A Stimulating Presentation: Reviewing Neurobiology, Consequences and Treatments of Methamphetamine Use

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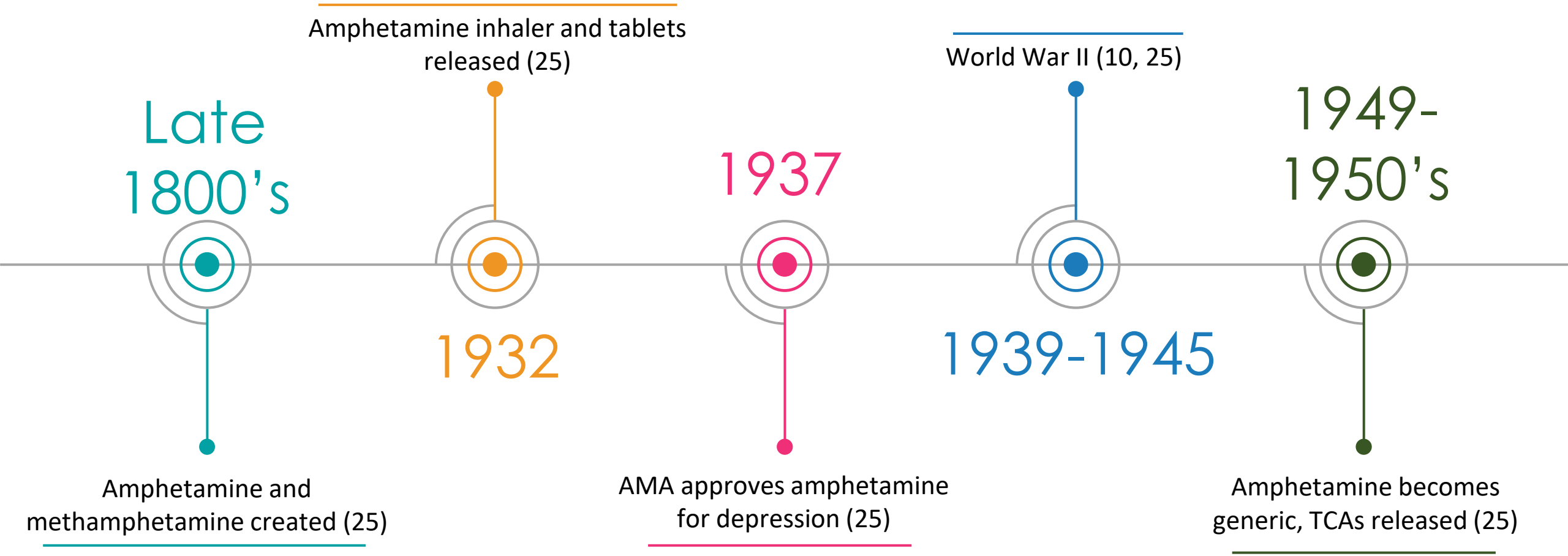
PRESENTATION OUTLINE

1. History of stimulants in the United States
2. Methamphetamine basics and neuropsychiatric consequences
3. Available treatments

