Commonwealth of Massachusetts Section 35 Commission Meeting

Expert Panel Presentation on Detoxification and Induction on MAT

Presenter: Maria Sullivan, MD, PhD.
Senior Medical Director, Clinical Research and Development, Alkermes Inc.

November 5, 2018

Extended-release injectable naltrexone

Therapeutic use in opioid dependence	Prevention of relapse to opioid dependence, following opioid detoxification[1]
Pharmacology	Opioid receptor antagonist[1]

Dosage and Administration

- The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks or once a month.
- The injection should be administered by a healthcare provider as an intramuscular (IM) gluteal injection, alternating buttocks for each subsequent injection, using the carton components provided.

Clinical considerations

- The administration of VIVITROL is not associated with the development of tolerance or dependence[1]
- Should only be used in patients who are opioid-free for a minimum of 7-10 days[1]
- Monthly injection[1]
- Please see important safety information at end of slide deck[1]

1. VIVITROL® (naltrexone for extended-release injectable suspension): US Prescribing Information. Waltham, MA: Alkermes, Inc.; December 2015.

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Induction onto XR-Naltrexone

Induction is the process of initial dosing with a medication for OUD treatment until the patient reaches a state of stability, also called initiation onto XR-NTX[1]

- Induction onto XR-NTX, VIVITROL® (naltrexone for extended-release injectable suspension) remains a challenge for many clinicians[2,3]
  - Prior to initiating VIVITROL, an opioid-free duration of a minimum of 7–10 days is recommended for patients, to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization[4]
- Clinical studies have evaluated various protocols for induction onto XR-NTX, in both inpatient and outpatient settings; success rates range 33-72%[3,5-9]
  - "If a more rapid transition from agonist to antagonist therapy is deemed necessary and appropriate by the healthcare provider, monitor the patient closely in an appropriate medical setting where precipitated withdrawal can be managed."[4]

NTX, naltrexone; OUD, opioid use disorder; XR-NTX, extended-release naltrexone

1. Center for Substance Abuse Treatment. Medications for Opioid Use Disorder. Treatment Improvement Protocol (TIP) Series 63. HHS Publication No. (SMA) 18-5063. Rockville, MD: Substance Abuse and Mental Health Services Administration, February 2018. 2. Bisaga A et al. Am J Addict. 2018;27:177-187. 3. Lee JD et al. The Lancet. 2018; 391:309-318. 4. VIVITROL® (naltrexone for extended-release injectable suspension): US Prescribing Information. Waltham, MA: Alkermes, Inc.; December 2015. 5. Bisaga A et al. Drug Alcohol Depend. 2018;187:171-178. 6. Sullivan M et al. Am. J. Psychiatry. 2017;174:459-467. 7. Mannelli P et al. Drug Alcohol Depend. 2014;138:83-88. 8. Rudolf G et al. Am J Drug and Alcohol Abuse. 2018;44:302-309. 9. Mogali S et al. Am. J. Addict. 2015;24:258-264.

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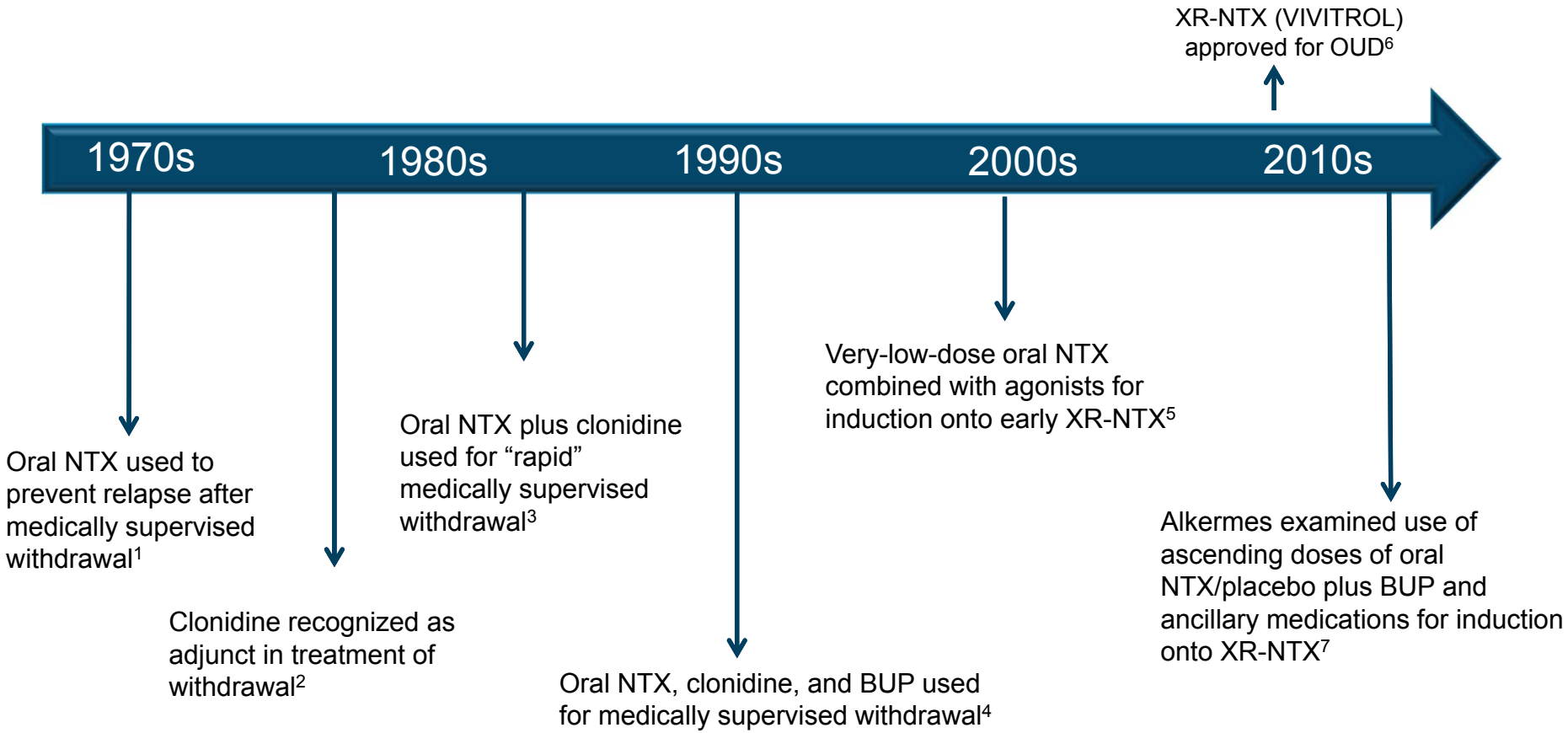
Historical Overview of Induction Strategies



