What Does the Science Tell Us About Evidence-Based Drug Treatment?

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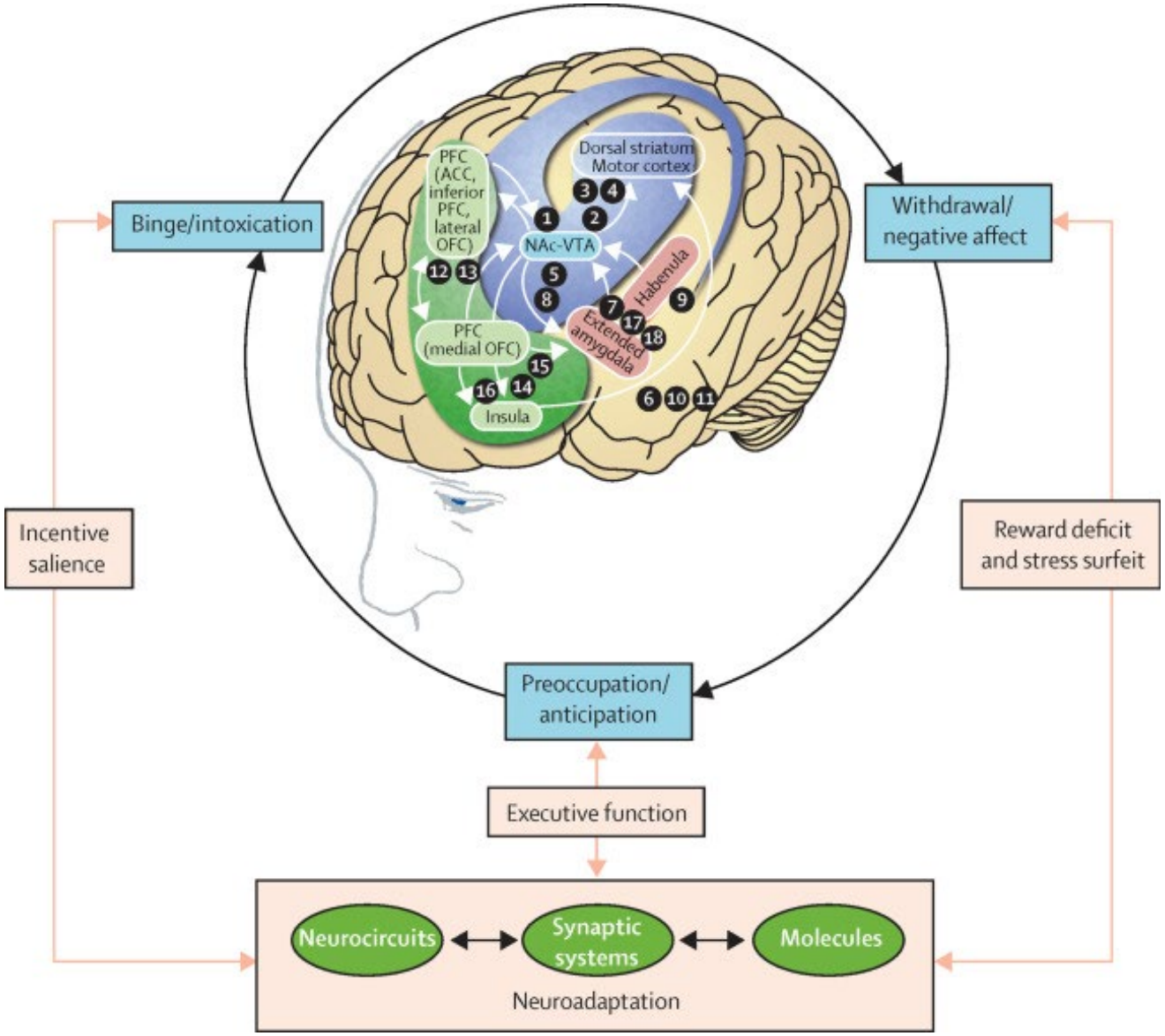
Brain Circuits Involved in the Addiction Cycle

