
Moving Buprenorphine-Naloxone Treatment for Short-term Medically Managed Opioid Withdrawal from a Phase Three National Multi-site RCT to Maryhaven, a Community Treatment Program

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NIDA
Clinical Trials Network

MARYHAVEN

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Introduction

- Since the mid-1990s, the prevalence of lifetime heroin use has increased for both adolescents and young adults (SAMHSA, National Survey on Drug Use and Health, 2002)
- Buprenorphine (BUP) is a partial mu-opioid agonist and new treatment option for managing opioid dependence.
- The Drug Addiction Treatment Act of 2000 (DATA 2000) expanded the clinical context of medication-assisted opioid treatment.
- In October of 2002 tablet formulations of buprenorphine (Subutex[®]) and buprenorphine-naloxone (Suboxone[®]) were approved for the treatment of opioid dependence by the Food and Drug Administration (FDA).
- This is a 2 part report presenting 1) data derived from a randomized clinical trial using a short-term taper using BUP for medically managed opioid withdrawal and 2) implementation of a similar protocol at a participating Community Treatment Program.

PART 1: Randomized Multi-site Clinical Trial

Bringing Buprenorphine/Naloxone Detoxification to Community Treatment Providers: The NIDA Clinical Trials Network Field Experience

Based on:

Amass, L., et al., *Bringing Buprenorphine-Naloxone Detoxification to Community Treatment Providers: The NIDA Clinical Trials Network Field Experience*. The American Journal on Addictions, 2004; 13: S42-S66.

NIDA's Clinical Trials Network



- Established in 1999.
- NIDA's largest initiative to blend research and clinical practice by bringing promising therapies to community treatment providers.
- Network of 17 University-based Nodes (RRTCs) involving over 100 Community Treatment Programs (CTPs) in 24 states, Washington D.C. and Puerto Rico.

Why Study Bup/Naloxone for Detox in the CTN?

- The shorter-term use of BUP/NX for opiate detoxification had not received much research attention. BUP/NX may offer an alternative to currently used short-term detoxification treatments in many community treatment settings.
- Provide guidance/training to providers.
- Enhance provider experience with planned marketed product in the U.S.
- The diversity of clinics in the CTN provided an unparalleled opportunity to conduct such a clinical endeavor.

Why Participate in This Trial?

“We must find a better way to treat these patients, more that half of them are not continuing with treatment”

Maryhaven Medical Director

NIDA CTN 001/002 Buprenorphine-Naloxone Detoxification Protocols

- Two, open-label, randomized clinical trials.
- Compared Buprenorphine-Naloxone (BUP/NX) and Clonidine for Short-Term (2 weeks) Opiate Detoxification in Residential or Outpatient Settings.
- Initiated in 8 Regional Nodes and 12 Community Treatment Programs.
- Inclusion criteria: healthy, at least 15 years old, opioid dependent, male and females desiring opioid detoxification.
- Exclusion criteria: serious medical or psychiatric conditions, allergy to study drugs, dependence on other substances requiring detoxification, pending legal action.

Community Treatment Programs

6 Residential

- 2 Therapeutic Communities
- 1 Free-standing, Chemical Dependency Hospital
- 2 Detox Units with Integrated Addiction and Mental Health Services
- 1 long term Residential