BUP, buprenorphine; NTX, naltrexone; OUD, opioid use disorder; XR-NTX, extended-release naltrexone

1. Martin WR et al. Arch Gen Psychiatry. 1973;28:784–791; 2. Gold MS et al. JAMA. 1980;243:343–346; 3. Charney DS et al. Am J Psychiatry. 1986;143:831–837; 4. O'Connor PG et al. Ann Intern Med. 1997;127:526–530; 5. Mannelli P, et al. Addict Biol. 2009;14:203–213; 6. Vivitrol Prescribing Information, available at: https://www.vivitrol.com/content/pdfs/prescribing-information.pdf. Accessed November 2017; 7. Bisaga A et al. Drug Alcohol Depend. 2018;187:171-178.

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Overview of Medically Supervised Withdrawal and XR-NTX Induction

- The available scientific and clinical evidence suggest that there is no single best detoxification method but rather a set of pharmacologic approaches and treatment settings that can be customized to individual patient needs[1]
  - Can be safely and effectively accomplished in both inpatient and outpatient settings

- Strategies for medically supervised withdrawal prior to induction onto XR-NTX:

Gradual opioid agonist taper[1]	Low-dose oral NTX[2-6]	Non-opioid ancillary medications[7-10]
(± ancillary medications)	*(+ancillary medications; ± BUP)*	*(± benzodiazepine)*

BUP, Buprenorphine; NTX, Naltrexone; XR-NTX, Extended-release injectable naltrexone

1. Sigmon SC, et al. Am J Drug Alcohol Abuse. 2012;38(3):187-199; 2. Mannelli P et al. Drug Alcohol Depend. 2014;138:83–88; 3. Sullivan M et al. Am J Psychiatry. 2017;174:459–467; 4. Bisaga A, et al. Drug Alcohol Depend. 2018;187:171-178; 5. Tompkins DA et al. Poster presented at the ASAM Annual Conference; April 12–15, 2018; San Diego, USA. Poster 33; 6. Mannelli P et al. Poster presented at the ASAM Annual Conference; April 12–15, 2018; San Diego, USA. Poster 31; 7. Krupitsky EM, et al. Ann Clin Case Rep. 2017;2:1297; 8. Rudolf G, et al. Am J Drug Alcohol Abuse. 2018;44(3):302-309; 9. Growing L., et al. Cochrane Database of Systematic Reviews 2016, Issue 5; 10. FDA approves the first non-opioid treatment for management of opioid withdrawal symptoms in adults. Accessed on July 4, 2018

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Long-Acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone Versus Buprenorphine

Maria A. Sullivan, Adam Bisaga, Martina Pavlicova, C. Jean Choi, Kaitlyn Mishlen, Kenneth M. Carpenter, Frances R. Levin, Elias Dakwar, John J. Mariani, Edward V. Nunes

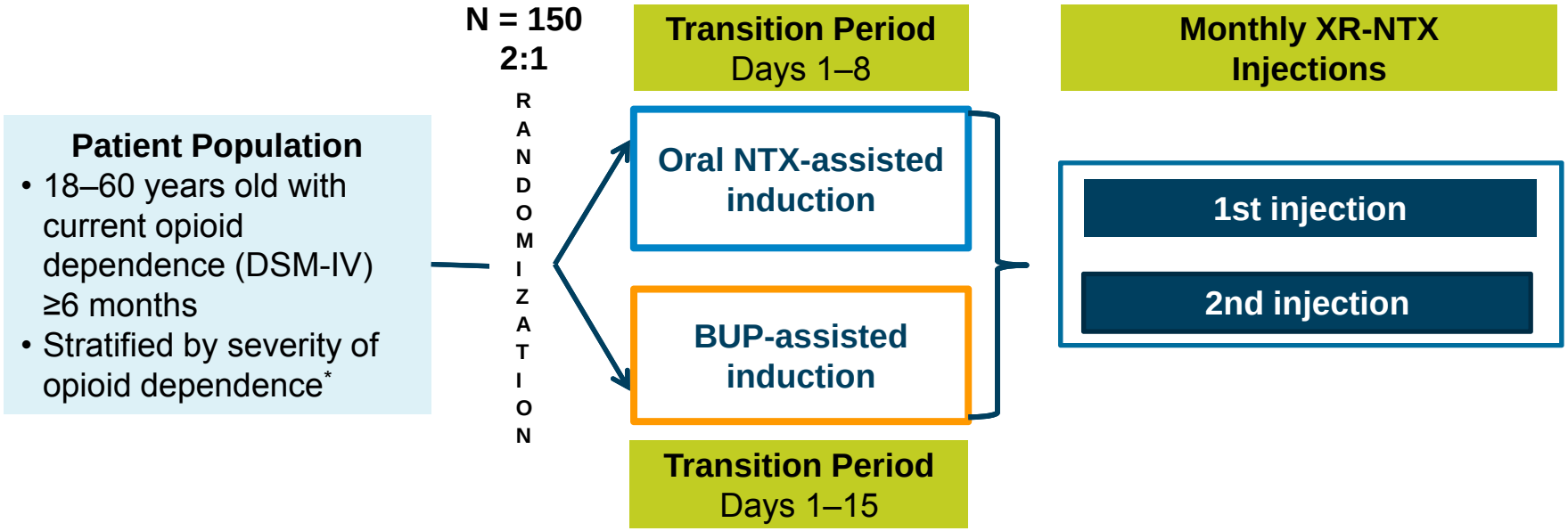
Sullivan MA et al. *Am J Psychiatry.* 2017;174:459–467

Oral NTX- vs BUP-assisted Induction Onto XR-NTX

Aims and Study Design

- A randomized trial in participants seeking treatment for heroin or prescription opioid dependence, to compare XR-NTX outpatient induction rates between two methods of opioid withdrawal management

Opioid Dependence*	Low Use	High Use
Patients, 150 (100%)	71 (47%)	79 (53%)



