Pharmaceutical Strategies for Treatment of Methamphetamine Use Disorder

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Learning Objectives

- Participants will review the outcome of a study with promising results for treatment of stimulant use disorder with bupropion and naltrexone
- Participants will learn about treatment modalities involving on-site injections or oral medications

Disclosures

Dr. Jha has received contract research grants from Acadia Pharmaceuticals and Janssen Research & Development, educational grant to serve as Section Editor of the Psychiatry & Behavioral Health Learning Network, consultant fees from Eleusis Therapeutics US, Inc, and honoraria for CME presentations from North American Center for Continuing Medical Education and Global Medical Education.

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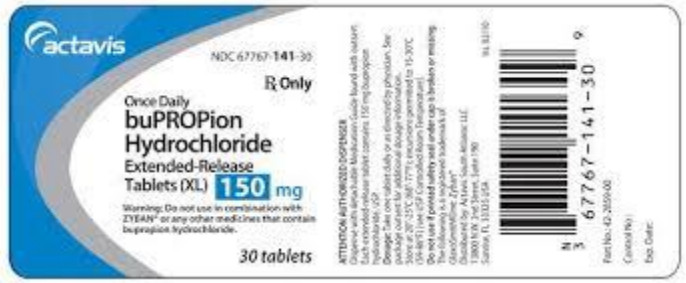
Background and Rationale

- No FDA approved medication for methamphetamine (MA) use disorder
- Promising candidates showing preliminary clinical utility include naltrexone and bupropion
- Combination of bupropion + naltrexone predicated on potentially complementary effects as shown in clinical research[1]
- CTN-0054 pilot trial: Open-label study using bupropion + naltrexone for MA dependent participants showed promising results

1. 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



Newton et al., 2004; Newton et al., 2006; Elkashef et al., 2008

ADAPT-2 Study Objectives

Primary Aim:

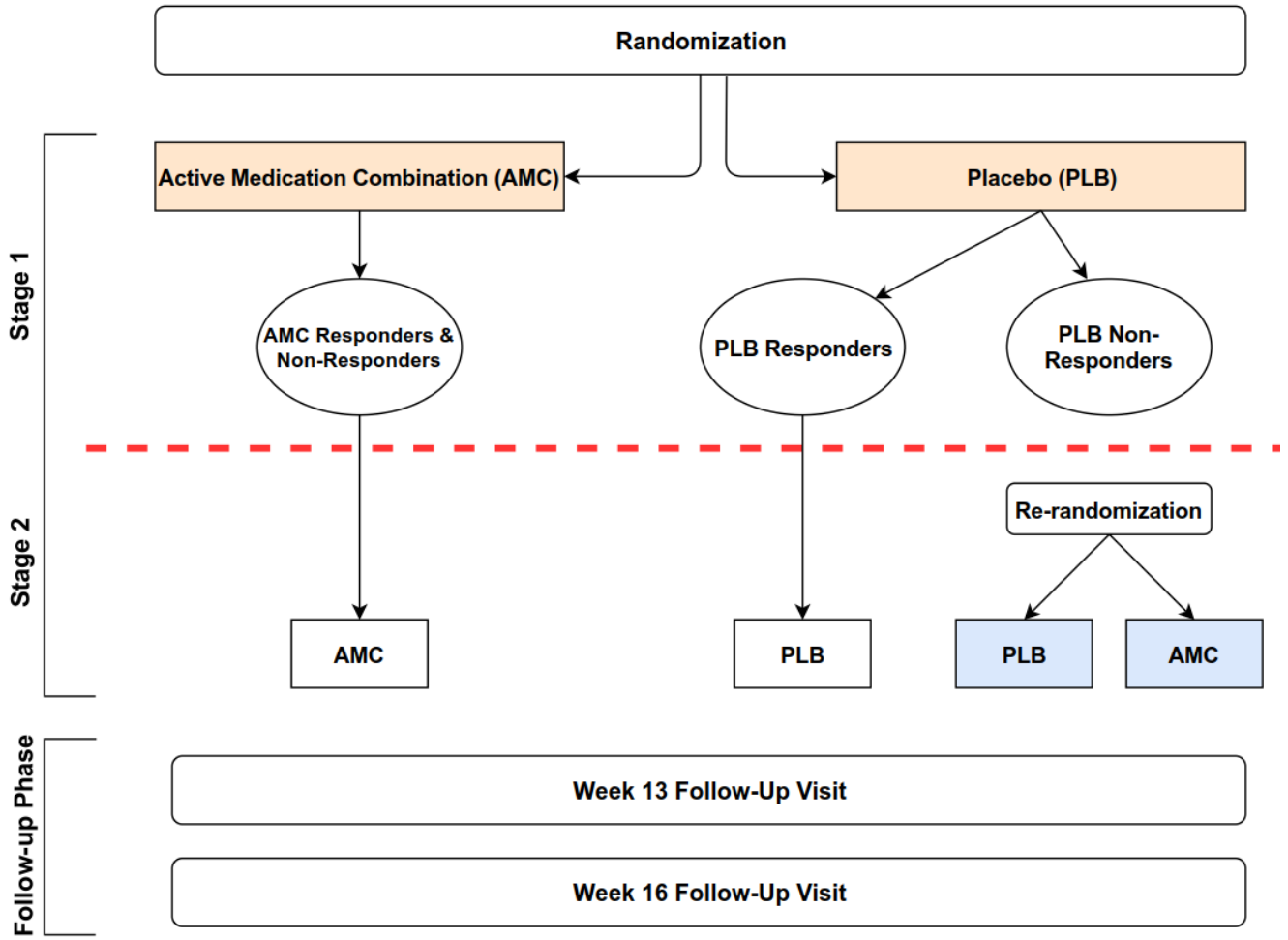
- Assess efficacy of extended-release injectable naltrexone (380 mg) + extended-release oral bupropion (450 mg) as combination pharmacotherapy for methamphetamine use disorder

