Treatment of Methamphetamine Use Disorder Using Injectable Naltrexone and Oral Bupropion

Madhukar H. Trivedi, M.D.

Presented at ASAM State of the Art Course 2021

Disclosure Information

Madhukar H. Trivedi, MD

In the last 36 months, Dr. Trivedi has served as a consultant or advisor for ACADIA PHARMACEUTICALS INC., Akili Interactive, ALKERMES INC (Pub Steering Comm-ALKS5461), Allergan Sales LLC, Alto Neuroscience, Inc. , Applied Clinical Intelligence, LLC (ACI), Axome Therapeutics, Boehringer Ingelheim, Engage Health Media, Gh Research, GreenLight VitalSign6, Inc., Heading Health, Inc., Health Care Global Village, Janssen – Cilag.SA, Janssen Research and Development, LLC (Adv Committee Esketamine), Janssen Research and Development, LLC (panel for study design for MDD relapse), Janssen - ORBIT, Legion Health, Jazz Pharmaceuticals, LUNDBECK RESEARCH U.S.A, Medscape, LLC, Merck Sharp & Dohme Corp., Mind Medicine (MindMed) Inc., Myriad Neuroscience, Neurocrine Biosciences Inc, Navitor, Pharmaceuticals, Inc., Noema Pharma AG, Orexo US Inc., Otsuka Pharmaceutical Development & Commercialization, Inc. (PsychU, MDD Section Advisor), Otsuka America Pharmaceutical, Inc. (MDD expert), Pax Neuroscience , Perception Neuroscience Holdings, Inc., Pharmerit International, LP, Policy Analysis Inc., Sage, Therapeutics, Rexahn Pharmaceuticals, Inc., Sage Therapeutics, Signant Health, SK Life Science, Inc., Takeda Development Center Americas, Inc., The Baldwin Group, Inc., and Titan Pharmaceuticals, Inc. Dr. Trivedi also received editorial compensation from Oxford University Press.

Session Learning Objectives

At the end of the session, you will be able to:

- Outline the current state of evidence for methamphetamine use disorder in the U.S.
- Describe the evidence for the efficacy of the combination of bupropion and extended-release naltrexone for the treatment of methamphetamine use disorder.
- Describe the evidence for the safety of the combination of bupropion and extended-release naltrexone for the treatment of methamphetamine use disorder.

Methamphetamine Crisis

- Methamphetamine use disorder is persistently rising in the United States.
- Methamphetamine is a leading cause of overdose deaths in the Midwest and West.
- Despite this crisis being identified as a public health goal, there is no FDA-approved medication for methamphetamine use disorder.

Hedegaard et al., 2017; Ellis et al., 2018; Ashok et al., 2017; Soares and Pereira, 2019

ADAPT-2 Background and Rationale

- Promising candidates showing preliminary clinical utility include naltrexone and bupropion
- Combination of bupropion + naltrexone predicated on potentially complementary effects as shown in clinical research
- CTN-0054 ADAPT-MD pilot trial: Open-label study using bupropion + naltrexone for MA dependent participants showed promising results