*Low use (≤5 bags (~10 mg) of heroin or ≤ 200 mg of morphine equivalents per day) and high use (>5 bags of heroin or >200 mg of morphine equivalents per day)
BUP, buprenorphine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; NTX, naltrexone; XR-NTX, extended-release naltrexone
Sullivan M et al. Am J Psychiatry. 2017;174:459–467

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Oral NTX- vs BUP-assisted Induction Onto XR-NTX

Dosing Regimen During Transition Period

	Day 1/2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 15
Oral NTX-assisted induction	BUP 2 mg sublingually every 1-2 hrs, up to 8 mg	Washout	NTX 1 mg	NTX 3 mg	NTX 12 mg	NTX 25 mg	**XR-NTX:** 380 mg IM	--
BUP-assisted induction		BUP 6 mg	BUP 4 mg	BUP 4 mg	BUP 2 mg	BUP 1 mg	--	**XR-NTX:** 380 mg IM
Ancillary medications*	clonidine, clonazepam, prochlorperazine, trazodone, zolpidem as needed							

* Ancillary medications offered included clonidine (0.1 mg q.i.d., plus every 4 hours as needed; maximum daily dose, 1.2 mg), clonazepam (0.5mg q.i.d.; maximumdaily dose, 2.0 mg), prochlorperazine (10 mg t.i.d.), trazodone(100 mg h.s.), and zolpidem (10 mg h.s.).

qid, 4 times daily; tid, three times daily; hs, at bedtime

BUP, buprenorphine; NTX, naltrexone; XR-NTX, extended-release naltrexone

Sullivan M et al. Am J Psychiatry. 2017;174:459–467

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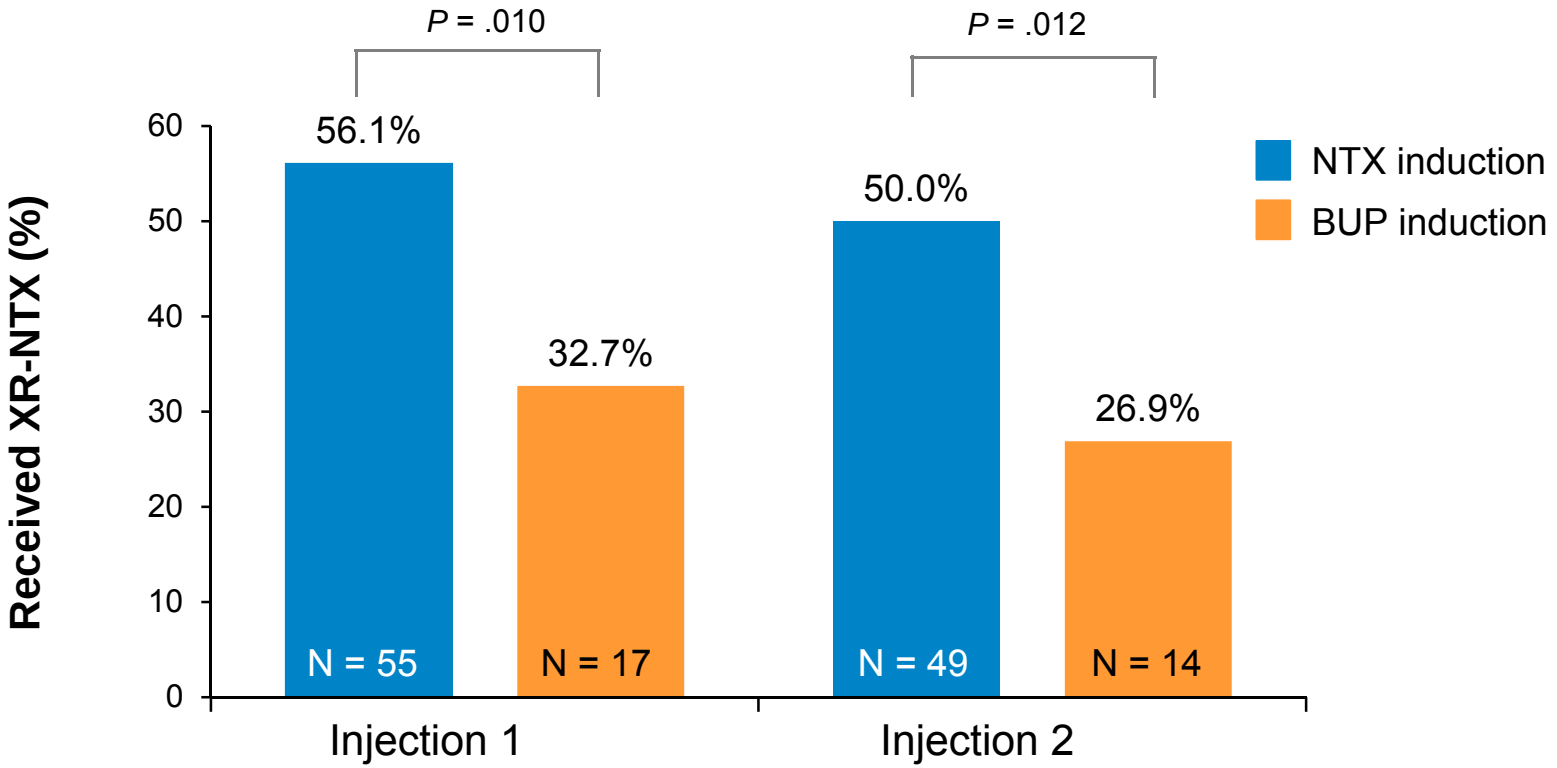
Oral NTX- vs BUP-assisted Induction Onto XR-NTX

Successful Induction on XR-NTX

- Withdrawal severity and treatment dropout during the induction period were comparable in the two treatment arms during the first 7 days of treatment



- Participants were significantly more likely to successfully initiate XR-NTX after a rapid 8-day oral NTX-assisted induction than after a standard 15-day BUP induction

BUP, buprenorphine; NTX, naltrexone; XR-NTX, extended-release naltrexone

Sullivan M et al. Am J Psychiatry. 2017;174:459–467

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Oral NTX- vs BUP-assisted Induction Onto XR-NTX

Successful Induction on XR-NTX

- Study limitations include: the study was non-blinded, and patients received more care than in typical practice.