HISTORY OF STIMULANTS



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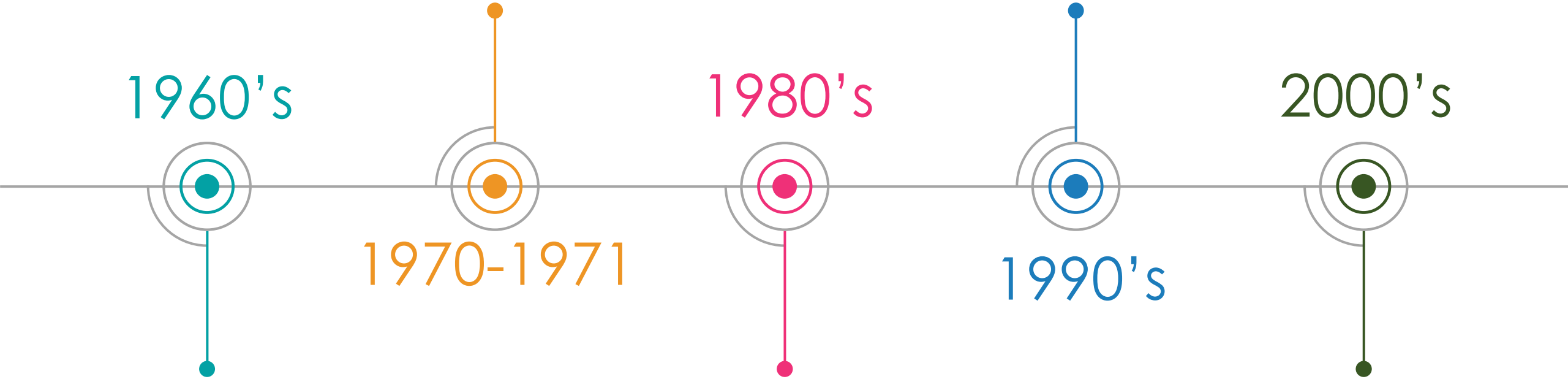
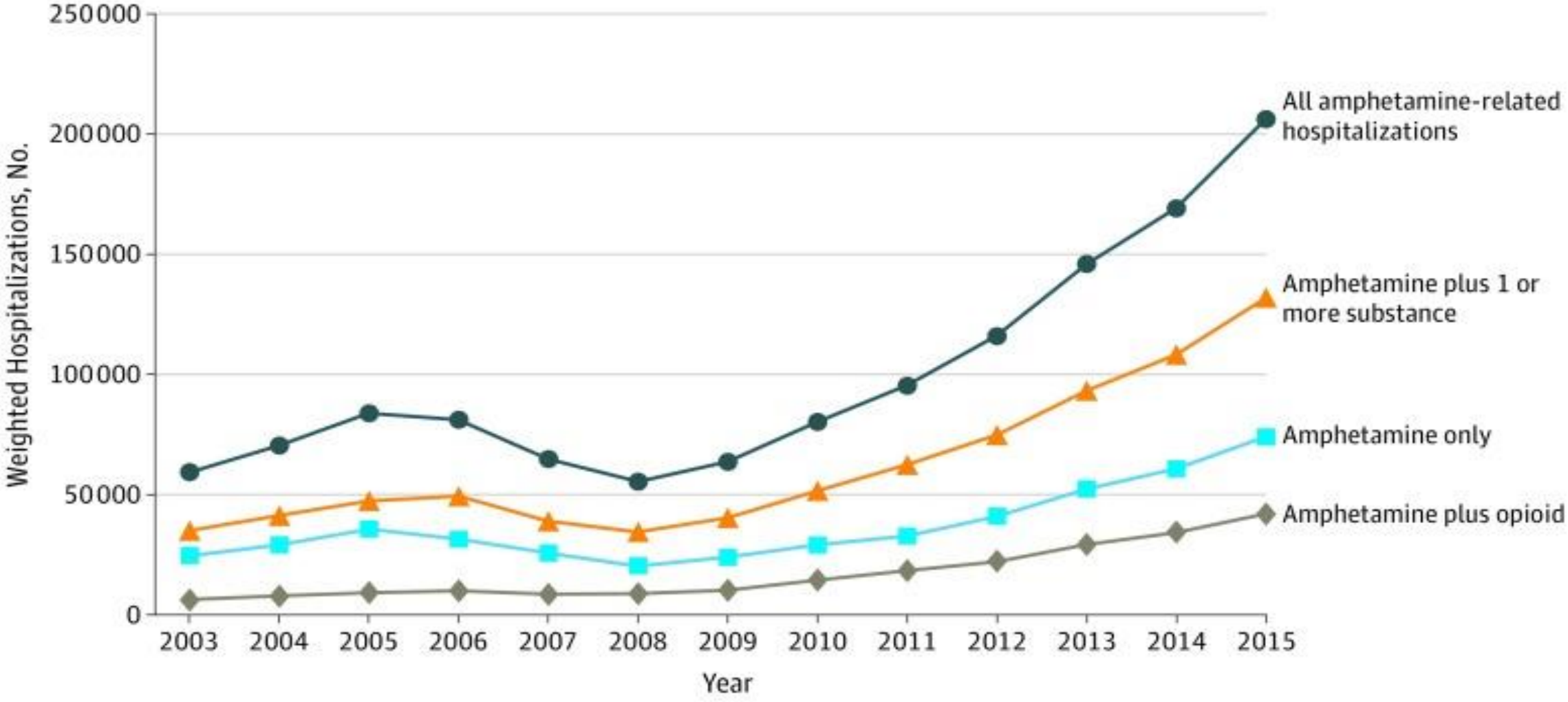


AMPHETAMINE RELATED HOSPITALIZATIONS(38)



