Long Acting Extended Release Naltrexone for Opioid Dependence: Implantable and Injectable

Evgeny Krupitsky

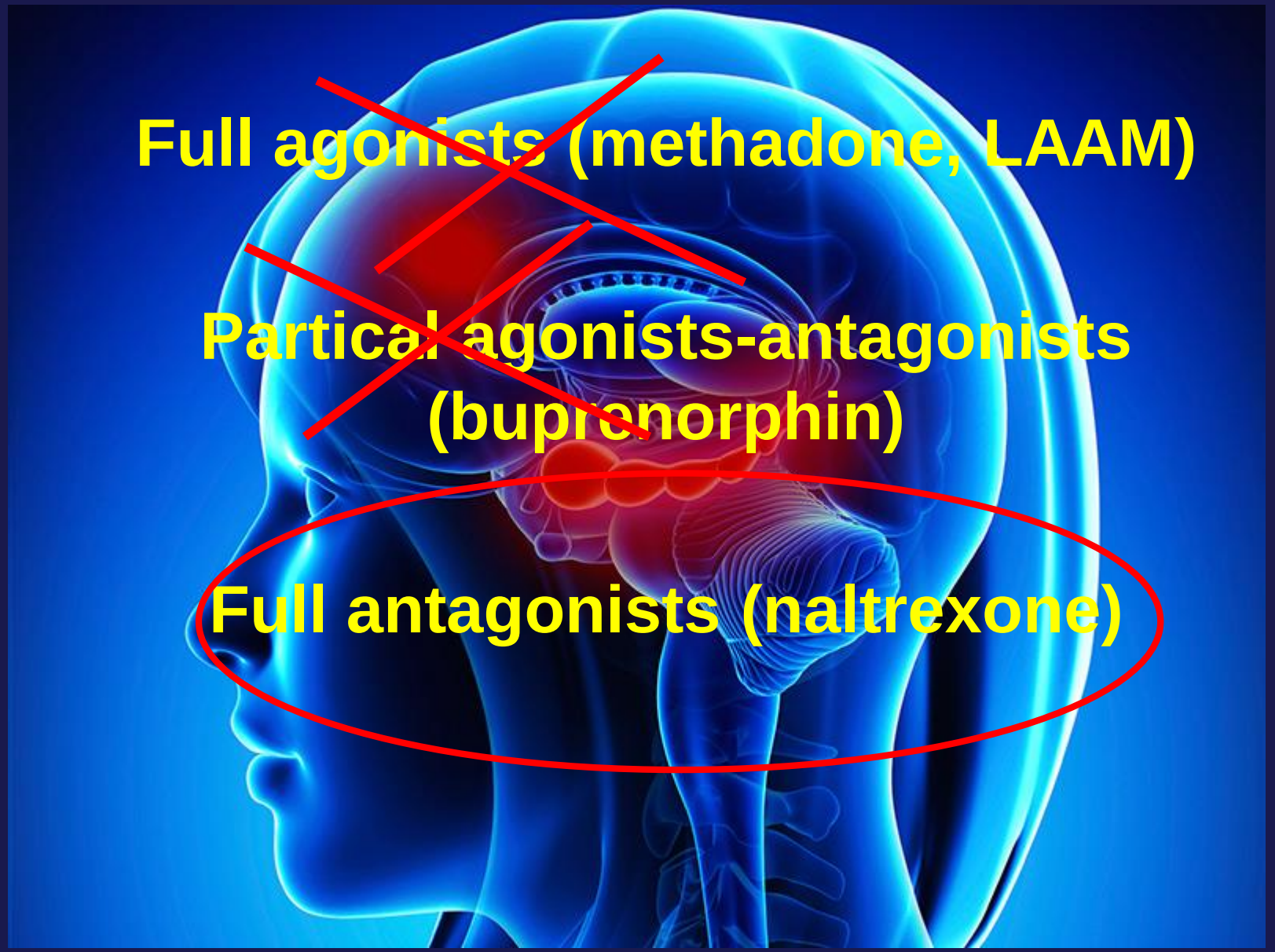
MD, PhD

V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology, St. Petersburg

First Pavlov State Medical University, St. Petersburg

University of Pennsylvania, Philadelphia

PHARMACOTHERAPY OF OUD



NALTREXONE

Different drug formulations:

1. Oral
2. Implantable
3. Injectable

ELSEVIER

Journal of Substance Abuse Treatment 26 (2004) 285–294

Journal of Substance Abuse Treatment

Regular article

Naltrexone for heroin dependence treatment in St. Petersburg, Russia

Evgeny M. Krupitsky, M.D., Ph.D.[a], Edwin E. Zvartau, M.D., Ph.D.[a],
Dimitry V. Masalov, M.D.[a], Marina V. Tsoi, M.D.[a], Andrey M. Burakov, M.D.[a],
Valent
Eva B. Iv

ELSEVIER

Journal of Substance Abuse Treatment xxx (2006) xxx–xxx

Journal of Substance Abuse Treatment

Regular article

Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia

Evgeny M. Krupitsky, (M.D Ph.D.)[a], Edwin E. Zvartau, (M.D., Ph.D.)[a],
Dimitry V. Masalov, (M.D.)[a], Mari
Valentina Y. Egorova, (M.D.)[a], Tatyan
Eva B. Ivanova, (M.D., Ph.D.)[a], Anton Y
Nikolai G. Neznanov, (M.D.,
Charles P. O'Brien, (M.

[a]St. Petersburg Scientific-Research Center of Addictions and Bekhterev Research Ps
[b]Department of Psychiatry and Veterans Aff

Received 1 March 2006; recei

ELSEVIER

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Naltrexone with or without guanfacine for preventing relapse to opiate addiction in St.-Petersburg, Russia

Evgeny Krupitsky[a,b], Edwin Zvartau[a,b], Elena Blokhina[a,b], Elena Verbitskaya[a,b], Marina Tsoy[a,b], Valentina Wahlgren[a,b], Andrey Burakov[a,b], Dimitry Masalov[a,b], Tatyana N. Romanova[a,b], Vladimir Palatkin[a,b], Arina Tyurina[a,b], Tatyana Yaroslavtseva[a,b], Rajita Sinha[c], Thomas R. Kosten[d,*]

[a] St.-Petersburg State Pavlov Medical University, St. Petersburg, Russia
[b] St.-Petersburg Bekhterev Research Psychoneurological Institute, St. Petersburg, Russia
[c] Yale University, Department of Psychiatry, CT, USA
[d] Baylor College of Medicine, TX, USA

Oral Naltrexone Summary

- Effective **if properly supervised**
- With patients with OUD getting older its **efficacy gradually goes down**
- Combination of Naltrexone with antidepressants or guanfacine **did NOT increase efficacy** dramatically

PROBLEM: ADHERENCE

“Drugs don’t work in patients who do not take them”

Everett Koop, MD

How can we improve naltrexone treatment?

National Institute on Drug Abuse

Research

monograph series

Narcotic Antagonists: The Search for Long-Acting Preparations

Editor
Robert Willette, Ph.D.
Division of Research
National Institute on Drug Abuse
January 1976

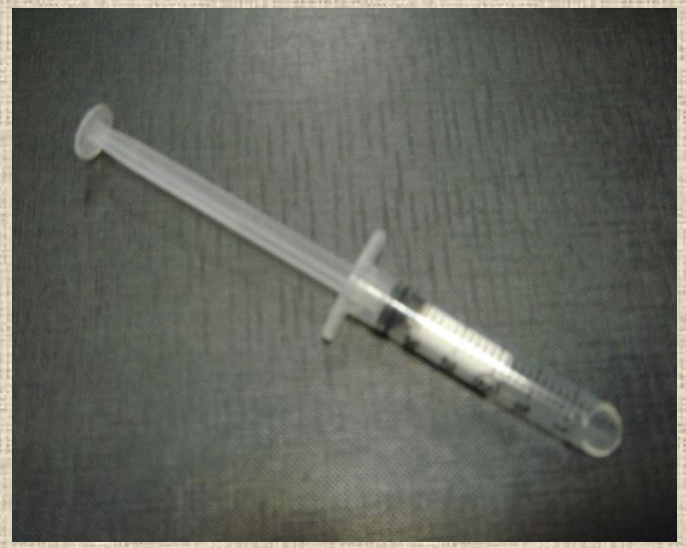
NALTREXONE

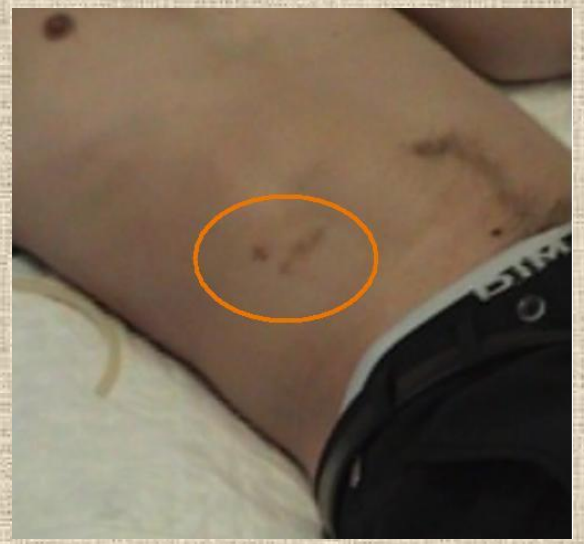
Different drug formulations:

1. Oral
2. Implantable
3. Injectable

Implantable Naltrexone: Route and Dosage

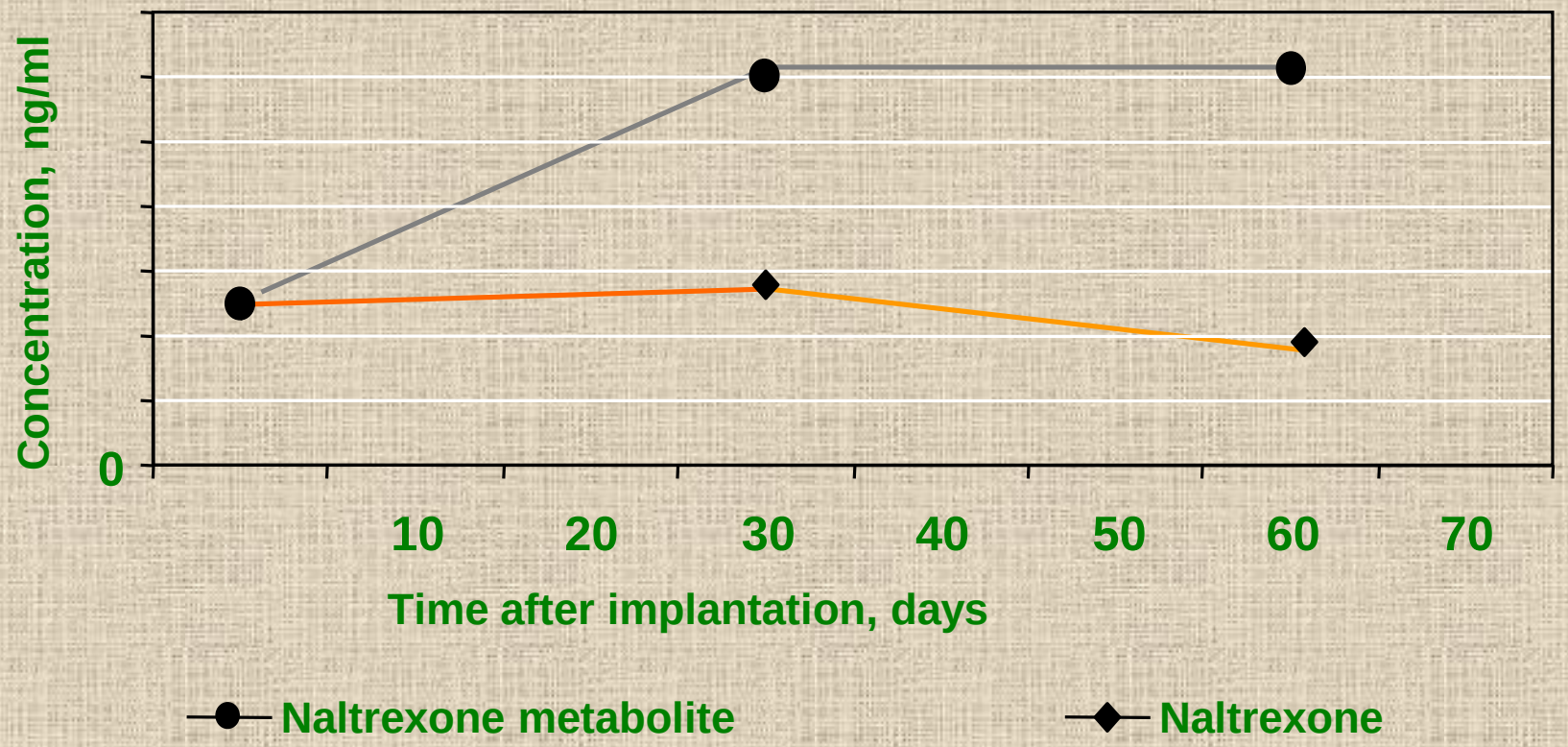
PRODETOXONE, tablets for implantation
1000 mg of naltrexone