Secondary Aims:

- Assess safety
- Assess efficacy on other SUD outcomes, depression symptom scores, quality of life ratings

ADAPT-2 Design & Unmasked Schema

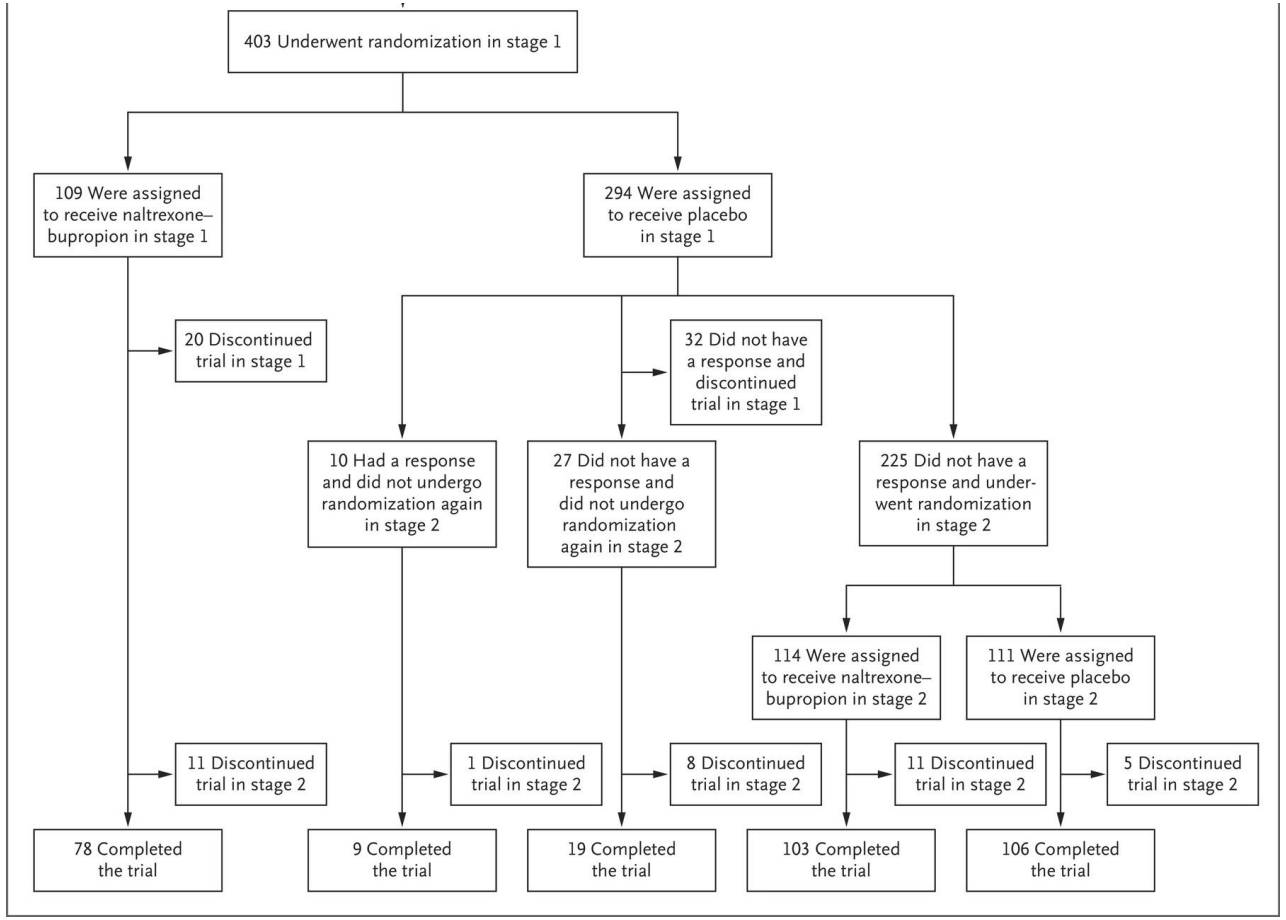
- Double-blind, placebo-controlled, randomized SPCD
- 8 study sites
- Randomized to AMC vs. PLB
- PLB non-responders **re-randomized** to AMC v. PLB
- 12 week Medication Phase
  - Visits: twice weekly
  - Oral meds: dispensed weekly
  - Injections: every 3 weeks



ADAPT Primary Outcomes

- **Primary efficacy outcome measure**
  - Meth-negative UDS results for AMC vs PLB
- "Responder": Any ppt who provided ≥3 (out of possible 4) meth-negative UDS during the evaluation period:
    - 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



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ADAPT Primary Outcome Results

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Baseline Demographics of Participants in the Intention-to-Treat Population

Characteristic	All Participants	Stage 1		Stage 2	
	Total (N=403)	Naltrexone–Bupropion (N=109)	Placebo (N=294)	Naltrexone–Bupropion (N=114)	Placebo (N=111)
Male — no. (%)	277 (68.7)	78 (71.6)	199 (67.7)	78 (68.4)	79 (71.2)
Age – yr	41.0±10.1	41.0±10.6	41.0±10.0	41.0±10.5	42.0±9.6
Hispanic or Latino ethnic group — no. (%)	55 (13.6)	13 (11.9)	42 (14.3)	20 (17.5)	18 (16.2)
Race or ethnic group — no. (%)					
White	287 (71.2)	82 (75.2)	205 (69.7)	84 (73.7)	69 (62.2)
Black	48 (11.9)	10 (9.2)	38 (12.9)	8 (7.0)	22 (19.8)
Other	68 (16.9)	17 (15.6)	51 (17.3)	22 (19.3)	20 (18.0)
High school diploma, GED, or lower education level — no. (%)	142 (35.2)	39 (35.8)	103 (35.0)	36 (31.6)	33 (29.7)