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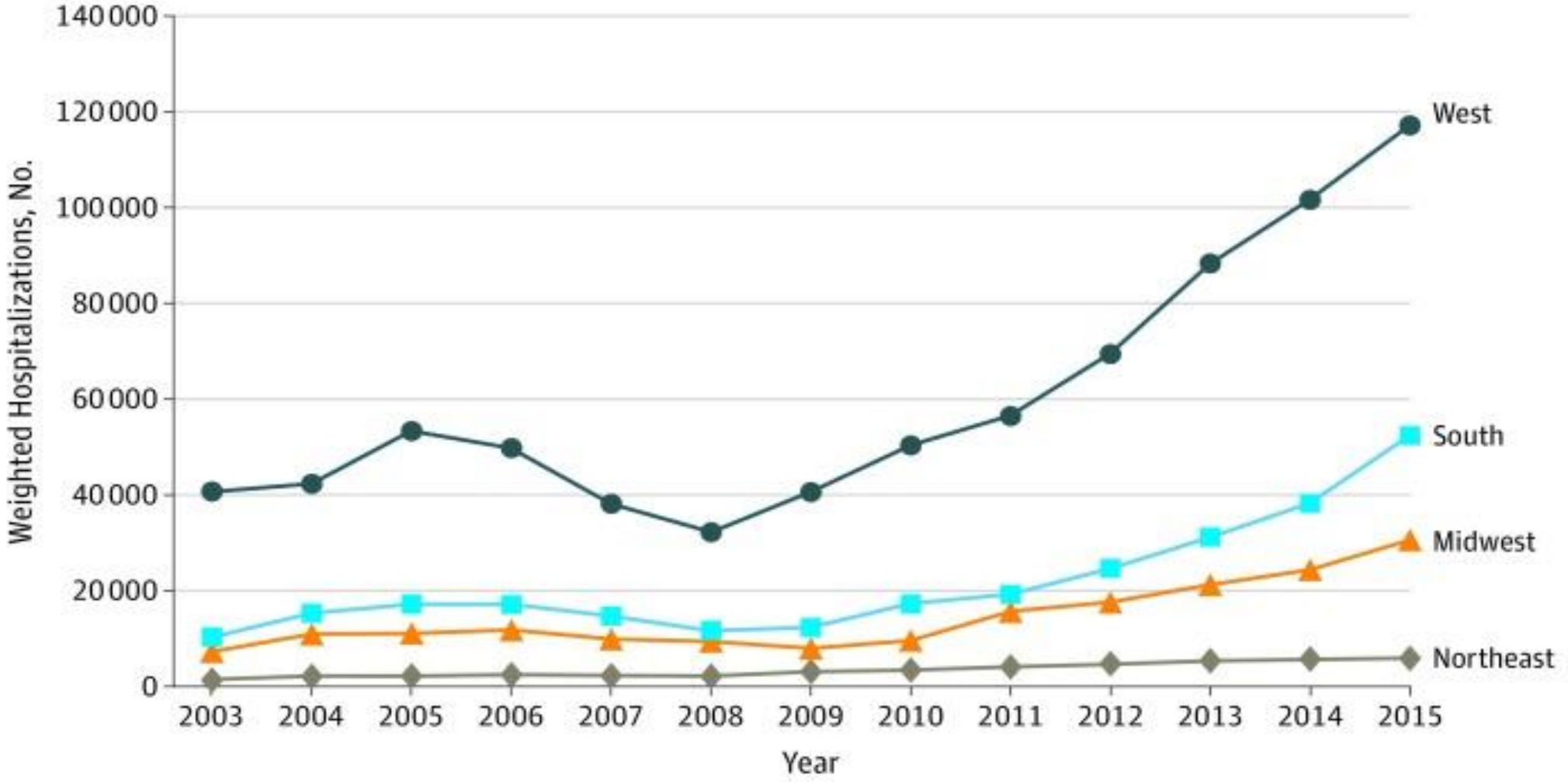
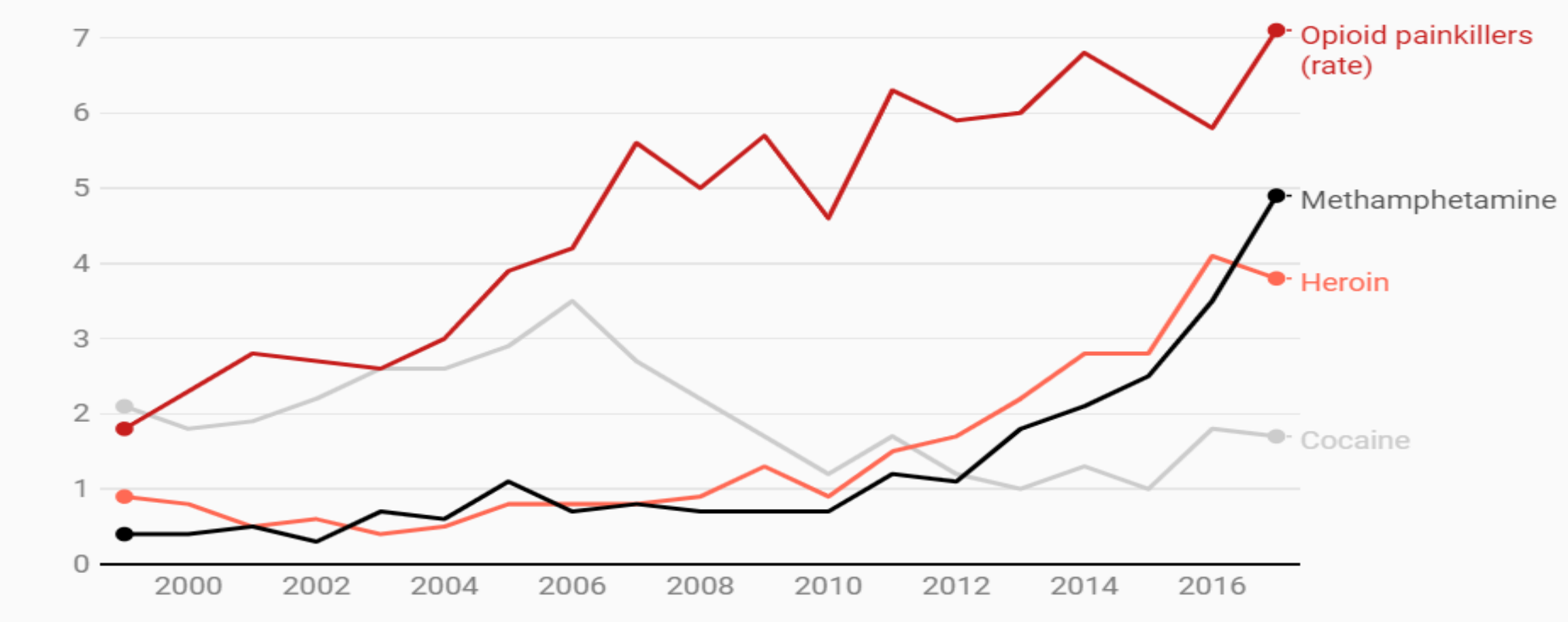


COLORADO DEATHS (13)