Pharmacokinetics of Prodetoxone

(data from the manufacturer)



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

ORIGINAL ARTICLE

Randomized Trial of Long-Acting Sustained-Release Naltrexone Implant vs Oral Naltrexone or Placebo for Preventing Relapse to Opioid Dependence

Evgeny Krupitsky, MD, PhD, DMedSci; Edwin Zvartau, MD, PhD, DMedSci; Elena Blokhina, MD, PhD; Elena Verbitskaya, PhD; Valentina Wahlgren, MD; Marina Tsoy-Podosenin, MD, PhD; Natalia Bushara, MD; Andrey Burakov, MD, PhD; Dmitry Masalov, MD; Tatyana Romanova, PsyD; Arina Tyurina, MD; Vladimir Palatkin, MD; Tatyana Slavina, MD, PhD; Anna Pecoraro, PsyD; George E. Woody, MD

Context: Sustained-release naltrexone implants may improve outcomes of nonagonist treatment of opioid addiction.

Objective: To compare outcomes of naltrexone implants, oral naltrexone hydrochloride, and nonmedication treatment.

Design: Six-month double-blind, double-dummy, randomized trial.

Setting: Addiction treatment programs in St Petersburg, Russia.

Participants: Three hundred six opioid-addicted patients recently undergoing detoxification.

Interventions: Biweekly counseling and 1 of the following 3 treatments for 24 weeks: (1) 1000-mg naltrexone implant and oral placebo (NI+OP group; 102 patients); (2) placebo implant and 50-mg oral naltrexone hydrochloride (PI+ON group; 102 patients); or (3) placebo implant and oral placebo (PI+OP group; 102 patients).

Main Outcome Measure: Percentage of patients retained in treatment without relapse.

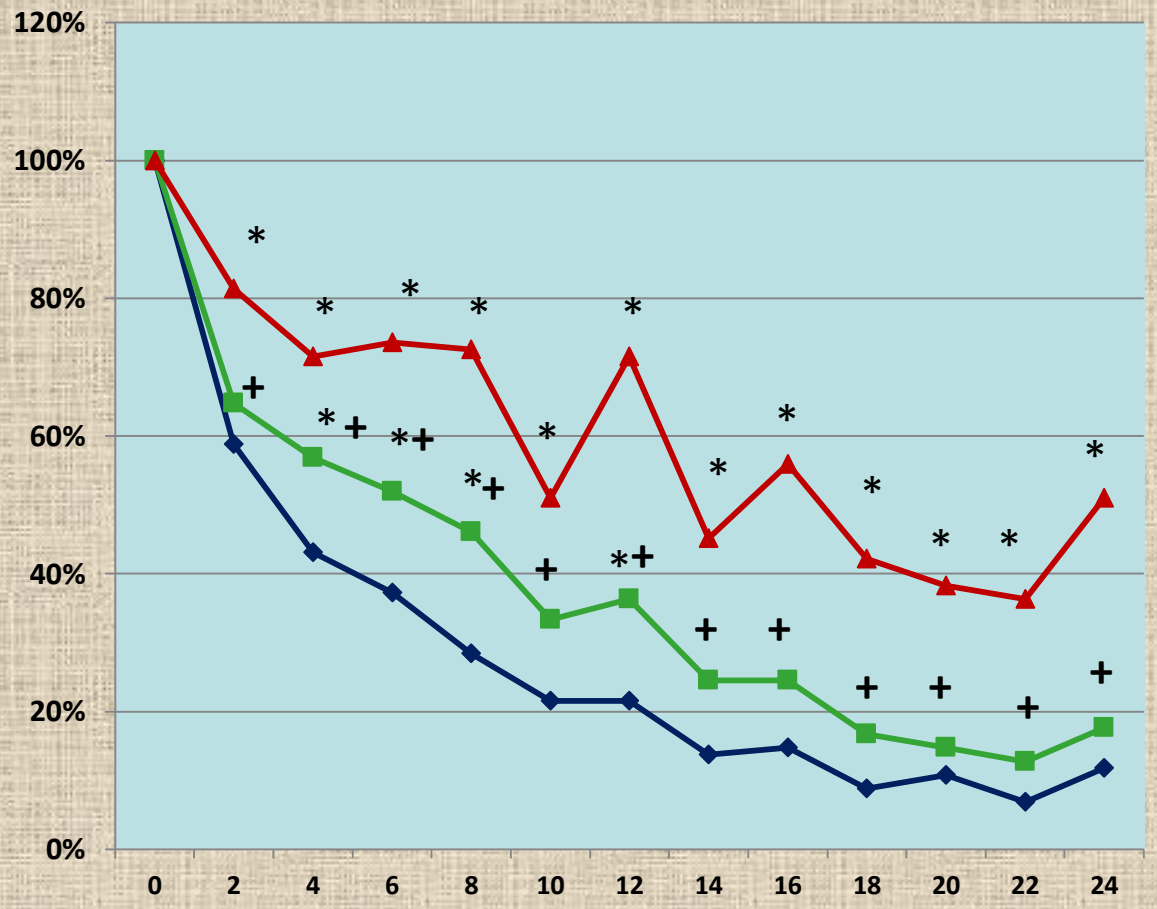
Results: By month 6, 54 of 102 patients in the NI+OP group (52.9%) remained in treatment without relapse compared with 16 of 102 patients in the PI+ON group (15.7%) (survival analysis, log-rank test, $P<.001$) and 11 of 102 patients in the PI+OP group (10.8%) ($P<.001$). The PI+ON vs PI+OP comparison showed a nonsignificant trend favoring the PI+ON group ($P=.07$). Counting missing test results as positive, the proportion of urine screening tests yielding negative results for opiates was 63.6% (95% CI, 60%-66%) for the NI+OP group; 42.7% (40%-45%) for the PI+ON group; and 34.1% (32%-37%) for the PI+OP group ($P<.001$, Fisher exact test, compared with the NI+OP group). Twelve wound infections occurred among 244 implantations (4.9%) in the NI+OP group, 2 among 181 (1.1%) in the PI+ON group, and 1 among 148 (0.7%) in the PI+OP group ($P=.02$). All events were in the first 2 weeks after implantation and resolved with antibiotic therapy. Four local-site reactions (redness and swelling) occurred in the second month after implantation in the NI+OP group ($P=.12$), and all resolved with antiallergy medication treatment. Other nonlocal-site adverse effects were reported in 8 of 886 visits (0.9%) in the NI+OP group, 4 of 522 visits (0.8%) in the PI+ON group, and 3 of 394 visits (0.8%) in the PI+ON group; all resolved and none were serious. No evidence of increased deaths from overdose after naltrexone treatment ended was found.

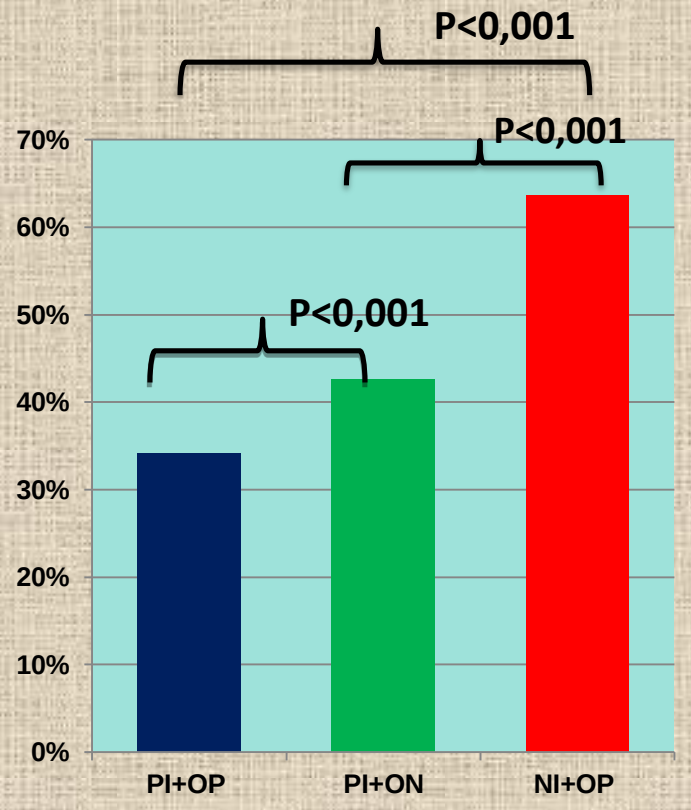
Conclusions: The implant is more effective than oral naltrexone or placebo. More patients in the NI+OP than in the other groups develop wound infections or local irritation, but none are serious and all resolve with treatment.

