Rapid Initiation of Naltrexone and Buprenorphine

Primary Outcome Findings from the NIDA CTN 0097 Study

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Disclosure Information

Rapid Initiation of Naltrexone and Buprenorphine: Primary Outcome Findings from the NIDA CTN

April 5, 2024, Concurrent Sessions #2

Dr. Adam Bisaga, MD

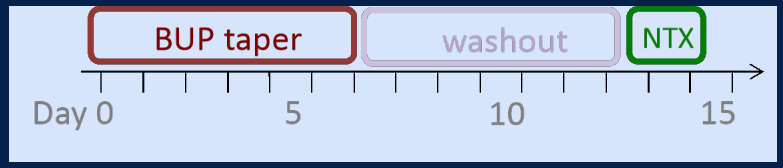
- Dr. Adam Bisaga has participated as an unpaid consultant to Alkermes, Inc., received grant funding (through the institution) from Alkermes, Inc., has served as an investigator on a multi-site clinical trial funded by Alkermes, Inc., and has received medication for NIDA-funded studies from Alkermes, Inc. and from Go Medical Industries Pty, He also consulted for Sophrosyne.

Learning Objectives and Background

- To describe the background and design of the study
- To illustrate the rapid procedure for initiation of treatment with XR-naltrexone
- To summarize the main findings of the study

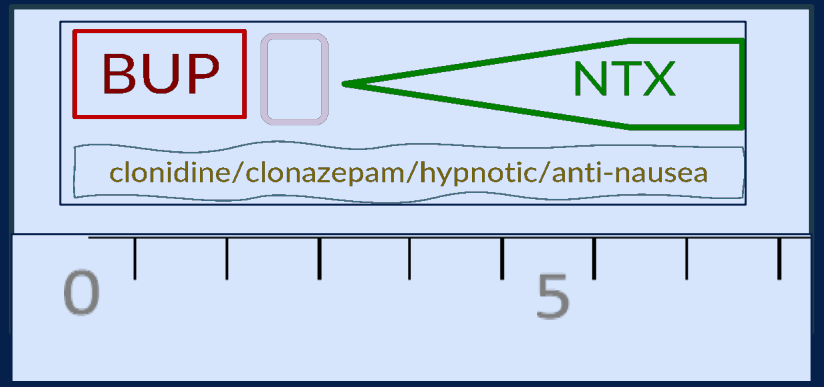
Background

- Difficulty with initiating standard XR-naltrexone treatment ("induction hurdle") is a major barrier
  - Prescribing Information for Vivitrol® recommends 10-14 day initiation procedure (Standard Approach)



- Alternative, shorter approaches were evaluated over the past 20 years
- An outpatient trial showed rapid induction approach (5-7 days) more successful than a standard approach for XR-naltrexone initiation (56% vs. 33%) *(Sullivan, Bisaga, et al., 2017)*

KEY Features of the Rapid Induction Protocol



- Buprenorphine (1-2 mg) administered as soon as opioid withdrawal emerges
  - the minimum necessary dose (avg. 6mg) with adjunctive medications for residual withdrawal
- Standing doses of adjunctive medication to prevent withdrawal
  - given before and during buprenorphine titration
  - scheduled dosing rather than *as needed*
  - combination of clonidine with clonazepam + ondansetron is particularly effective
- Low starting doses of oral naltrexone (0.5-3mg) to minimize precipitated withdrawal while accelerating time to the full dose tolerability
  - start with lower dose if fentanyl positive
  - given in divided doses to assess tolerability
  - once 6mg is tolerated, it is safe to administer XR-naltrexone
- Protocol may be modified depending on the tolerability of NTX titration (4-7 days)