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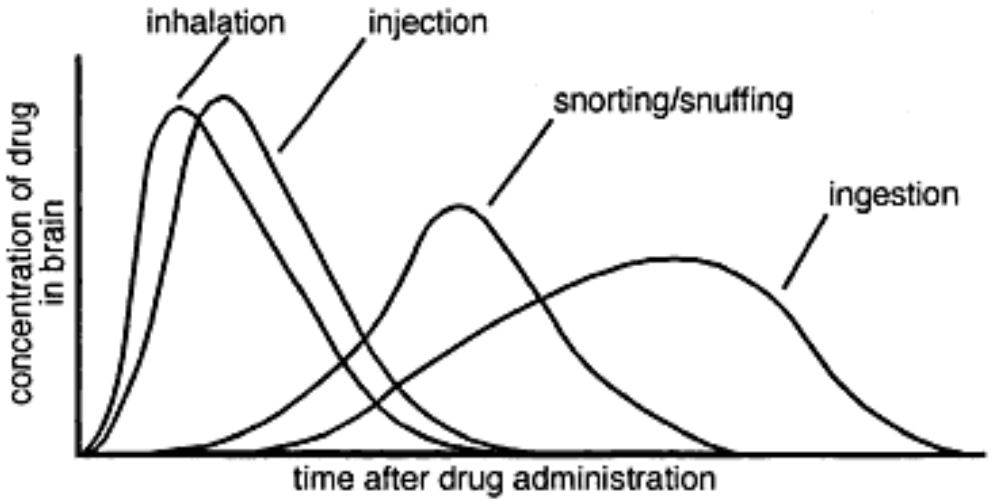
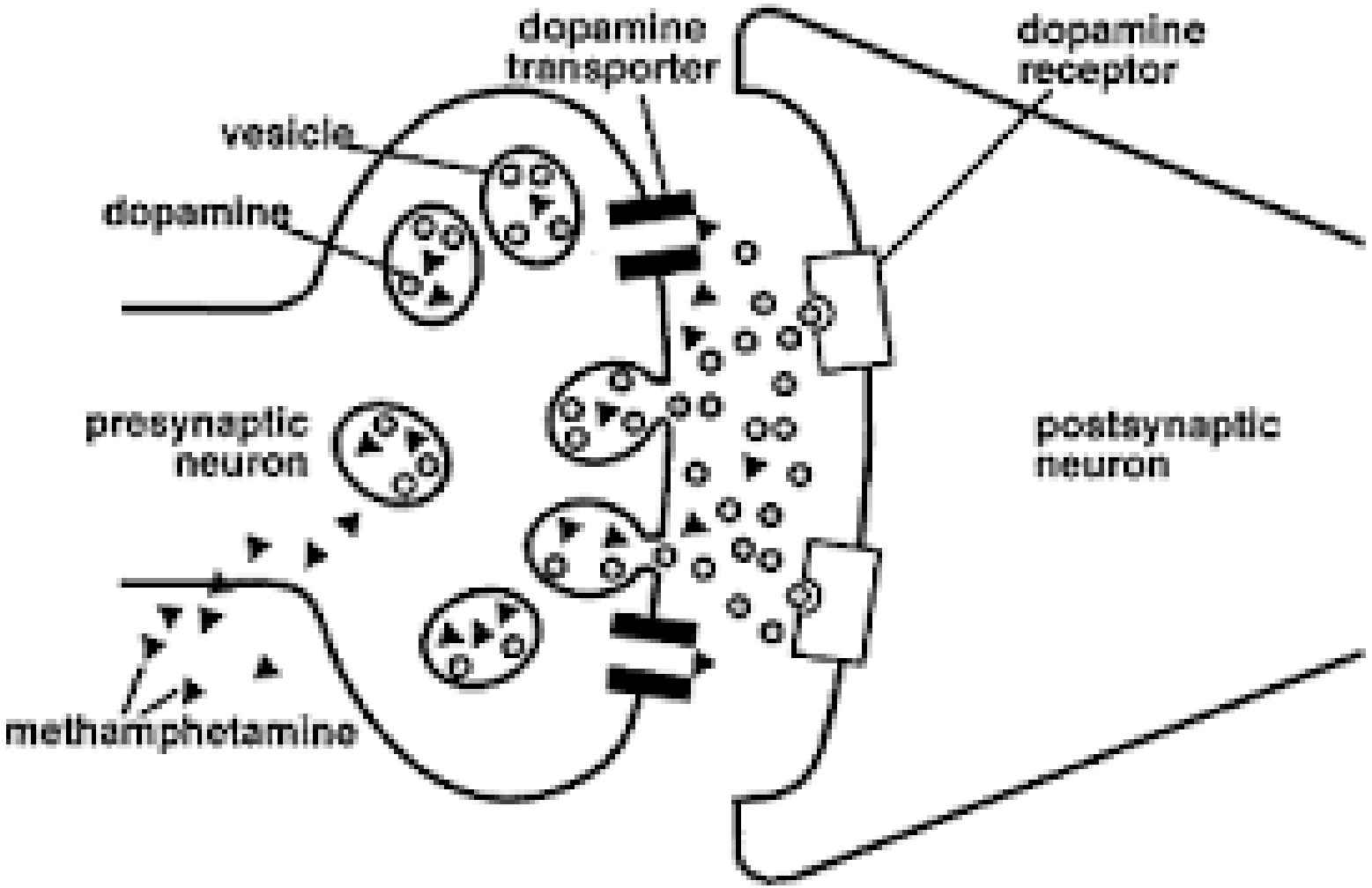
METHAMPHETAMINE BASICS

- Dopamine, Norepinephrine, Serotonin Activation. Affects salience and reward circuit of brain. (5,24, 34)
- Blocks dopamine transporter (DAT) **AND** increases dopamine release
- Half life 12 hours (24, 29)
- More lipophilic than amphetamine: cross BBB (24)
- Route of ingestion matters (24)
  - Smoke inhalation: 6-8 seconds
  - IV use: 10-15 seconds
  - Intranasal: 3-5 minutes
  - Oral: peak level 3 hours



METHAMPHETAMINE BASICS



https://www.youtube.com/watch?time_continue=50&v=TTMNXzL4O4s (21)

INTOXICATION (4)

- Euphoria
- Increased energy/alertness
- Decreased appetite
- Increased psychomotor activity, skin picking, teeth grinding
- Delusions, Hallucinations
- Increased Autonomic Signs
- Increased risk taking: **hypersexuality**, agitation