Trial Registration: clinicaltrials.gov Identifier: NCT00678418

Arch Gen Psychiatry. 2012;69(9):973-981

Opiate negative visits

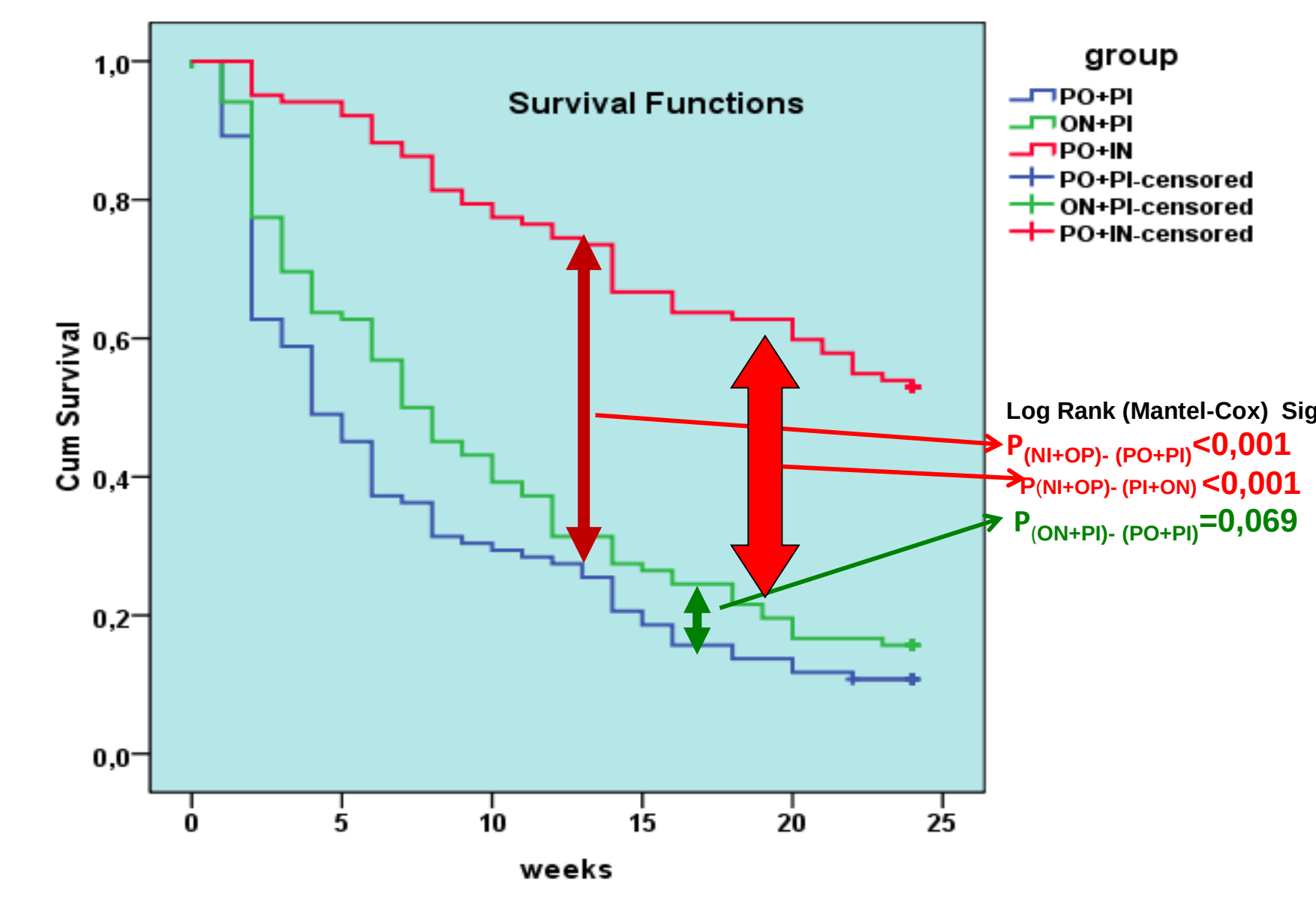




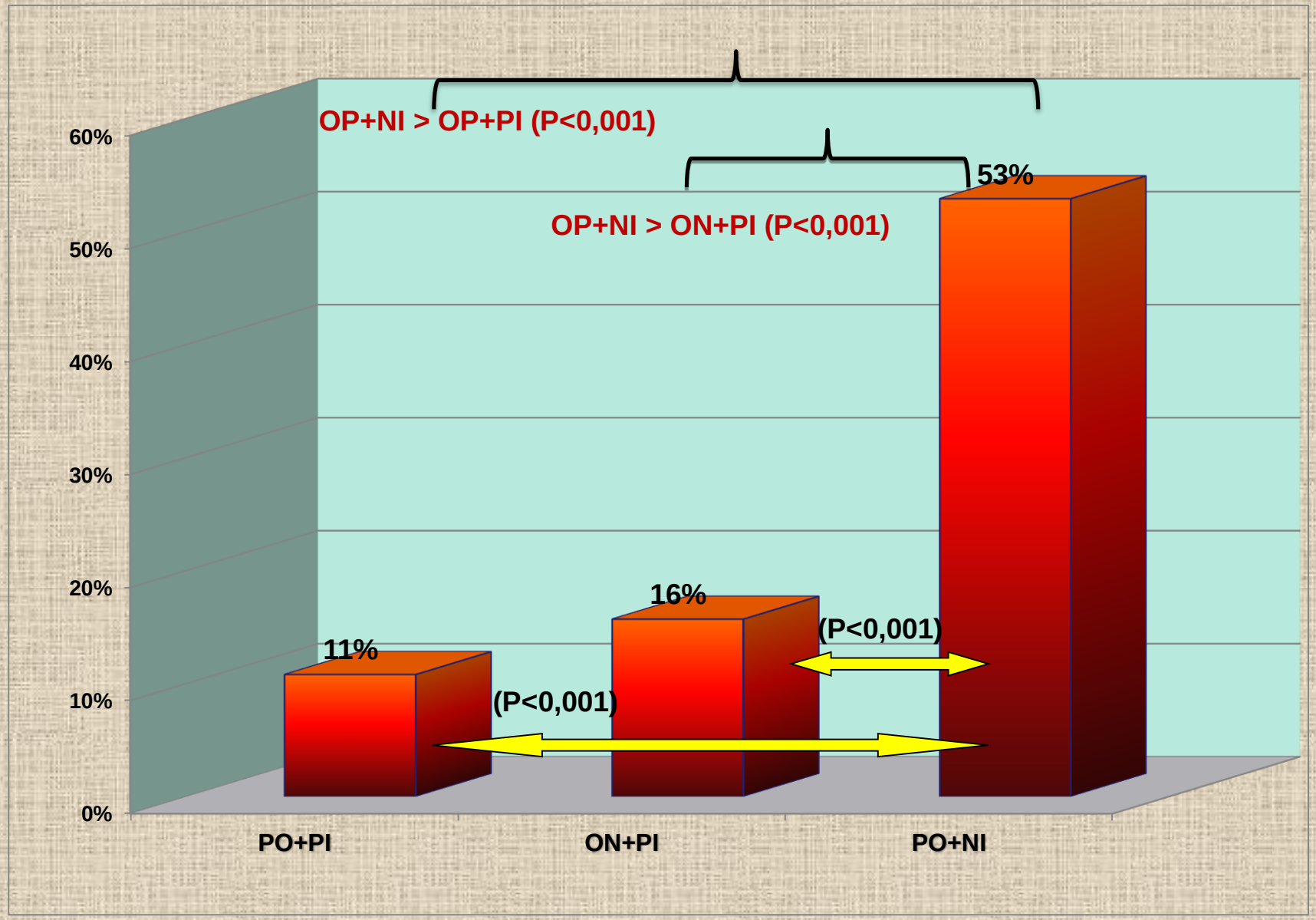
*- P<0,01 Fisher's Exact Test to placebo

+ - P<0,01 Fisher's Exact Test to Ntxn implant group

Kaplan-Meier Survival Functions: Drop out

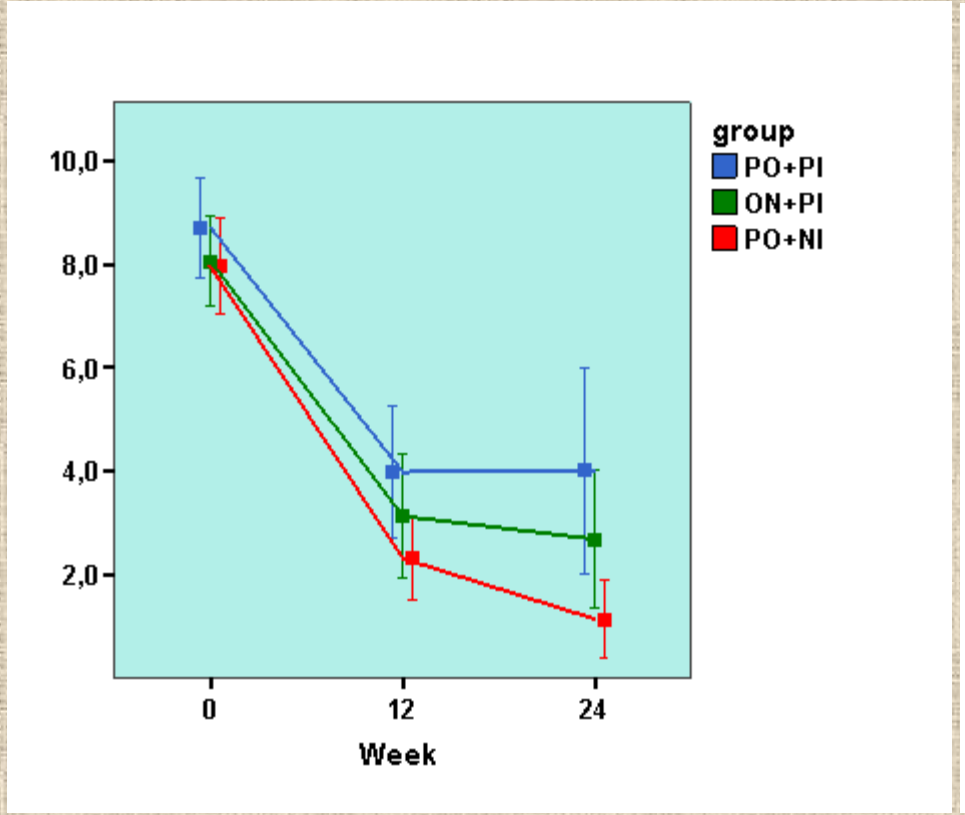


Retention: End of treatmernt (6 months)