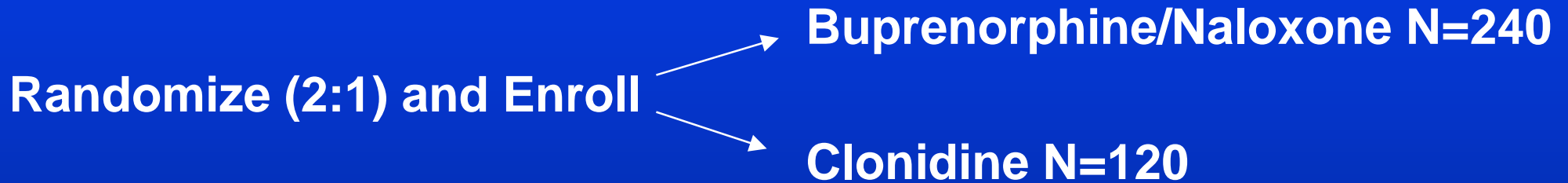
6 Outpatient

- 4 Opioid Treatment Programs
- 1 HMO
- 1 Community Mental Health Center

Usual care approaches: 50% methadone, 50% clonidine

Usual care approaches: mostly methadone and clonidine in HMO

Study Design



- 13 Days taper with follow-ups at 1 month, 3 and 6 months
- Ancillary Medications:
 - Physicians at CTPs were surveyed to determine what they normally use to treat withdrawal symptoms.
 - A fixed range of OTC and prescription medications were available during the 13-day detoxification to help manage: Anxiety and restlessness, Bone pain and arthralgias, Nausea, Diarrhea, Insomnia
- Psychosocial Services
 - Standard counseling procedures used at each clinic.
 - Self-help detoxification handbooks provided to all patients.

BUP-NX Detoxification Schedule

Study Day	BUP-NX Dose (mg of bup)
1	4 plus 4 more if not contraindicated
2	8
3	16
4	14
5	12
6	10
7	8
8-9	6
10-11	4
12-13	2

- Patients required to abstain from heroin for at least 6 hours and to be in mild withdrawal before starting buprenorphine on day 1.
- Observers verified withdrawal status before giving first dose.
- In outpatient protocol, benzodiazepine-negative U/A was required before dosing on day 1.
- λ All patients required to provide a methadone-negative U/A before dosing on day 1.

Patient Demographics

N	237
Gender	69% male
Mean Age	37 years
Regular Opioid Use	8.6 years
IVDU	65%
Mean # Prior Drug Tx	2.8