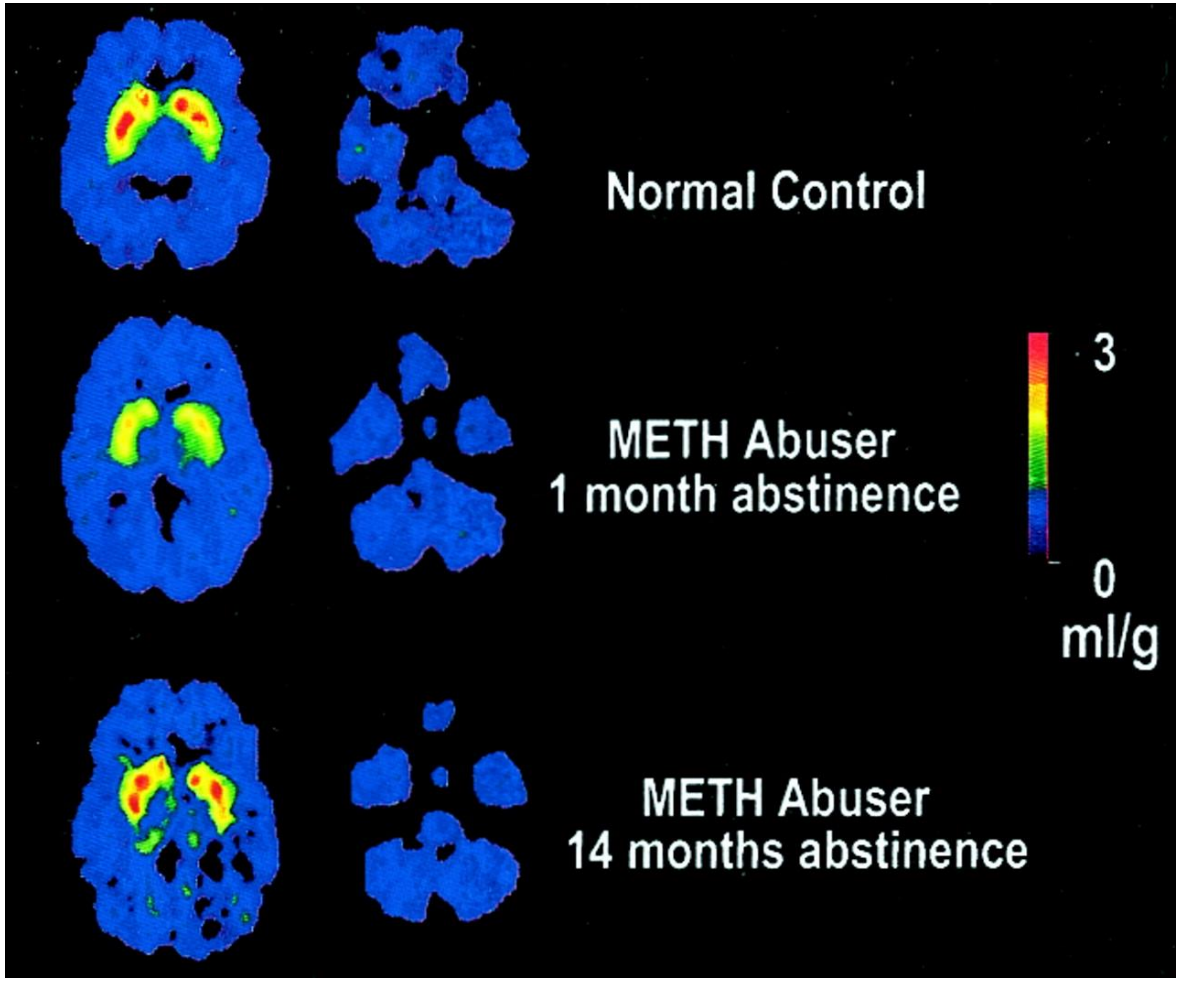
WITHDRAWAL (4)

- Dysphoria, anhedonia
- Fatigue
- Increased appetite
- Slowed psychomotor activity

NEUROPSYCHIATRIC HEALTH CONSEQUENCES

- Acute: sustained sympathetic activation (29)
  - Strokes, seizures, hyperthermia
  - Psychosis related to dopamine increase
- Chronic: sustained/repeated monoamine release (29)
  - High dopamine + hyperthermia= neurotoxic nerve terminal damage
  - Fine motor movements deficit (11)
  - Impairments in neuropsychological testing: most notably verbal learning, **executive function, episodic memory** (28, 36)

Dopamine Transporter (DAT) Recovery



PET scan using dopamine transporter radioligand

- Meth toxicity leads to less DAT (40 yrs aging) and lowered metabolism in some regions of the brain (22, 37)
- DAT and metabolism can recover with protracted abstinence (22, 36, 37)
- Neuropsychological function recovery variable depending on study. Thalamus metabolism perhaps related to improved verbal memory and motor tasks. (36, 37)

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MEDICATIONS RESEARCHED FOR METHAMPHETAMINE USE (3, 12,17, 20)

- Replacement therapy (methylphenidate, dextroamphetamine, modafinil)
- **BUPROPION (9, 31)**
- Partial D2 agonist (aripiprazole)
- D2 antagonists (quetiapine, risperidone)
- GABA agents (baclofen, gabapentin, vigabatrin)
- Imipramine
- Ondansetron
- Food supplements (creatinine, citicoline)
- Cholinesterase Inhibitors (donepezil, rivastigmine)
- SSRI (fluoxetine, paroxetine, **SERTRALINE) (32)**
- **MIRTAZAPINE (12, 17)**
- **NALTREXONE/VIVITROL (7, 14, 15, 16)**
- (13.6% with naltrexone–bupropion and 2.5% with placebo Trivedi NEJM 2021)
- N-acetylcysteine
- Topiramate
- Calcium Channel blockers (amlodipine, israpidine)

PSYCHOTHERAPIES

- Most of the drug treatment studies utilized some version of CBT based therapy, often in group format.
- Mostly 3 month duration, some 6 month
- MATRIX model (26,27)
  - Combines individual therapy, CBT group therapy, family education groups, drug testing, 12 step meetings, relapse prevention therapy, social support therapy.
- Contingency Management (23,33)
  - Incorporates structure for monetary/prize earnings into component of treatment plan such as UDS.

TAKE HOME POINTS

- Methamphetamine use never went away and has been worsening.
- Methamphetamine use results in neurotoxic damage and cognitive impairments, although some potential for recovery.
- No FDA approved medications. Therapy is most important intervention at this time but need to prioritize keeping patients engaged since that correlates with clinical improvement.