Study Objectives

SWIFT

CTN-0097

Surmounting Withdrawal to Initiate (Fast) Treatment with Naltrexone

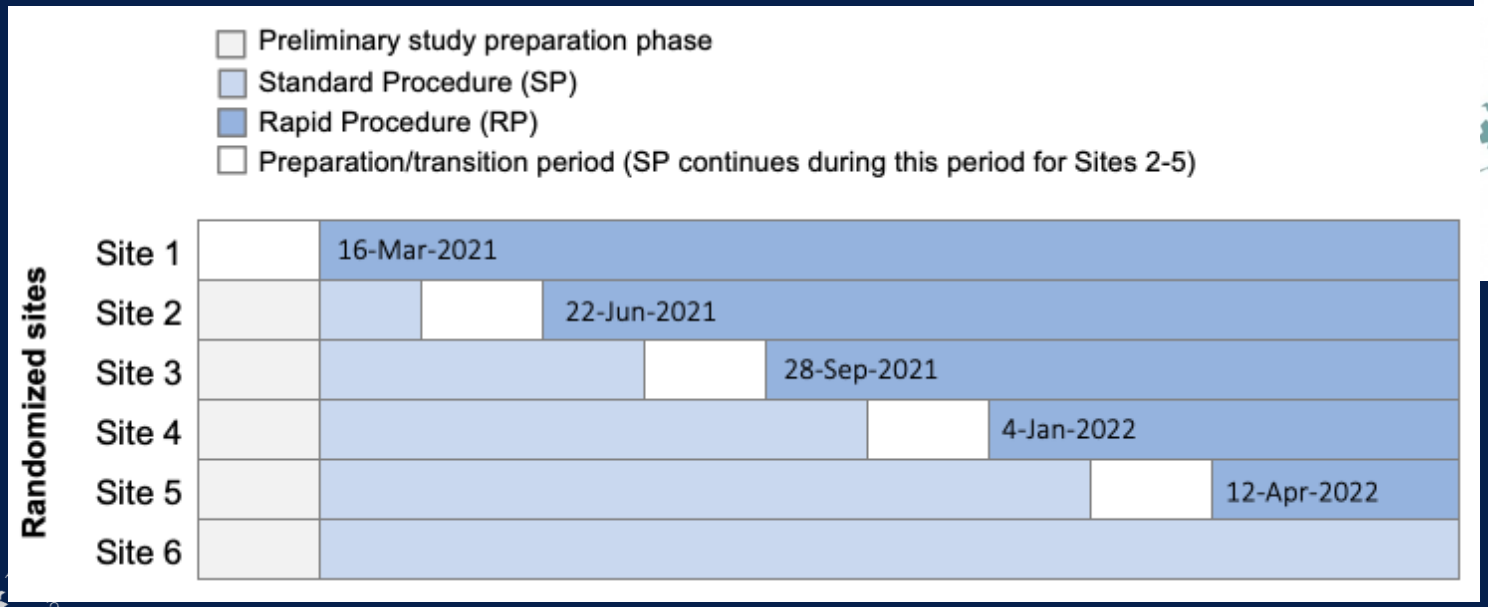
CTN-0097 was supported by the **NIH HEAL Initiative**

Type 1 Hybrid Effectiveness-Implementation Trial

- To determine whether the Rapid Procedure (RP) is **non-inferior** to a Standard Procedure (SP) on the successful initiation of XR-naltrexone
- To study barriers and facilitators to RP implementation and to develop an Implementation Strategy for dissemination of RP

Study Design

- Open-label, multisite, optimized stepped-wedge, randomized trial
- Five 14-week steps
- Six, community-based inpatient sites (N=450)



Study Outcomes

PRIMARY OUTCOME

- Received 1st XR-naltrexone injection while inpatient

PRIMARY HYPOTHESIS

- RP will be non-inferior to SP in the proportion of XR-naltrexone initiation
- 55% in SP vs. 70% in RP (10% NI margin, Odds Ratio of 0.67)

- **SECONDARY OUTCOMES**

Effectiveness

- Time to 1st injection, craving, withdrawal, safety

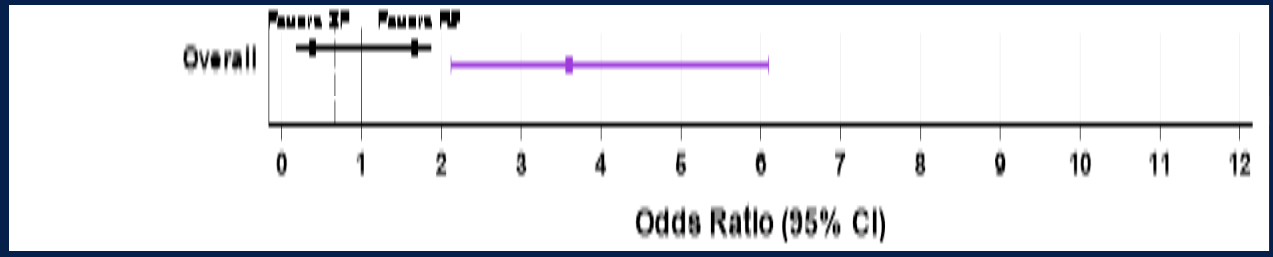
Implementation:

- Feasibility and acceptability of RP
- Implementation facilitators and barriers

Results: Primary Outcome

Received 1st XR-NTX injection

Induction Procedure	Number Enrolled	First Injection Administered While on the Unit	Odds Ratio
Rapid	225	141 **(62.7%)**	**3.60**
Standard	190	68 **(35.8%)**	
Total	415	209 (50.4%)	



- **Both noninferiority and superiority were demonstrated**
- Non-inferiority of RP to SP was demonstrated with OR of 3.60 with a 95% CI of 2.12–6.10
- With non-inferiority established, superiority of RP was tested and demonstrated (p<0.0001**)**
  - 95% CI for the odds ratio was above 0.67 and also above 1;
- The fixed effect of step was not significant (p=0.371)
- No interactions with demographic characteristics

