

Naltrexone Revisited

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History of Naltrexone

Naltrexone Pharmacology

Opioid antagonist (no effects in non-dependent person, precipitated withdrawal in opioid dependent person)

No agonist properties; no reinforcing effects to add to the patient's motivation to continue taking naltrexone

Effectively blocks effects of opioids (e.g., heroin)

Good oral bioavailability

Long duration of action

Naltrexone Efficacy

Highly effective in controlled, inpatient studies

Can be taken daily or three times per week

Compliance and treatment retention are poor in general in outpatient clinical trials

Compliance is better in motivated patients (e.g., physicians, business professionals)

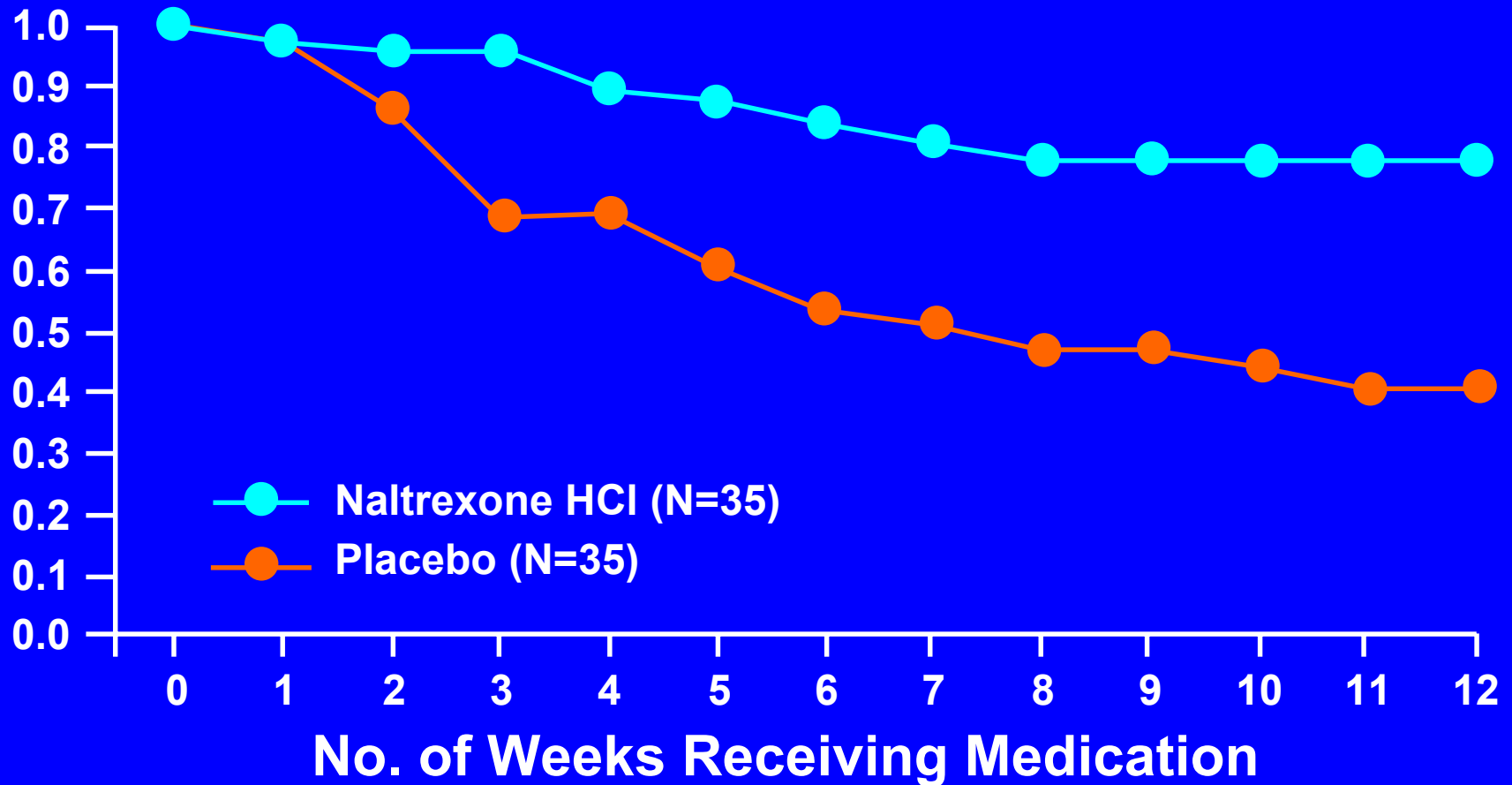
Naltrexone Safety and Side Effects

Very safe in usual dose range

Higher than usual doses may produce increases in liver function tests (LFTs)

Most commonly reported side effects are abdominal complaints and dysphoria (although both are rare)

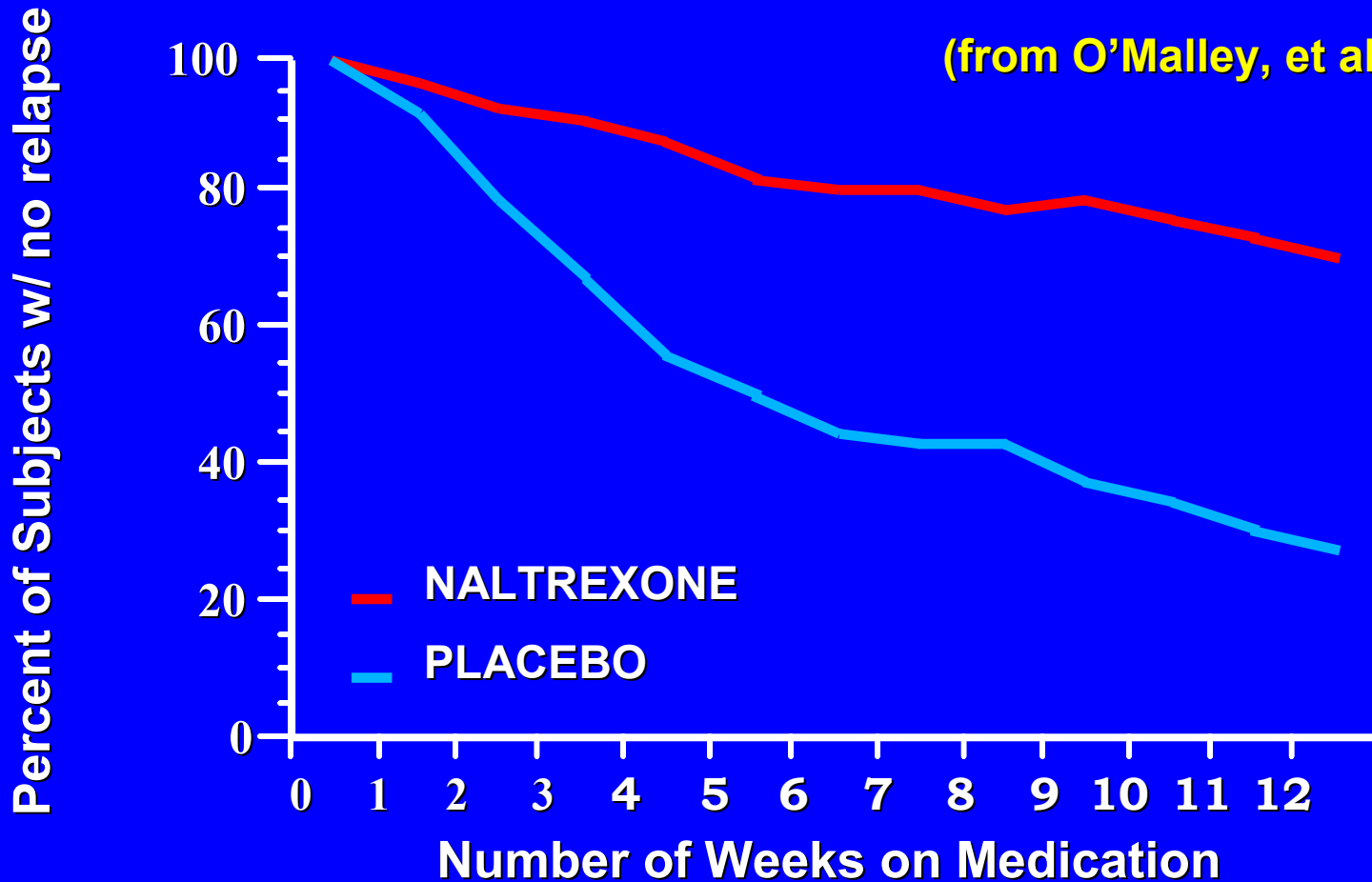
Naltrexone in the Treatment of Alcohol Dependence