Questions?

Thanks to the ECHO team!

Resources

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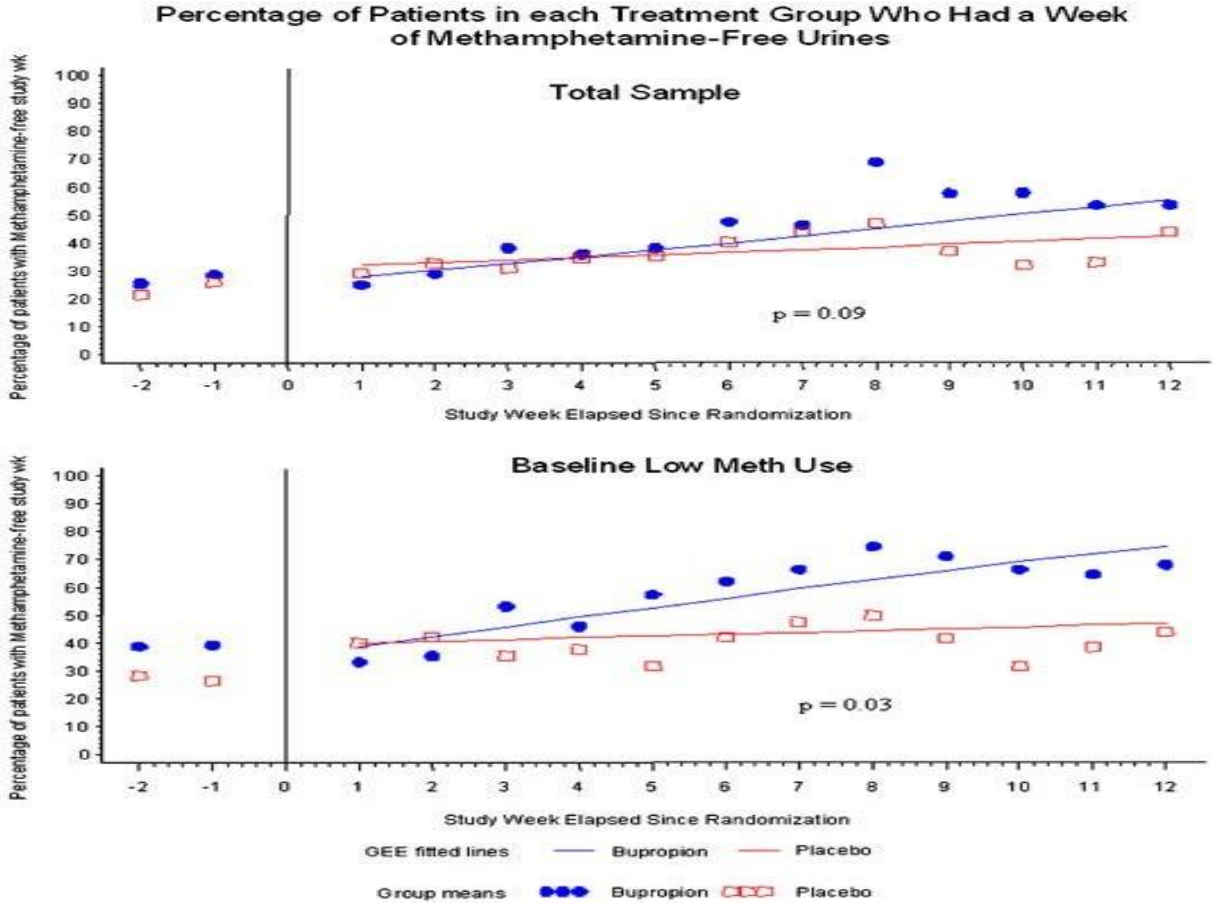
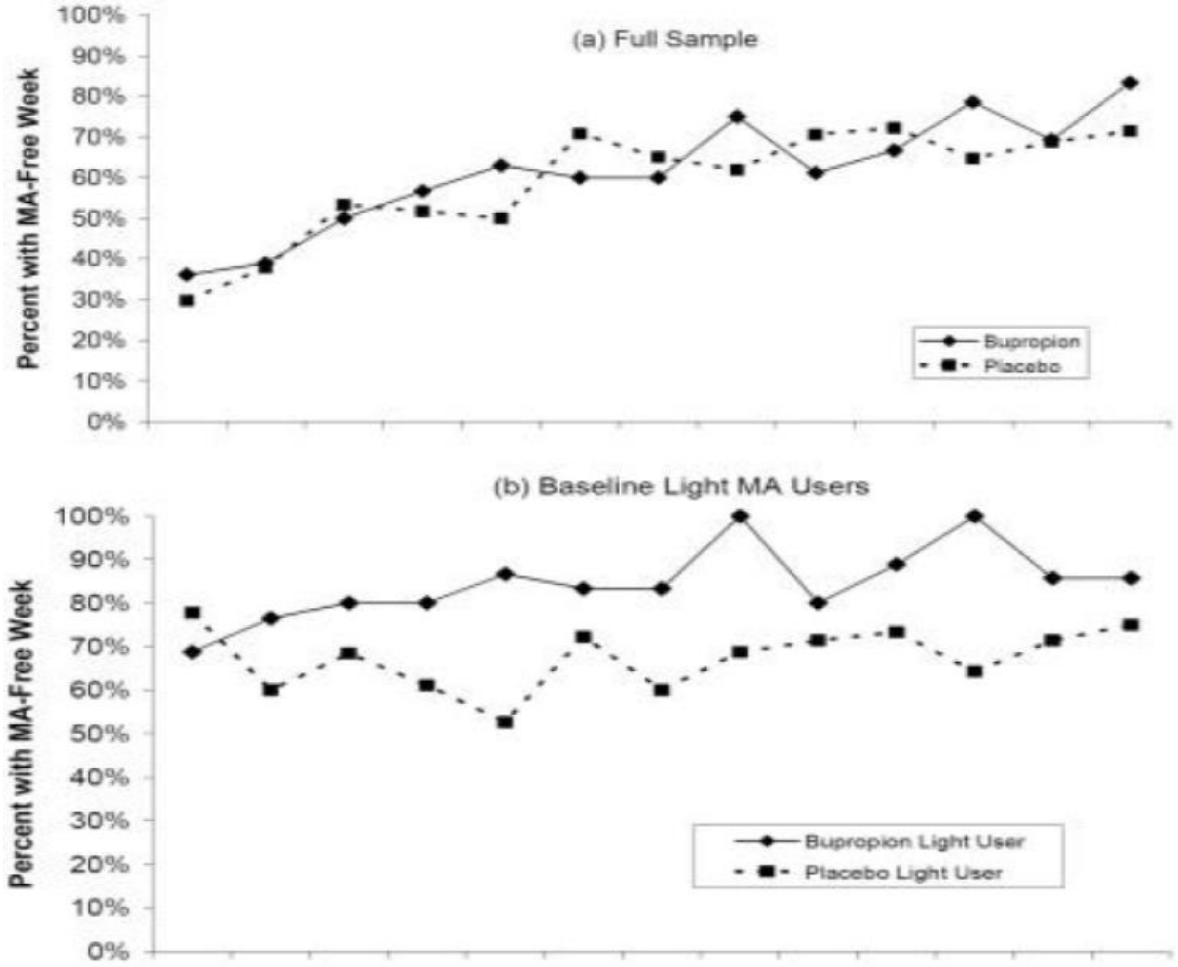
FUTURE CONSIDERATIONS