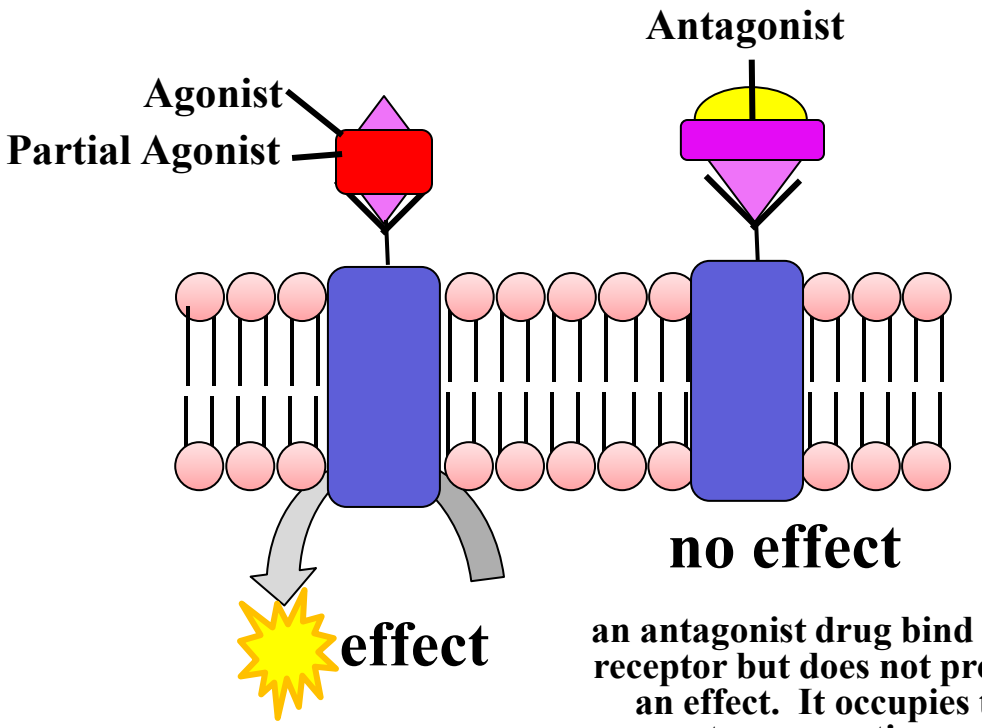


Koob and Volkow, Lancet Psychiatry 2016.

