Methamphetamine Neurological Consequences

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CASE STUDY

- Patient is a 29 yo male with long history of opioid use disorder currently on MAT and doing well. One year ago patient was introduced to methamphetamine and progressed from intermittent use to daily use. He presents to your office with feelings that he is being monitored by the FBI. He notes that the same car keeps driving by to monitor him and he is getting calls on his cell phone that when he answers are silent. He reports he last used methamphetamine last week. He still trusts you and is here for a refill of his buprenorphine.
- He has presented in a similar manner before

CASE STUDY

You have been working with him for several months on stopping the methamphetamine. He reports he is able to stop for 1-4 days but then feels so bad he starts to have cravings that are nearly impossible to overcome. He really wants to stop but seems unable to

Has been admitted twice for drug induced psychosis, placed on antipsychotics (last time depo antipsychotic). Always motivated to stop on discharge but relapses within one week.

DISCUSSION QUESTION

- What clinical questions does a case like this raise?

DISCUSSION QUESTION

- Why does methamphetamine cause psychosis
- How do you interact with a patient with underlying MAP delusions
- Are there any medications that can reduce his delusions
- Will continued methamphetamine use result in long term effects
- Is there anything that can help him with methamphetamine withdrawal or cravings which seem to lead to relapse

METHAMPHETAMINE ASSOCIATED PSYCHOSIS (MAP)

- Neurophysiolosy of Psychosis
- Prevalence of MAP
- Characteristics
- Predictors
- How do you interact
- Treatment
- Methamphetamine withdrawal, symptoms and management

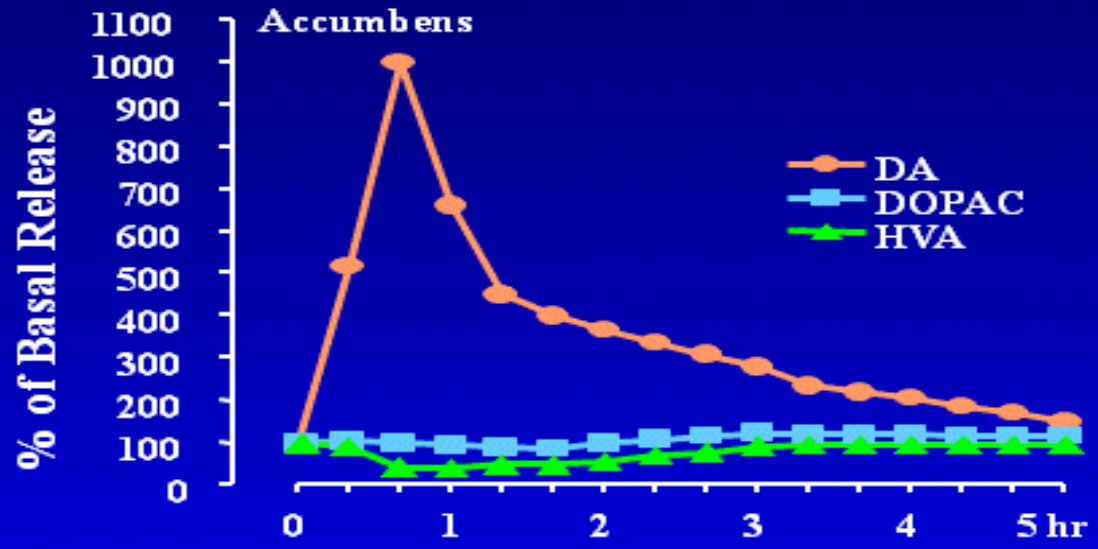
Reward Pathway (Nucleus acumbens/ventral striatum)