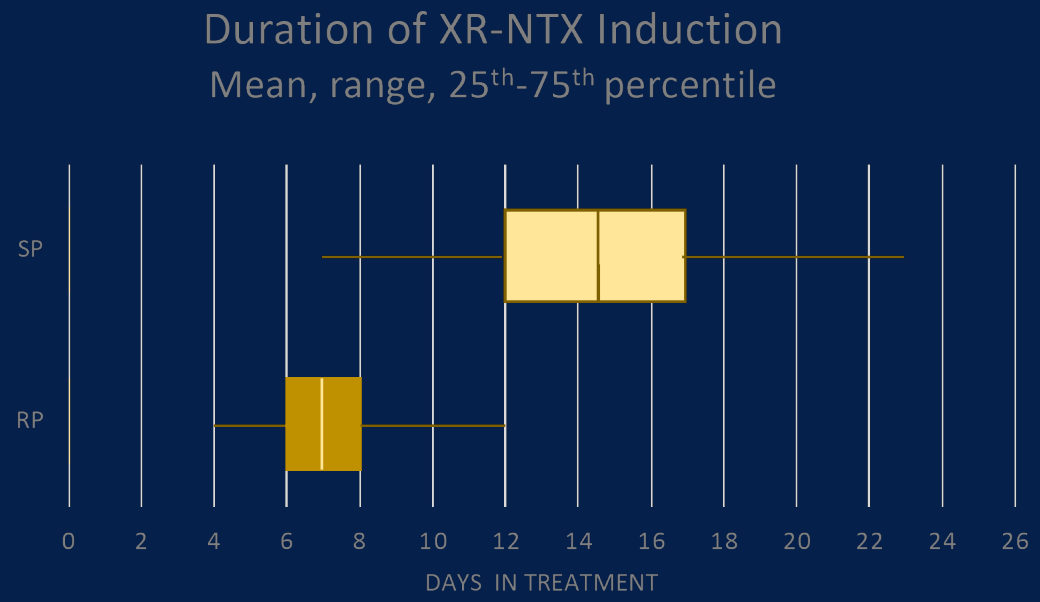
Time to Receipt of First XR-Naltrexone Injection

Standard Procedure:

Mean = **14.5 days**; SD 3.57 (7 – 23)

Rapid Procedure:

Mean = **7 days**; SD 1.42 (4 – 12)



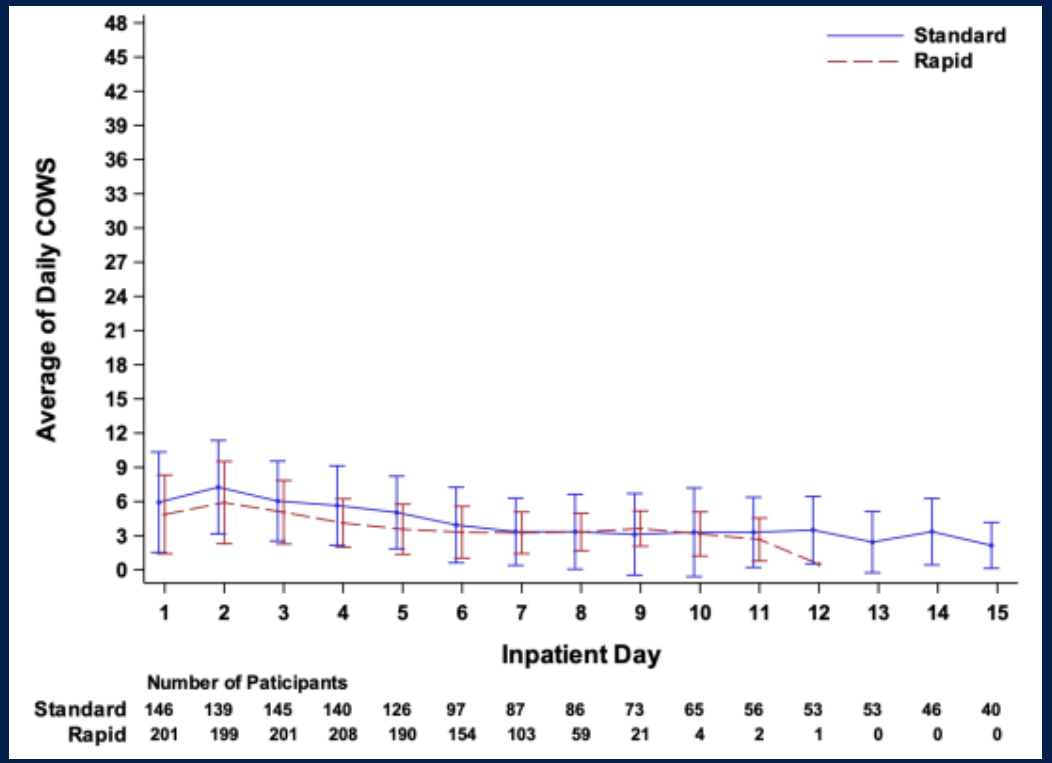
- RP Hazard Ratio (HR) was 25.4 times the HR in SP (95% CI: 11.9 – 54.1)