Baseline Demographics of Participants in the Intention-to-Treat Population

Characteristic	All Participants	Stage 1		Stage 2	
	Total (N=403)	Naltrexone–Bupropion (N=109)	Placebo (N=294)	Naltrexone–Bupropion (N=114)	Placebo (N=111)
Marital status — no. (%)					
Married or living with partner	93 (23.1)	26 (23.9)	67 (22.8)	25 (21.9)	25 (22.5)
Never married	204 (50.6)	49 (45.0)	155 (52.7)	60 (52.6)	59 (53.2)
Divorced, separated, widowed, or unknown — no. (%)	106 (26.3)	34 (31.2)	72 (24.5)	29 (25.4)	27 (24.3)
Employed — no. (%)	156 (38.7)	43 (39.4)	113 (38.4)	46 (40.4)	44 (39.6)

Baseline Methamphetamine Use Characteristics

Characteristic	All Participants	Stage 1		Stage 2	
	Total (N=403)	Naltrexone–Bupropion (N=109)	Placebo (N=294)	Naltrexone–Bupropion (N=114)	Placebo (N=111)
No. of days that methamphetamine was used in the 30 days before consent	26.7±4.1	27.0±3.9	26.5±4.2	26.7±4.1	26.1±4.3
Most frequent route of use — no. (%)					
Smoking	293 (72.7)	80 (73.4)	213 (72.4)	83 (72.8)	79 (71.2)
Intravenous	77 (19.1)	23 (21.1)	54 (18.4)	21 (18.4)	22 (19.8)
Nasal or oral	33 (8.2)	6 (5.5)	27 (9.2)	10 (8.8)	10 (9.0)
Participants reporting intravenous use ≥1 days in the 30 days before consent — no. (%)	135 (33.5)	39 (35.8)	96 (32.7)	38 (33.3)	36 (32.4)
Intensity of craving	66.1±22.3	65.7±22.2	65.8±21.6	66.7±21.3	63.7±21.9
Age of first use — yr	24.8±9.9	24.7±10.7	24.8±9.6	25.5±10.9	24.8±9.1