Cocaine
- blocks the reuptake of dopamine

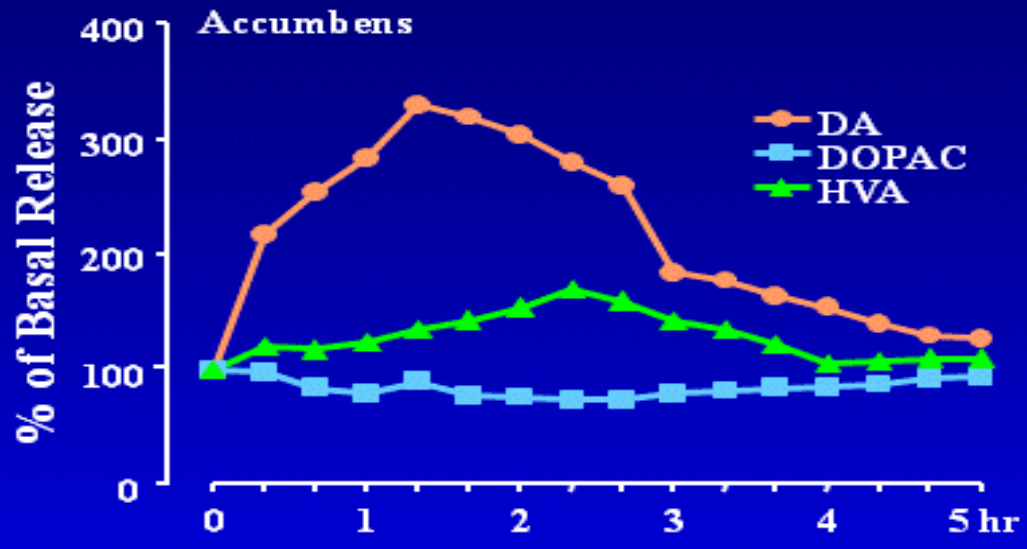
Methamphetamine
- blocks the reuptake of dopamine and
- binds to presynaptic DA neuron membranes and cause release
- binds to the presynaptic DA vesicles (VMAT)and causes release DA
- binds to the presynaptic DAT and causes release of DA
- blocks the breakdown of dopamine via the MAO pathway

Effects of Drugs on Dopamine Release

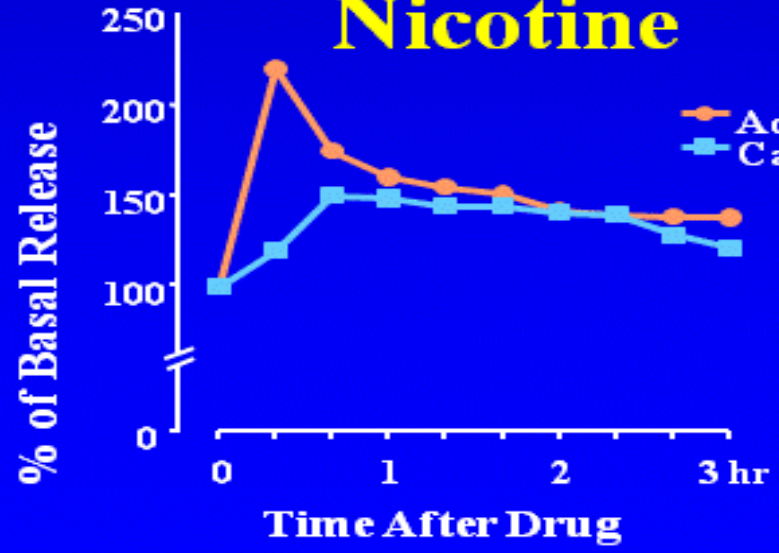
Amphetamine



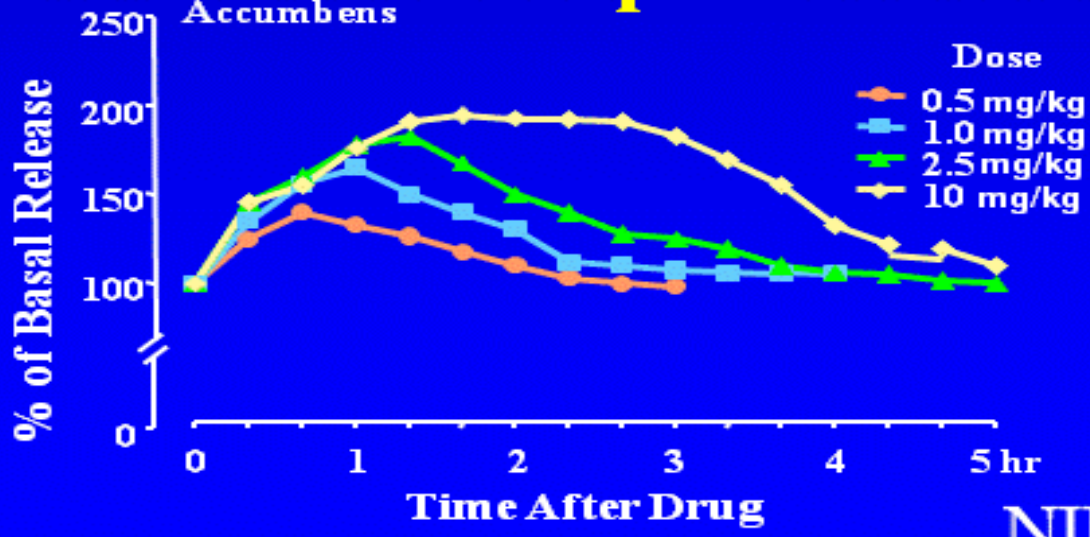
Cocaine



Nicotine



Morphine



Di Chiara and Imperato, PNAS, 1988

NIDA

Journal of Experimental Biology

Volume 224, Issue 13

July 2021

INSIDE JEB | 06 JULY 2021

Freshwater methamphetamine pollution turns brown trout into addicts FREE

Kathryn Knight

+ Author and article information

J Exp Biol (2021) 224 (13): jeb242971.