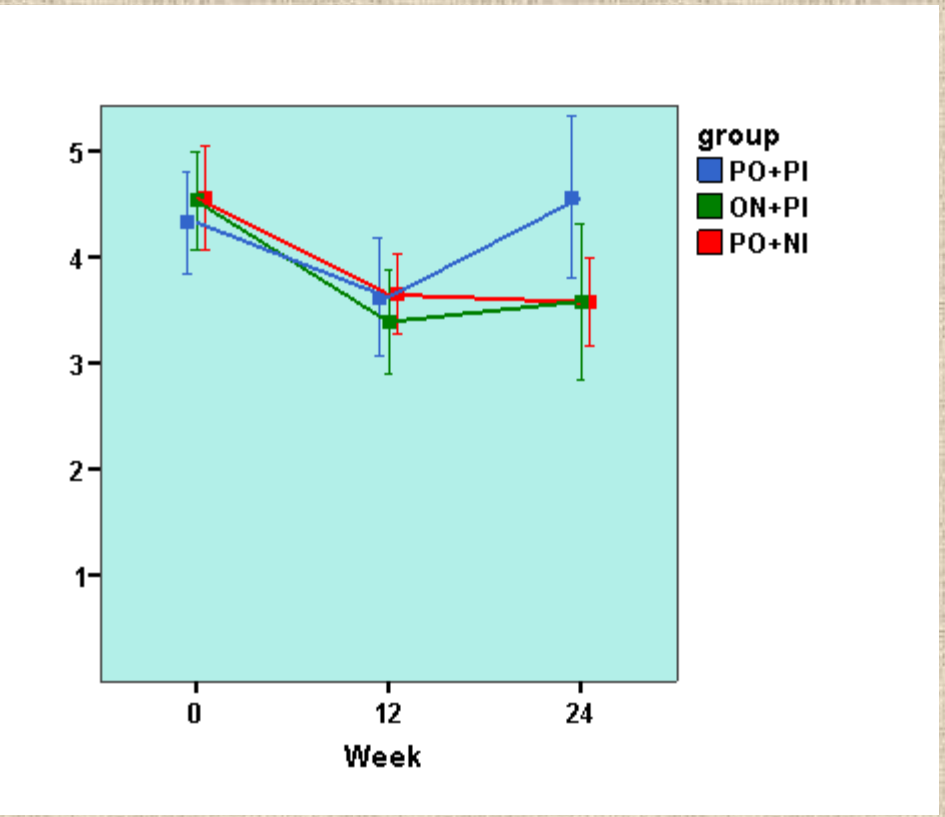


Naltrexone implant
HIV Risk Assessment Battery

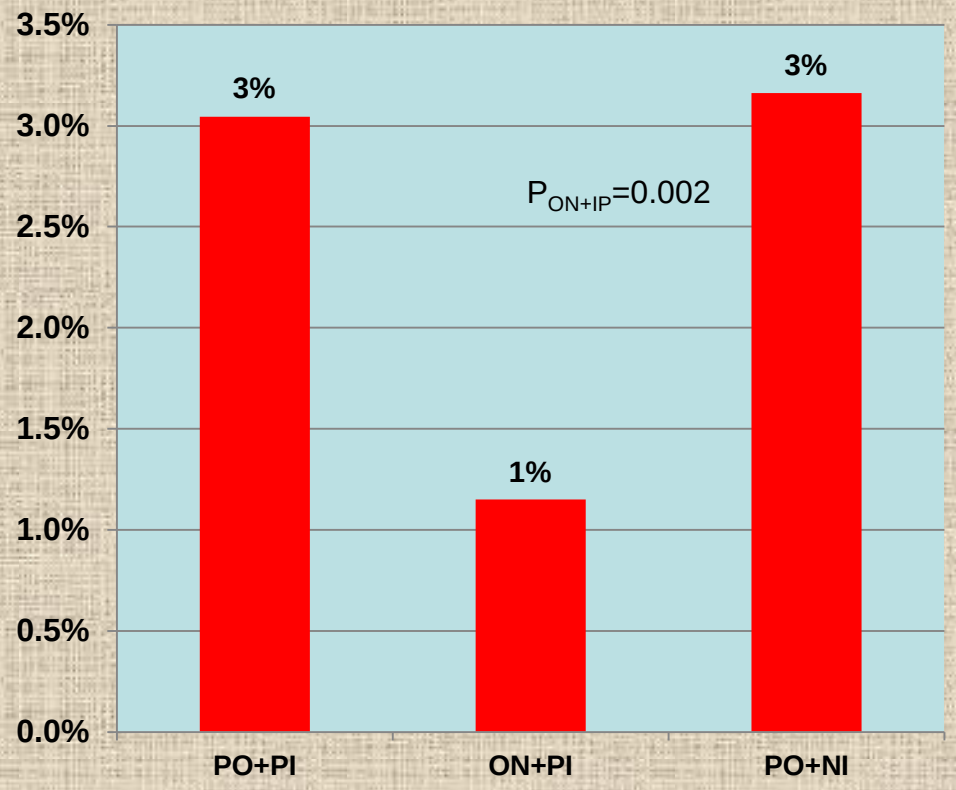
RAB drug risk



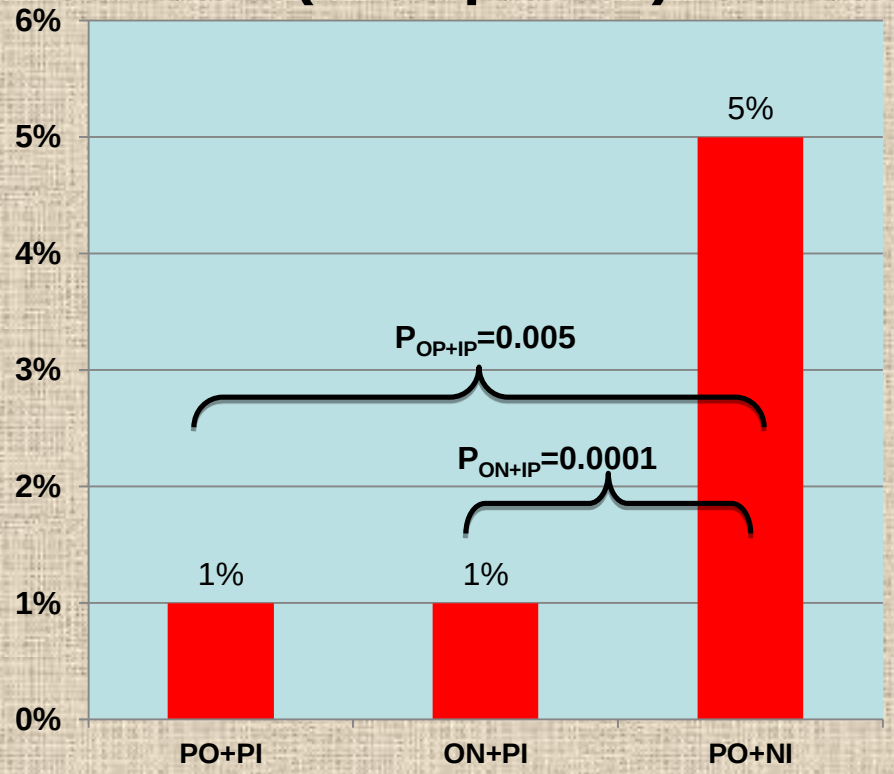
RAB sex risk



AE (non-surgical) (% visits)



AE (surgical – wound infection) (% implants)



Only one SAE in PI+OP group: the holecystectomia due to the stones in gallbladder .

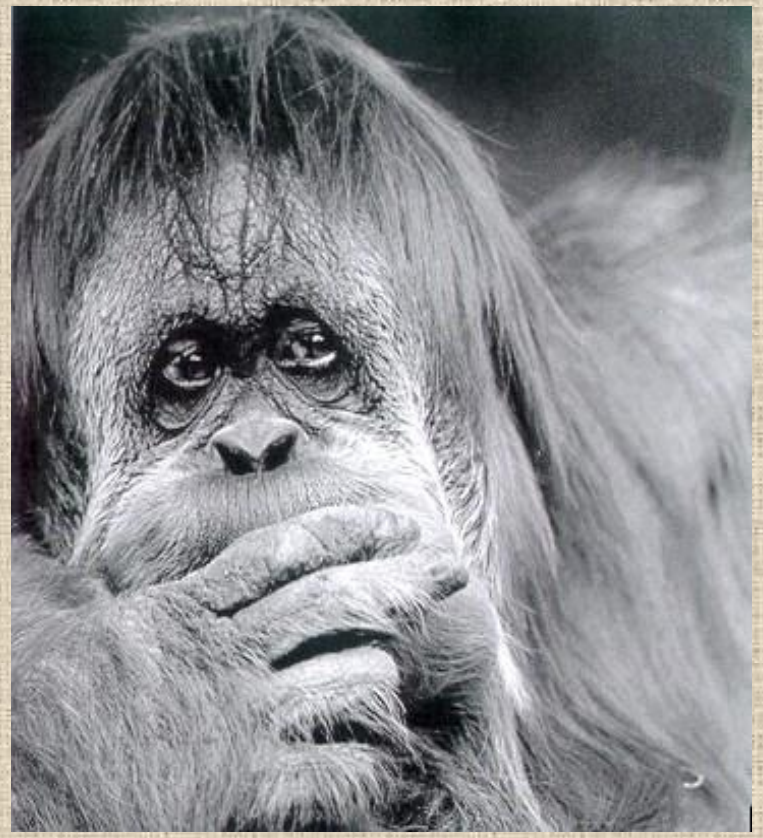
Naltrexone Implant Summary

- Implantable naltrexone demonstrated greater effectiveness in the treatment of opioid dependence in comparison to oral naltrexone and placebo.
- Implantable naltrexone is basically comparable to oral naltrexone and placebo in terms of safety and tolerability except surgical adverse events (wound infection at the implantation site).

LIMITATIONS for PRODETOXONE

1. Surgical procedure
2. Wound infections (particularly in HIV+ individuals)
3. Cosmetic defects
4. Relatively easy to take out within the first few weeks after implantation
5. Dos not provide 2 months long blockade in some patients (small proportion)

Is there another way to improve naltrexone therapy ?

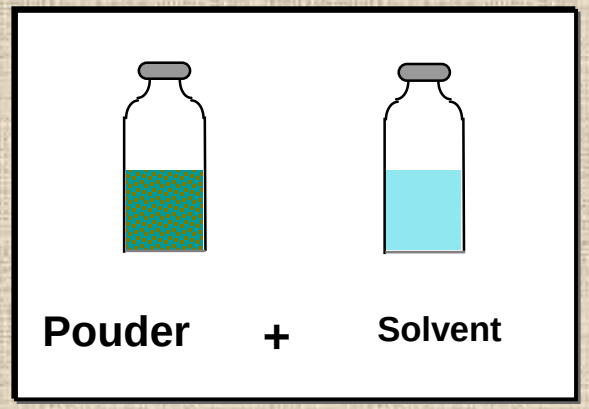


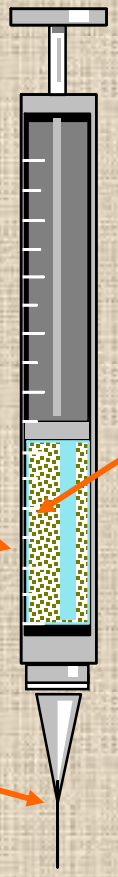
NALTREXONE

Different drug formulations:

1. Oral
2. Implantable
3. Injectable

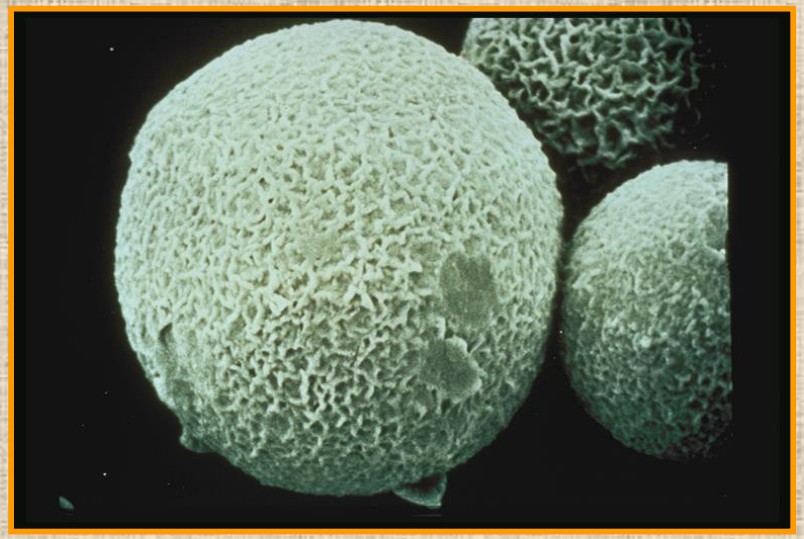
Extended Release Injectable Naltrexone





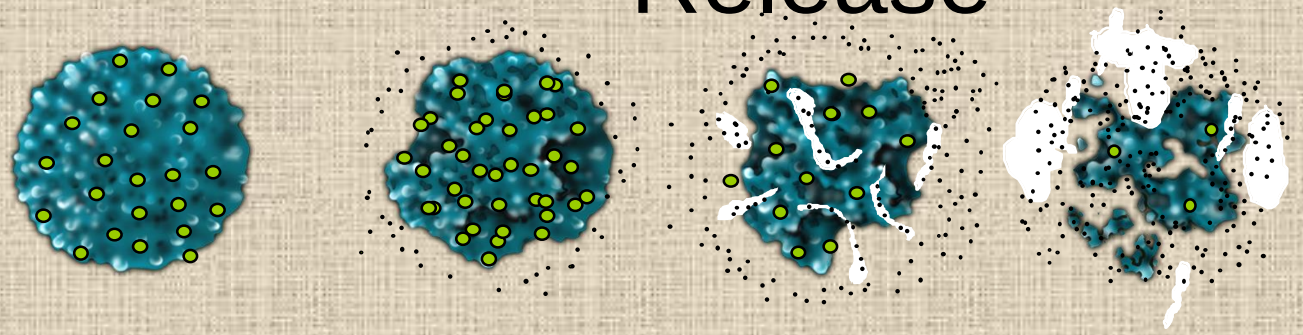
Microspheres (Suspension)

Needle



- **Monthly injection**

Medisorb®: Mechanism of Drug Release

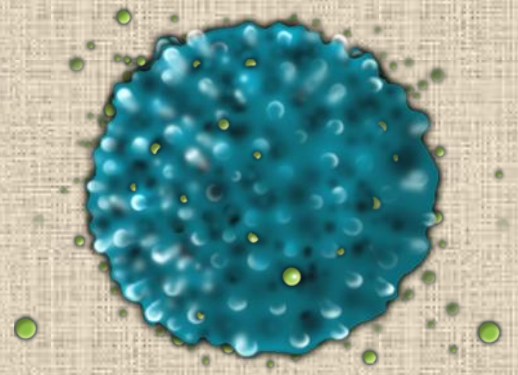


Initial Release:

Drug at or near the surface dissolves and diffuses away

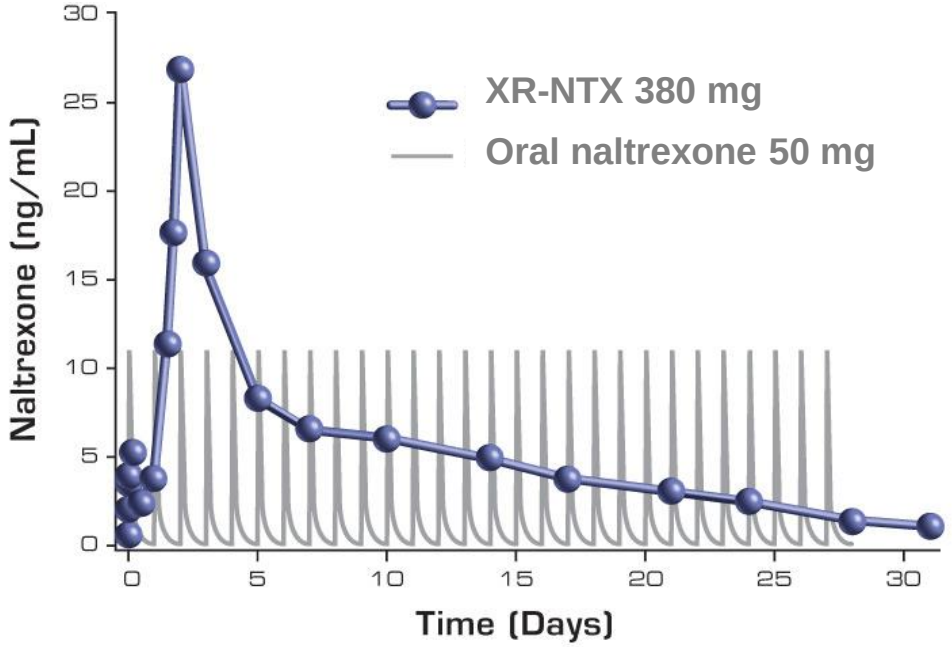
Sustained Release:

PLGA degrades, creating pores for drug diffusion and release from microspheres



Pharmacokinetics

Mean steady-state naltrexone concentration following monthly XR-NTX 380 mg compared to daily oral dosing



- **Steady state by 2nd dose**
- **Minimal accumulation 6β-naltrexol**
- **Limited 1st pass metabolism by liver**
- **Monthly naltrexone (380 mg vs 1,500 mg)**

Dean RL. *Front Biosci*. 2005 Jan 1;10:643-655.
Dunbar JL, et al. *Alc Clin Exp Res.* 2006;30:480-490.
Data on File, Alkermes, Inc.