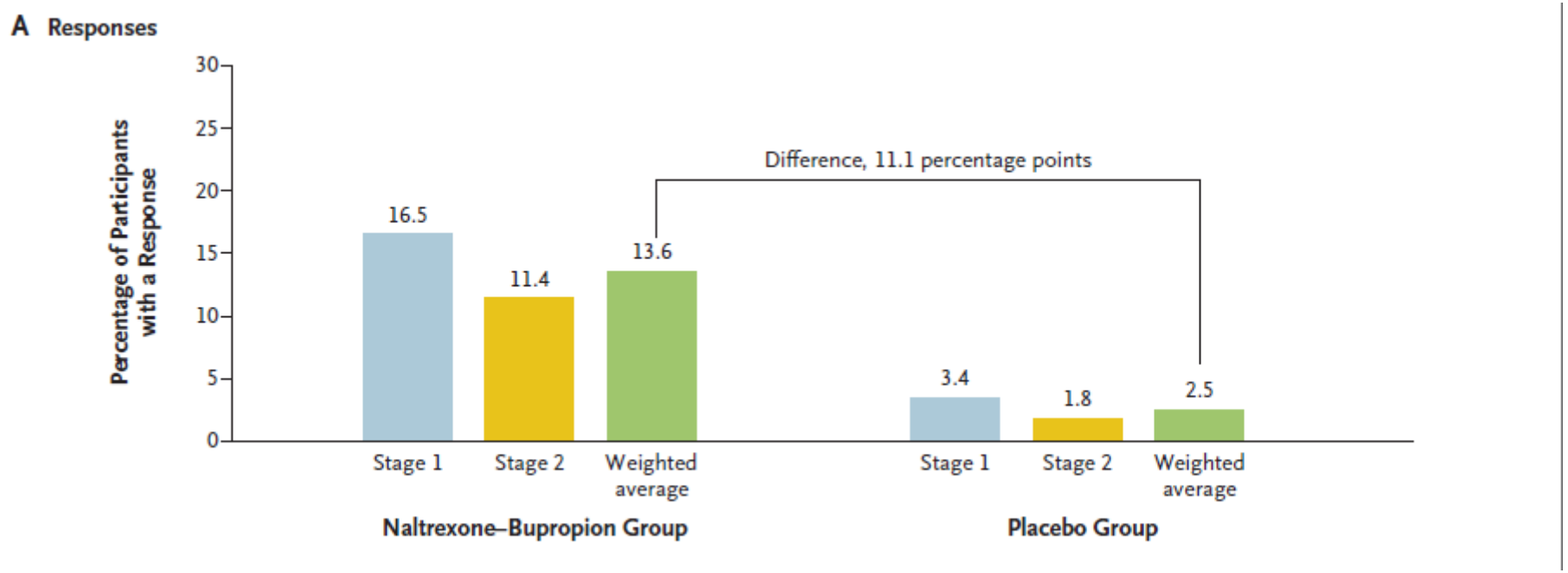
Primary Outcome Results

The primary efficacy outcome was **statistically significant**

Primary Outcome Analysis by Stage and Treatment Arm								
Stage 1			Stage 2			Results		
N	PLB Responder Rate	AMC Responder Rate	N	PLB Responder Rate	AMC Responder Rate	Treatment effect *h*	p-value	Number Needed to Treat