https://doi.org/10.1242/jeb.242971

Related content

This is a related article to: Methamphetamine pollution elicits addiction in wild fish

OTHER DOPAMINE PATHWAYS

- Reward Pathway (Nucleus Accumbens) – excessive dopamine
- Nigrostriatal : deficiency of dopamine→ Parkinsons, dystonias
  excessive dopamine→ tics, bruxism
- Mesolimbic : excessive dopamine → + symptoms of schizophrenia
  antipsychotics- block dopamine
- Mesocortical: deficiency dopamine→ neg symptoms of schizophrenia
- Tuberinfudibular: excessive dopamine inhibits prolactin

The Schizophrenia – Methamphetamine link

- The excessive dopamine levels seen with methamphetamine use are not localized to the reward pathways
- The excessive dopamine in the mesolimbic pathways can results in a schizophrenic like state (Psychosis, delusions, positive symptoms)

Methamphetamine Associated Psychosis

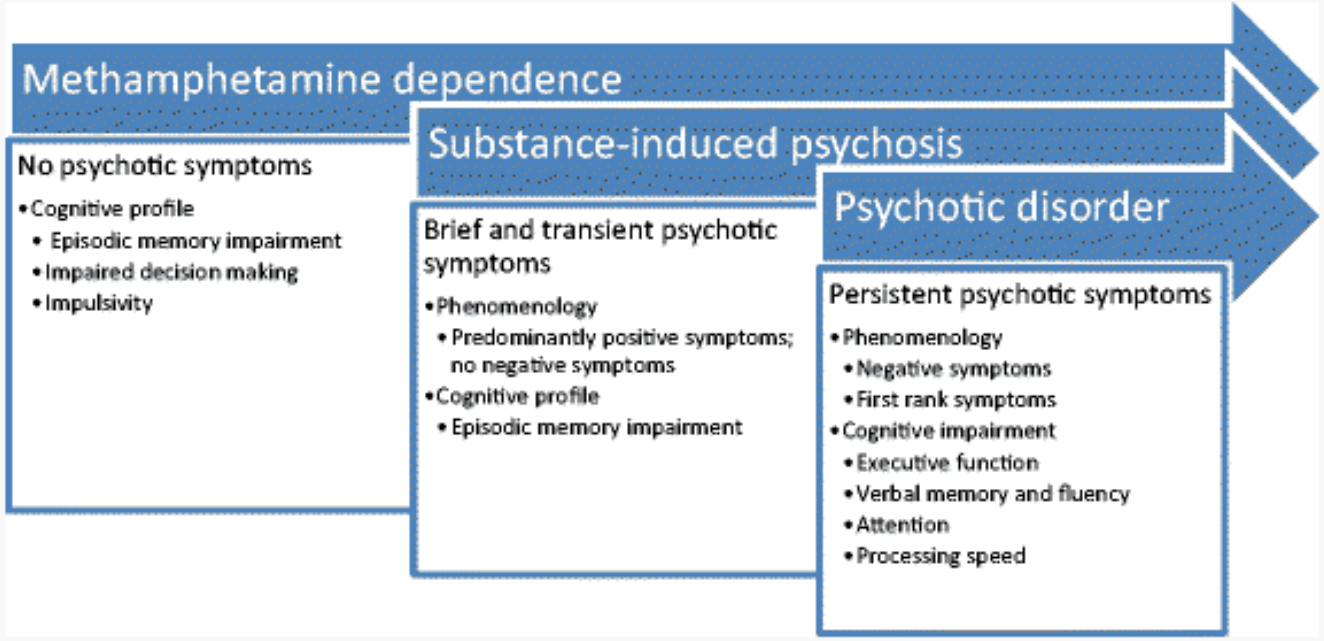


Fig. 1
MAP spectrum

The prevalence of psychotic symptoms among methamphetamine users: Rebecca McKetin, et. Al., Addiction , Sept , 2006

- Cross sectional survey of 309 methamphetamines users looking at prevalence of psychosis and variables associated with psychosis

- 13% screened positive for history of psychosis within last year
- 23% had experiences clinically significant thoughts of suspicion, unusual thought content or hallucinations,
- 18% of those without a diagnosis of psychotic disorder