Sullivan M et al. Am J Psychiatry. 2017;174:459–467

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Outpatient Transition to Extended-Release Injectable Naltrexone for Patients With Opioid Use Disorder: A Phase 3 Randomized Trial

Adam Bisaga, Paolo Mannelli, Miao Yu, Narinder Nangia, Christine E. Graham, D. Andrew Tompkins, Thomas R. Kosten, Sarah C. Akerman, Bernard L. Silverman, Maria A. Sullivan

Bisaga A, et al. *Drug Alcohol Depend*. 2018; 187:171-178

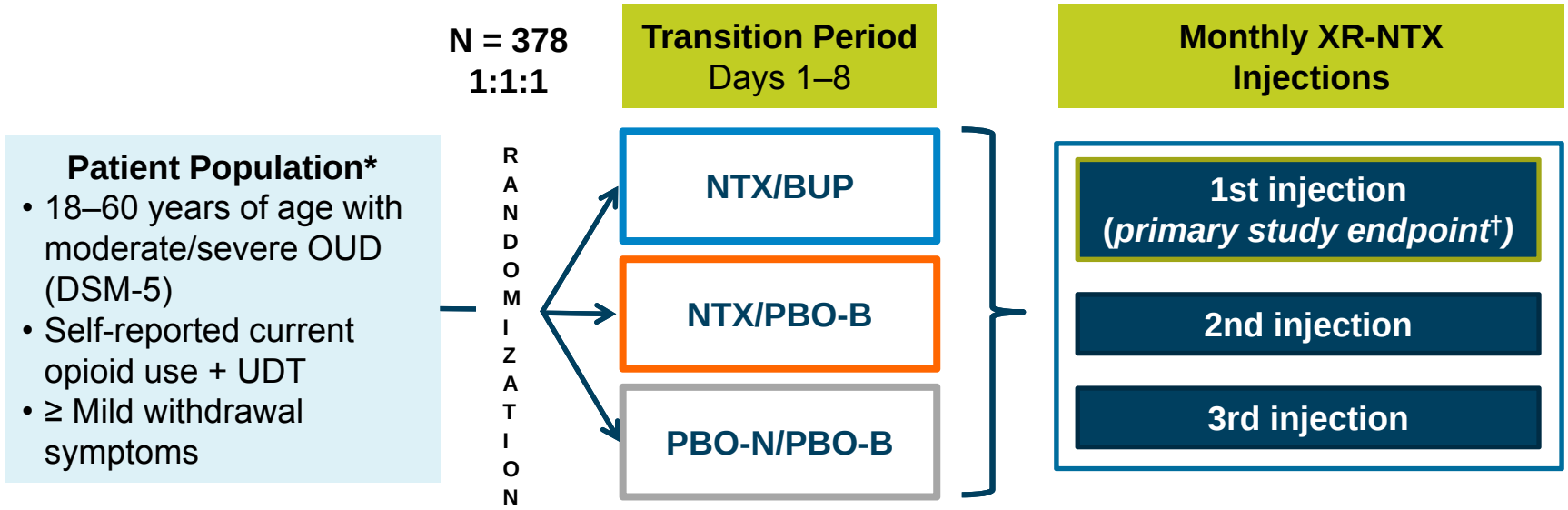
Tompkins DA et al. Poster presented at the ASAM Annual Conference; April 12–15, 2018; San Diego, USA. Poster 33

Financial support for the conduct of the research and preparation of this article was provided by Alkermes, Inc.

Bisaga: Heroin or Prescription Opioids: Transition to XR-NTX
Aim and Study Design

- Phase 3, multicenter, randomized, double-blind, PBO controlled study to examine safety and efficacy of low-dose oral NTX, combined with BUP and standing ancillary medications, to transition patients with OUD onto XR-NTX

Opioid Dependence*	Prescription Opioid	Heroin
Patients, 378 (100%)	136 (36%)	242 (64%)



*Baseline patient characteristics were similar across transition-protocol groups
†Primary endpoint: The proportion of patients who received and tolerated a XR-NTX injection
BUP, buprenorphine; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; NTX, naltrexone; OUD, opioid use disorder; PBO-B, placebo for buprenorphine; PBO-N, placebo for naltrexone; UDT, urine drug test; XR-NTX, extended-release naltrexone
Bisaga A et al. Drug Alcohol Depend. 2018;187:171-178

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Bisaga: Heroin or Prescription Opioids: Transition to XR-NTX *Dosing Regimen During Transition Period*

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
1st and 2nd Dose NTX or PBO-N	0.25 mg	0.25 mg	0.5 mg	1.5 mg	3 mg	7.5 mg	15 mg	**XR-NTX:** 380 mg IM
BUP or PBO-B	2 mg + 2 mg†	2 mg	2 mg	--	--	--	--	
Standing Ancillary Medications*	fixed doses of clonidine, clonazepam, trazodone							

*Standing ancillary medications included fixed doses of clonidine (0.1 mg tid), clonazepam (0.5 mg tid), trazodone (100 mg qhs)
2nd dose administered ≥1h after 1st dose; †Optional 2 mg buprenorphine at home
BUP, buprenorphine; NTX, naltrexone; PBO-B, placebo for buprenorphine; PBO-N, placebo for naltrexone
Bisaga A et al. Drug Alcohol Depend. 2018;187:171-178