403	10/294 (3.4%)	18/109 (16.5%)	225	2/111 (1.8%)	13/114 (11.4%)	0.11	**<0.0001**	**9**

Note: Rate of continuation into Stage 2 among PLB non-responders was 0.7923

Weighted outcome primary result



Trivedi MH, et al. *N Engl J Med*. 2021;384(2):140-153.

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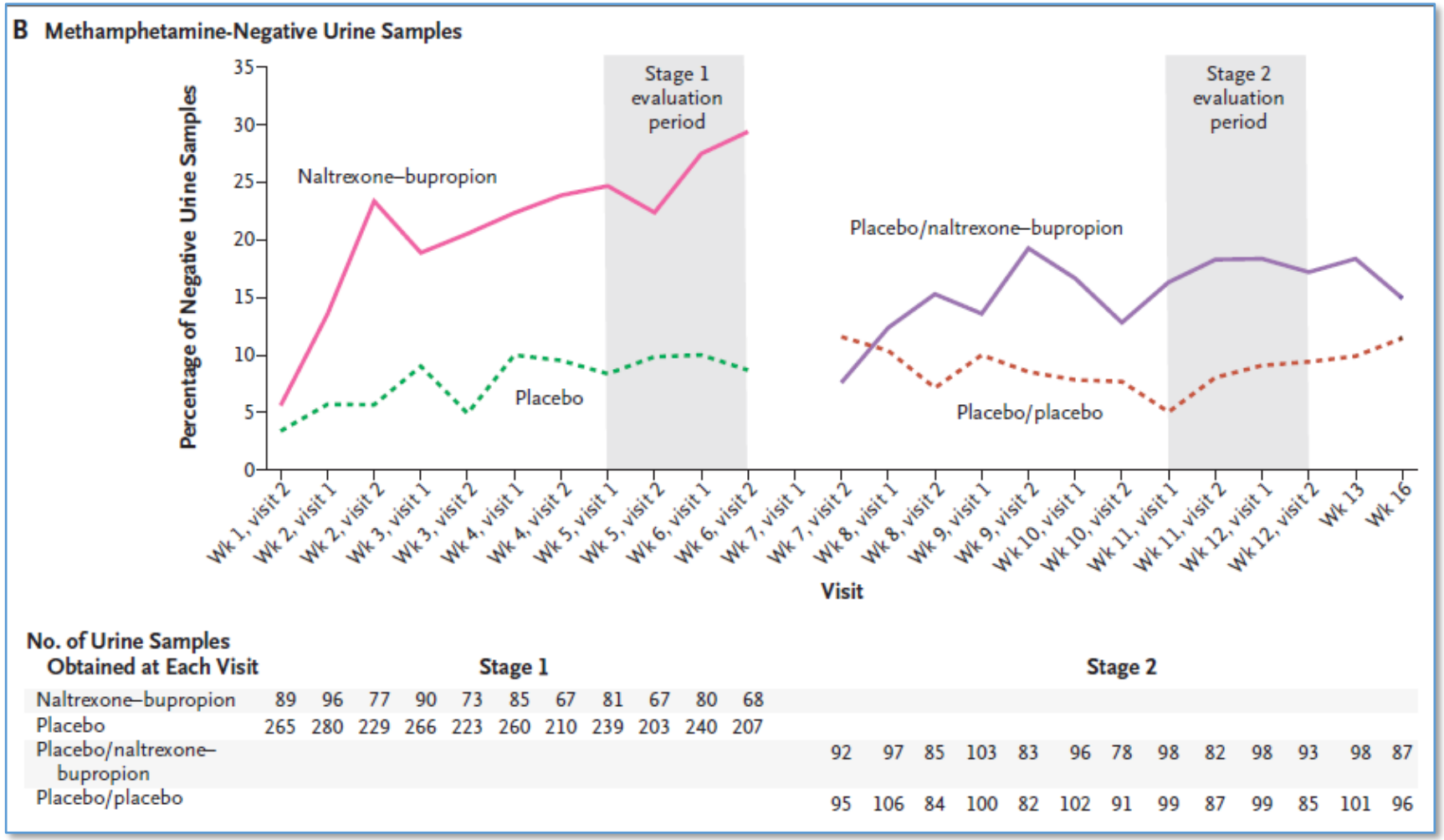
Meth Negative UDS by Stage & Arm, ITT Population