A Systematic Review of the Symptom Profile and Course of Methamphetamine-Associated Psychosis: Alexandra Voice, et. Al., Substance Use and Misuse, Vol 54 (4), 2019

- Retrospective review of 49 articles involving 7387 patients with methamphetamine induced psychosis
- 25% of patients had persistent psychosis after one month

The prevalence of psychotic symptoms among methamphetamine users: Rebecca McKetin, et. Al., Addiction , Sept , 2006

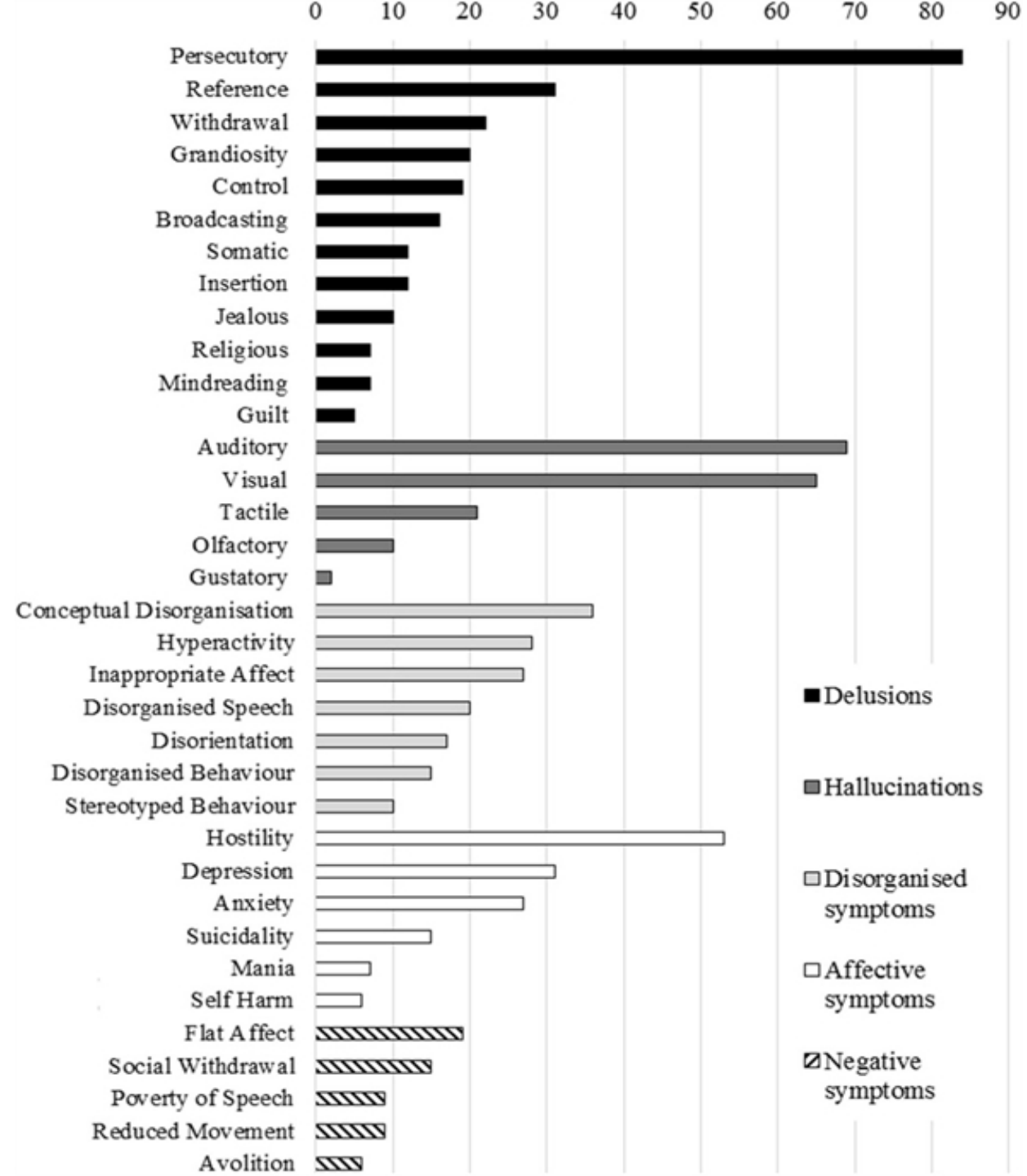
	Odds ratio (95% CI)	*P-value*
History of schizophrenia	15.1 (4.0–57.0)	< 0.001
History of other psychotic disorder[a]	3.7 (1.3–10.9)	0.016
Dependence on methamphetamine	3.1 (1.6–5.9)	< 0.001

