergey Dvoryak, M.D., George E. Woody, M.D., and colleagues

Kiev City Narcological Hospital and Kiev City AIDS Center

Primary Aims

- 1) Measure acceptability and compliance with a 3-month course of methadone maintenance of 25 HIV+ and 25 HIV- patients in Kiev
- 2) Measure the impact of a 3-month course of methadone treatment in HIV+ and HIV- on reducing opioid use
- 3) Measure the impact of a 3-month course of methadone treatment in HIV+ and HIV- on reducing HIV risk behavior

Secondary Aims

- 1) Assess the degree to which the 3-month course of methadone maintenance reduces illegal activities and improves employment and psychiatric symptoms
- 2) Determine short term outcome after completion of methadone treatment
- 3) Obtain pilot data on the prevalence of hepatitis B and C among study patients

Additional Work: Possible by NIDA Supplement

Field test & implement on a small scale:

- 1) Intervention developed by Dr. Dvoryak and colleagues to facilitate access of IDUs receiving MAT to ART
- 2) HIV medication adherence intervention (Life Steps) developed by Safren and colleagues

Aims of Supplement

- These 2 interventions to be piloted with approximately ten patients in the R21
- Then applied to additional 25 HIV+ IDUs who will be started on MAT as part of supplement.
- Expected that methadone, when used in combination with the intervention developed by Dr. Dvoryak and colleagues will facilitate entry of MAT treated HIV+ IDUs into ART
- Once on ART, Life Steps will be well accepted and associated with meaningful adherence.

Preliminary Results

- Approximately 30 patients started on parent study since 7/08
- Methadone very well-accepted; patients want to continue it
- More HIV+ than HIV- IDUs at Kiev site
- Supplement to begin after training at end of May, 2009

New Studies (hopefully!)

- Naltrexone implant in heroin addicted patients just starting ART in St. Petersburg/Leningrad Region as way to reduce relapse & improve adherence to ART
- Daily Suboxone vs. methadone for reducing HIV risk and injecting use in Subutex injectors in Tbilisi in collaboration with Otiashvili, Piralishvili, and others
- Extended release methylphenidate (Concerta) for reducing HIV sex risk and marijuana abusing adolescents in Porto Alegre