Methamphetamine Negative UDS Results in Stage 1 and Stage 2 in ITT Population



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

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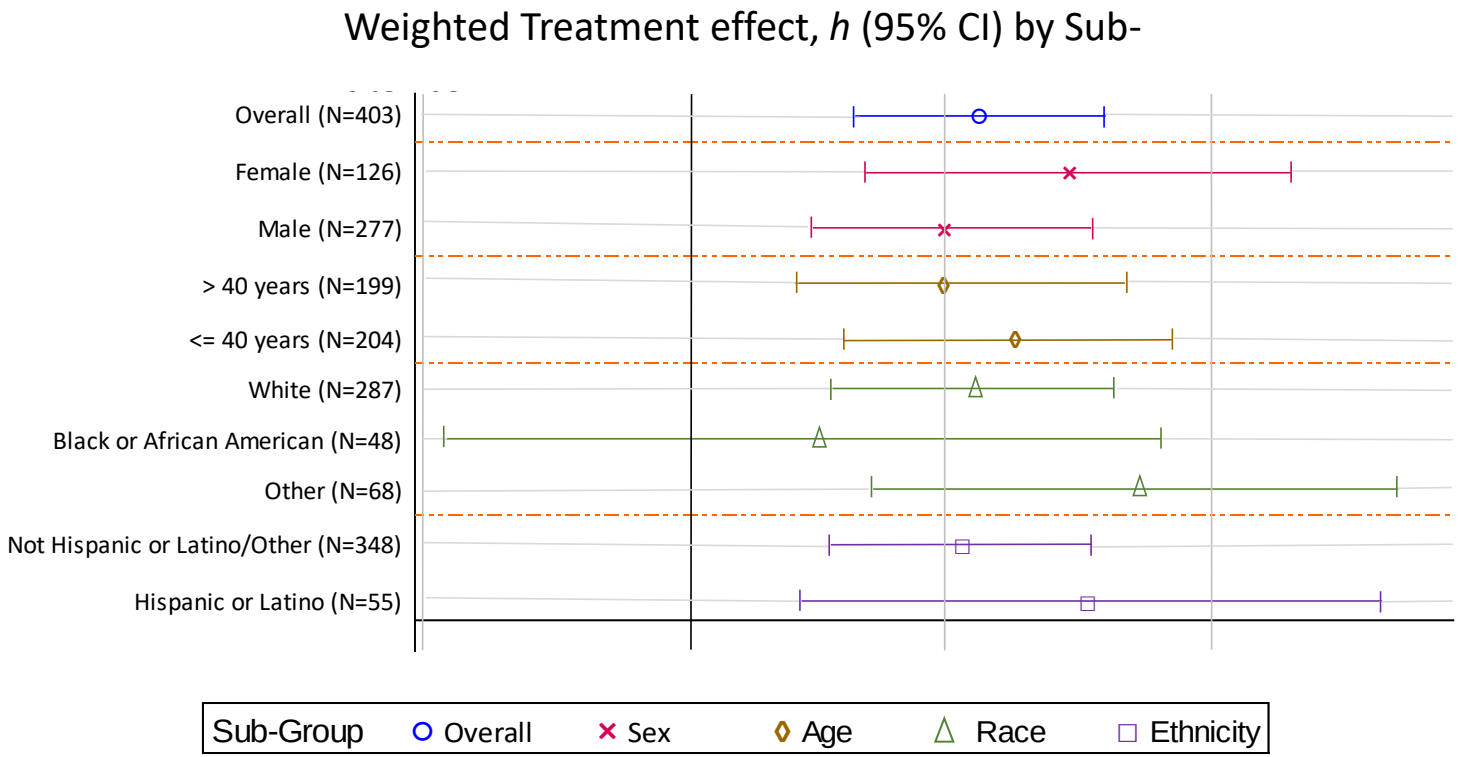
Repeated primary analysis, separately by Sex, Age, Race, Ethnicity