Hanson, 2004; Newton et al., 2006; Ornellas & Chavez, 2011

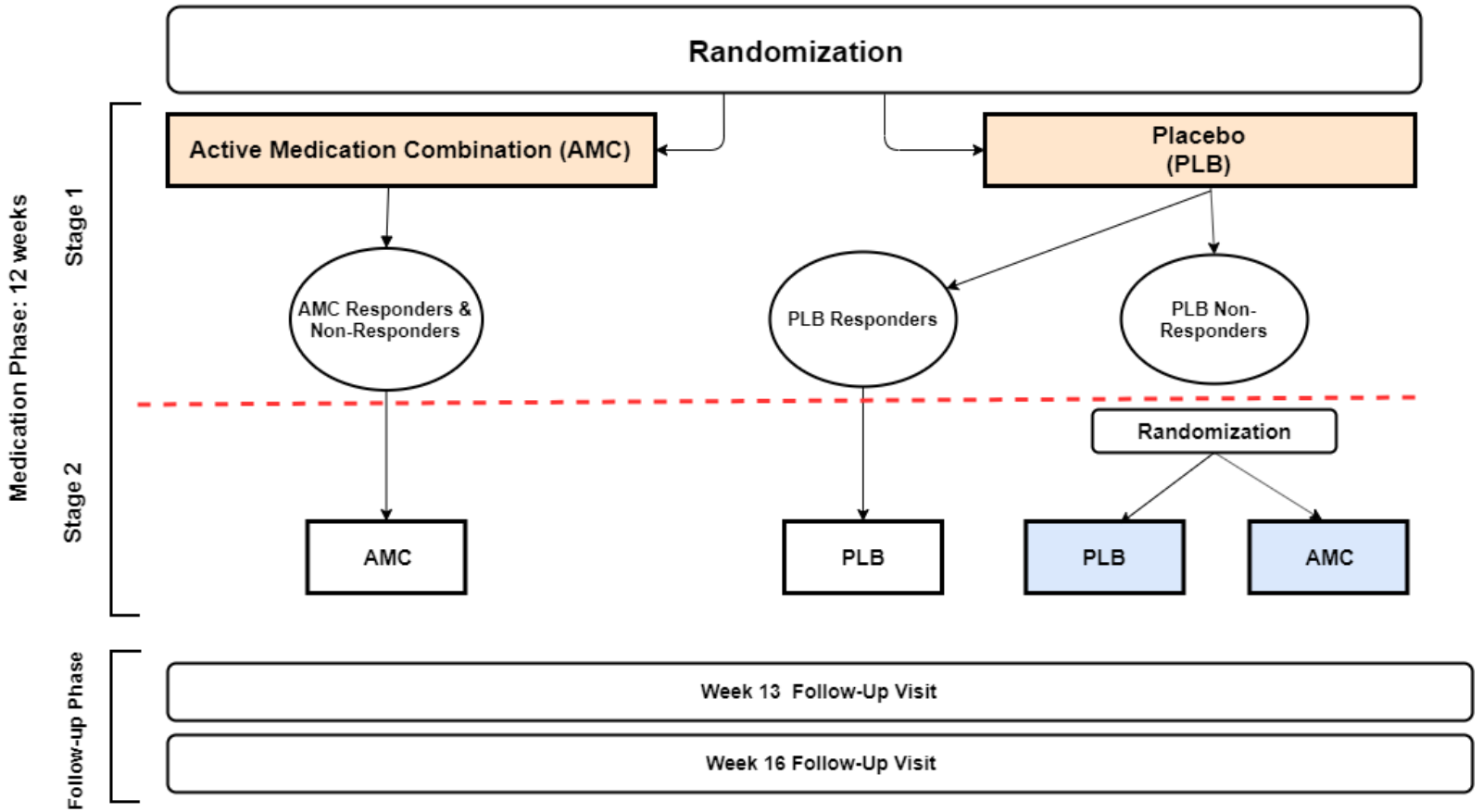
ADAPT-2 Study Medications

- **Naltrexone** appears to:
  - Reduce reinforcing effects of amphetamine
  - Reduce likelihood of relapse
  - Decrease craving

- **Bupropion** (typically 300mg/day) appears to:
  - reduce cue-craving
  - decrease methamphetamine use