Methamphetamine Induced Psychosis

- Risk factors
  - history of concurrent psychotic disorder
  - increased frequency, dose and length
  - family hx of schizophrenia (5x)
  - concurrent depression, sexual abuse
  - premorbid schizoid or schizotypical personality

CHARACTERISTICS OF METHAMPHETAMINE INDUCED PSYCHOSIS

- Typically last hours to one week
- Typically cluster around three dimensions
  - Positive psychotic symptoms (delusions and hallucinations)
  - Affective symptoms (depression, hostility)
  - Psychomotor agitations (hyperactivity, bizarre behavior)
- Typically lack the negative symptoms seen in schizophrenia
- Typically last less then one month but 10-20% will persist past that
- If persistent see more negative symptoms emerge



A Systematic Review of the Symptom Profile and Course of Methamphetamine-Associated Psychosis: Alexandra Voice, et. Al., Substance Use and Misuse, Vol 54 (4), 2019

Characteristic ($N = 526$)	No. (%)	
	Current	Lifetime
Any psychiatric disorder (excluding drug disorders, alcoholism)	179 (34.0)	182 (34.6)
Affective disorders		
Major depression	80 (15.2)	***
Major depression, recurrent	***	48 (9.1)
Dysthymic disorder	19 (3.6)	***
Mania	21 (3.9)	45 (8.5)
Hypomania	13 (2.4)	49 (9.3)
Any affective disorder	117 (22.2)	129 (24.5)
Anxiety disorders		
Panic disorder	14 (2.6)	43 (8.1)
Agoraphobia	14 (2.6)	***
Social anxiety disorder	45 (8.5)	***
Generalised anxiety disorder	65 (12.3)	***
Obsessive-compulsive disorder	40 (7.6)	***
Post-traumatic stress disorder	31 (5.8)	***
Any anxiety disorder	123 (23.4)	***
Eating disorders		
Anorexia nervosa	0 (0.0)	***
Bulimia nervosa	13 (2.4)	***
Psychotic disorders	26 (4.9)	67 (12.7)
Antisocial personality disorder	***	136 (25.8)
Suicide attempts	***	151 (28.7)

- Mood disorder – 35%
- Anxiety disorder- 43%
- Psychosis- 12%

- Overall- 48%

Psychopathology in methamphetamine-dependent adults 3 years after treatment. Glasner-Edwards et al., Drug Alcohol Rev 2010 Jan:29(1) 12-20

Delusions : fixed beliefs that conflict with reality

- Paranoid
- Delusions of reference (things are about him/her)
- Thought broadcasting (thoughts can be heard)
- Grandeur
- Guilt (they are responsible for something)
- Persecutory
- Somatic (body is somehow diseased)
- Erotomanic (convinced someone loves them)

When interacting with a patient who presents with delusions what Do’s and Don’ts would you recommend?

How to interact with a patient with delusions

- DO
  - Maintain the therapeutic relationship for future engagement
  - Ask questions about their delusion in an unemotional manner, gain a better understanding of the delusion (it gives you a sense of how deep the delusion, it builds therapeutic relationship, and forces the patient to examine their logic)
  - Try to keep the focus on the emotional impact of the delusion
  - Can ask them if there is anything that could change their mind
  - If the patient is well enough open the possibility of doubt by offering alternatives (I am willing to look at your side of the story but I would need more evidence / I understand your belief but this is why I believe this other explanation)

- DON'T
  - Ignore it
  - Argue or try convince the person out of their delusion
  - Just agree with their delusion
  - Avoid emotional reactions

Are there preferred medications to treat the acute psychosis

Efficacy and dropout rates of antipsychotic medications for methamphetamine psychosis: A systematic review and network meta-analysis: Manit Srisurapanont, et.al., Drug and Alcohol Dependence, 219, Feb 2021

- Metanalysis of 6 randomized controlled trials involving 395 patients
- Six studied antipsychotics were aripiprazole, haloperidol, olanzapine, paliperidone extended-release, quetiapine, and risperidone.
- They all were effective in managing the acute psychosis of MAP
- Individually the studies did not show any superior antipsychotic
- This meta analysis suggest slight superiority of olanzapine and quetiapine

ARE THERE MEDICATIONS THAT ARE HELPFUL IN METHAMPHETAMINE USE DISORDER

- If methamphetamine addiction is caused by excessive dopamine release what about using long term antipsychotics (dopamine blockers) to reduce the reward and cravings of methamphetamine

The patient asks you to place him on low dose Vyvanse (lisdexampfetamine) as he feels that will control his cravings and allow him to focus on his recovery