THE LANCET

Volume 377 · Number 9776 · Pages 1465–1542 · April 30–May 6, 2011 www.thelancet.com

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

Evgeny Krupitsky, Edward V Nunes, Walter Ling, Ari Illeperuma, David R Gastfriend, Bernard L Silverman

Lancet 2011; 377: 1506–13

Published Online
April 28, 2011
DOI:10.1016/S0140-6736(11)60358-9

See Comment page 1468

Bekhterev Research Psychoneurological Institute, St Petersburg State Pavlov Medical University, St Petersburg, Russia (Prof E Krupitsky MD); **New York State Psychiatric Institute and Department of Psychiatry, Columbia University, New York, NY, USA** (Prof E V Nunes MD); **Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA, USA** (Prof W Ling MD); **and Alkermes, Waltham, MA, USA** (A Illeperuma MA, D R Gastfriend MD, B L Silverman MD)

Correspondence to:
Prof Evgeny Krupitsky, Department of Addictions, St Petersburg Bekhterev Psychoneurological Research Institute, Bekhtereva Street 3, St Petersburg 192019, Russia
kruenator@gmail.com

Summary

Background Opioid dependence is associated with low rates of treatment-seeking, poor adherence to treatment, frequent relapse, and major societal consequences. We aimed to assess the efficacy, safety, and patient-reported outcomes of an injectable, once monthly extended-release formulation of the opioid antagonist naltrexone (XR-NTX) for treatment of patients with opioid dependence after detoxification.

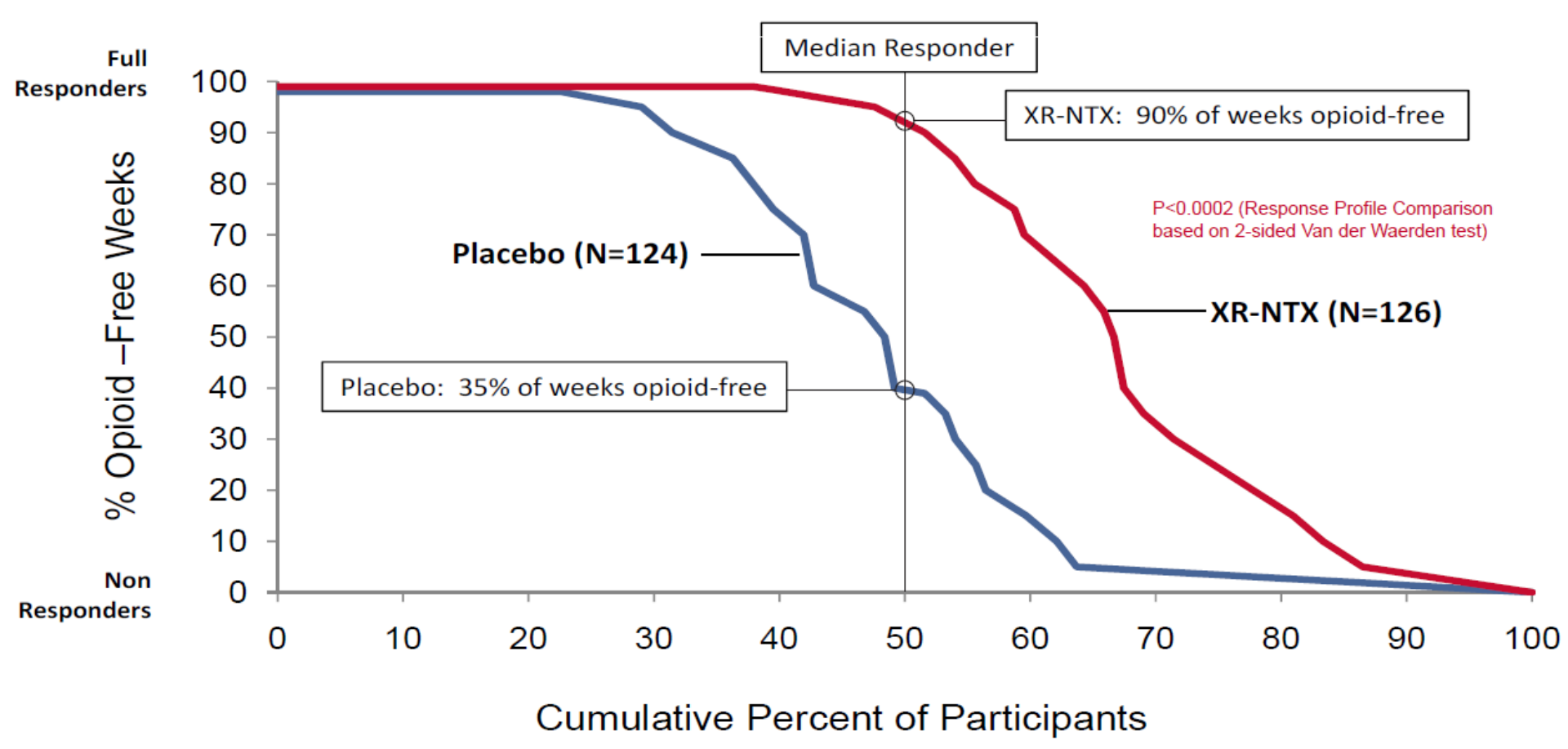
Methods We did a double-blind, placebo-controlled, randomised, 24-week trial of patients with opioid dependence disorder. Patients aged 18 years or over who had 30 days or less of inpatient detoxification and 7 days or more off all opioids were enrolled at 13 clinical sites in Russia. We randomly assigned patients (1:1) to either 380 mg XR-NTX or placebo by an interactive voice response system, stratified by site and gender in a centralised, permuted-block method. Participants also received 12 biweekly counselling sessions. Participants, investigators, staff, and the sponsor were masked to treatment allocation. The primary endpoint was the response profile for confirmed abstinence during weeks 5–24, assessed by urine drug tests and self report of non-use. Secondary endpoints were self-reported opioid-free days, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence. Analyses were by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00678418.

Findings Between July 3, 2008, and Oct 5, 2009, 250 patients were randomly assigned to XR-NTX (n=126) or placebo (n=124). The median proportion of weeks of confirmed abstinence was 90·0% (95% CI 69·9–92·4) in the XR-NTX group compared with 35·0% (11·4–63·8) in the placebo group (p=0·0002). Patients in the XR-NTX group self-reported a median of 99·2% (range 89·1–99·4) opioid-free days compared with 60·4% (46·2–94·0) for the placebo group (p=0·0004). The mean change in craving was –10·1 (95% CI –12·3 to –7·8) in the XR-NTX group compared with 0·7 (–3·1 to 4·4) in the placebo group (p<0·0001). Median retention was over 168 days in the XR-NTX group compared with 96 days (95% CI 63–165) in the placebo group (p=0·0042). Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the XR-NTX group (p<0·0001). XR-NTX was well tolerated. Two patients in each group discontinued owing to adverse events. No XR-NTX-treated patients died, overdosed, or discontinued owing to severe adverse events.

Interpretation XR-NTX represents a new treatment option that is distinct from opioid agonist maintenance treatment. XR-NTX in conjunction with psychosocial treatment might improve acceptance of opioid dependence pharmacotherapy and provide a useful treatment option for many patients.

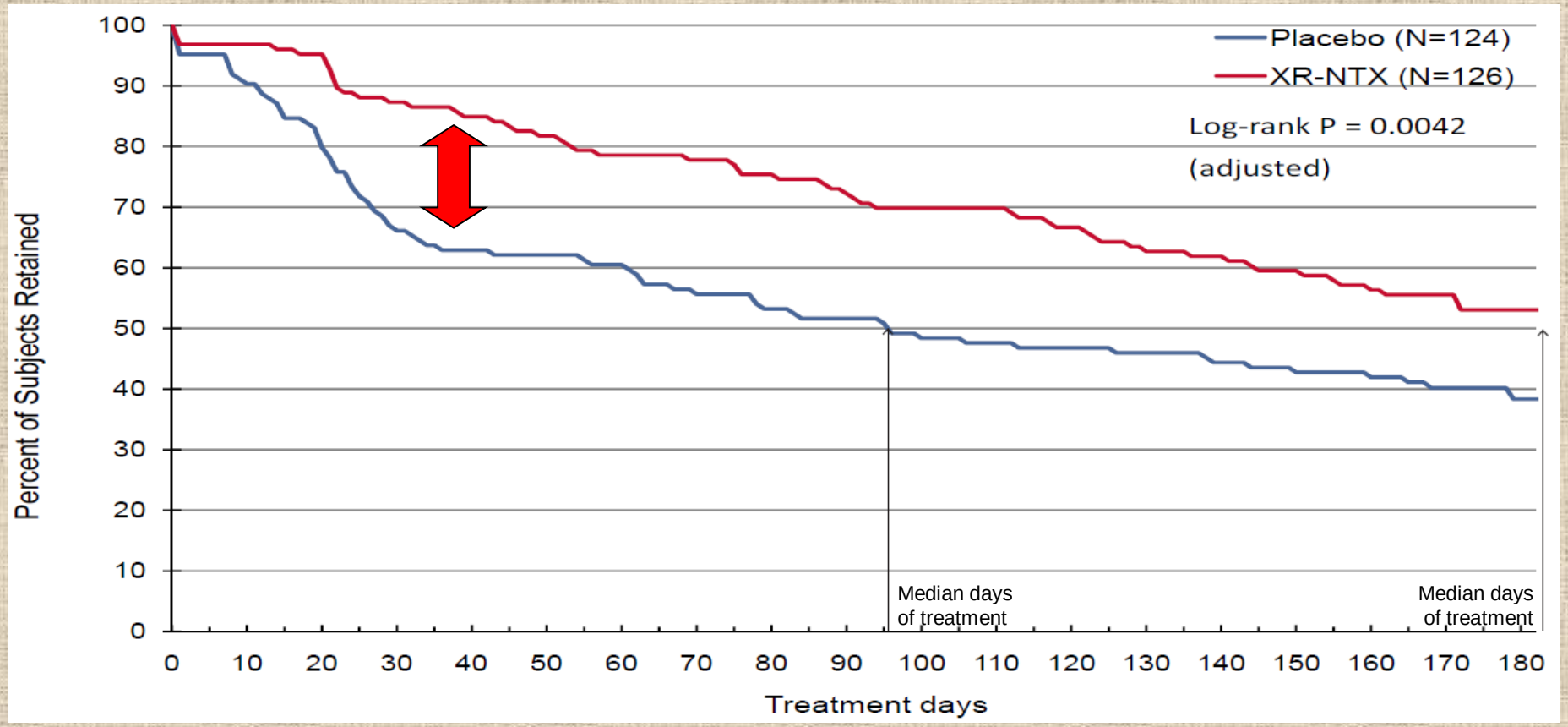
Response Profile

Cumulative % of Participants at Each Rate of Weekly Confirmed Abstinence: XR-NTX 380 mg *vs.* Placebo