Trivedi et al., 2021

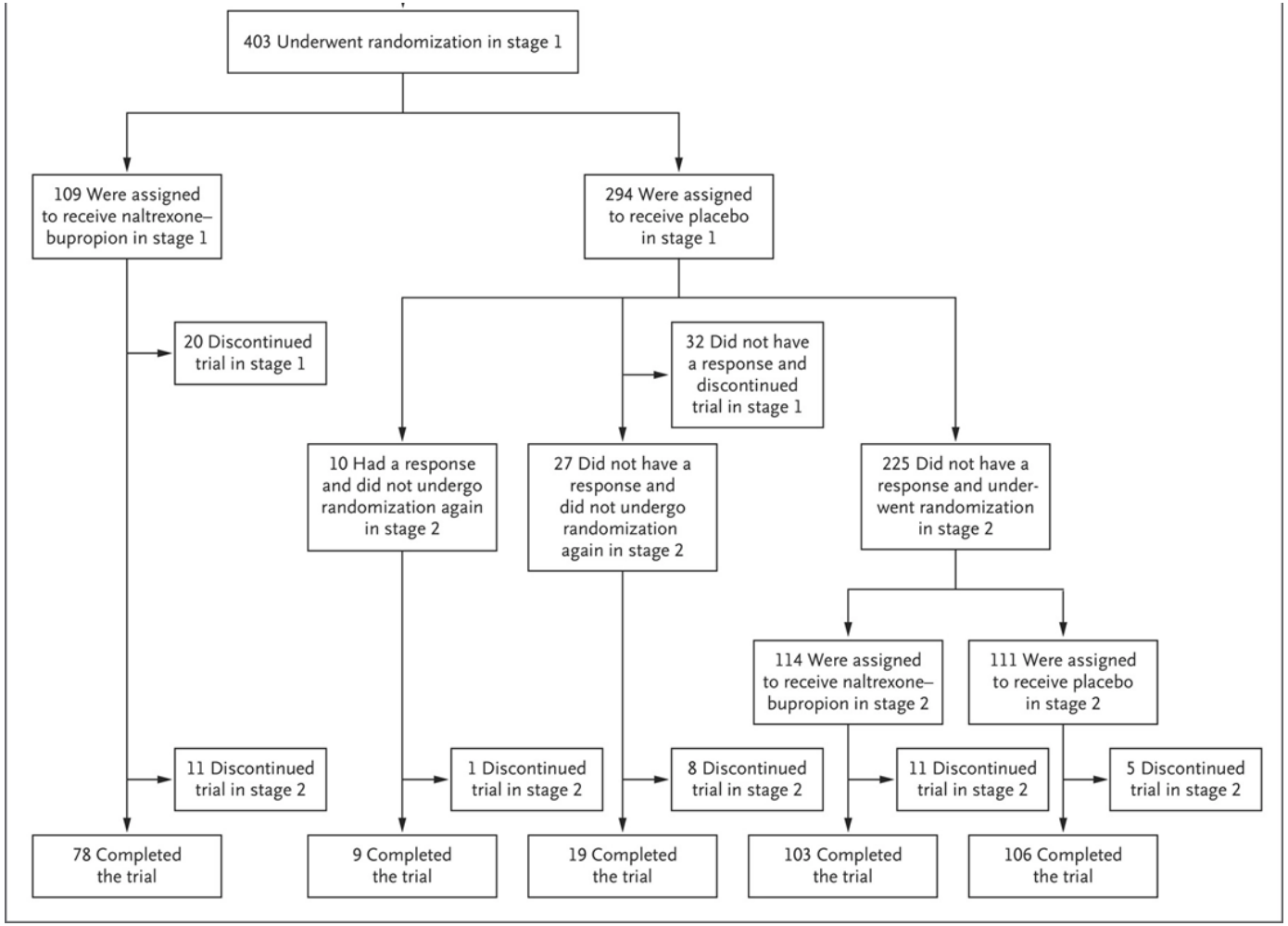
ADAPT-2 Study Schema: Unmasked



Primary Outcomes

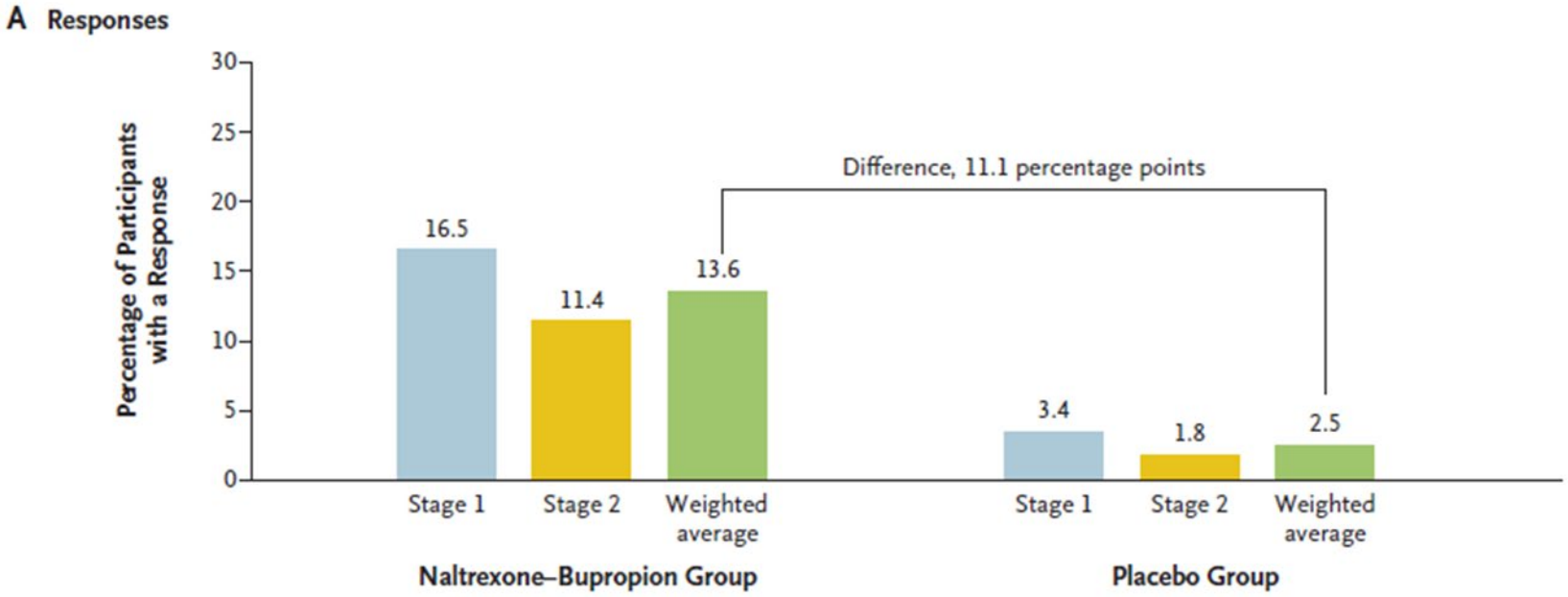
- **Primary** efficacy outcome measure
  - Methamphetamine negative UDS results in Medication Phase (AMC vs PLB)
- "**Responder**": Participants who provide at least 3 of 4 total UDS negative for methamphetamine during evaluation periods
  - Stage 1 evaluation period: Weeks 5 and 6
  - Stage 2 evaluation period: Weeks 11 and 12
- **Primary safety outcomes**: Adverse Events and Serious Adverse Events