Drugs evaluated for use in stimulant use disorder

- Dexamphetamine
- Methylphenidate
- Lisdextroamfetamine
- Risperidone
- Aripiprazole
- Modafinil
- Bupropion
- Baclofen
- Vigabatrin
- Buprenorphine
- Ondansetron
- Varenicline
- Amlodipine
- Atomoxetine
- Imipramine
- Amantadine
- Bromocriptine
- Pergolide
- Acamprosate
- Naltrexone
- N=acetyl Cysteine
- Mirtazapine
- Sertraline
- Fluoxetine
- Flumazenil
- Gabapentin
- Topiramate
- Quetiapine
- Creatine
- Disulfiram
- Oxytocin
- Vaccine
- Carbamazepine
- Valproic Acid
- Olanzapine
- Memantine
- Riluzole

Pharmacotherapy for methamphetamine/ amphetamine use disorder- a system review and meta-analysis

Chan, B., et al, Addiction (Early view), July 2019

- Studies up to April 2019 not included in previous systemic reviews
- 18 studies related to 17 different pharmacotherapies
- Review of level II (RCT with placebo)

Methylphenidate

Study	N		Primary outcome	Negative urines
Miles et al, 2013	40 methylphenidate 39 Placebo -27 (28%) completed the trial)	-22 weeks -daily attendance required	% positive UDS collected 2/week	-23% drug -26% placebo
Konstenius et al 2010	12 methylphenidate 12 placebo - 71% retention (requirement of 4 weeks drug free prior to enrollment)	-use disorder + ADHD -twice weekly visits -12 weeks	% positive UDS collected 2/week -self reports	-10.6% drug -8.6% placebo
				-

Bupropion

Study	N		Primary outcome	Negative urines
Shoptaw, et al 2008	-36 bup -37 Placebo 36% completion rate	12 weeks	3 / week UDS	-35% negative urines Bupropion -31% negative in the placebo
Heinzerling et al 2014	-40 bupropion -40 placebo 36 (47%) completion rate	16 weeks	3/week UDS (EOT)	-29% negative urines bupropion -14% placebo
Elkshef et al 2007	-79 bupropion -7 7 placebo 79 (52%) completion rate	16 weeks	3/week UDS	-54% bupropion 44% placebo (1 week of – UDS)

Naltrexone and Bupropion

Study	N		Primary outcome	
Madhukar, H., et al	1st 6 weeks - 109 medications - 294 placebo 2nd 6 weeks - 114 medications - 111 continued placebo	12 weeks	UDS testing 2 / week	Stage 1 -18/109 (16.5%) -10/294 (3.4%) Stage 2 - 13/114 (3.4%) -2/111 (1.8%)

Pharmacotherapy for Amphetamine use disorder

- There is no strong or consistent evidence of benefit on MA use, abstinence or treatment retention
- There are some individual studies which suggests improved outcomes (retention, cravings, UDS)

DSM-V METHAMPHETAMINE WITHDRAWAL

- Dysphoric mood and two (or more) of the following physiological changes, developing within a few hours to several days after Criterion A:
- Fatigue.
- Vivid, unpleasant dreams.
- Insomnia or hypersomnia.
- Increased appetite.
- Psychomotor retardation or agitation.
- **C**. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

METHAMPHETAMINE WITHDRAWAL

- Acute phase (crash) : 1-7 days
  -increased sleep
  -increased appetite
  -fatigue
  -depression / anhedonia
  -inactivity
  -cravings
- Subacute phase 1-2 weeks
  -anxiety
  -poor sleep +/-
  -cravings
  -anhedonia
  -poor concentration, irritability

The patient presents 4 days after stopping. He describes staying in bed, feeling depressed, no interest in doing anything. Starting to have spontaneous cravings.

Would it be reasonable to start an antidepressant?

MANAGEMENT

- No standard treatment approach
- Predominately psycho-social support
- Outpatient
- No approved medications
  -mirtazapine
  -modafinil
  -bupropion

- WHAT COMPONENTS OF METHAMPHETAMINE ADDICTION TREATMENT THAT ARE IMPORTANT TO HAVE IN PLACE

Some observations regarding treatment

- Longer term then 12 weeks of IOP, intense
- Trigger identification
  - people (sex partners, “friends who understand”)
  - places (specific using environment)
  - things (stimulus checks)
  - times (weekends→ daily)
- Cyclical pattern: use—anhedonia---cravings—use (immediate reward)
- More frequent follow up
- Isolation from recovery support systems and activities
- Paranoia and difficulty in getting into treatment *strong therapeutic alliance
- More concurrent mental health issues (anxiety, depression)