Volpicelli et al. Arch Gen Psychiatry. 1992;49:876-880

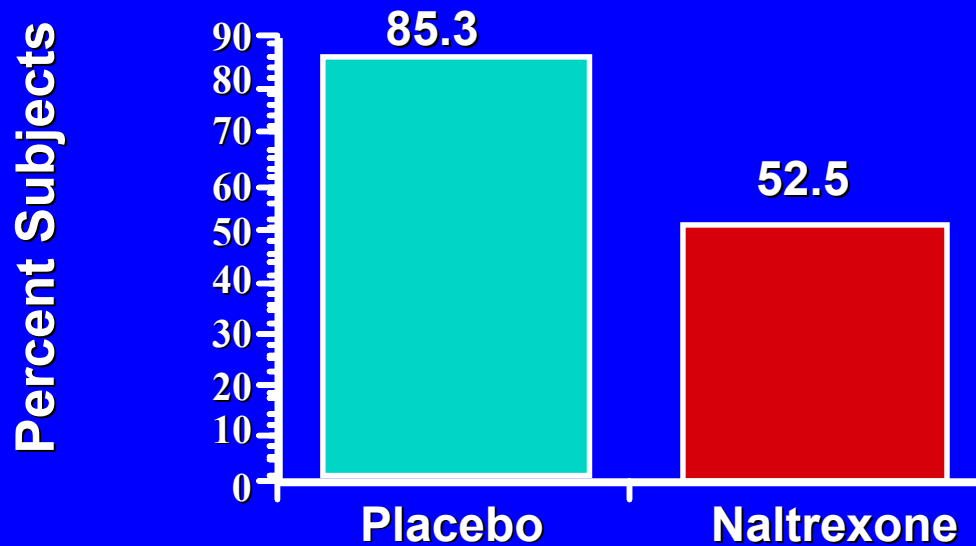
Relapse Rates

(from O'Malley, et al., 1992)



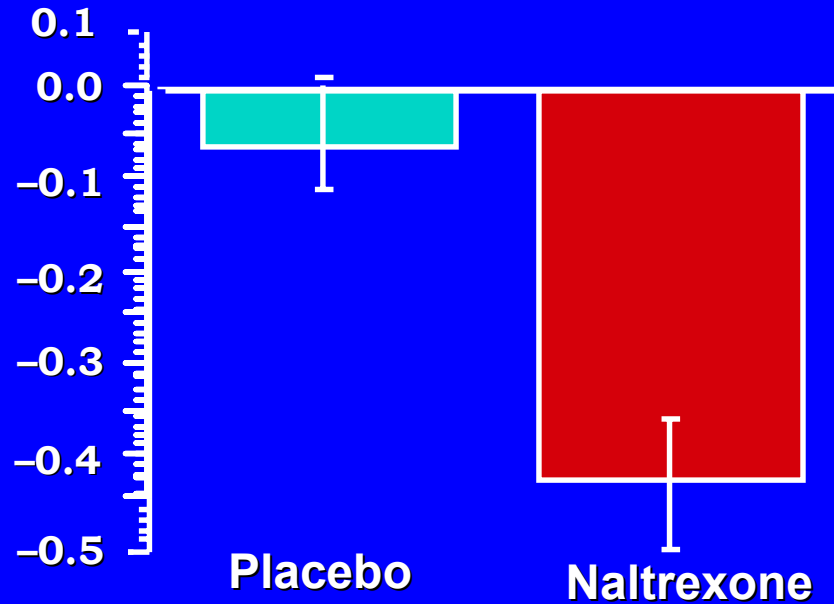
Subjects Who Relapsed After “Slipping”

(Volpicelli 1992, 1994)



Subjective “High”

(Volpicelli 1992, 1994)



+1 = increased high;
0 = no change in high;
-1 = decreased high

Naltrexone Maintenance and Opiate Dependence

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Standing Detox Orders

- **Buprenorphine 8 mg SL q 8 pm on MON & TUES (Nursing observation X 10 min. after dose)**
- **Naltrexone 12.5 mg po at 10 am on THURS only (Mouth check after dose, please)**
- **Klonopin 1 mg po q BID TUES-SAT**
- **Klonopin 0.5 mg BID SUN**
- **Clonidine 0.2 mg TID (please check VS prior to administering; hold if SBP<100, DBP<60) (MDD=0.6 mg)**

Standing Detox Orders, cont

- Prochlorperazine 10 mg po at 9 am on THURS -SAT
- Naltrexone 25 mg po at 10 am on FRI only (Mouth check after dose, please)
- Naltrexone 50 mg po at 10 am on SAT, SUN and MON (Mouth check after dose, please)
- Multivitamin 1 tab q am
- Ranitidine 150 mg po BID
- Nicoderm Patch 21 mg q am (apply to arm; patient may participate in smoking walks)

PRN Medications

- **Acetaminophen 650 mg q 4-6 hrs. prn headache, muscle pain (MDD=1300 mg)**
- **MOM 30 cc po q 8 hrs. prn constipation (MDD=90cc)**
- **Compazine 10 mg po/IM q 8 hrs. prn nausea (MDD=30 mg)**
- **Ondansetron 8 mg po q day prn nausea (please call MD before administering)**
- **Clonidine 0.2 mg po q 6 hrs. prn w/d (please check VS prior to administering; hold if SBP<105, DBP<60) (MDD=0.8 mg)**

PRN Medications, cont

- Clonazepam 1.0 mg po q 4 hrs prn severe anxiety (MDD=5 mg)
- Ketorolac tromethamine 30 mg IM q 12 hrs. prn severe muscle pain (MDD=2 doses)
- 8) Mylanta 30 cc po q 4-6 hrs. prn GI upset (MDD=90 cc)
- 9) Trazodone 50 mg po q hs prn insomnia; may repeat X 1 after one hour
- 10) Nicorette gum 1 piece q 1-2 hrs prn nicotine craving (MDD=12 sticks)
- 11) Immodium 2 mg 2 capsules after loose stool (MDD=16 mg)

Management Issues In Detox

- **Contraband/Searching the Patient**
- **Smoking/Nicotine Withdrawal**
- **Addressing Insomnia**
- **Handling Withdrawal**
- **Emerging Mood and Character Symptoms**

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Substance Treatment and Research Services (S.T.A.R.S.)