Screening and Randomization



Trivedi et al., 2021

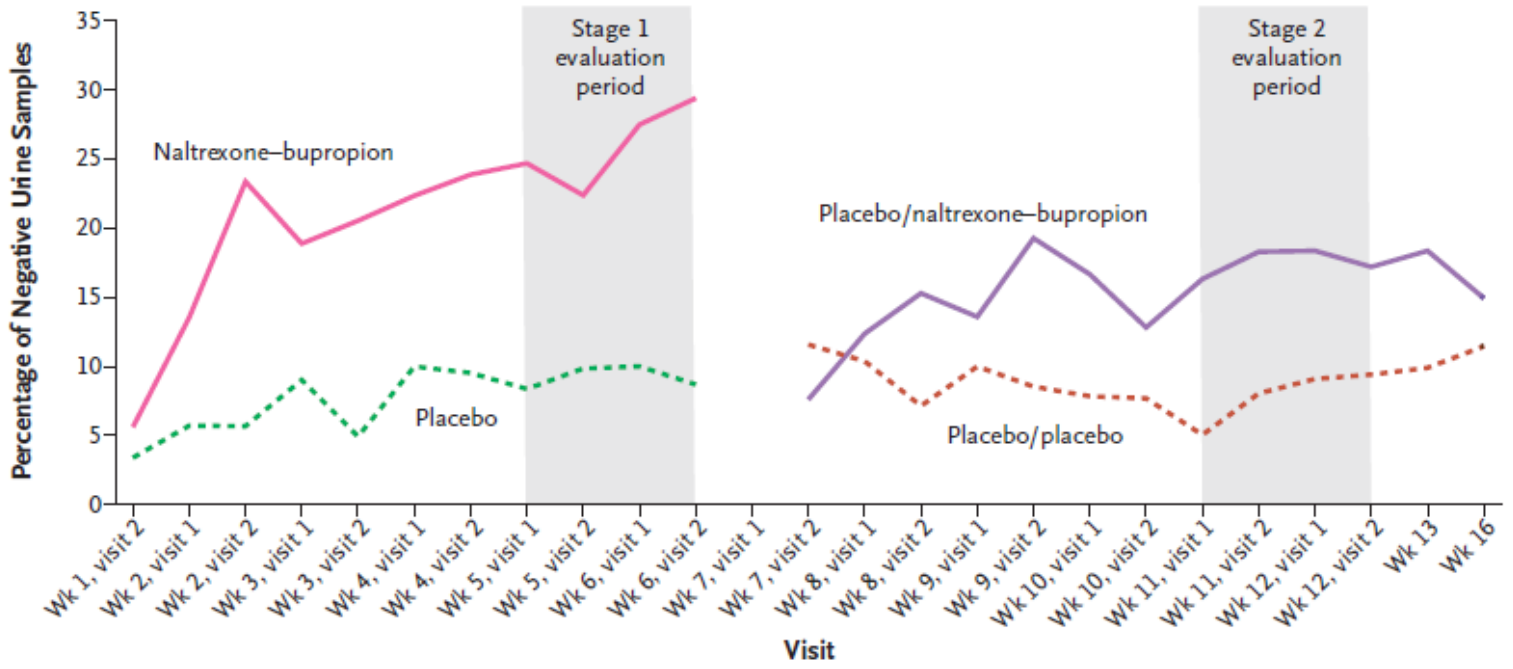
Weighted Outcome Primary Result



Trivedi et al., 2021

Weighted Outcome Primary Result

B **Methamphetamine-Negative Urine Samples**

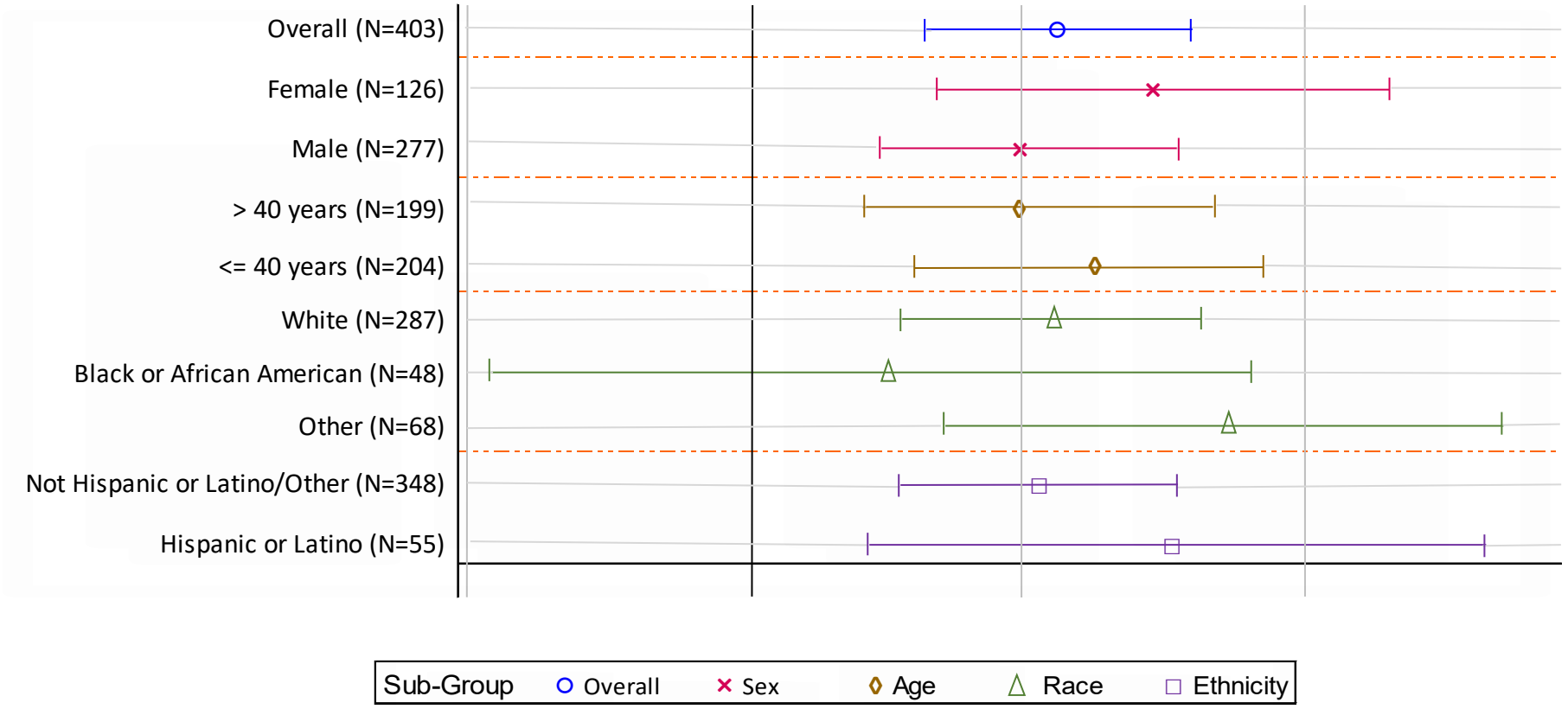


No. of Urine Samples Obtained at Each Visit	Stage 1											Stage 2												
Naltrexone–bupropion	89	96	77	90	73	85	67	81	67	80	68													
Placebo	265	280	229	266	223	260	210	239	203	240	207													
Placebo/naltrexone–bupropion												92	97	85	103	83	96	78	98	82	98	93	98	87
Placebo/placebo												95	106	84	100	82	102	91	99	87	99	85	101	96

Trivedi et al., 2021

Repeated Primary Analysis, Separated by Sex, Age, Race, Ethnicity

Weighted Treatment effect, *h* (95% CI) by Sub-Groups



Primary Outcome Covariate Adjusted Analysis Results: ITT Population		
Model Results	Treatment Effect	p-value
Treatment Effect	0.1095	**<0.0001**
Other Covariates in the Model		
Site		0.1108
Age at onset of methamphetamine use		0.3037
Baseline number of methamphetamine use days self-reported		0.3154
Baseline IV methamphetamine use self-reported		0.0911
Number of DSM-5 criteria met during screening		0.1859
Baseline number of days of cigarette or e-cigarette use self-reported		0.1573
Baseline Treatment Effectiveness Assessment Score		0.2301
Baseline average Visual Analog Craving Scale Score		0.8640

Covariate adjusted model showed results consistent with the primary outcome analysis.

ADAPT Secondary Outcome Results

Other Methamphetamine UDS-Derived Results

Treatment Effectiveness Score (TES) – proportion of 12 UDS that are MA-negative, within each stage:

Stage 1		Stage 2		Results		
PLB Mean TES	AMC Mean TES	PLB Mean TES	AMC Mean TES	Treatment Effect	Std. Error H	*p*-Value