- Continue to develop potential medications.
- Medication combinations?
- Therapy combinations?
- Duration of treatment should be in line with neuroscience understanding

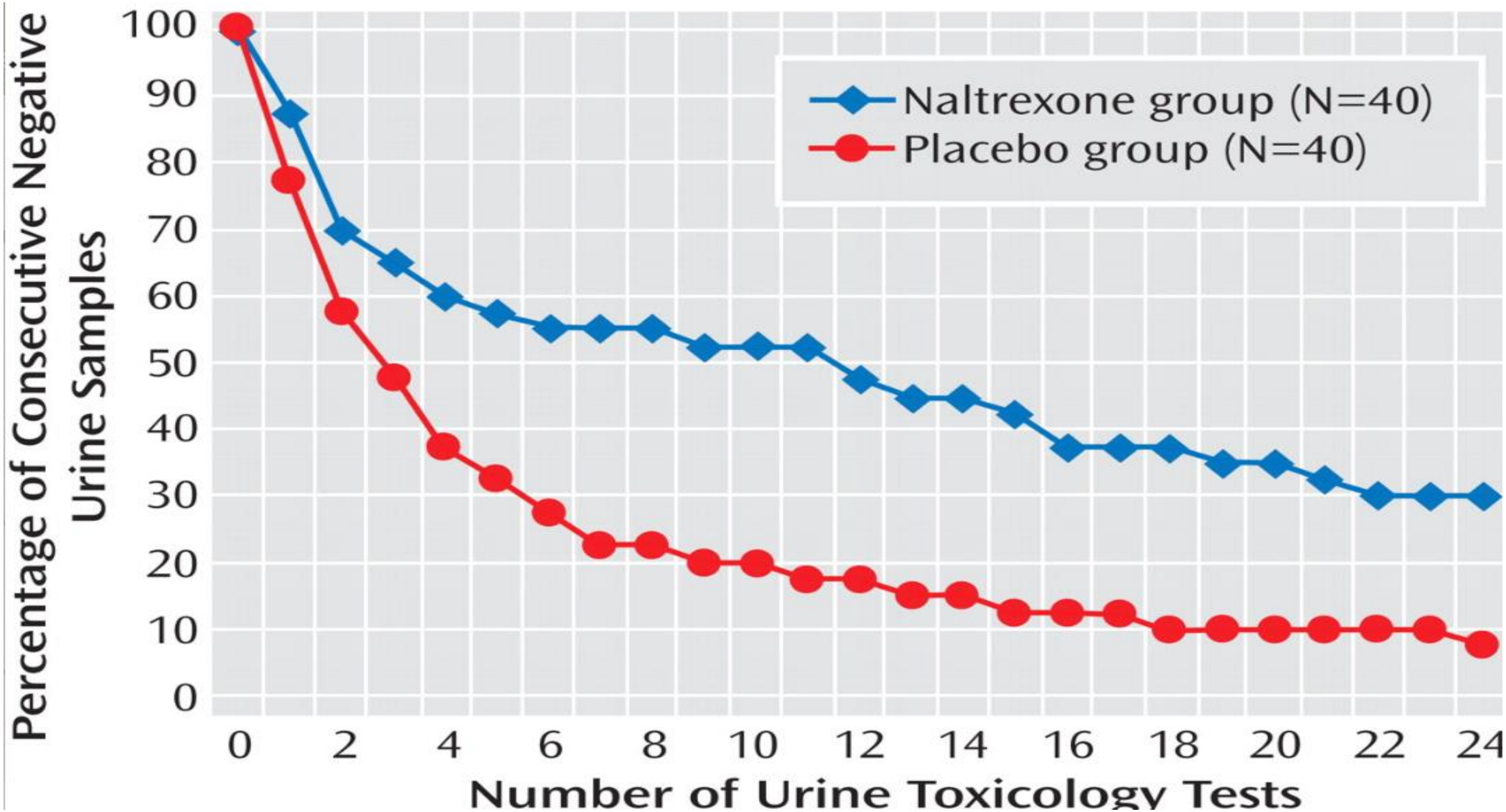
- Bupropion 150mg SR BID
  - N=151, 12 week double blind placebo controlled with 1 month f/u, Decrease in meth positive urines 10% in MALE low-moderate users (used 18 or less days/month) (9)
    - Lack of inter-rater reliability, high drop out rate