- **NIDA-funded, treatment-outcome research programs**
- **Providing combination of pharmacological and psychotherapeutic interventions for a variety of substance abuse disorders including cocaine, heroin, alcohol and marijuana dependence**
- **Importance of addressing comorbid psychiatric diagnoses**
- **Inclusion of adjunct, manual-guided psychotherapy**

Clinical Implications of Naltrexone Maintenance

- Naltrexone, when taken regularly, blocks the reinforcing effects of heroin and helps extinguish use of opiates. Further, it is an important alternative to agonist-maintenance and drug-free treatments which, although effective, are limited.
- Problems with naltrexone remain, however, and include:
 - Difficulty with induction given precipitated withdrawal;
 - Poor compliance, and;
 - Relapse is high without adequate psychotherapeutic context (Kosten and Kleber, 1984).
- Efforts to improve compliance with naltrexone are warranted.

Efforts to Improve Treatment with Naltrexone for Opiate Dependence

- The goal of our clinical-research team has been to develop and test a novel behavioral psychotherapy, Behavioral Naltrexone Therapy (BNT)
- Goals of BNT: encourage long-term abstinence from opiates by promoting adherence to naltrexone and lifestyle changes in heroin-dependent individuals.
- BNT integrates several manualized psychotherapy interventions with demonstrated efficacy for substance abusers to promote compliance and retention in treatment, and ultimately reduce relapse rates.

Overview of Behavioral Naltrexone Therapy (BNT):

- **Six-month treatment program for heroin dependence and naltrexone maintenance**
- **Integration of manualized psychotherapy interventions with demonstrated efficacy**
- **Aims of BNT: abstinence from heroin; adherence to naltrexone; lifestyle changes**
- **Three Phases of BNT: Induction, Stabilization, and Maintenance**
- **Twice-weekly therapy sessions: One Individual, One Network**
- **Network member is trained to monitor medication**

BNT: Integration of empirically supported therapy interventions for substance abusers

- **Cognitive-Behavioral Relapse Prevention Therapy (Marlatt & Gordon, 1985; Carroll et al., 1994)**
- **Network Therapy (NT; Galanter, 1993)**
- **Community Reinforcement Approach (CRA; Hunt & Azrin, 1973; Meyers & Smith, 1995)**
- **Contingency Management (Higgins et al.1991, 1993, 1994)**
- **Motivational Enhancement Therapy (Miller & Rollnick, 1991).**

What is CBT?

- **Behaviors are learned; reinforced by positive/negative consequences**
- **Learning Theories: Classical Conditioning; Operant Conditioning; Modeling**
- **Techniques include: self-monitoring or increased attention/awareness to thoughts and behaviors; identifying antecedents/ consequences; re-shaping new behaviors**
- **Interactive, team-oriented therapy**
- **Practice exercises in/out of sessions**
- **Goal-oriented and Time-limited**

Relapse Prevention Therapy

- **Short-term, Cognitive-Behavioral Approach**
- **Structured and Goal Oriented**
- **Flexible, Individualized Approach**
- **Assumes Drug Use is Learned Behavior**
- **Coping with Cravings: Increase Awareness/Monitoring of Triggers and Cues**

Critical Tasks of RPT:

- **Functional Analysis: Exploration of External and Internal Triggers; Pros/Cons of use**
- **Skills Training (e.g., Cope with Craving; Refusal Skills; Manage Negative Thinking)**
- **Foster Motivation and Commitment to Stop**
- **Identify Past/Future High-Risk Situations**
- **Psychoeducation**
- **Examine cognitions and affects related to substance use**

Goals of RPT

- **Recognize**
- **Avoid**
- **Cope**
 - **Self Talk**
 - **Refusal Skills**
 - **Decision Delay**
 - **Talking Through**

Network Therapy

- **Involves one or more non-drug-using significant others in network**
- **Review and rehearsal of RPT skills**
- **Supports integrity of network by improving communication, diffusing interpersonal conflict, and encouraging drug avoidance skills**
- **Network members participate in weekly sessions, monitor adherence to medication (e.g. naltrexone), and record compliance on monitoring diaries**

Community Reinforcement Approach (CRA)

- **Intensive goal setting**
- **Identify and promote competing reinforcers**
- **Active, collaborative therapy approach**
- **Use of in-session exercises (e.g., Happiness Scale; Goal Setting; Communication Exercises)**
- **Importance of Homework/Practice Exercises**
- **Voucher Program**

CRA: Goals of Counseling

- **Family/Social Relationships**
- **Recreational Activities**
- **Social networks**
- **Employment**
- **Psychological**
- **Legal**
- **Medical**

Contingency Management

- **Contingent reinforcement for positive change**
- **Provides vouchers for positive behaviors (e.g. adherence to medication; abstinence) and awarded to both identified patients and network members/ medication monitors**
- **Vouchers are reviewed in treatment and exchanged for a variety of goods and services**

Motivational Enhancement Therapy

- Encourage internally driven change and self-efficacy
- Precursor to RPT
- Diffuse ambivalence with MET techniques
- Mobilize the patient's resources:
 - MET: Why change?
 - RPT: How change?

MET Techniques

**Stages of Change: Precontemplation;
Contemplation; Determination; Action**

Techniques:

Reflection

Roll with Resistance

Avoid Argumentation

Double-Side Reflection

Core Sessions:

Orientation to the Program, Rapport-Building
Functional Analysis of Drug Use
Coping with Cravings (e.g., Self-monitoring)
Managing Thoughts about Drug Use
Problem-Solving Skills
Refusal Skills
Planning for Emergencies
Seemingly Irrelevant Decisions
Building a Supportive Network
Termination

Elective Sessions:

- **Social Skills Training**
- **Relationship Enhancement Training (e.g., Communication Skills)**
- **Management of Mood and Emotions: Recognition and Management of Anxiety**
- **Increasing Pleasant Activities**
- **Enhancing Social Support Networks**
- **Job-Seeking Skills**

Monitoring Integrity of Interventions in BNT

- **Rigorous didactic and clinical training**
- **Weekly individual and group supervision**
- **Audio- and videotaping of sessions**
- **Therapist Session Checklist: Measure of Adherence**
- **Therapist Skillfulness Form: Measure of Competence**
- **Inter-rater reliability of Therapist Session Checklists by independent evaluator**

Three Phases of BNT

- **Induction (screening and detoxification)**
- **Stabilization (Weeks 1-4)**
- **Maintenance (Weeks 5-24)**

Induction Phase:

- **Recruitment and assessment of eligibility for BNT**
- **Detoxification and induction to naltrexone; first two weeks clinic-based administration to ensure compliance**
- **Transition from inpatient to outpatient treatment**
- **Additional goals: convening network, providing education and support, securing motivation for treatment and adherence to naltrexone maintenance**