0.114	0.196	0.126	0.184	0.068	0.016	**<0.001**

Note: N=403, Weight used 0.43, continuation rate 0.792, test statistic Z 4.254

ADAPT Secondary Outcome Results

Other Methamphetamine UDS-Derived Results

Number of visits with methamphetamine negative UDS results, within each stage:

Stage 1		Stage 2		Results	
PLB # Visits MA-Negative UDS	AMC # Visits MA-Negative UDS	PLB # Visits MA-Negative UDS	AMC # Visits MA-Negative UDS	Treatment Effect	*p*-Value
1.474	2.449	1.613	2.309	0.815	**<0.001**

Note: N = 403, Weight 0.43, continuation rate 0.792, test statistic (z) 4.026

ADAPT Secondary Outcome Results

Other Methamphetamine UDS-Derived Results

Number of consecutive visits with methamphetamine negative UDS:

Stage 1		Stage 2		Results	
PLB # Consecutive Visits MA-Negative UDS	AMC # Consecutive Visits MA-Negative UDS	PLB # Consecutive Visits MA-Negative UDS	AMC # Consecutive Visits MA-Negative UDS	Treatment Effect	*p*-Value
1.300	2.126	1.373	2.052	0.742	**<0.001**

Note: N = 403, Weight 0.43, continuation rate 0.792, test statistic (z) 3.761

Self-Reported Changes in Methamphetamine Use & Craving

Use from Timeline Follow Back (TLFB)

Stage 1: Mean Change from Baseline		Stage 2: Mean Change from End of Stage 1		Results	
PLB Days of MA Use	AMC Days of MA Use	PLB Days of MA Use	AMC Days of MA Use	Treatment effect	p-value
0.140	0.272	0.160	0.253	0.110	**<0.001**

Note: Weight 0.43, continuation rate 0.792, test statistic (Z) 5.666

Craving from VAS

Stage 1: Mean Change from Baseline		Stage 2: Mean Change from End of Stage 1		Results	
PLB Days of MA Use	AMC Days of MA Use	PLB Days of MA Use	AMC Days of MA Use	Treatment effect	p-value
-21.860	-29.599	-20.119	-31.339	-9.724	**<0.001**