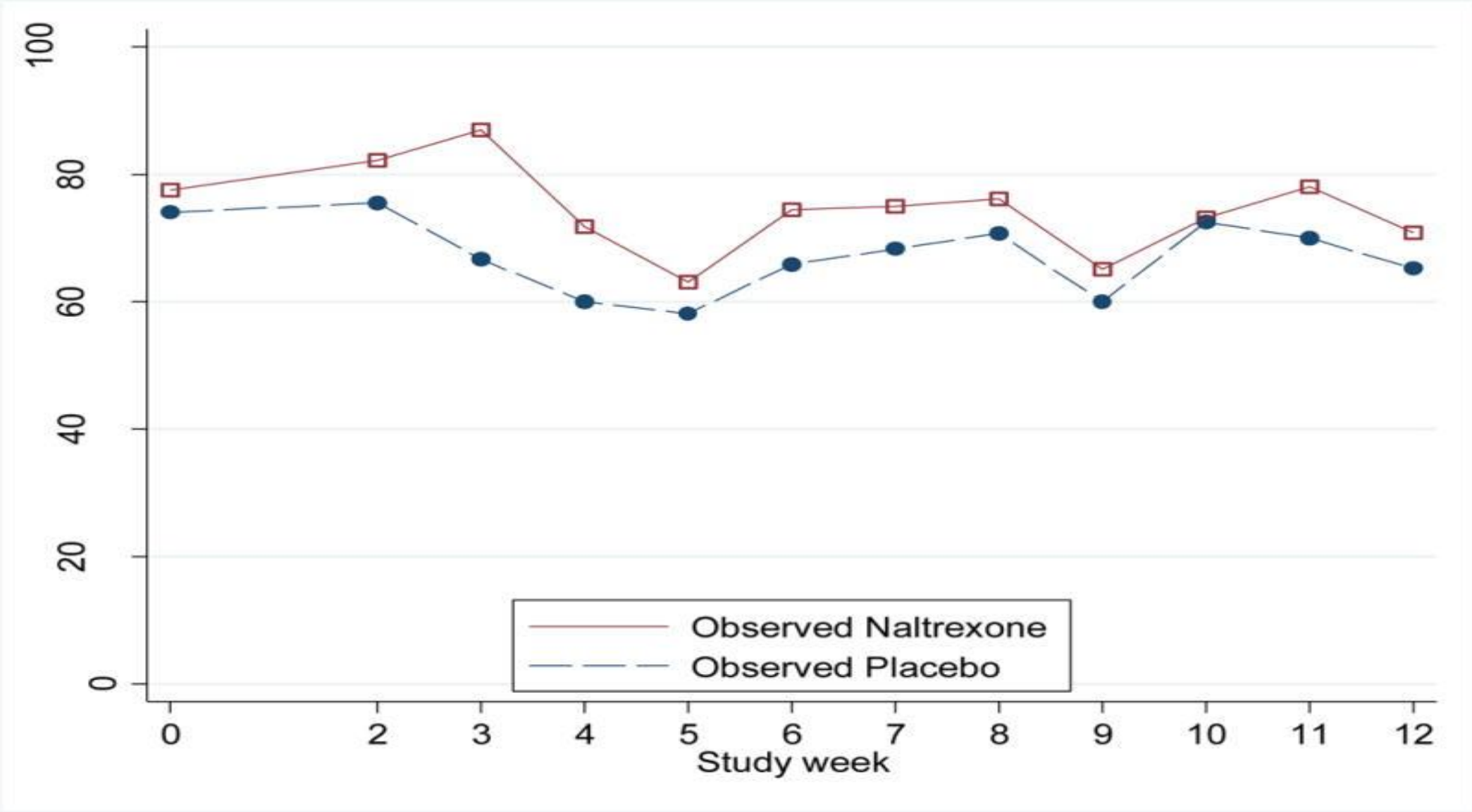
- Bupropion 150mg SR BID
  - N=73, 12 week randomized double blind placebo controlled, Decrease in methamphetamine and reported cigarette use (28)
    - High dropout rate



- Naltrexone 50mg PO daily



- Vivitrol 380mg IM monthly (7)



- Mirtazapine (12, 16)
  - 2 studies showing no effect on use
  - Decrease in risky sexual behaviors as well as extent of methamphetamine use

- Sertraline 50mg BID (29)
  - N=229, 12 week double blind placebo controlled trial looking at combinations of sertraline with Contingency Management, showed sertraline having adverse affect on retention rate and methamphetamine abstinence.

MATRIX Model

- Original model 6 months with 6 weeks 12 step group follow up. Superior to inpatient hospitalization or 12 step alone. (27)
- MATRIX model vs TAU (26)
  - 8 multi-site comparison, 16 week duration, N=978
  - 38% more likely to stay in treatment, 31% more likely to have drug free urine during treatment
  - About 40% completion rate in MATRIX group
  - **No difference** in chance of neg UDS at final meeting or 6 month f/u (66% vs 69%).
  - **No difference** in change in decrease of number days using meth in past month (11 down to 4). This persisted at 6 month f/u.

CONTINGENCY MANAGEMENT

- N=111, 12 week meeting x3/week, steady increase credits for UDS (33)
  - Cost per patient $800, average 42% drug free urine samples
  - 60% completed 4 weeks, 30% completed 12 weeks
  - No therapy component
- N=415, 12 week 2 group comparison (CM, non-CM),UDS x2/week, lottery based system (2)
  - No difference from placebo group for average clean urine samples
  - 49% CM group completed 12 weeks, 35% non-CM group
  - Had group therapy component