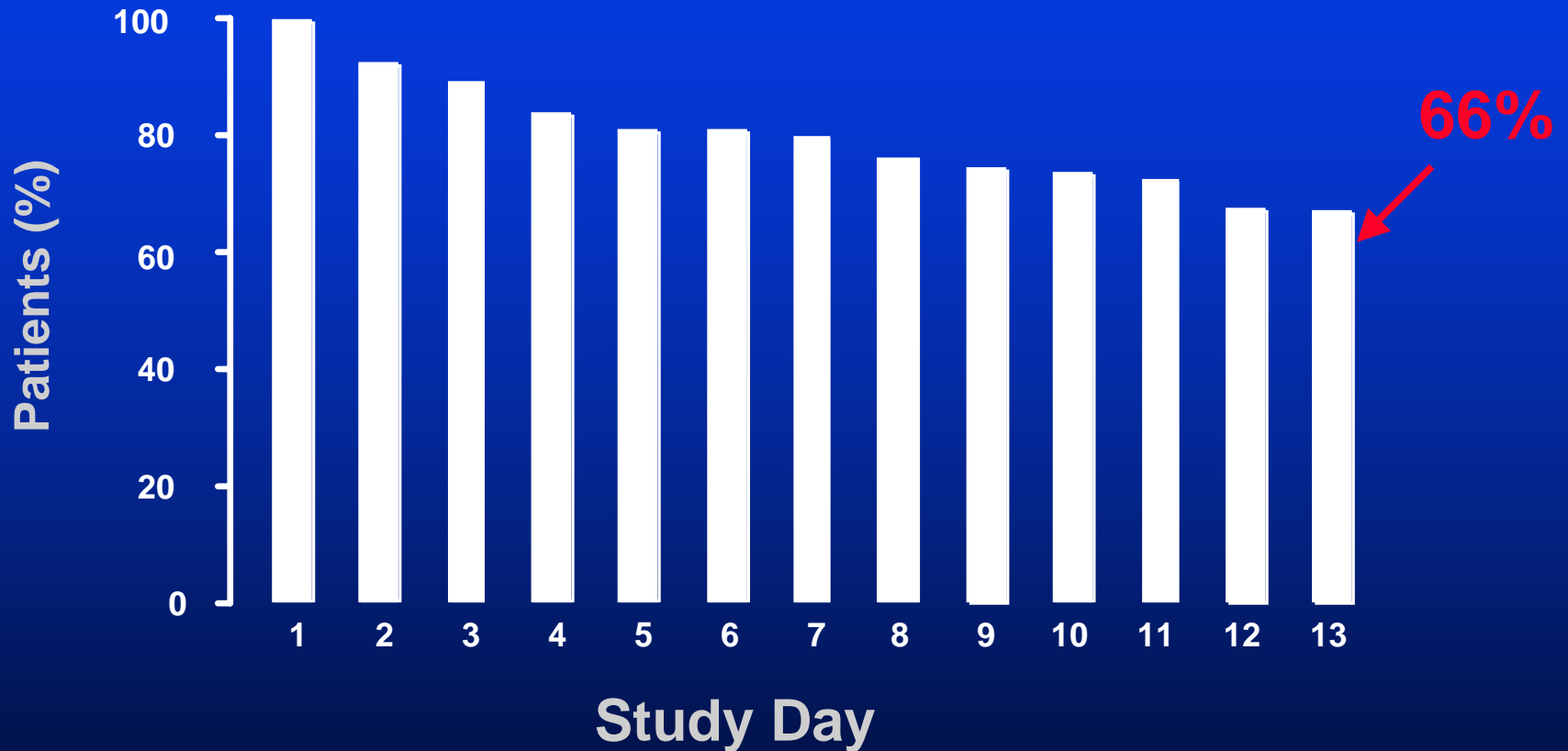
RACE

African-American	30%
White	45%
Latino	19%

Primary Other Current DSM IV Dx

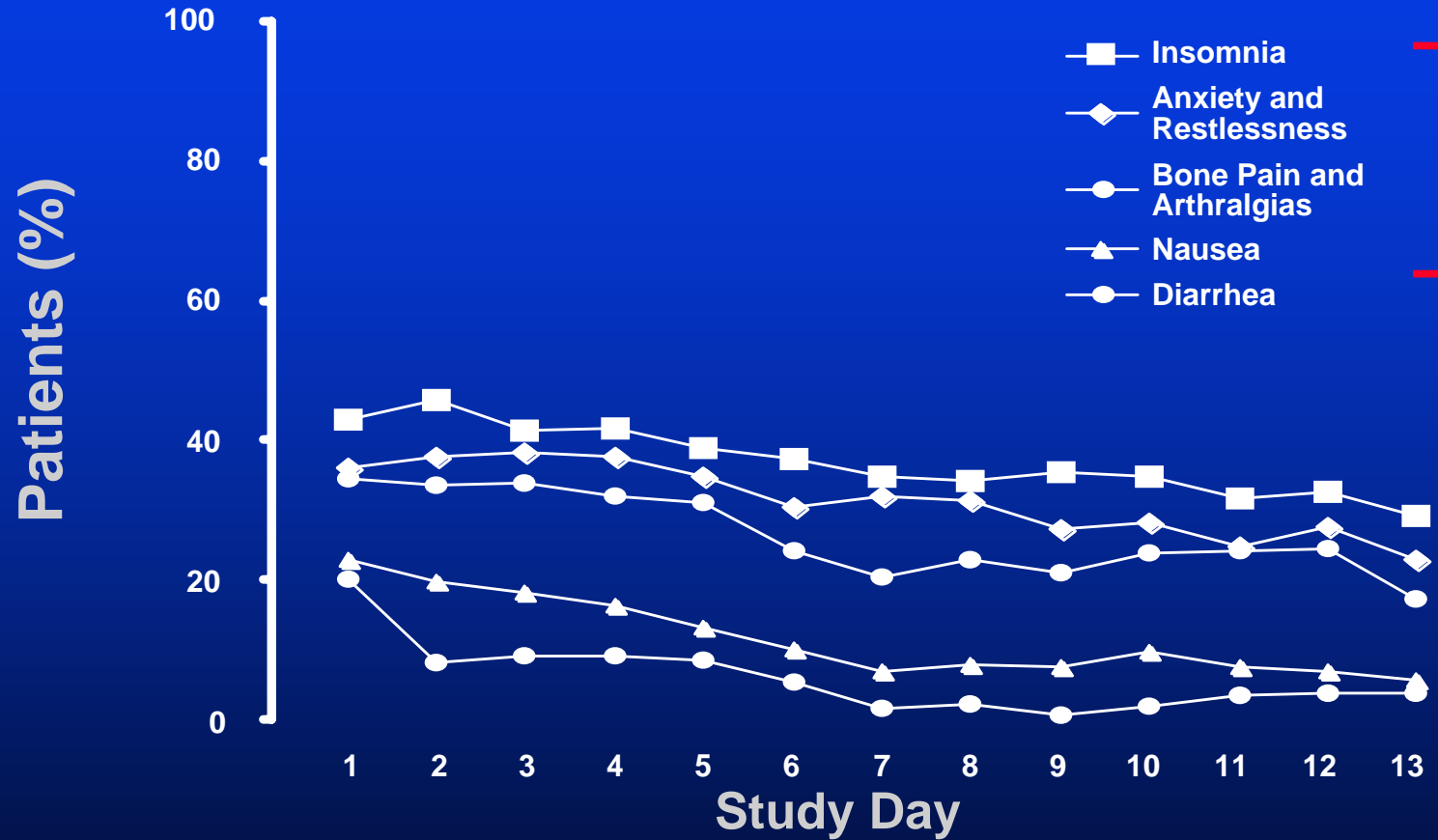
Cocaine	19%
Nicotine	29%

BUP/NX Compliance



Percent of patients taking the expected dose as indicated in the 13-day detoxification schedule. On day 13, 66% of patients were still enrolled and compliant with BUP dosing.

Ancillary Medication Use



The most commonly reported conditions where ancillary medications were used by participants as a function of study day.

BUP/NX Safety Profile was Excellent

- λ Side effects were primarily related to signs/symptoms of opioid withdrawal
- λ 18 total SAEs: 17 for hospitalization; 1 death at follow-up
- λ All but one SAE not drug related
- λ 83% (15/18) of SAEs captured at follow-up
- λ 61% (11/18) of SAEs expected events mostly for hospitalization related to drug relapse

FOUR KEY FINDINGS

1. Direct induction with BUP/NX is acceptable to a majority of opioid users. Close to 90% of patients completed induction, reaching a target dose of 16 mg within 3 days.
2. A substantial number of patients completed the short-term detox, regardless of setting or program philosophy. This program thus met a major goal of many programs to improve early treatment engagement. Short-term treatment can also help to establish an effective therapeutic alliance with local care providers.
3. Ancillary medications appear to have been used to manage more protracted abstinence symptoms as opposed to symptoms caused by the buprenorphine taper itself.
4. BUP/NX is safe for use in a wide range of community treatment settings. There were few serious adverse events and most were not related to BUP/NX.

Lessons Learned & Conclusions

- Lessons Learned:
 - Patient interest in the BUP/NX detox was high and some programs developed waiting lists, suggesting that the combination mixture will not deter patients from seeking buprenorphine treatment.