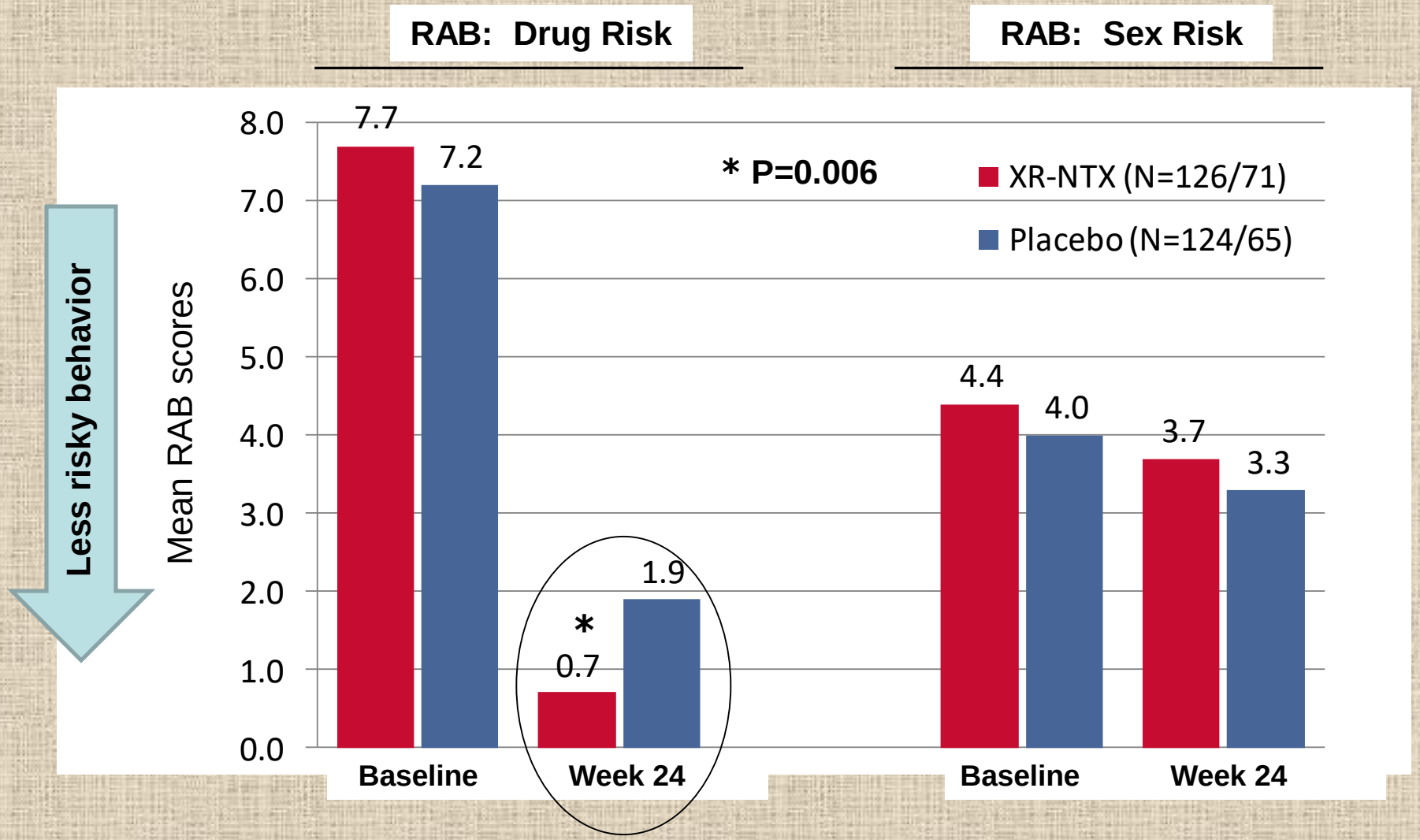
- Total abstinence (100% opioid-free weeks) during Weeks 5-24 was reported in 45 (35.7%) of subjects in the XR-NTX group versus 28 (22.6%) subjects in placebo group (P=0.0224).

Retention: Kaplan-Meier Analysis of Time-to-Discontinuation



- Median days on treatment was significantly longer for patients in the XR-NTX *vs.* placebo group: >168 days *vs.* 96 days in the placebo group (P=0.0042, log-rank test, adjusted for multiplicity)

Risk Assessment Battery (RAB): Baseline and LOCF-endpoint Scores



P-value based on Van der Waerden test for XR-NTX vs. Placebo

Treatment-emergent Adverse Events: Clinical Events With Incidence ≥5%; and Incidence of Severe and Serious Events

Adverse Event, N (%)	XR-NTX 380 mg N=126	Placebo N=124
Nasopharyngitis	9 (7.1)	3 (2.4)
Insomnia	8 (6.3)	1 (0.8)
Injection site pain	6 (4.8)	1 (0.8)
≥ 1 adverse event	63 (50.0)	40 (32.3)
≥ 1 **severe** adverse event	0 (0)	0 (0)
≥ 1 **serious** adverse event *	3 (2.4)	4 (3.2)
Discontinued due to **serious** adverse event	0 (0)	2 (1.6)
Liver function tests, mean change at endpoint		
ALT, IU/L	+6.9	+5.6
AST, IU/L	+3.8	+6.7

- In the XR-NTX group, 3 patients reported 4 SAEs consisting of infectious processes, e.g., AIDS/HIV or other infection.
- In the Placebo group, 4 patients reported 5 SAEs: 2 infectious, 1 drug dependence, 1 psychotic disorder and 1 peptic ulcer.

FDA NEWS RELEASE

For Immediate Release: Oct. 12, 2010
Media Inquiries: Shelly Burgess, 301-796-4651 , shelly.burgess@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves injectable drug to treat opioid-dependent patients

The U.S. Food and Drug Administration today approved Vivitrol to treat and prevent relapse after patients with opioid dependence have undergone detoxification treatment.

Vivitrol is an extended-release formulation of naltrexone administered by intramuscular injection once a month. Naltrexone works to block opioid receptors in the brain. It blocks the effects of drugs like morphine, heroin, and other opioids. It was approved to treat alcohol dependence in 2006.

"Addiction is a serious problem in this country, and can have devastating effects on individuals who are drug-dependent, and on their family members and society," said Janet Woodcock, M.D., director of FDA's Center for Drug Evaluation and Research. "This drug approval represents a significant advancement in addiction treatment."

The safety and efficacy of Vivitrol were studied for six months, comparing Vivitrol treatment to placebo treatment in patients who had completed detoxification and who were no longer physically dependent on opioids. Patients treated with Vivitrol were more likely to stay in treatment and to refrain from using illicit drugs. Thirty-six percent of the Vivitrol-treated patients were able to stay in treatment for the full six months without using drugs, compared with 23 percent in the placebo group.

Patients must not have any opioids in their system when they start taking Vivitrol; otherwise, they may experience withdrawal symptoms from the opioids. Also, patients may be more sensitive to opioids while taking Vivitrol at the time their next scheduled dose is due. If they miss a dose or after treatment with Vivitrol has ended, patients can accidentally overdose if they restart opioid use.

Side effects experienced by those using Vivitrol included nausea, tiredness, headache, dizziness, vomiting, decreased appetite, painful joints, and muscle cramps. Other serious side effects included reactions at the site of the injection, which can be severe and may require surgical intervention, liver damage, allergic reactions such as hives, rashes, swelling of the face, pneumonia, depressed mood, suicide, suicidal thoughts, and suicidal behavior.

Vivitrol should be administered only by a health care provider as an intramuscular injection, using special administration needles that are provided with the product. Vivitrol should not be injected using any other needle. The recommended dosing regimen is once a month.

Consumers and health care professionals are encouraged to report adverse events to the FDA's MedWatch program at 800-FDA-1088 or online at www.fda.gov/medwatch/how.htm.

Vivitrol is manufactured by Alkermes, Inc.

For more information:

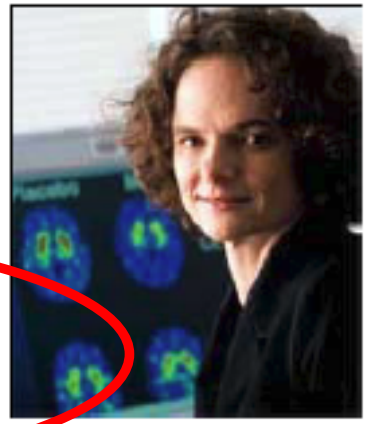
- Drugs@FDA

#

Message from the Director on Important Treatment Advances for Addiction to Heroin and other Opiates

Heroin addiction afflicts an estimated 810,000 people in this country, the great majority of who do not either seek or receive treatment. Further, in 2008 1.85 million people in the U.S. met the diagnostic criteria for abuse or dependence on opioid pain relievers, such as Oxycontin and Vicodin (NSDUH, 2009). In fact, opioid abuse (including heroin) is a worldwide problem, with between 12.8 and 21.9 million people abusing opiates in the past year (UNODC, 2010). Two recent developments in the treatment of opioid addiction herald important advances for addressing this worldwide epidemic.

First, the U.S. Food and Drug Administration (FDA) today announced its approval of Vivitrol®



Nora D. Volkow, M.D., Director, NIDA

(http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229109.htm) for the treatment of opioid addiction. Vivitrol is an extended release formulation of naltrexone, an opioid receptor antagonist. Double-blind, placebo controlled clinical trials have shown Vivitrol to be effective in preventing not only relapse to drug use

How to Order Free Publications

- NIDA DrugPubs - Online Ordering

Additional Resources:

- NIDA Addiction Science and Clinical Practice - a peer-reviewed journal
- NIDA Notes

UNODC
United Nations Office on Drugs and Crime

World Health Organization

INTERNATIONAL STANDARDS FOR THE TREATMENT OF DRUG USE DISORDERS

DRAFT FOR FIELD TESTING
March 2016

Acknowledgements

The United Nations Office on Drugs and Crime (UNODC) would like to acknowledge the following for their invaluable contribution to the process of publication of these standards:

The group of international experts for providing the relevant scientific evidence, technical advice and developing the main draft of the standards, including (in alphabetical order):

Dr. David Basangwa, Uganda; Dr. Adam Bisaga, United States; Dr. Willem Van Den Brink, Netherlands; Dr. Sandra Brown, United States; Mr. Thom Browne, United States; Dr. Kathleen Carroll, United States; Mr. Humberto Carvalho, United States; Dr. Michael Clark, United States; Dr. Steve Gust, United States; Dr. Loretta Finnegan, United States; Dr. Gabriele Fischer, Austria; Dr. Hendree Jones, United States; Dr. Martien Kooyman, Netherlands; Dr. Evgeny Krupitsky, Russia; Dr. Otto Lesch, Austria; Dr. Icro Maremanni, Italy; Dr. Douglas Marlowe, United States; Dr. Andrew Thomas McLellan, United States; Dr. Edward Nunes, United States; Dr. Isidore Obot, Nigeria; Dr. John Strang, United Kingdom; Dr. Emilis Subata, Lithuania; Dr. Marta Torrens, Spain; Dr. Roberto Tykanori Kinoshita, Brazil; Dr. Riza Sarasvita, Indonesia; Dr. Lucas George Wiessing, Netherlands.