Note: N = 392, Weight 0.43, continuation rate 0.792, test statistic (z) -4.69

Outcomes Related to Life Quality

- **Treatment Effectiveness Assessment (TEA)**
  - More improvement (from baseline) in AMC than PLB, in both stages
  - **Overall significant effect ($p<0.0001$)**

- **QoL Outcomes**
  - 3 separate types: Physical Health, Mental Health, Activities
  - More improvement (from baseline) in AMC than PLB, in both stages
  - Not significant

Depressive Symptoms from PHQ-9

Stage 1: Mean Change from Baseline		Stage 2: Mean Change from End of Stage 1		Results	
PLB PHQ-9	AMC PHQ-9	PLB PHQ-9	AMC PHQ-9	Treatment effect	p-value
-2.946	-4.458	-3.362	-4.042	-1.039	0.016

Note: N = 403, Weight 0.43, continuation rate 0.792, test statistic (z) -2.41

Treatment Effectiveness Assessment (TEA)

Stage 1: Mean Change from Baseline		Stage 2: Mean Change from End of Stage 1		Results	
PLB TEA Score	AMC TEA Score	PLB TEA Score	AMC TEA Score	Treatment effect	p-value
2.178	6.495	2.450	6.222	4.006	**<0.001**

Note: N=306, Weight 0.43, continuation rate 0.792, test statistic (z) 4.558

PHQ-9: Suicide Endorsement

PHQ-9: Suicide Item #9:

Over the past 2 weeks, how often have you been bothered by thoughts that you would be better off dead, or thoughts of hurting yourself in some way?

Stage 1		Stage 2		Results		
Placebo Rate	AMC Rate	Placebo Rate	AMC Rate	Treatment effect	p-value	NNT
0.029	0.025	0.030	0.021	-0.007	0.693	-140.1

Note: N=403, Weight 0.43, randomization fraction 0.37, continuation rate 0.792, test statistic (z) -0.504, 95% Lower limit -0.035

Oral Bupropion Blood Levels

Summary of Oral Medication Blood Levels in AMC Participants by Stage				
		Stage 2		
	Stage 1	Re-randomized	Not Re-randomized	Total
	AMC (N=109)	Placebo/AMC (N=114)	AMC (N=109)	(N=223)
Bupropion adherence[1]				
Visit 0401	72/76			
Visit 0701	65/68			
Visit 1001		73/80	50/56	123/136
Visit 1202		77/80	55/55	132/135
Hydroxybupropion adherence[2]				
Visit 0401	75/76			
Visit 0701	68/68			
Visit 1001		79/80	54/56	133/136
Visit 1202		77/80	55/55	132/135

[1] A participant was considered adherent if bupropion blood level was greater than 0.500 ng/mL.
[2] A participant was considered adherent if hydroxybupropion blood level was greater than 1.00 ng/mL.

Final Takeaways

- Even in face of grim mortality rates due to methamphetamine disorder in the US, there is still no FDA-approved treatment.
- This is the first large study to present promising results.
- A treatment that involves multiple on-site injections would be more promising than sending patients home with oral medication, where there is no confirmation of consumption.
- Future directions include examination other interventions to increase adherence and/or are fast acting.

References

1. Hedegaard H, Bastian BA, Trinidad JP, Spencer MR, Warner M. Regional differences in the drugs most frequently involved in drug overdose deaths: United States, 2017. Natl Vital Stat Rep 2019; 68:1-16.
2. Ellis MS, Kasper ZA, Cicero TJ. Twin epidemics: the surging rise of methamphetamine use in chronic opioid users. Drug Alcohol Depend 2018; 193: 14-20.
3. Ashok AH, Mizuno Y, Volkow ND, Howes OD. Association of stimulant use with dopaminergic alterations in users of cocaine, amphetamine, or methamphetamine: a systematic review and meta-analysis. JAMA Psychiatry 2017; 74: 511-9.
4. Mooney LJ, Hillhouse MP, Thomas C, et al. Utilizing a two-stage design to investigate the safety and potential efficacy of monthly naltrexone plus once-daily bupropion as a treatment for methamphetamine use disorder. J Addict Med 2016; 10: 236-43.
5. Trivedi MH, Walker R, Ling W, et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. N Engl J Med. 2021;384(2):140-153.

Questions?

Madhukar H. Trivedi, M.D.
Madhukar.Trivedi@utsouthwestern.edu