Stabilization Phase:

- **First month of outpatient treatment**
- **Focus continues to be securing motivation and commitment to treatment**
- **Training and rehearsal for network to monitor adherence to naltrexone**
- **Review of avoidance/relapse-prevention skills to deter immediate slip to heroin use**
- **Coping with protracted withdrawal symptoms**

Maintenance Phase:

- **Remaining months of outpatient treatment**
- **Long-term lifestyle changes are promoted (e.g., Social Skills; Job-Seeking; Relationship Enhancement Skills)**
- **Termination: facilitate transition for ongoing treatment and naltrexone maintenance beyond six-month program**

Management of Slips and Relapses in BNT

- **Slips explored as learning experiences**
- **Review high-risk situations encountered**
- **Skill-building/emergency plans to prevent future slips**
- **Elicit support of network**
- **Promote continuation of medication compliance (return to clinic-based administration)**
- **Avoid punitive responses**

Review of efforts to manage slips and promote compliance in BNT

- **With slips, return to clinic-based administration to promote continued compliance and avoid relapse**
- **Network members closely monitor medication compliance and reinforce treatment efforts**
- **Confirm compliance with riboflavin markers, blood levels, and recording sheets completed by network**
- **Voucher rewards for compliance to reinforce behavior**

Efficacy of BNT

- **Pilot Trial: Initially, 47 participants entered a pilot trial of BNT during which time a working treatment manual was constructed, therapist training procedures and therapist competency and adherence measures were developed. Preliminary evaluation demonstrated 31% of patients completed trial and based on findings, BNT was modified to better address severe depressive symptoms and methadone use at baseline, two significant predictors of premature attrition in our pilot sample.**
- **Randomized Trial: Currently, 74 participants have entered randomized trial in which one is assigned to either BNT or Compliance Enhancement Therapy (CE), a control therapy intended to simulate standard outpatient psychiatry**

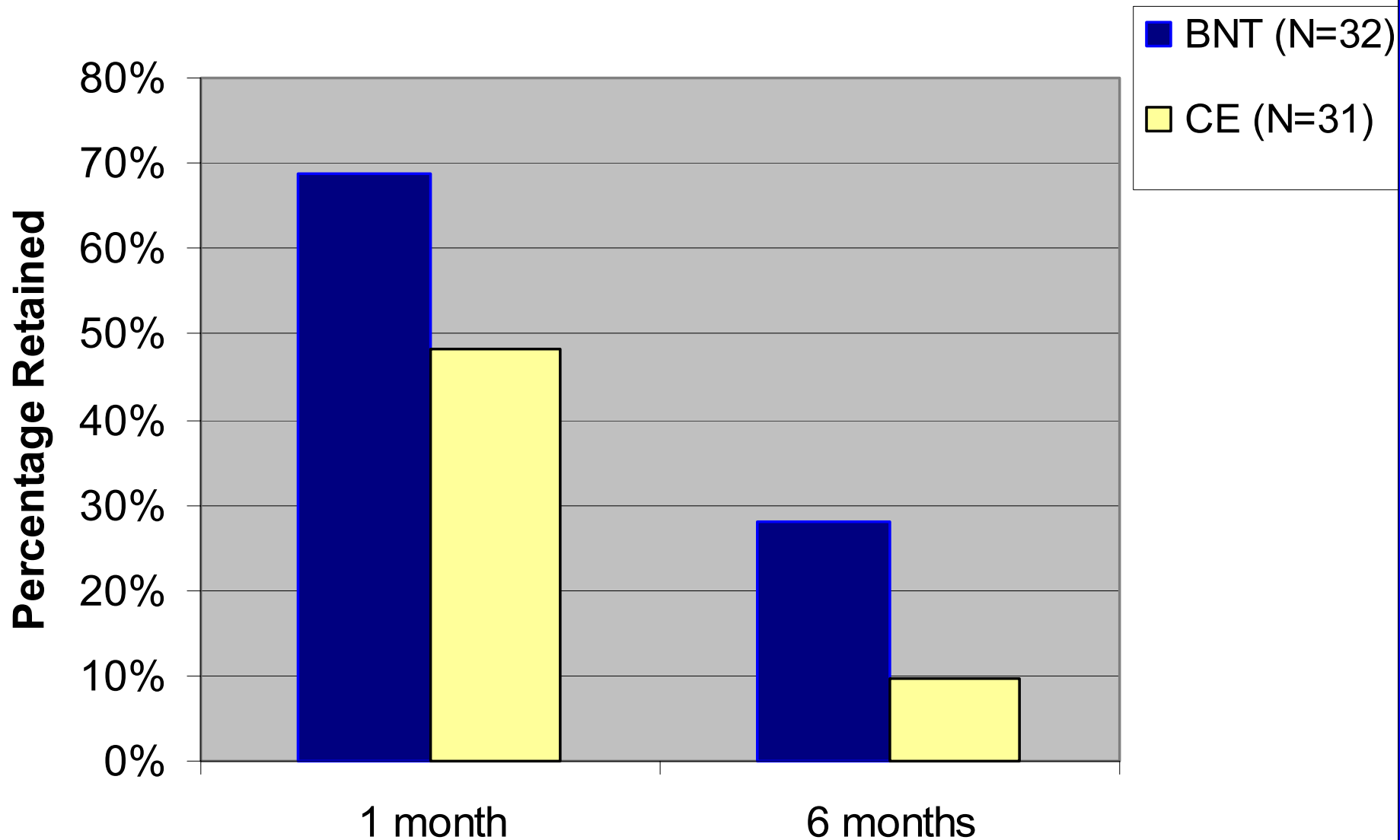
Eligibility for BNT

- *Inclusion Criteria:*
 1. ≥ 18 years of age.
 2. Meets criteria for opiate dependence as measured by SCID-IV criteria, urine toxicology, and naloxone challenge if diagnosis is unclear.
 3. Has a non-substance abusing significant other who is eligible and willing to participate in network therapy.
- *Exclusion Criteria:*
 1. Unstable medical conditions such as active liver disease.
 2. Diagnosis of Bipolar Mood Disorder or Psychosis.
 3. Suicidality/Homicidality.
 4. Regular methadone use.

Outcome Measures

- **Treatment retention (weeks in treatment)**
- **Naltrexone compliance (% of pills taken)**
- **Abstinence from opiates (% of opiate-free urines)**

Figure 1. Percentage Retained To One Month and Six Months



Conclusions and Plans

- Preliminary findings suggest that a greater percentage of patients in BNT are retained in treatment, perhaps by securing a network that promotes consistent adherence to naltrexone. It is likely that patients in CE, who self-monitor compliance, discontinue their medication, relapse to heroin use, and stop attending treatment visits. This hypothesis continues to be examined with collection of follow-up data.
- Future randomized trials are being planned that will involve a depot formulation of naltrexone during detoxification. This is in an effort to improve methods to prevent premature attrition and promote retention in treatment which occurs in both groups.