Overall conclusion

(15-year studies of 1132 patients with OUD treated with different formulations of naltrexone)

Oral naltrexone:

- Effective **if supervised**
- With patients with OUD getting older its **efficacy gradually goes down**
- Combination of Naltrexone with antidepressants or guanfacine **does NOT increase efficacy** dramatically

Long acting sustained-release Naltrexone:

Naltrexone **implant** (Prodetoxone):

- More effective than oral Naltrexone
- Long working (2-3 months)
- Minor surgery => Risk of surgical AEs

Injectable naltrexone (Vivitrol):

- Easier to use
- Good tolerability
- Works shorter (1 month) than implant

Naltrexone treatment reduces HIV drug risk behavor and thus prevents HIV spread

HYPOTESIS TO BE TESTED

CAN EXTENDED RELEASE NALTREXONE IMPROVE ADHRENCE TO ANTIRETROVIRAL THERAPY IN PATIENTS WITH OUD - AND ART's EFFICACY

THE LANCET
HIV

Slow-release naltrexone implant versus oral naltrexone for improving treatment outcomes in people with HIV who are addicted to opioids: a double-blind, placebo-controlled, randomised trial

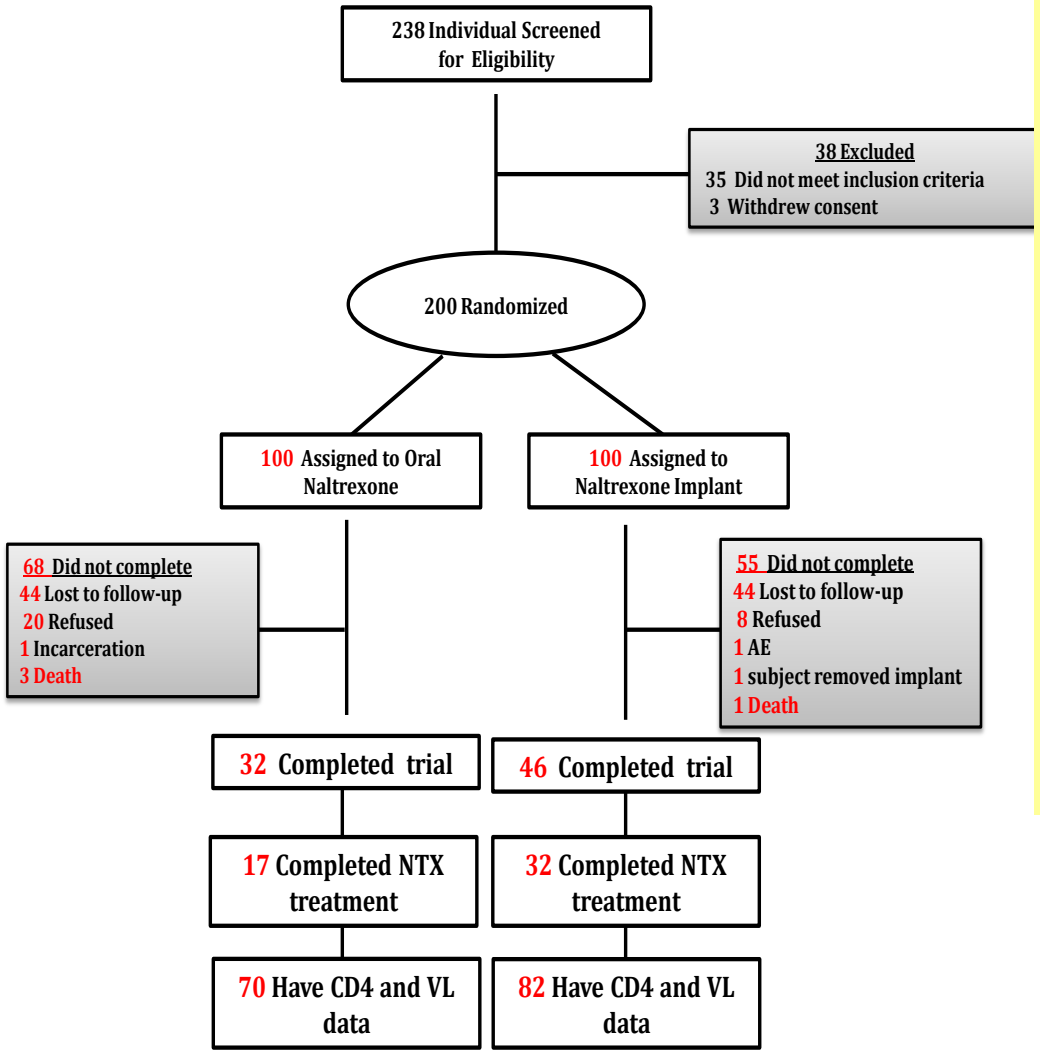
Evgeny Krupitsky, Elena Blokhina, Edwin Zvartau, Elena Verbitskaya, Dmitri Lioznov, Tatiana Yaroslavtseva, Vladimir Palatkin, Marina Vetrova, Natalia Bushara, Andrei Burakov, Dmitri Masalov, Olga Mamontova, Daniel Langleben, Sabrina Poole, Robert Gross, George Woody

Lancet HIV 2019

Published Online
March 14, 2019
http://dx.doi.org/10.1016/S2352-3018(18)30362-X

STUDY FLOW CHART

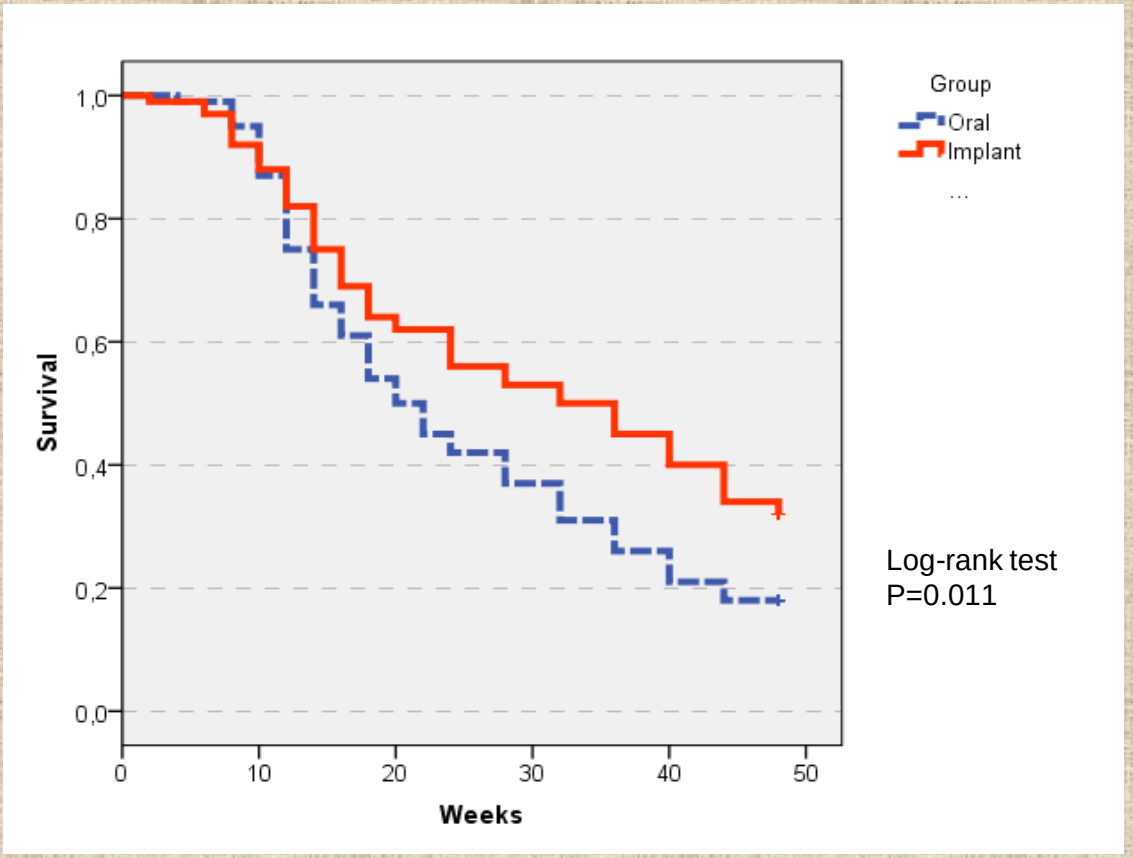
Figure 1. Study Flow Diagram



Methods:

- 200 recently detoxified HIV+ ART naïve opioid addicted patients
- Randomized 1:1 to 12 months of NI+ON placebo and ART, or ON+NI placebo and ART
- All were offered every other week drug and adherence counseling

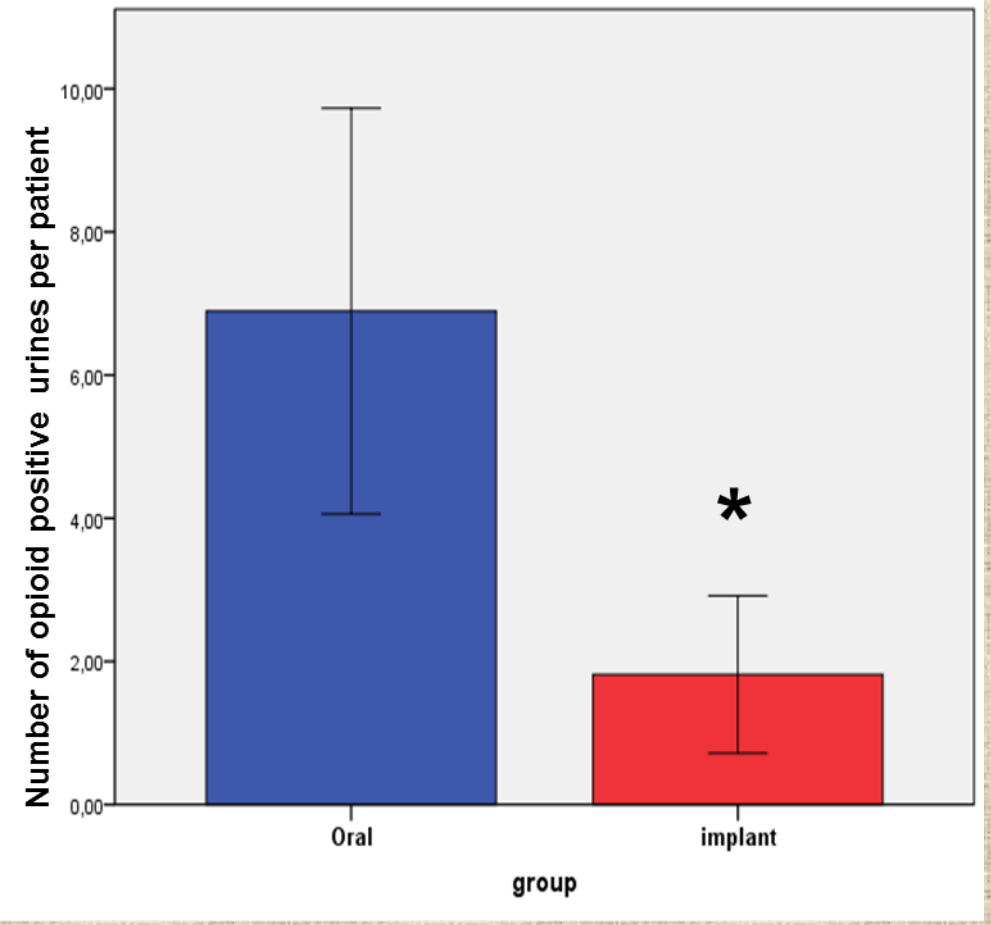
Retention in addiction treatment
Kaplan Meier Survival Functions