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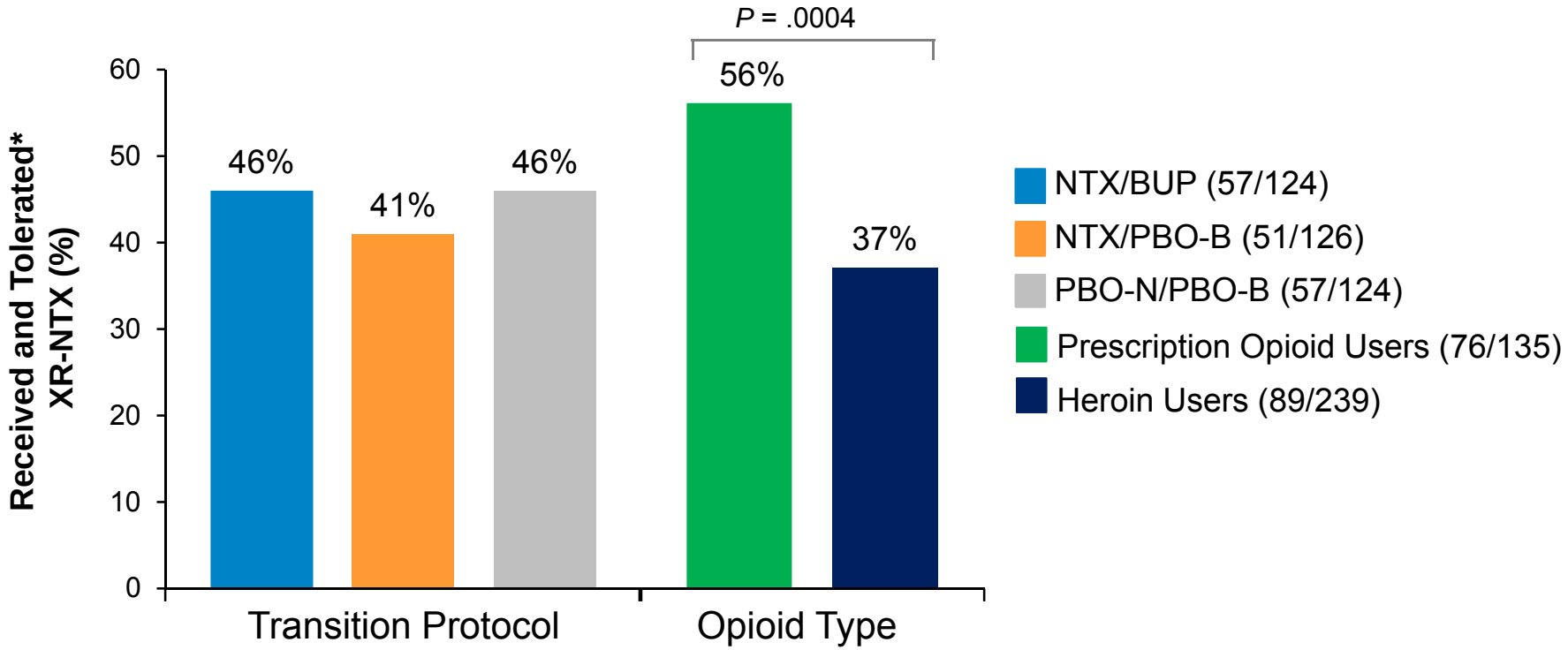
Bisaga: Heroin or Prescription Opioids: Transition to XR-NTX

Successful Induction onto XR-NTX



- Transition to XR-NTX was similar regardless of transition protocol (*P* > .383)
  - Primary study endpoint was not met
- Prescription opioid users were more likely to transition to XR-NTX than heroin users (*P* = .0004)
- Majority (57.3%) who passed naloxone challenge and received XR-NTX had opioid-positive UDT on day of induction

*Tolerance was demonstrated by mild withdrawal scores with COWS score ≤12 or SOWS score ≤10.
BUP, buprenorphine; NTX, naltrexone; PBO-B, placebo for buprenorphine; PBO-N, placebo for naltrexone; XR-NTX, extended-release naltrexone; UDT, urine drug test
Bisaga A et al. Drug Alcohol Depend. 2018;187:171-178

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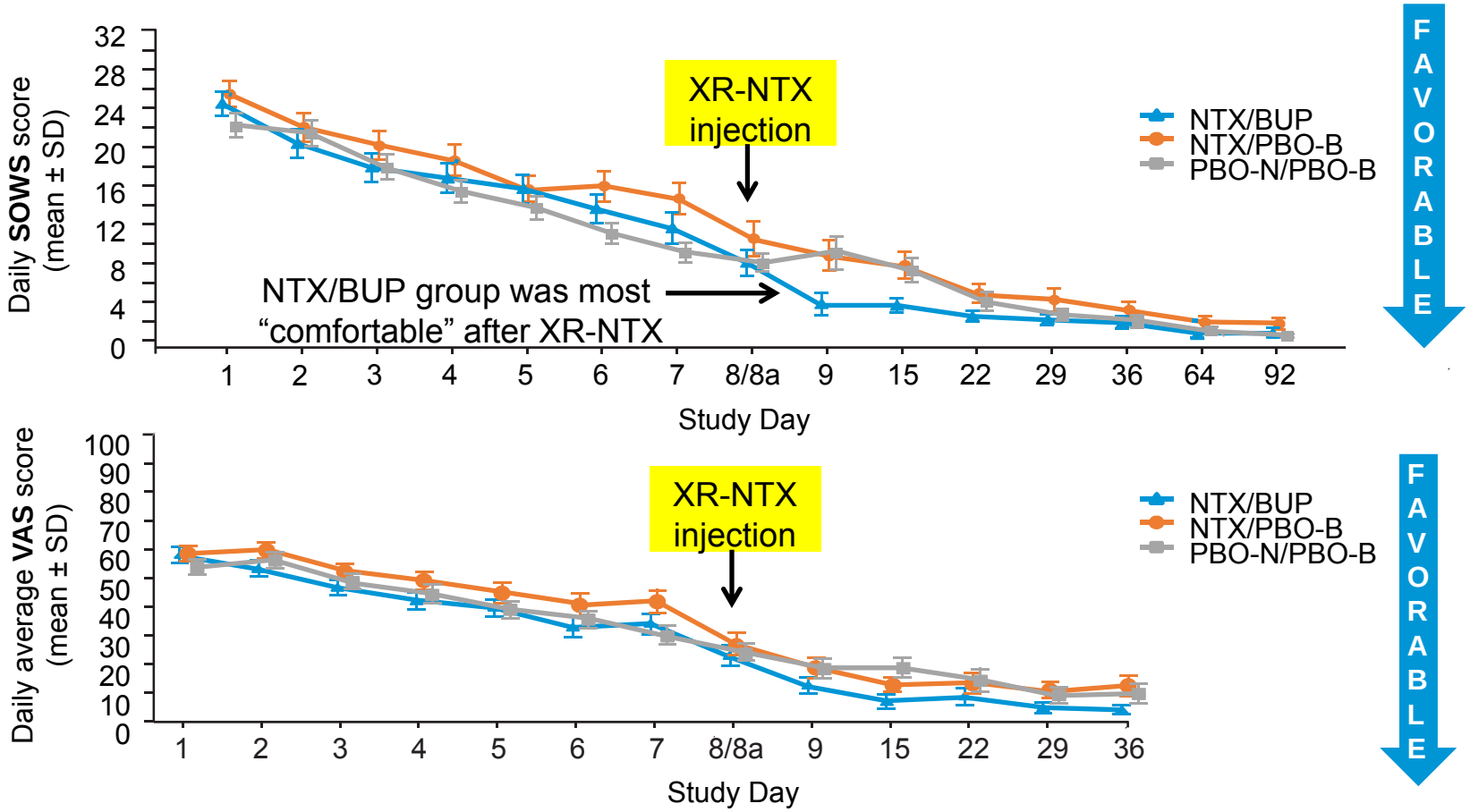
Bisaga: Heroin or Prescription Opioids: Transition to XR-NTX *Withdrawal and Craving Scores*



- Changes in COWS and SOWS were similar. Overall withdrawal scores were mild to moderate during the transition period. Craving scores declined steadily

BUP, buprenorphine; NTX, naltrexone; PBO-B, placebo-buprenorphine; PBO-N, placebo-NTX; SD, standard deviation; SOWS, Subjective Opioid Withdrawal Scale; VAS, visual analog scale; XR-NTX, extended-release naltrexone .