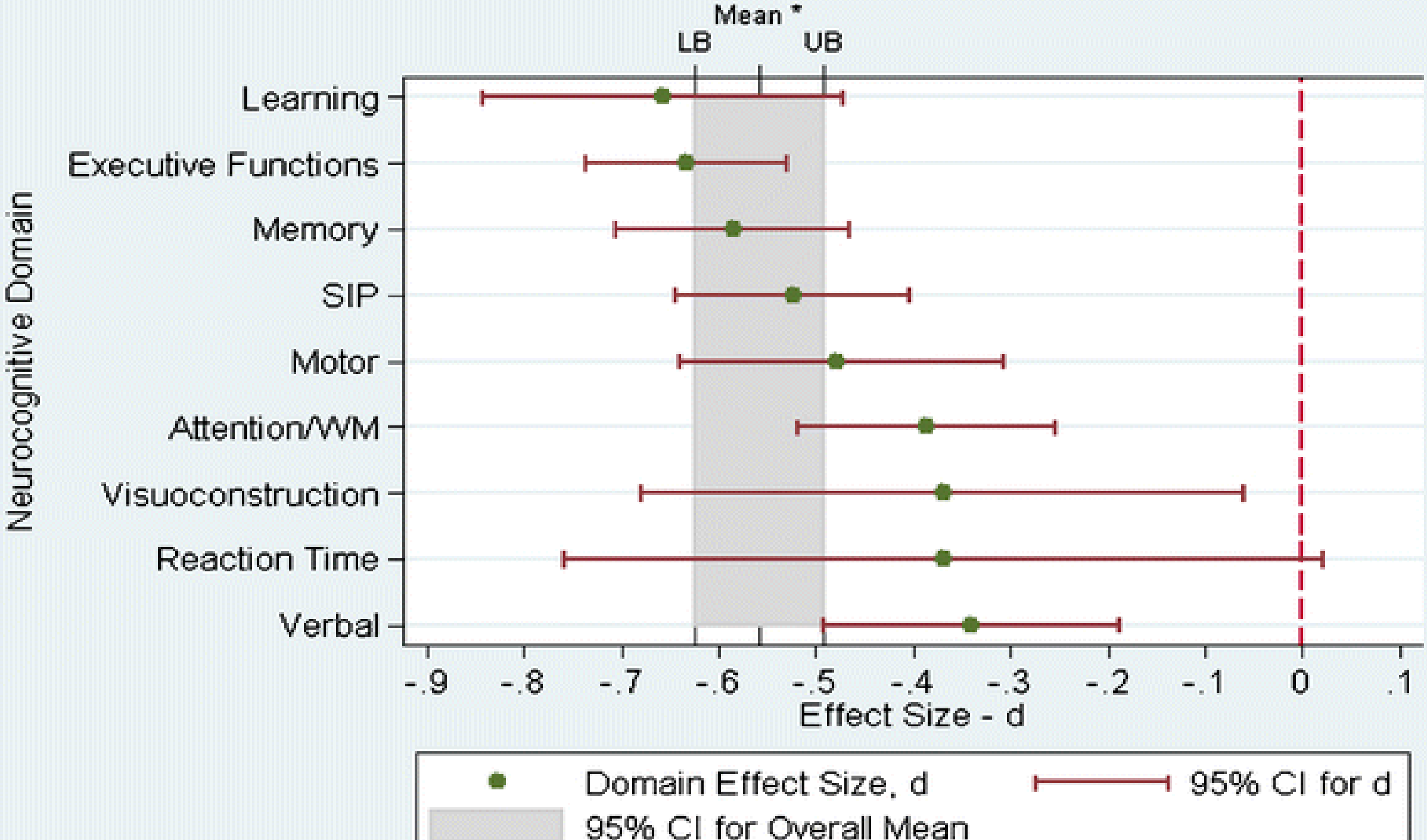
METHAMPHETAMINE IS A NEUROTOXIC AGENT

AND IT IS NOT JUST NEUROTRANSMITTERS

- Increased evidence of neuroinflammation (increased microglial activation) resulting in neurotoxicity
- Disruption of the blood brain barrier that blocks toxins
- Mitochondrial dysfunction resulting in oxidative stress
- Breaks in the DNA single and double strands
- Increase in inflammatory ct
- Focal cerebral perfusion deficits

Neurocognitive Effects of Methamphetamine : A Critical Review and Meta-analysis. Scott JC., et al., Neuropsychology Review 17, 275-297 (2007)

- Review of literature that had neuropsychological testing results
- 18 studies (487 subjects, 464 controls)