 - All sites expected patients to attend counseling regularly. Whether short-term BUP/NX detox would fare as well in primary care or office based settings where such services are not on site is not known.
- Conclusions:
 - BUP/NX is practical, acceptable and safe for use in a wide range of community treatment settings.
 - These sites include those with no prior experience using agonist therapy and/or limited experience with medical detoxification for opioid dependence.
 - The NIDA CTN can successfully conduct clinical trials of new therapies in community treatment settings.

PART 2: Community Treatment Program Adoption

Integrating Buprenorphine-Naloxone Tablet Treatment for Short-term Withdrawal from Opioids into a Residential Integrated Addiction and Mental Health Service

Based on CPDD 2004 Poster:

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Maryhaven, Columbus, OH;

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and**

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Why Adopt BUP/NX?

- “The difference is unbelievable these patients now have a fair chance at TX & recovery”

Rehab nurse

- “It’s amazing you can sort them out by who is sick and who is ready to participate in treatment”

Detox Counselor

Do Research Findings Translate into Clinical Care?

- Following completion of the NIDA CTN 001 clinical trial Maryhaven considered implementation of buprenorphine-naloxone (BNX) in its detoxification program
- Maryhaven held meetings with clinical staff and community stake holders to discuss the value of this new treatment
- State, County and private funding was acquired to train staff and support the treatment of 104 patients in a one year period
- The following report is based on a retrospective chart review of the first 64 BNX patients and Maryhaven data for 384 additional admissions for opioid-dependence prior to and after BNX became available at Maryhaven.