Bisaga A et al. Drug Alcohol Depend. 2018;187:171-178

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Bisaga: Heroin or Prescription Opioids: Transition to XR-NTX *Withdrawal and Craving Scores*

- Study limitations include: frequency and duration of study visits exceeded those common in outpatient practice, generalizability to real-world patient populations may be limited, and doses of oral naltrexone used in the study are not commercially available or FDA approved.

Bisaga A et al. Drug Alcohol Depend. 2018;187:171-178

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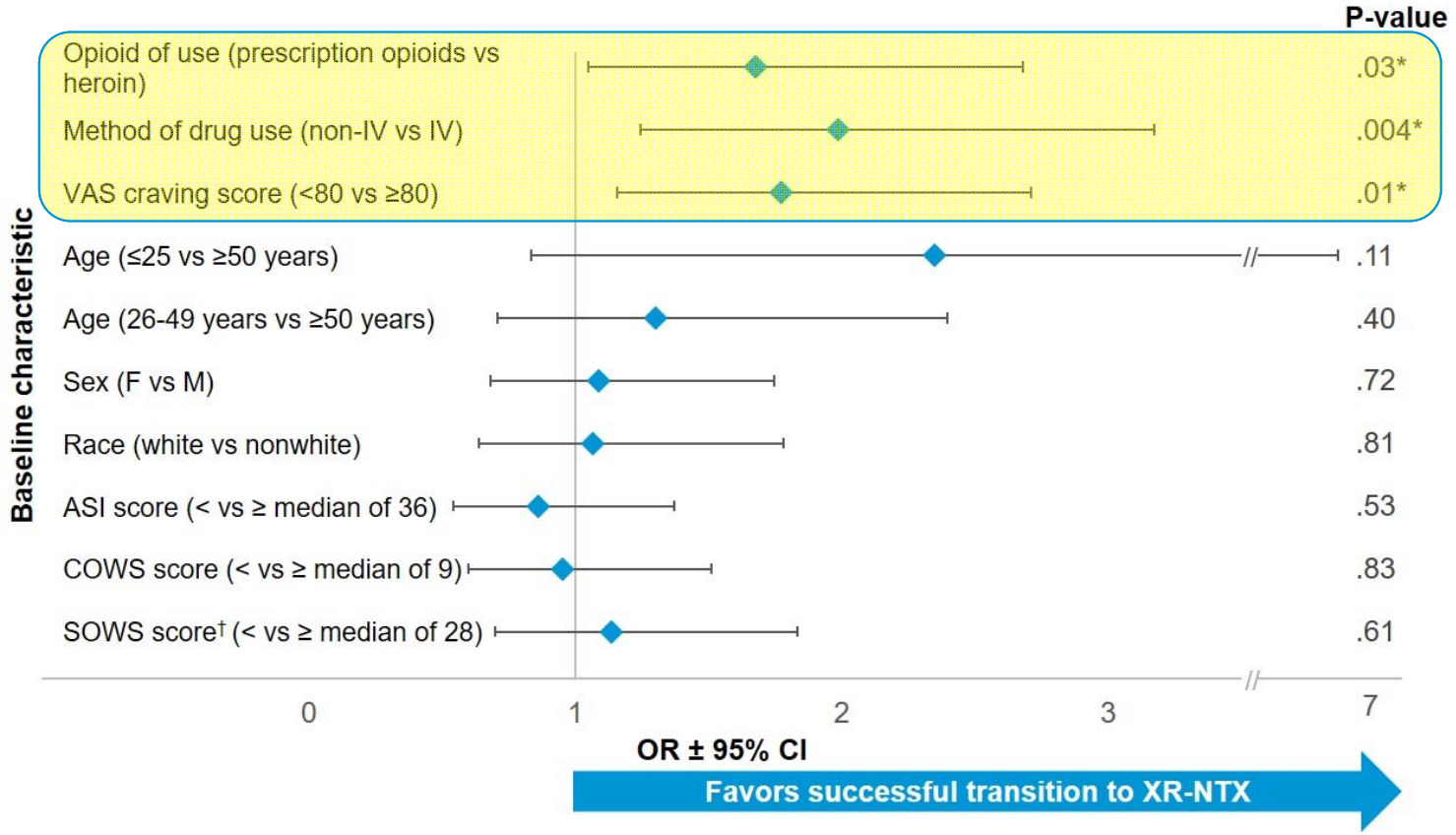
Tompkins: Heroin or Prescription Opioids: Transition to XR-NTX

Baseline Predictive Factors



- Baseline prescription opioid use, non IV drug use, and VAS score <80‡ were significantly associated with successful induction onto XR-NTX

ASI, Addiction Severity Index; CI, confidence interval; COWS, Clinical Opiate Withdrawal Scale; F, female; IV, intravenous; M, male; OR, odds ratio; SOWS, Subjective Opiate Withdrawal Scale; VAS, visual analog scale; XR-NTX, extended-release naltrexone

*P values indicate statistical significance at α = 0.05

†Accounts for the n = 41 subjects who were missing SOWS score at baseline; ‡Compared to ≥ median score of 80

Tompkins DA et al. Poster presented at the ASAM Annual Conference; April 12–15, 2018; San Diego, USA.

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Tompkins: Heroin or Prescription Opioids: Transition to XR-NTX
Baseline Predictive Factors

- Study limitations include: this was a post hoc analysis and the parent study evaluated a 7-day outpatient regimen with standing ancillary medications; therefore the findings may not be generalizable to other protocols or settings

Tompkins DA et al. Poster presented at the ASAM Annual Conference; April 12–15, 2018; San Diego, USA.