Mean *
LB
UB
Learning
Executive Functions
Memory
SIP
Motor
Attention/WM
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Reaction Time
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-.4
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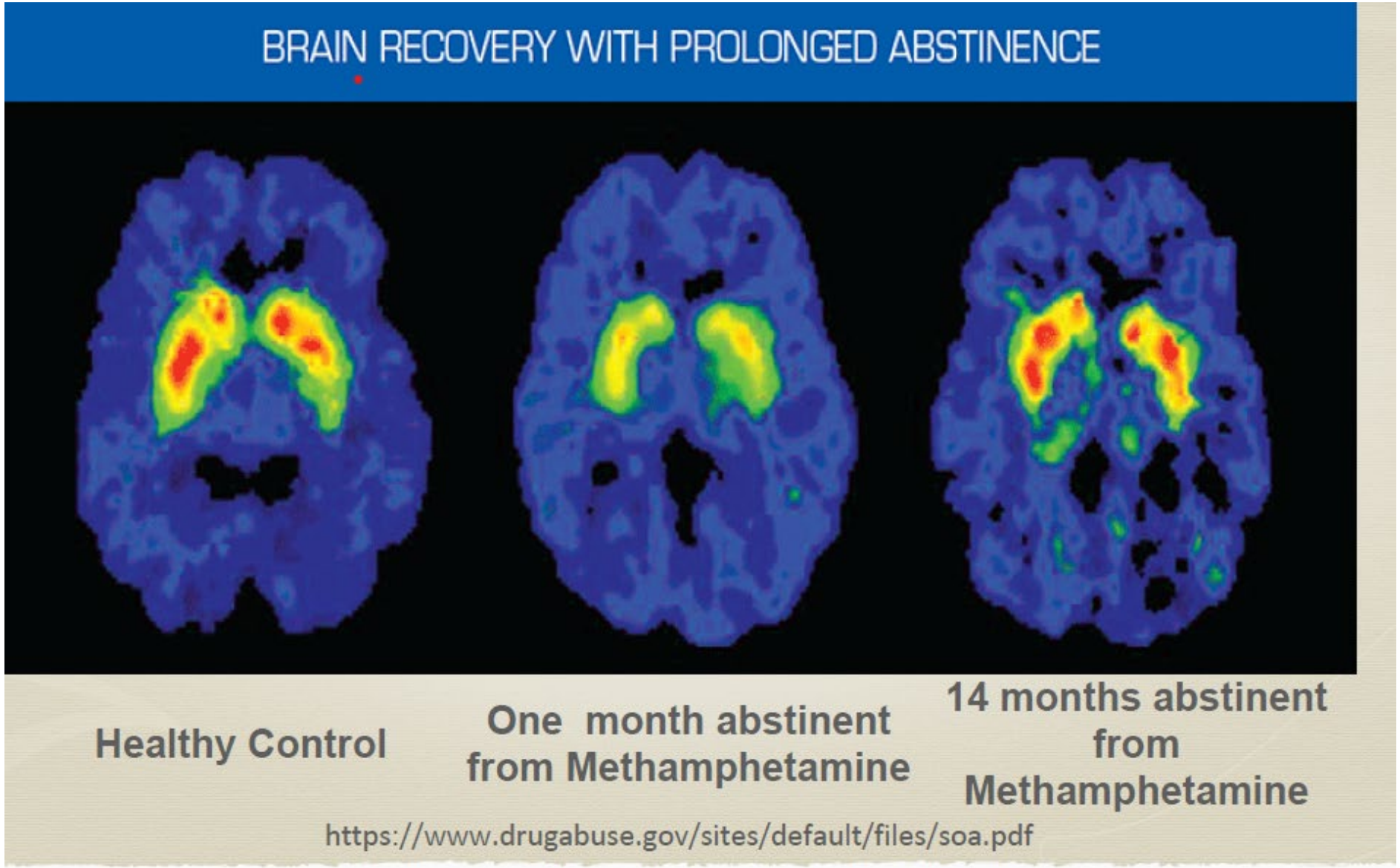
-.2
-.1
0
.1
Effect Size - d
Domain Effect Size, d
95% CI for d
95% CI for Overall Mean

DURATION OF THE DEFICITS

- Persist into abstinence
- May worsen initially (5-14 days)
  * one study suggested individuals in early abstinence actually performed worse than those who continued to use methamphetamine)

Dopamine transporter (DAT) levels may return to normal in 12 months but mild cognitive impairments may persist longer

HOW LONG WILL THE IMPAIRMENTS LAST



ARE THERE IMPLICATIONS FOR TREATMENT

- Unclear how much these impairments impact cognitive driven treatments
- Evidence based treatment
  - contingency management (immediate reward)
  - cognitive based treatments (matrix model)
- May need to develop specific strategies that address the deficits of impaired memory, learning and executive function