Research to Practice... **a providers perspective**

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Research to Practice Problems

- **Access to research**
- **Interpretation of findings**
- **Relevancy for treatment**
- **Concrete implementation strategies**
- **Individualized program design**
- **Staff resistance to change**
- **Time constraints**

Research to Practice Needs

- **Clearing House**
- **Empirical experience**
- **Implementation**
 - **Pragmatic steps that can be modified**
 - **Staff engagement**
 - **Staff training**

Research to Practice Project

- NIAAA, OASAS, and ASAP “Researcher in Residency Program”
 - Nationally recognized researcher paired with a treatment provider to affect a technology transfer:
 - Naltrexone Adjunct Therapy for Craving Reduction in Alcoholics - an evidence based treatment approach that has been underutilized

Fundamentals of Researcher in Residency Program

- **Planning**
- **Reimbursement**
- **TIPS manuals**
- **2 Day residency**
- **Orientation of Stakeholders**
 - **physicians, administration, clinical staff**
- **Technical Assistance**

Implementation Site: Inpatient Rehabilitation Unit

- **Abstinent (at least 5 days)**
- **H & P (within 24 hours)**
- **Liver function tests**
- **Side effects**
- **Compliance**
- **Patient education**

Note 50-70% with co-occurring disorder

Initial Implementation Process

- **Protocol developed**
- **Monitoring & education tools**
 - **Side effects monitoring form**
 - **Craving index form**
 - **Drinking episodes calendar**
 - **Medic Alert Cards**
 - **Information packets**

Protocol Initiated by Counseling Staff on Admission

- **Determine appropriateness**
 - **Alcohol use primary**
 - **Patient willing**
- **R/O contraindications**
 - **Acute hepatitis**
 - **Current opioid, methadone, LAAM use**
 - **Active opioid withdrawal**
 - **Pregnancy/breast feeding**
 - **Adolescent**

Protocol Continued

- **Administer craving index**
- **Schedule MD appointment**
 - **Prescribe as appropriate**
 - **education brochures & medic alert card**
- **Activate focused care treatment plan**
- **Monitor side effects (1st week)**
- **Administer craving index weekly**
 - **Monitor progress/craving reduction**

Implementation Ups and Downs

- **Momentum high first 6 months**
- **50% on Naltrexone**
- **Naltrexone implemented in outpatient**
- **Staff satisfied with process**
- **Evident success**

Implementation Ups and Downs continued

- **Momentum decreased second 6 months**
- **20% on Naltrexone**
- **Staff blocks emerge:**
 - **Not integrated as routine**
 - **Recommended by exception**
 - **Asked would you vs. we suggest**
 - **No motivational counseling**
 - **Viewed as medical**

Implementation Ups and Downs Continued

- **Physician arbitrary**
 - **Spread thin**
- **Documentation break down**
 - **No reasons given for non-use**
 - **Usual explanation “the patient refused”**

Action Taken

- **Eliminated craving index form on intake**
- **Assigned screening to RN's**
 - **In nursing assessment vs. stand alone**
- **Computerized template**
- **Policy & procedure formalized**
- **Maintained focus with staff**

Ongoing Activities

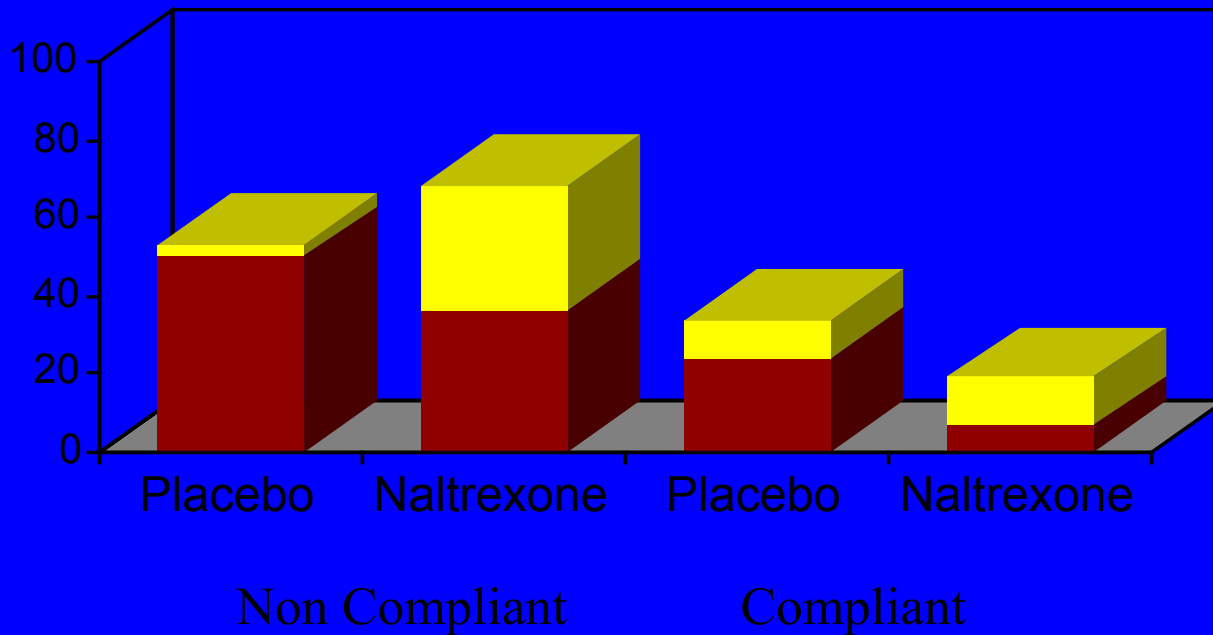
- **Several anecdotal success stories reviewed at case conference meetings**
- **Outcome monitors added to quality improvement plan**
- **Involved in statewide and regional research to practice groups**