Treatment Approaches for Substance use Disorders

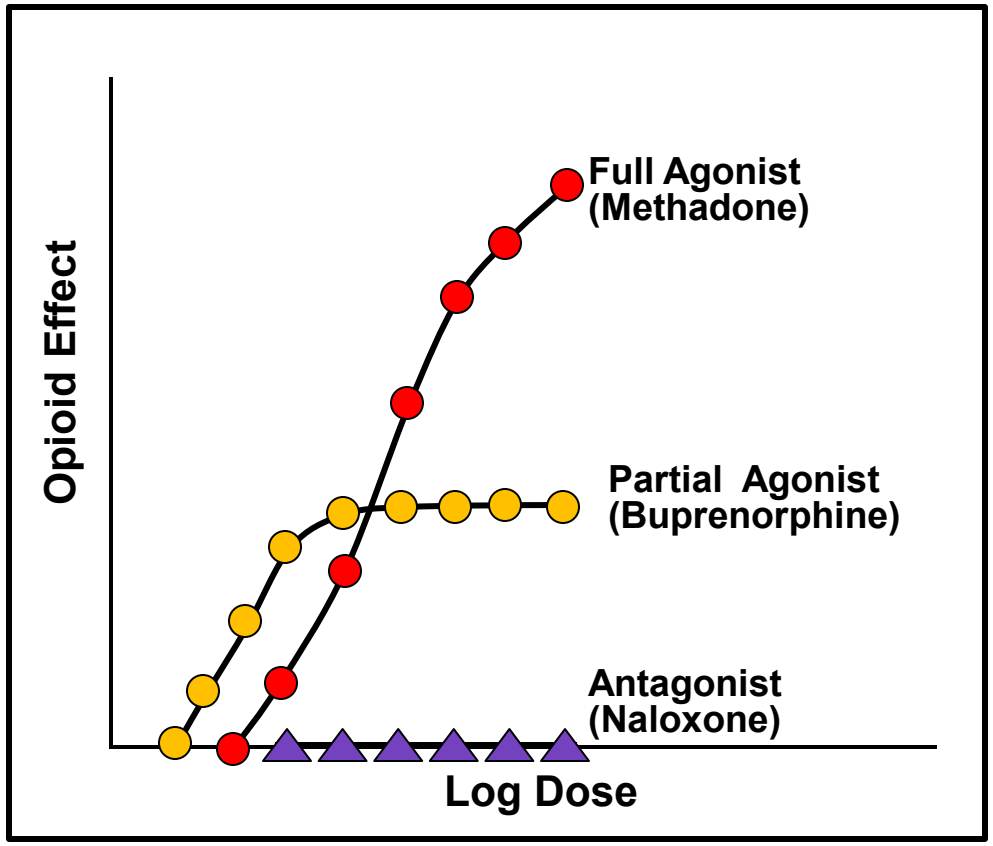
- Medications (FDA approved)
  - Nicotine Addiction
    - Nicotine Replacement Therapies (NRT)
    - Bupropion
    - Varenicline
  - Alcohol Use Disorder
    - Disulfiram
    - Naltrexone
    - Acamprosate
  - Opioid Use Disorder
    - Methadone
    - Naltrexone
    - Buprenorphine
- Behavioral therapies
- Neuromodulation

Full and Partial Agonists vs Antagonists Treatment Strategies for Opioid Addiction



an agonist and a partial agonist drugs bind to the receptor activating the signaling cascade with effects that can be stronger or weaker (partial agonist)

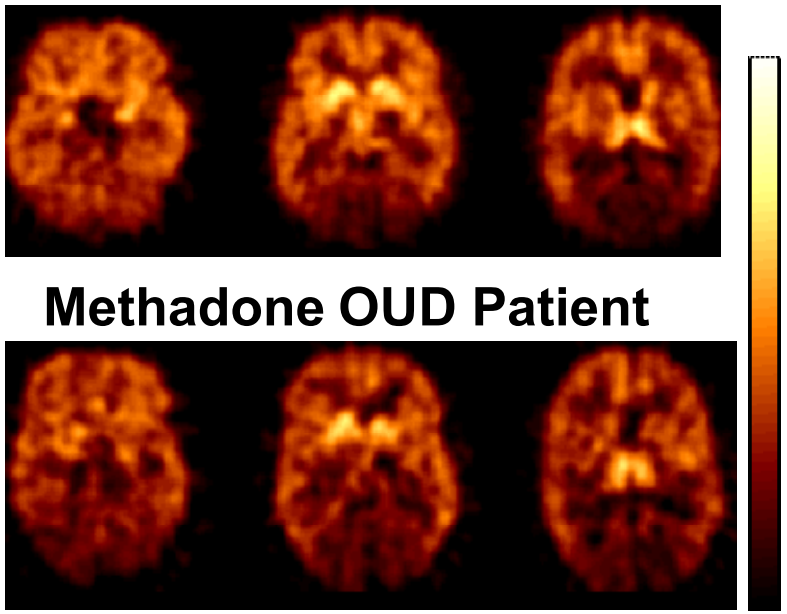
an antagonist drug bind to the receptor but does not produce an effect. It occupies the receptor preventing opioid agonists from binding