Project Background

- Maryhaven is a free standing comprehensive integrated addiction and mental healthcare treatment program founded in 1953 and located in Columbus, Ohio:
 - 7,205 admissions in July 1, 2002 to June 30, 2003
 - Programs offered include: adult and adolescent residential, outpatient and sub-acute medical detoxification programs
- Maryhaven is a CTP in the Ohio Valley Node,
 - Maryhaven's usual care for medical management of opioid withdraw is residential administration of Clonidine and Darvocet supplemented with ancillary medications
 - Maryhaven participated as a site in NIDA CTN 001
 - All patients receiving detoxification services are encouraged to engage in continued treatment

Residential Medically Managed Opiate Withdraw Admission Criteria

- Opioid-dependent and age 18 or older
- Appropriate for sub-acute medical management
- BNX Specific:
 - Non-pregnant and non-lactating
 - Willing to commit to a 13 day taper and continued treatment
 - Not in need of additional detoxification protocol
 - If on methadone, current dose ≤ 30 mg
 - No allergy or sensitivity to buprenorphine or naloxone
- Other reasons opioid dependent patients may not have received BNX include: did not want to wait for admission, declined participation in pre-admission screening, were not informed of the availability of BNX, received BNX on a previous admission or, refused to accept BNX treatment

Current BUP/NX Taper at Maryhaven

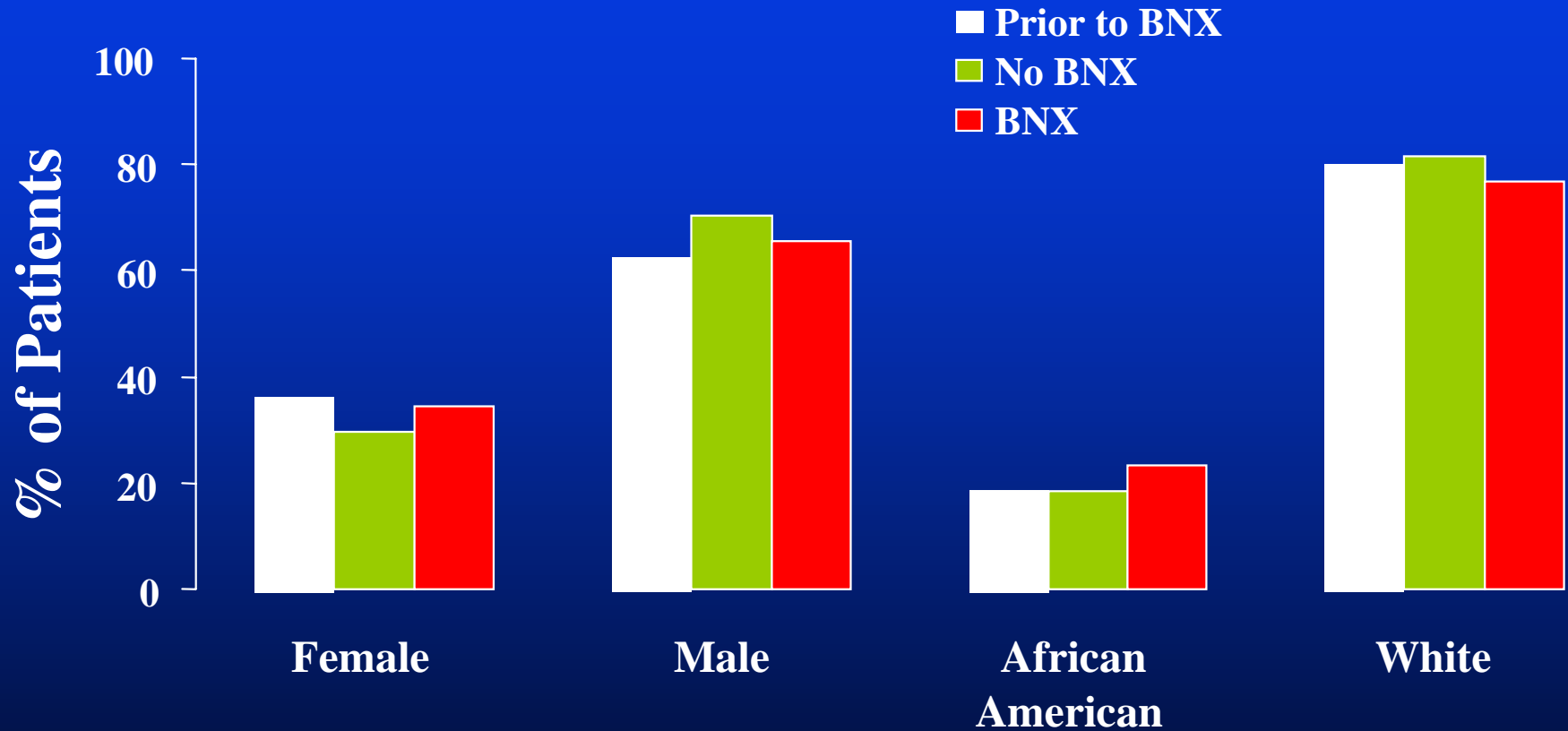
Day	BNX Dose (mg of bup)
0	Darvocet N 100, Clonidine 0.1mg po tid & Lorazepam 1 mg.
1	4 plus 4 more if not contraindicated (subutex for 1st dose if long-acting)
2	8
3	16
4	14
5	12
6	10
7	8
8-9	6
10-11	4
12-13	2