Initial Outcomes

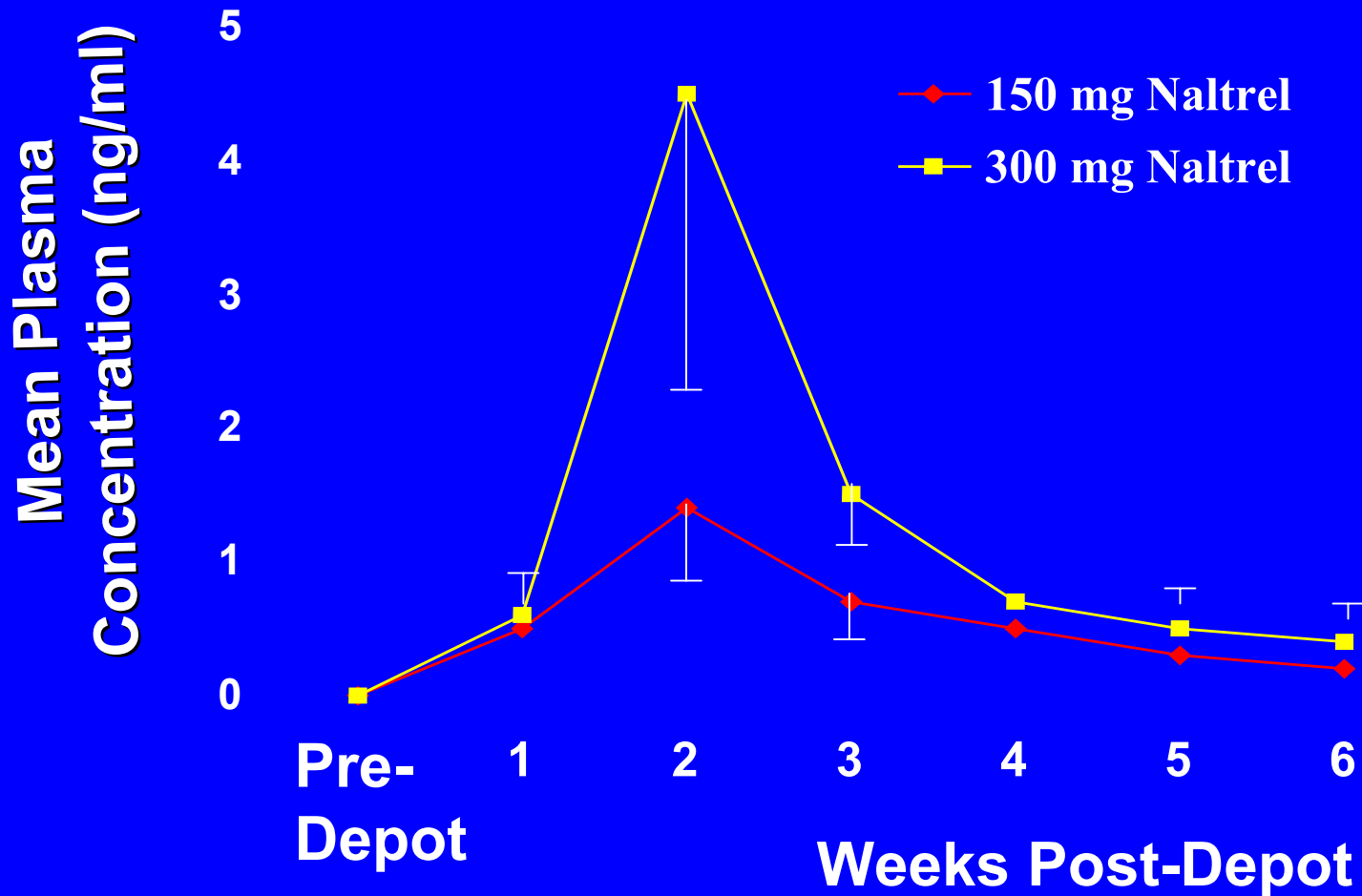
- **“Not a magic bullet”**
 - research indicates a 12-19% enhanced efficacy
- **Well tolerated with the co-occurring population on psychotropic medications**
- **Several reported successes**
 - Reduction in drinking episodes or full abstinence
- **Infrequent incidence of side effects**
- **Cost covered by N.Y. Medicaid**
 - Some commercial insurance

Compliance with Treatment and Treatment Outcome

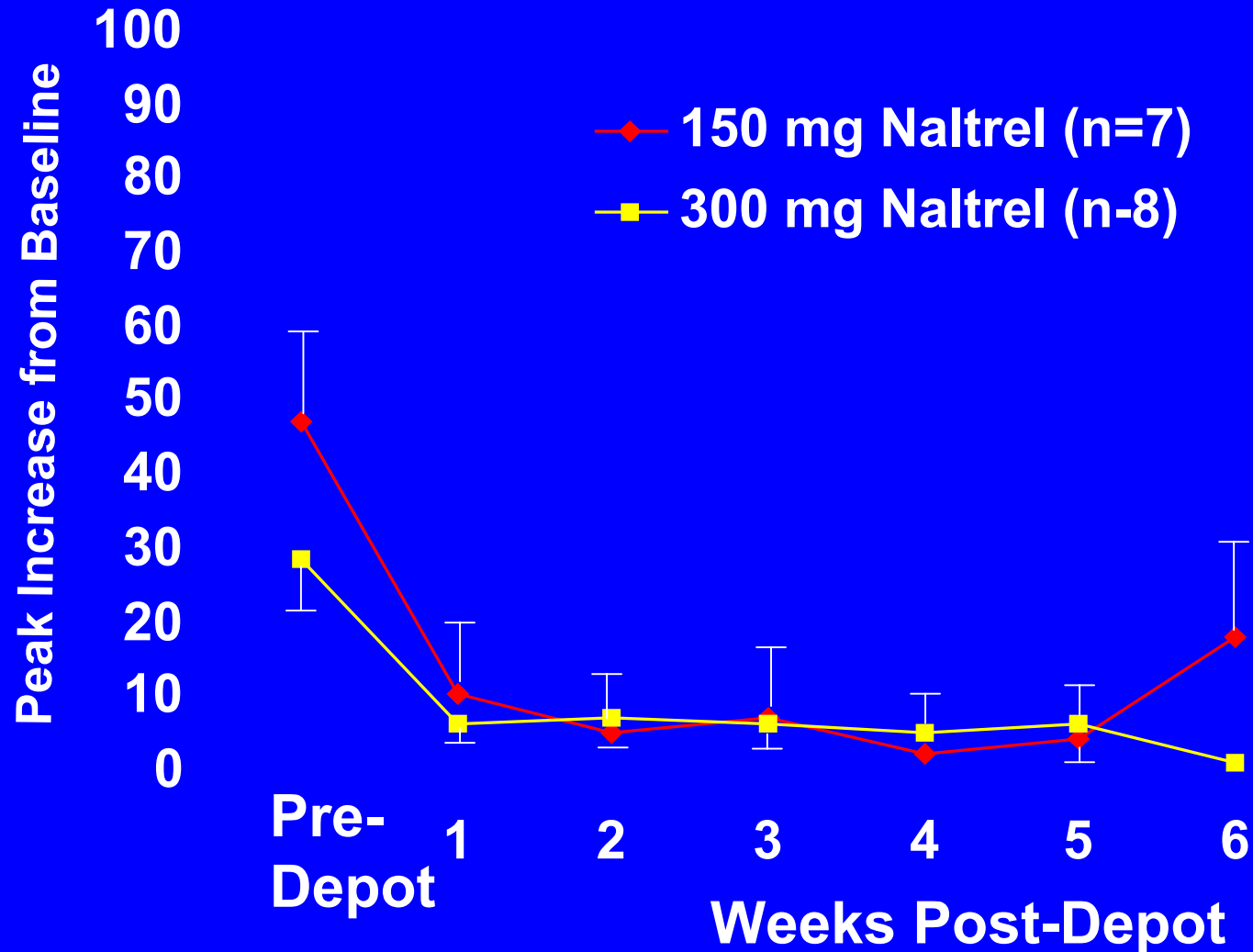
■ Relapsed ■ Slipped



Plasma Levels of Naltrexone



Hydromorphone Response - Drug Effect VAS



Criminal Justice Population

A substantial proportion of parolees/ probationers are opioid dependent

- Frequently these individuals receive little or no treatment;
and treatment itself has proven to be only modestly successful.
- A recent evaluation conducted by Dr. Zanis found a 28%, 6 month outpatient treatment rate for opioid dependent parolees

Forensic Intensive Recovery (FIR)

Only 175/475 (37%) of clients completed the required minimum 6 months of drug treatment