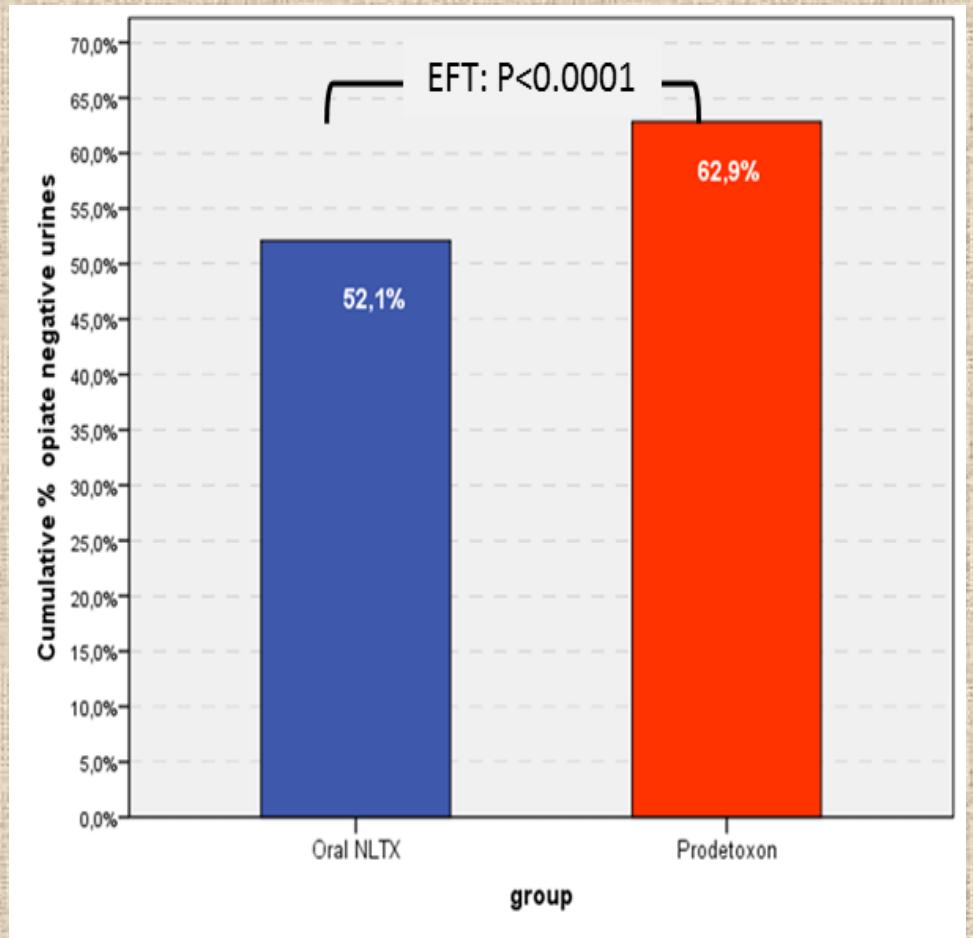
Secondary Outcomes:

Addiction treatment more often completed in NI than in ON group (32% vs 17%, p<0.05)

Mean number of opioid positive visits per patient

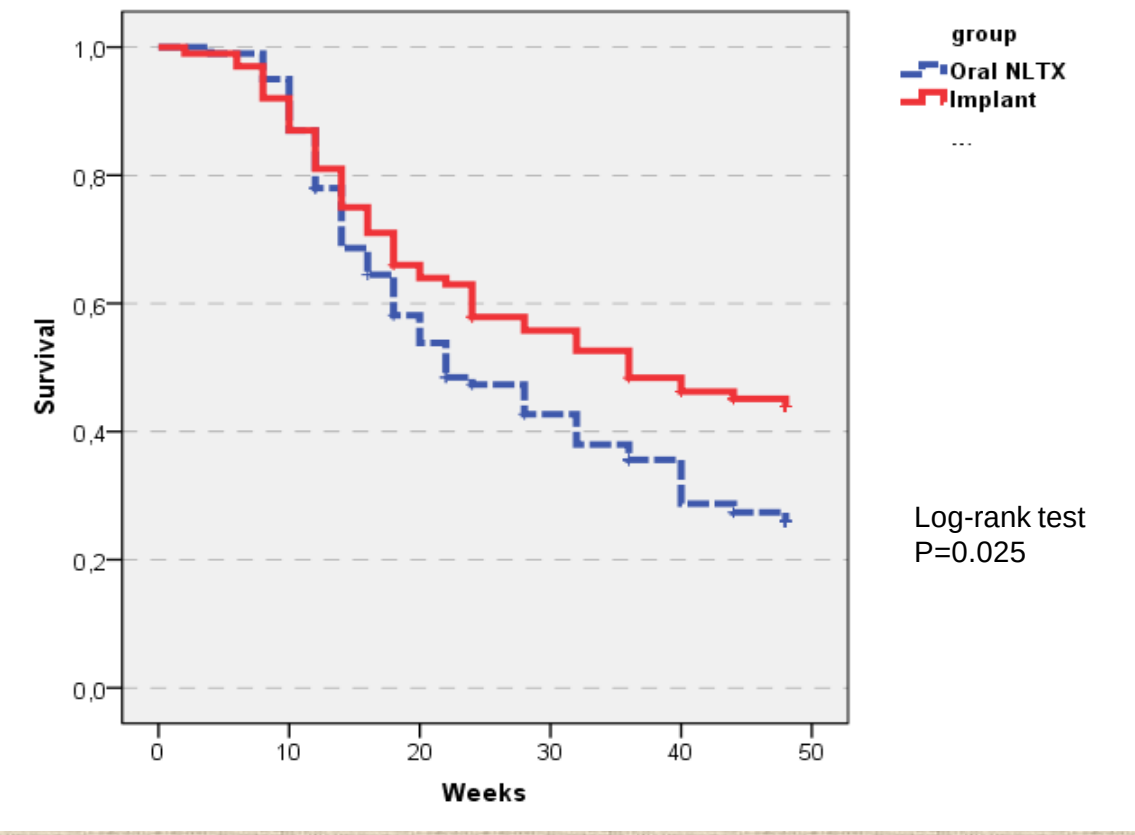


Cumulative % of opioid negative urines



Retention in ART

Kaplan Meier Survival Functions



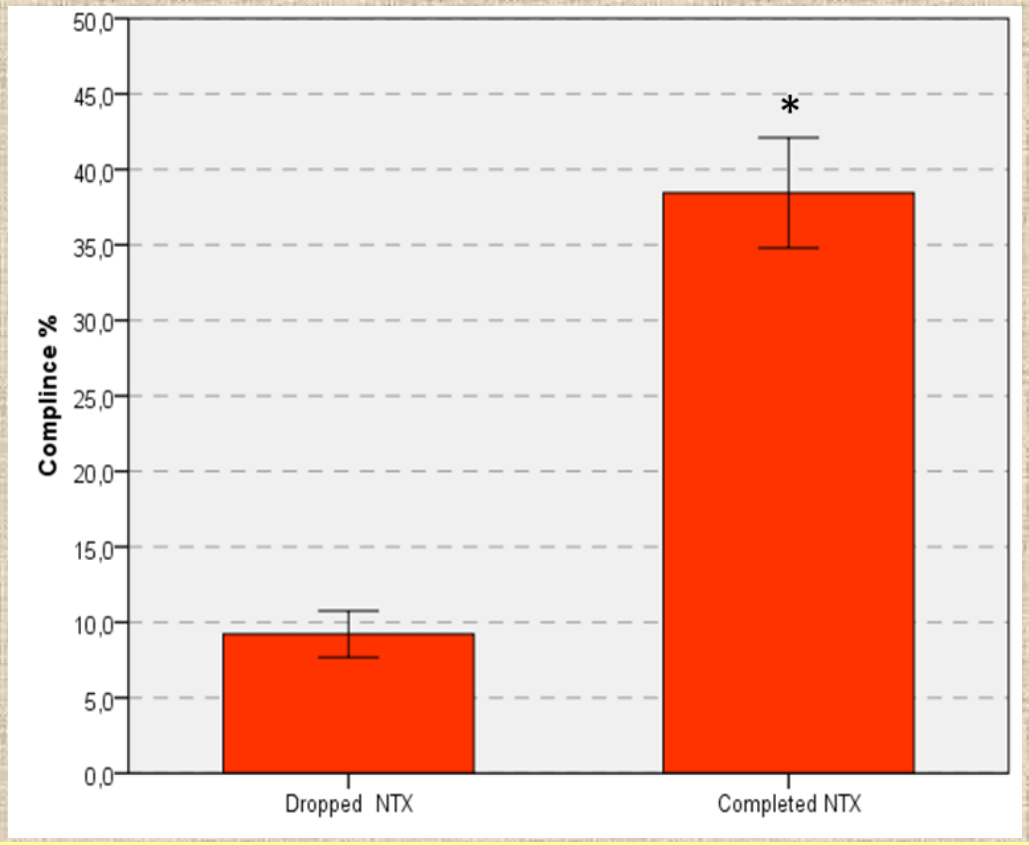
Secondary Outcomes:

ART retention was better in NI group than in ON group (46% vs 32%, p<0.05)

MEMS cups opening

Proportion of taken ART pills

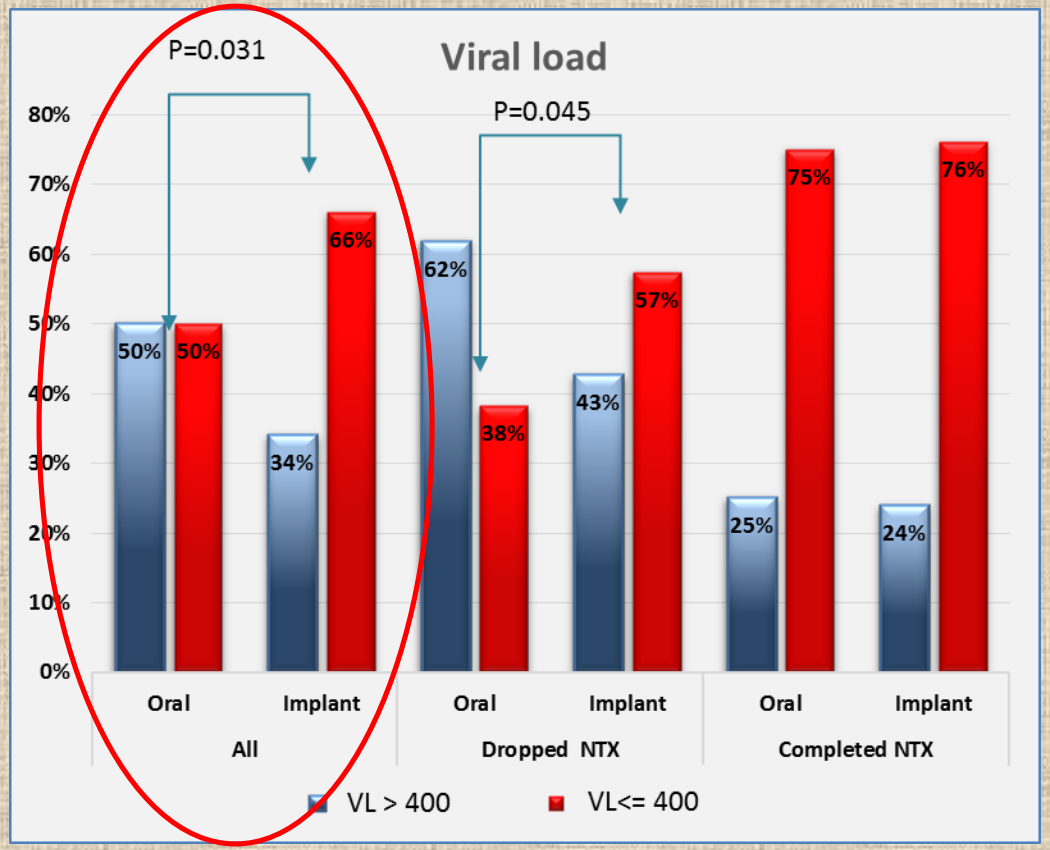
(calculated on the basis of the number of pills that patient supposed to take within a year)



Secondary Outcomes:

MEMS cup openings higher in those who continued naltrexone, regardless of group assignment (Mean±SD): 9,22%±8,52% vs. 38,45%±16,20%; ANOVA (F1=268.46, P<0.001)

Viral Load



Primary Outcome: More HIV suppression in NI than ON [66% vs 50%; OR (95%CI)=1.94 (1.10-3.43)]

CONCLUSION

Naltrexone implant:

- Prevents relapse to opioids

and

- Improves HIV treatment outcomes in patients with OUD

LIMITATION

Curr Psychiatry Rep (2010) 12:448–453
DOI 10.1007/s11920-010-0135-5

Use of Naltrexone to Treat Opioid Addiction in a Country in Which Methadone and Buprenorphine Are Not Available

Evgeny Krupitsky · Edwin Zvartau · George Woody

Acknowledgement

First Pavlov State Medical University of St. Petersburg , Russia:

Zvartau E, Blokhina E, Verbitskaya E, Lioznov D, Yaroslavtseva T, Palatkin V, Vetrova M, Bushara N, Burakov A, Masalov D, Mamontova O, Romanova T.

University of Pennsylvania, Department of Psychiatry:

Poole S, Gross R, Woody G

National Institute Drug Abuse

NIDA Grants


THANK YOU!!!