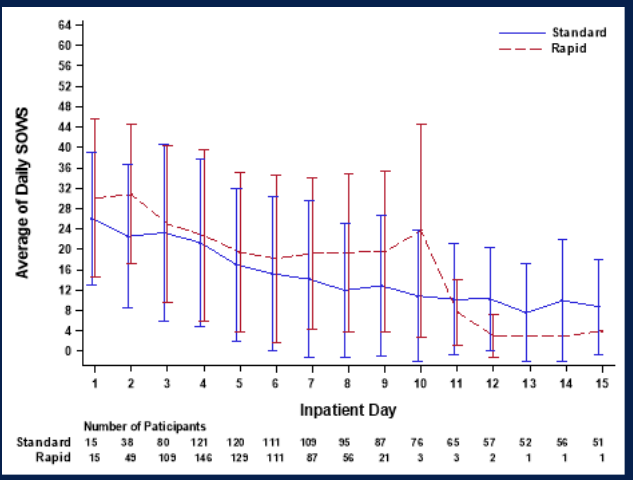
Opioid withdrawal and craving during induction phase

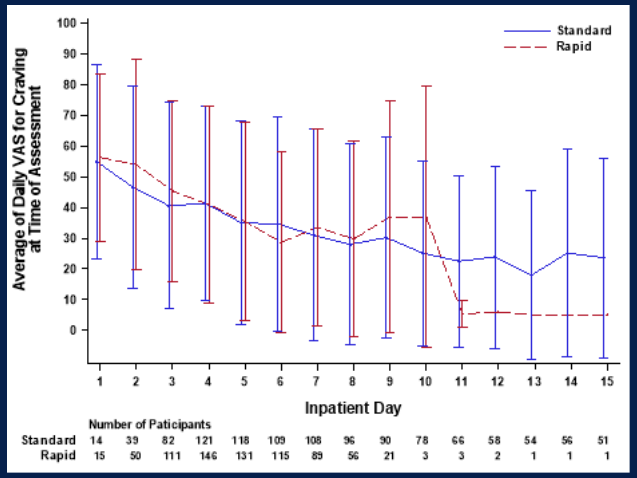
Longitudinal COWS, SOWS, and craving scores were analyzed using mixed-effects models

The effect of induction procedure was not significant for:

- COWS (p=0.54)
- SOWS (p=0.43)
- craving (p=0.07)







Early Induction Terminations by Procedure

	Standard (N=190)	Rapid (N=225)
Number of early induction terminations	122 (64.2%)	84 (37.3%)
Reason for early induction termination		
Left detox unit early ("I gotta leave")	**86 (70.5%)**	**52 (61.9%)**
Prefers other medication (buprenorphine or methadone)	25 (20.5%)	18 (21.4%)
Withdrawal symptoms were too uncomfortable	6 (4.9%)	12 (14.3%)

Safety and Adverse Events: Induction Phase

Serious Adverse Events (SAE)	Standard (N=190)	Rapid (N=225)	Fisher's P
# of participants with at least one SAE	2 (1.1%)	3 (1.3%)	1.00
Overdose	0	1	
Suicidal Ideation/ Attempt	0	1	
Medical complications (decreased level of consciousness, infectious ileitis, seizures)	2	1	

Targeted Safety Events (TSE)			
# of participants with a TSE	4 (2.1%)	12 (5.3%)	0.124
Fall event	0	4	
Acute change in mental status	1	0	
Acute medical complication likely exacerbated by the stress of w/d	3 seizures during withdrawal (1) precipitated withdrawal (2)	8 vomiting (5) precipitated withdrawal (2) wheezing/SOB* (1)	
Acute psychiatric symptoms	0	0	

Implications and Future Directions

- Expand approach of shared decision-making and rapid MOUD initiation to encompass buprenorphine and methadone as well as XR-naltrexone
  - Claims data showed only 20% admitted with OUD leave on MOUD
- Re-engineer “detoxification units” as “medication initiation units”
- More work needed on adherence to MOUD after discharge

References

1. Sullivan M, Bisaga A, Pavlicova M, et al. Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine. *Am J Psychiatry*. 2017;174(5):459-467. doi:10.1176/appi.ajp.2016.16050548