Of the 82 with opioid dependence,
23 (28%) completed

Pilot Study - increased treatment effectiveness

- 51 mostly male (90%), opioid dependent probationers/parolees
- Randomized to oral naltrexone + counseling (N=34) *or* counseling alone (N=17)

Outcome Measures:

- Retention
- Urine drug screens
- Re-Incarceration

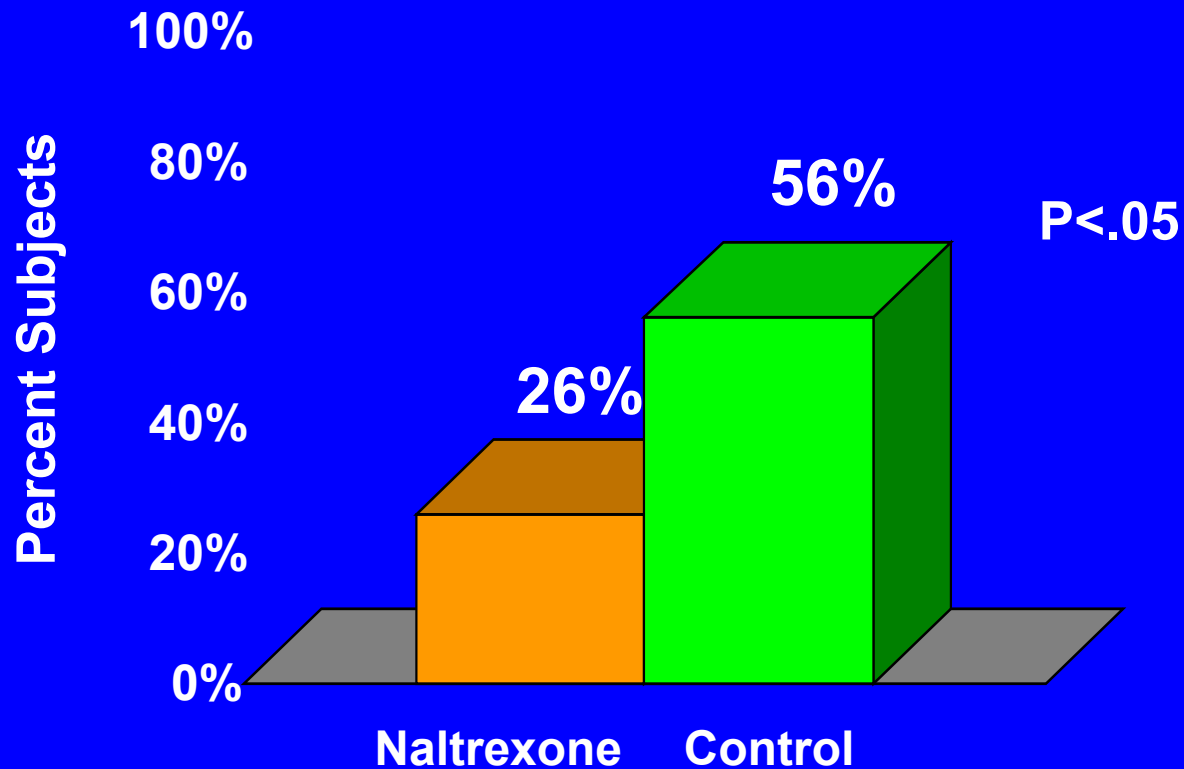
Mean Percent Positive Urines

Pilot Study

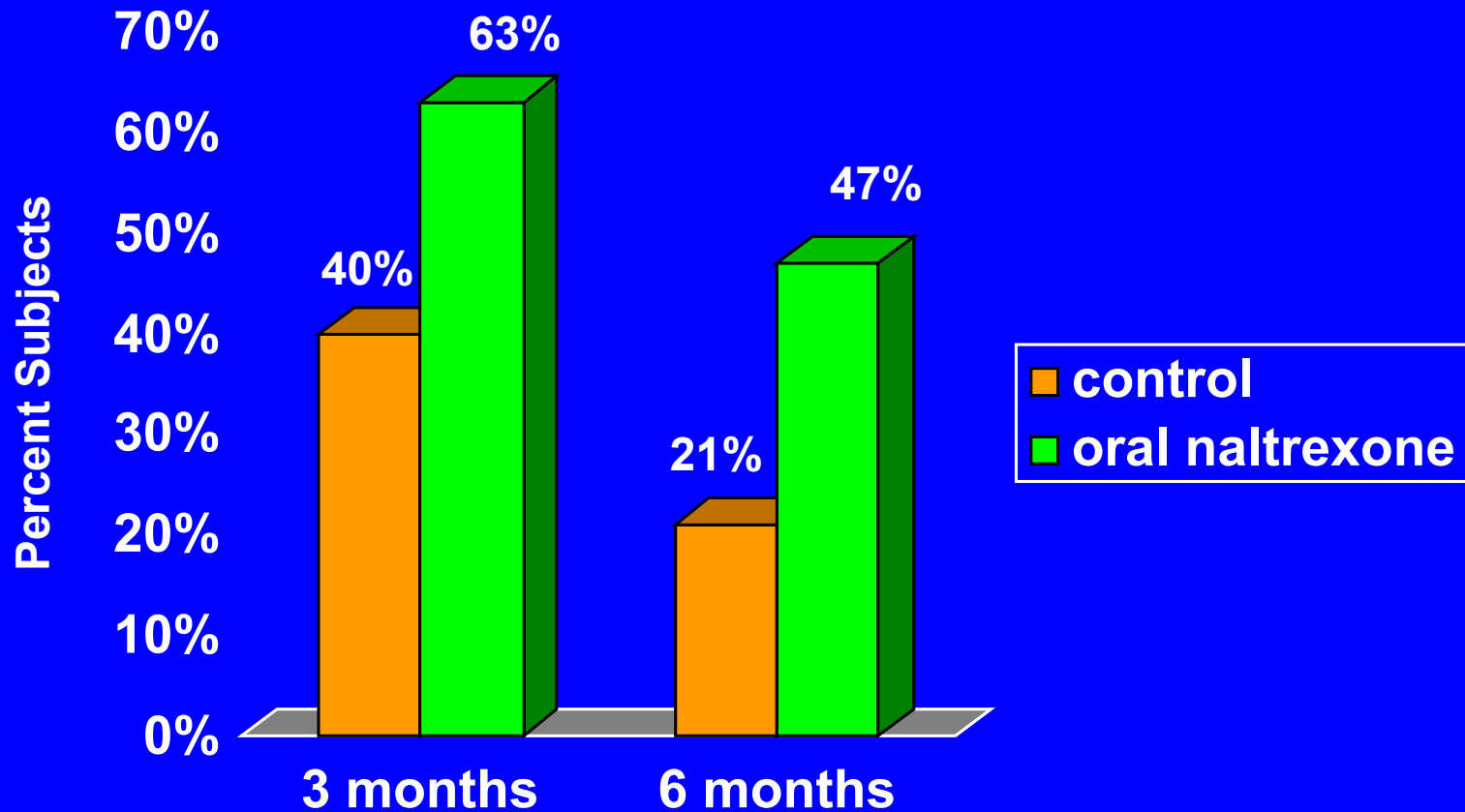
Substance	Oral Nltx (N=34)	Control (N=17)	Sig.
Opiate	8%	30%	p<.05
Cocaine	33%	49%	NS
Amphetamine	0%	1%	NS
Benzodiazepine	2%	6%	NS
Marijuana	13%	19%	NS
Alcohol	2%	4%	NS