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Bisaga: Heroin or Prescription Opioids: Transition to XR-NTX
Safety Analysis

Category	NTX/BUP (N = 126) n (%)	NTX/PBO-B (N = 126) n (%)	PBO-N/PBO-B (N = 126) n (%)	Total (N = 378) n (%)
Any TEAE	44 (34.9)	31 (24.6)	48 (38.1)	123 (32.5)
TEAE by severity				
Mild	23 (18.3)	12 (9.5)	15 (11.9)	50 (13.2)
Moderate	17 (13.5)	13 (10.3)	25 (19.8)	55 (14.6)
Severe	4 (3.2)	6 (4.8)	8 (6.3)	18 (4.8)
AE leading to discontinuation	1 (0.8)	2 (1.6)	1 (0.8)	4 (1.1)
Any SADR	0	1 (0.8)	0	1 (0.3)

- Most AEs were mild to moderate in severity
  - In addition, in a poster presentation most common TEAEs presented were: diarrhea (5.8%), anxiety (5.0%), nausea (4.0%)
- Four patients (1.1%) discontinued study due to AE
- No overdoses or deaths occurred during the study

AE, adverse event; BUP, buprenorphine; NTX, naltrexone; PBO-B, placebo for buprenorphine; PBO-N, placebo for naltrexone; SADR, serious adverse drug reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Bisaga A et al. Drug Alcohol Depend. 2018;187:171-178; Bisaga A et al. Poster presented at the AAAP Annual Meeting; December 7-10, 2018; San Diego, USA.

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Induction Strategy: Non-opioid, Benzodiazepine-free Protocols

Medication	Study
Pregabalin	Krupitsky et al. 2017[1]
Clonidine	
Gabapentin	Rudolf et al. 2018[2]
Tizanidine	
Hydroxyzine	
Lofexidine	Gorodetsky et al. 2017[3]

- These studies have proposed non-opioid, non-benzodiazepine regimens[1-3]

1.Krupitsky EM et al. Ann Clin Case Rep. 2017;2:1297; 2.Rudolf G, et al. Am J Drug Alcohol Abuse. 2018;44(3):302-309; 3. Gorodetzky et al. Drug and Alcohol Dependence 176 (2017) 79–88.

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Summary

- The available scientific and clinical evidence suggest that there is no single best detoxification method but rather a set of pharmacologic approaches and treatment settings that can be customized to individual patient needs[1-13]
- A component of successful induction onto XR-NTX may be medical management of withdrawal with ancillary medications[4-13]

Strategies for medically supervised withdrawal prior to induction onto XR-NTX:

Gradual opioid agonist taper[3] *(± ancillary medications)*	Low-dose oral NTX[4-8] *(+ancillary medications; ± BUP)*	Non-opioid ancillary medications[9-12] *(± benzodiazepine)*

BUP, Buprenorphine; NTX, Naltrexone; XR-NTX, Extended-release injectable naltrexone; HCP, healthcare provider

1. Bisaga A et al. Am J Addict. 2018;27:177-187. 2. Lee JD et al. The Lancet. 2018; 391:309-318. 3. Sigmon SC, et al. Am J Drug Alcohol Abuse. 2012;38(3):187-199; 4. Mannelli P et al. Drug Alcohol Depend. 2014;138:83–88; 5. Sullivan M et al. Am J Psychiatry. 2017;174:459–467; 6. Bisaga A, et al. Drug Alcohol Depend. 2018;187:171-178; 7. Tompkins DA et al. Poster presented at the ASAM Annual Conference; April 12–15, 2018; San Diego, USA. Poster 33; 8. Mannelli P et al. Poster presented at the ASAM Annual Conference; April 12–15, 2018; San Diego, USA. Poster 31; 9. Krupitsky EM, et al. Ann Clin Case Rep. 2017;2:1297; 10. Rudolf G, et al. Am J Drug Alcohol Abuse. 2018;44(3):302-309; 11.Growing L., et al. Cochrane Database of Systematic Reviews 2016, Issue 5. 12. FDA approves the first non-opioid treatment for management of opioid withdrawal symptoms in adults. Accessed on July 4, 2018; 13. Gorodetzky et al. Drug and Alcohol Dependence 176 (2017) 79–88

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VIVITROL®

(naltrexone for extended-release injectable suspension)

Product Safety Information

For complete prescribing information please visit
https://www.vivitrol.com/content/pdfs/prescribing-information.pdf

VIVITROL®
(naltrexone for extended-release injectable suspension)

- VIVITROL is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL
  - Patients should not be actively drinking at the time of initial VIVITROL administration
- VIVITROL is indicated for the prevention of relapse to opioid dependence, following opioid detoxification
  - Opioid-dependent patients and opioid-using patients, including those being treated for alcohol dependence, should be opioid-free for a minimum of 7–10 days before starting VIVITROL
- Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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Contraindications

- Patients receiving opioid analgesics
- Patients with current physiologic opioid dependence
- Patients in acute opioid withdrawal
- Any individual who has failed the nalaxone challenge test or has a positive urine screen for opioids
- Patients who have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other component of diluent

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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Warnings and Precautions

- Vulnerability to opioid overdose
- Injection site reactions
- Unintended precipitation of opioid withdrawal
- Hepatotoxicity
- Depression and suicidality
- When reversal of VIVITROL blockade is required for pain management

- Eosinophilic pneumonia
- Hypersensitivity reactions
- Intramuscular injections
- Alcohol withdrawal
- Interference with laboratory tests

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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Warnings and Precautions
Vulnerability to Opioid Overdose: Reduced Tolerance

- Reduced tolerance to opioids after detox
  - VIVITROL blockade of exogenous opioids wanes and eventually dissipates
    - VIVITROL-treated patients may respond to lower doses of opioids than previously used
    - Previously tolerated opioid doses could be life-threatening
    - Fatal outcomes reported in patients who used opioids
      - at the end of a dosing interval
      - after missing a scheduled dose
      - after discontinuing treatment

Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after VIVITROL treatment is discontinued

Family members and caregivers should be alerted to this important information

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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Warnings and Precautions (cont'd)
Vulnerability to Opioid Overdose: Overcoming Blockade

- Attempts to overcome the opioid blockade effect of VIVITROL
  - Blockade effect of VIVITROL to exogenous opioids is surmountable
  - Potential risk to patients who attempt to overcome blockade by administering large amounts of exogenous opioids
  - Any attempt by a patient to overcome the antagonism by taking opioids is especially dangerous and may lead to life-threatening opioid intoxication or fatal overdose