The BUP/NX taper is the same as described by Amass et. al., 2004 except for the addition of Day 0 when clients are admitted to the unit and treated with Darvocet N 100, clonidine and Lorazepam according to Maryhaven's standard detoxification protocol. Clients were observed for withdrawal symptoms prior to initiating BUP/NX on Day 1. Patients also receive the usual residential counseling and support services and ancillary medications.

Comparison Groups

- Prior to BNX implementation, $n = 157$
 - Admitted prior to BNX Implementation between 6/10/03 - 8/24/03
- After BNX implementation but no BNX, $n = 227$
 - Admitted between 8/25/03 - 1/31/04, but did not take BNX
- Received BNX, $n = 64$
 - Admitted between 8/25/03 - 1/31/04 and received BNX

Patient Demographics



Demographic characteristics of opioid dependent clients admitted to Maryhaven's residential detoxification program by group

Demographics (cont)

A. Age By Group

	Mean (range)
Prior to BNX	35.9 (19-65)
No BNX	35.9 (18-62)
BNX	36.8 (21-55)

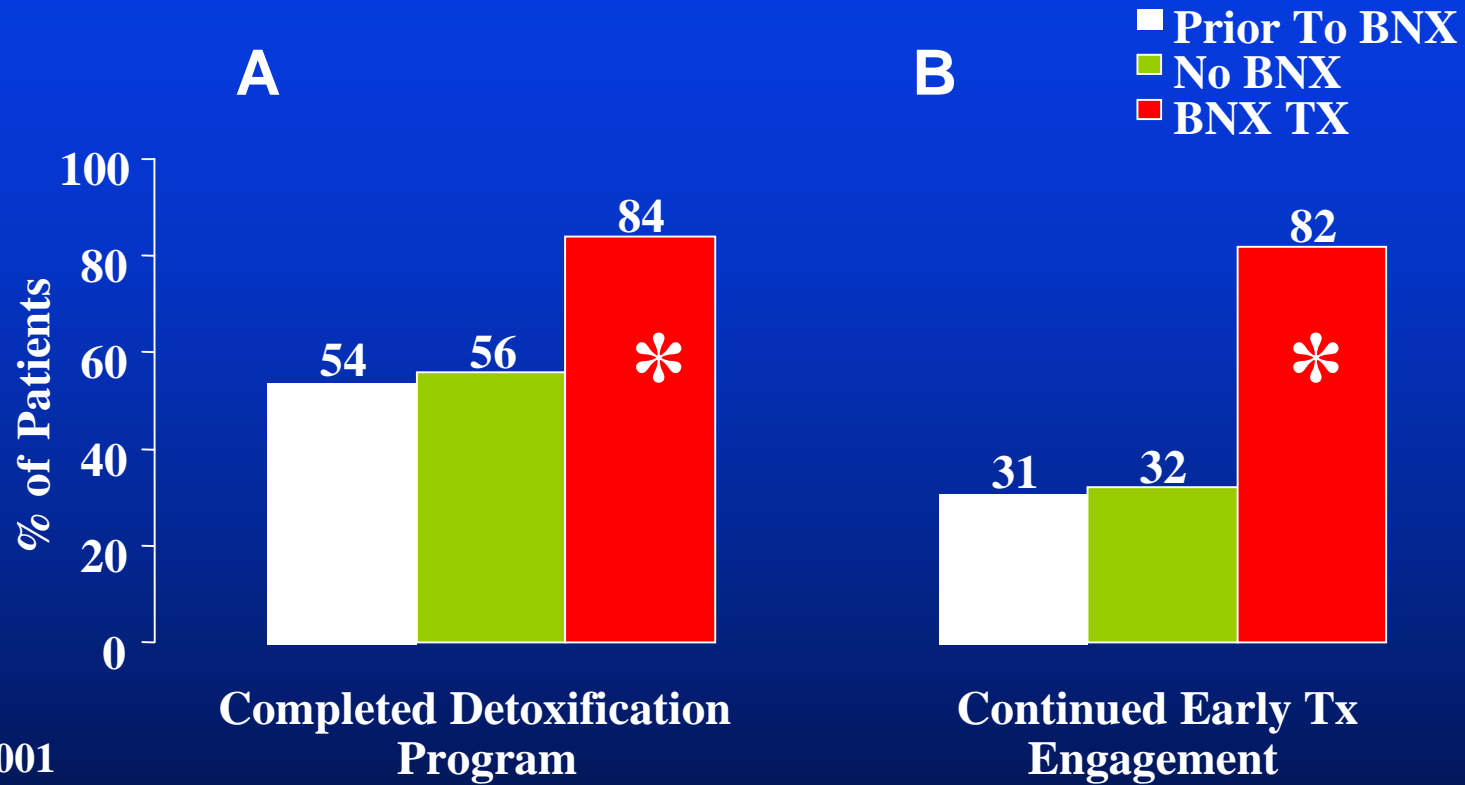
B. BUP/NX Group: Dose and Retention

	Mean (S.D.)	Range
BNX Dose (mg) n=58	22.8 (10.2)	0-32
# Days on BNX n=63	14.5 (6.9)	1-22

A. Breakdown of patients by age and treatment group.

B. Mean BUP/NX dose and treatment retention

Treatment Completion & Engagement



Percentage of patients, by treatment group, (A) completing detoxification and (B) engaging in treatment (i.e. accepting a referral and attending at least one day of treatment) beyond detox within a Maryhaven treatment program.

Observations

- Differences between the physician training (flexible dosing up to 32 mg.) and the clinical trials protocol (fixed maximum 16 mg.) caused some confusion