Subject Re-Incarceration

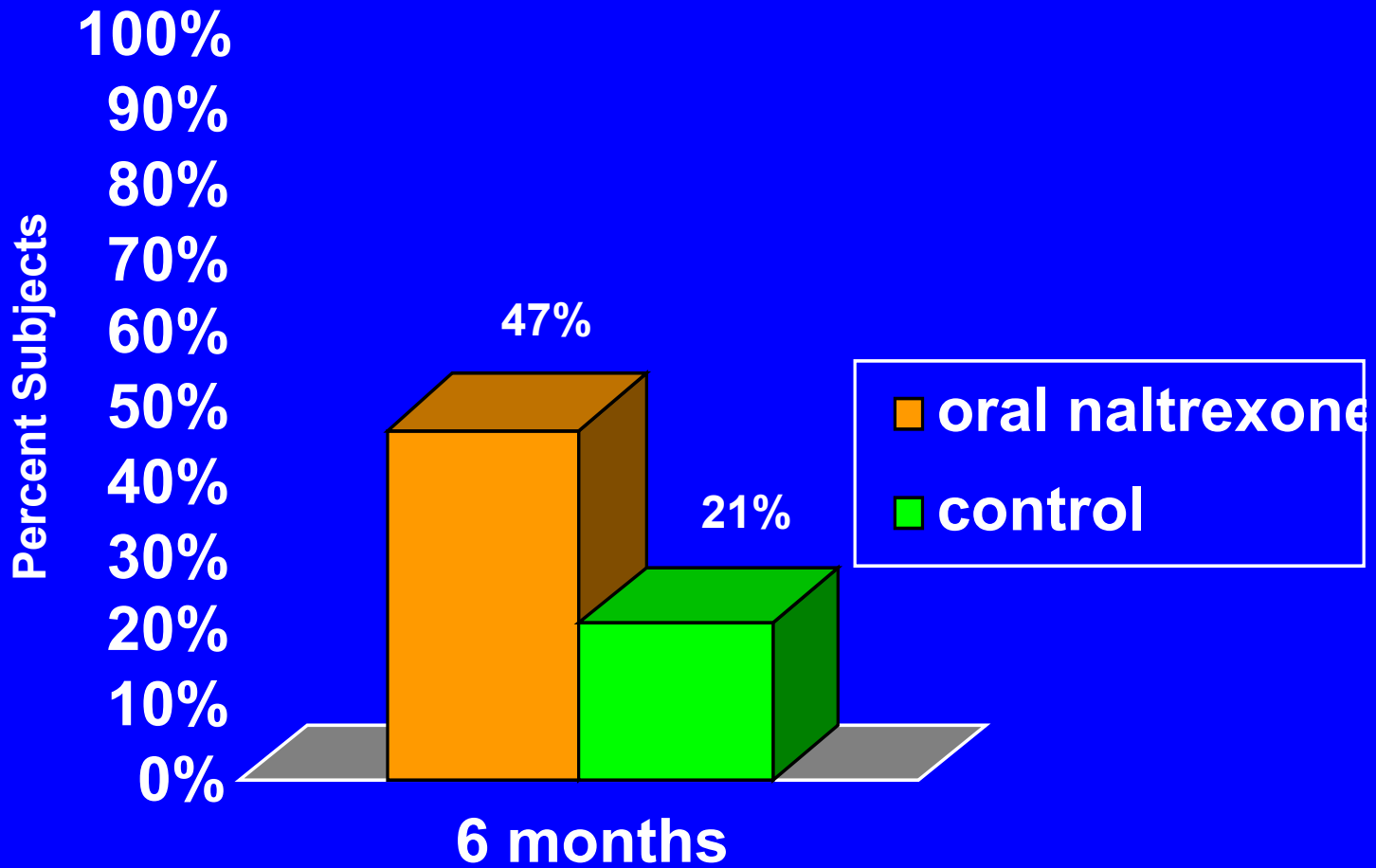
Pilot Study



Retention Rate

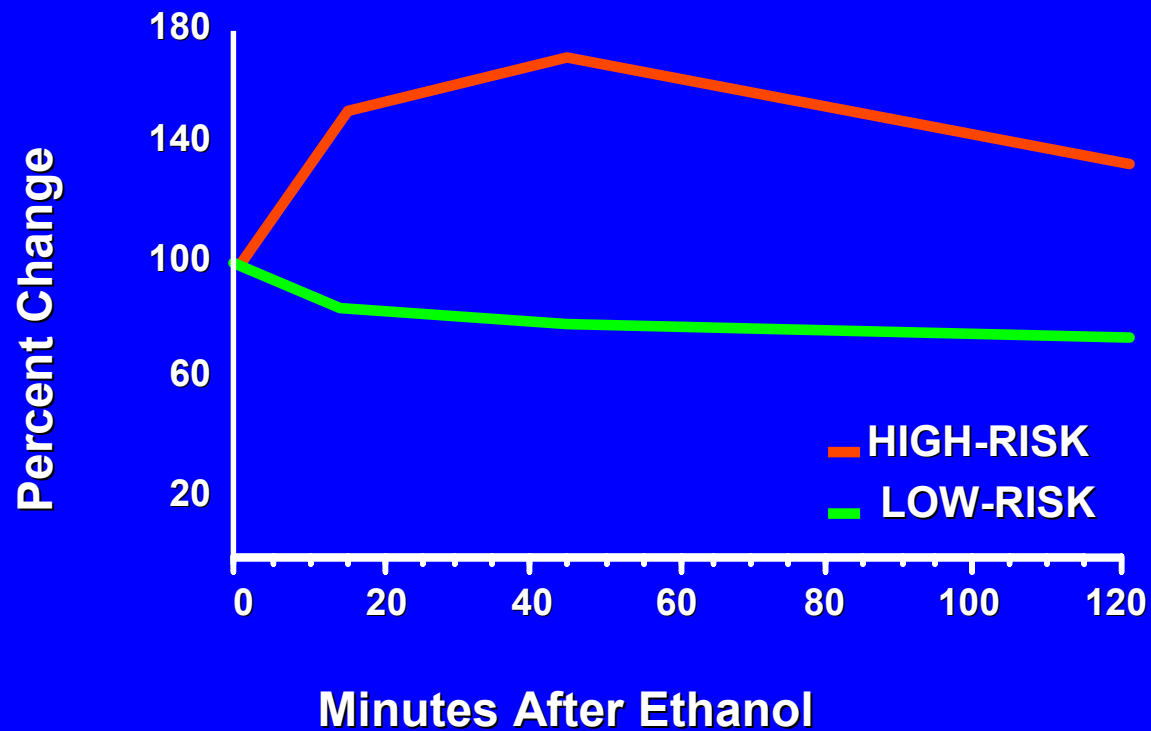


Retention Rate



Change in Beta-Endorphin After Alcohol

(from Gianoulakis, et al., 1990)



Beta-Endorphin Levels After Alcohol

(from Gianoulakis, et al., 1990)