Patients should be told of the serious consequences of trying to overcome the opioid blockade

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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Warnings and Precautions
Injection Site Reactions

- VIVITROL injections may be followed by:
  - pain, tenderness, induration, swelling, erythema, bruising, pruritus
  - some injection site reactions may be very severe
- Additional cases of injection site reactions in postmarketing period:
  - induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis

Patients should be informed that any concerning injection site reactions should be brought to attention of the healthcare provider

Patients exhibiting signs of abscess, cellulitis, necrosis, or extensive swelling should be evaluated by a physician to determine if referral to a surgeon is warranted

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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Warnings and Precautions
Unintended Precipitation of Opioid Withdrawal

- Opioid-dependent patients, including those treated for alcohol dependence should be opioid free (including tramadol) for a minimum of 7-10 days before starting VIVITROL treatment
  - to prevent occurrence of precipitated withdrawal in patients dependent on opioids, or exacerbation of a preexisting subclinical abstinence syndrome
  - patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for as long as two weeks
- Patients may experience precipitated withdrawal despite having a negative urine toxicology screen or tolerating a naloxone challenge test
- Patients treated for alcohol dependence with VIVITROL should be assessed for underlying opioid dependence and for any recent use of opioids prior to initiation of treatment with VIVITROL
- Patients necessitating a more rapid transition from agonist to antagonist therapy should be closely monitored in an appropriate medical setting where precipitated withdrawal can be managed

Healthcare providers should always be prepared to manage withdrawal symptomatically with non-opioid medications

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

Alkermes

Warnings and Precautions
Hepatotoxicity

- Cases of hepatitis and clinically significant liver dysfunction were observed in association with VIVITROL exposure during the clinical development program and in the postmarketing period.
- Transient, asymptomatic hepatic transaminase elevations were also observed
  - potential causative or contributory etiologies
    - pre-existing alcoholic liver disease
    - hepatitis B and/or C infection
    - concomitant usage of other potentially hepatotoxic drugs

Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis

Use of VIVITROL should be discontinued in the event of symptoms and/or signs of acute hepatitis

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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Warnings and Precautions
Depression and Suicidality

- Opioid- and alcohol-dependent individuals, including those taking VIVITROL, should be monitored for the development of depression or suicidal thinking
- Families and caregivers of patients being treated with VIVITROL should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's healthcare provider

Alcohol Dependence

- **Controlled clinical trials:** adverse events of a suicidal nature were infrequent overall, but were more common in patients treated with VIVITROL than in placebo treated patients (1% vs 0)
- **24-week, placebo-controlled pivotal trial:** adverse events involving depressed mood were reported by 10% of patients treated with VIVITROL 380 mg as compared to 5% of patients treated with placebo injections

Opioid Dependence

- **Open-label, long-term safety study:** adverse events of a suicidal nature were reported by 5% of opioid-dependent patients treated with VIVITROL 380 mg and 10% of opioid-dependent patients treated with oral naltrexone.
- **24-week, placebo-controlled pivotal trial:** adverse events involving depressed mood or suicidal thinking were not reported by any patient in either treatment group (VIVITROL 380 mg or placebo)

1. VIVITROL Prescribing Information. Alkermes, Inc.; 2013.
2. Garbutt JC, et al. *JAMA.* 2005;293:1617-1625.
3. Krupitsky E, et al. *Lancet.* 2011:377;1506-1513.

Warnings and Precautions
Reversal of VIVITROL Blockade for Pain Management

- In an emergency situation involving patients receiving VIVITROL, suggestions for pain management include:
  - regional analgesia
  - non-opioid analgesics
- If opioid therapy is required as part of anesthesia or analgesia
  - patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of a surgical or diagnostic procedure
  - opioid therapy must be administered by individuals specifically trained in the use of anesthetic drugs and the management of respiratory effects of potent opioids
    - specifically, establishment and maintenance of a patent airway and assisted ventilation

Irrespective of the drug chosen to reverse VIVITROL blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

Alkermes

Warnings and Precautions
Eosinophilic Pneumonia

- **Eosinophilic pneumonia**
  - Clinical trials: one diagnosed case, one suspected case:
    - Both cases required hospitalizations, and resolved after treatment with antibiotics and corticosteroids
    - Similar cases reported in postmarketing use
  - Diagnosis should be considered if patients develop progressive dyspnea and hypoxemia

Patients should be warned of the risk of eosinophilic pneumonia, and advised to seek medical attention should they develop symptoms of pneumonia

Clinicians should consider the possibility of eosinophilic pneumonia in patients who do not respond to antibiotics

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

Alkermes

Warnings and Precautions
Hypersensitivity

- **Hypersensitivity reactions (including anaphylaxis)**
  - Cases of urticaria, angioedema, and anaphylaxis have been observed with use of VIVITROL in the clinical trial setting and postmarketing use

Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis

In the event of a hypersensitivity reaction, patients should be advised to seek immediate medical attention in a healthcare setting prepared to treat anaphylaxis. The patient should not receive any further treatment with VIVITROL

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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Warnings and Precautions

Intramuscular Injections, Alcohol Withdrawal, Interference with Laboratory Tests

- **Intramuscular injections**
  - As with any intramuscular injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder (e.g., hemophilia and severe hepatic failure)
- **Alcohol withdrawal**
  - Use of VIVITROL does not eliminate or diminish alcohol withdrawal symptoms
- **Interference with laboratory tests**
  - VIVITROL may be cross-reactive with certain immunoassay methods for the detection of drugs of abuse (especially opioids) in urine
  - For further information, reference to the specific immunoassay instructions is recommended

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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Most Frequent Adverse Reactions

Alcohol Dependence[1] (occurring in ≥5%)

- nausea
- vomiting
- injection site reactions (including induration, pruritus, nodules and swelling)
- muscle cramps
- dizziness or syncope
- somnolence or sedation
- anorexia
- decreased appetite or other appetite disorders

Opioid Dependence[2] (occurring in ≥2%)

- hepatic enzyme abnormalities
- injection site pain
- nasopharyngitis
- insomnia
- toothache

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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Possible Serious Adverse Reactions

- Severe injection site reactions
- Eosinophilic pneumonia
- Serious allergic reactions
- Unintended precipitation of opioid withdrawal
- Accidental overdose
- Depression and suicidality

VIVITROL Prescribing Information. Alkermes, Inc.; 2013.

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