- The initial flexible dosing schedule was difficult for nursing staff to implement – and may have contributed to patient malingering
- Some patients engaged in diversion of BNX which resulted in increased monitoring of drug administration
- Patients receiving higher doses of BNX (>16 mg) complained of greater withdraw symptoms following conclusion of the taper
- Some patients refused BNX at admission after hearing rumors about withdraw symptoms
- There were no statistically significant within group differences on treatment completion or engagement based on gender, age or, race

Limitations

- Not a randomized trial
 - groups may be different on unknown factors affecting outcomes
- BNX taper was implemented as a program
 - no ability to analyze contribution of individual components to outcome
- The program continues to change. The maximum 16 mg dosing schedule has been in place since 1/01/2004

Conclusions

- Buprenorphine can be successfully used in a “drug free” substance abuse treatment facility for short-term medically assisted opioid withdrawal
- Patients receiving the buprenorphine-naloxone taper have significantly better rates of completion & early treatment engagement

Part 1: Collaborators

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Benefits of Adopting a Science Based Treatment

- **Pride of staff in offering state-of-the-science treatment to AOD patients**
- **Prestige of being recognized as a leader in the treatment community**
- **Increased staff satisfaction**
- **More competitive for available funding**
- **The acid test:**
 - **Improved patient care!**