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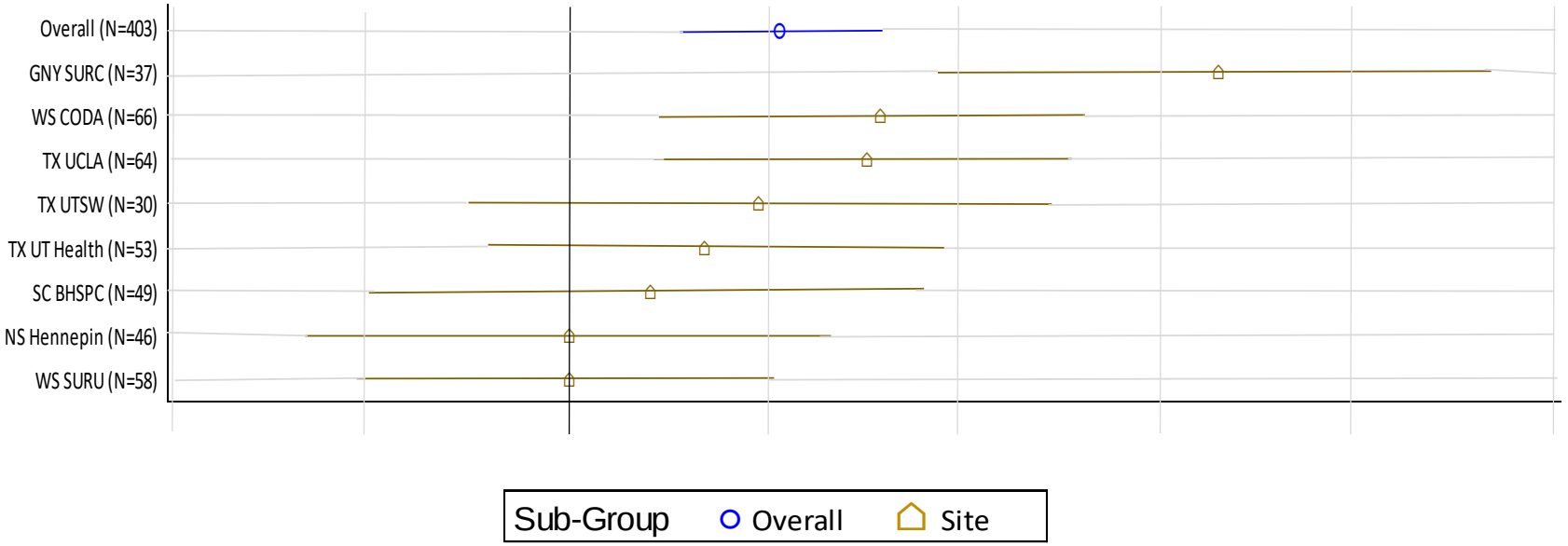
Repeated primary analysis, separately by site

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



Covariate adjusted model showed results consistent with the primary outcome analysis

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

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.