MOR Occupancy by Methadone, Buprenorphine and Naltrexone Measured with PET

METHADONE

Normal Control (no treatment)



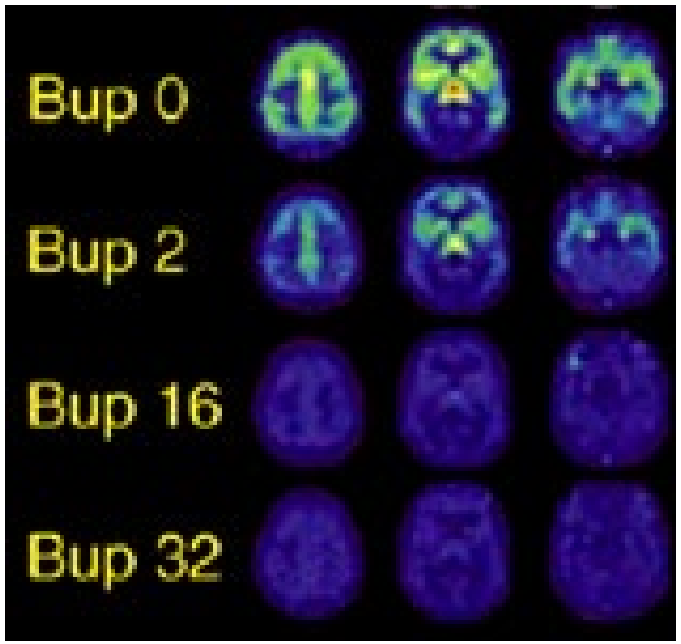
Methadone OUD Patient

[^{18}F]cyclofoxy

30-35% MOR occupancy for methadone doses >80 mg day

Source: Kling et al., JPET, 2000.

BUPRENORPHINE



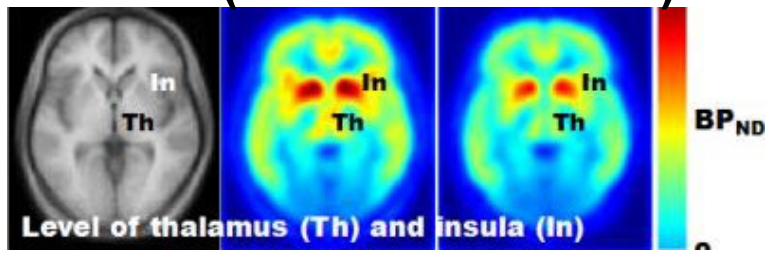
[^{11}C]carfentanil

27-47% occupancy by 2mg Bup
85-92% occupancy by 16 mg Bup
94-98% occupancy by 32 mg Bup

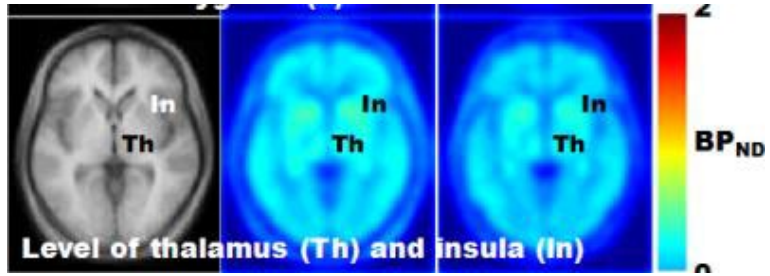
Greenwald, MK et al., Neuropsychopharm. 2003.

NALTREXONE

Alcoholic (before treatment)



Alcoholic (naltrexone treatment)



[^{11}C]carfentanil

Weertset al., Addict Biol. 2014.

90% occupancy for 32 and 48 mg chronic naltrexone
90% occupancy 150 mg single dose

Ye et al., JNM 2007.

Cognitive and Psychomotor Effects of Methadone

Methadone treatment has been associated with impairments in various cognitive functions including psychomotor speed, reaction time, attention, eye-hand coordination, information processing, working memory, decision making, and problem solving

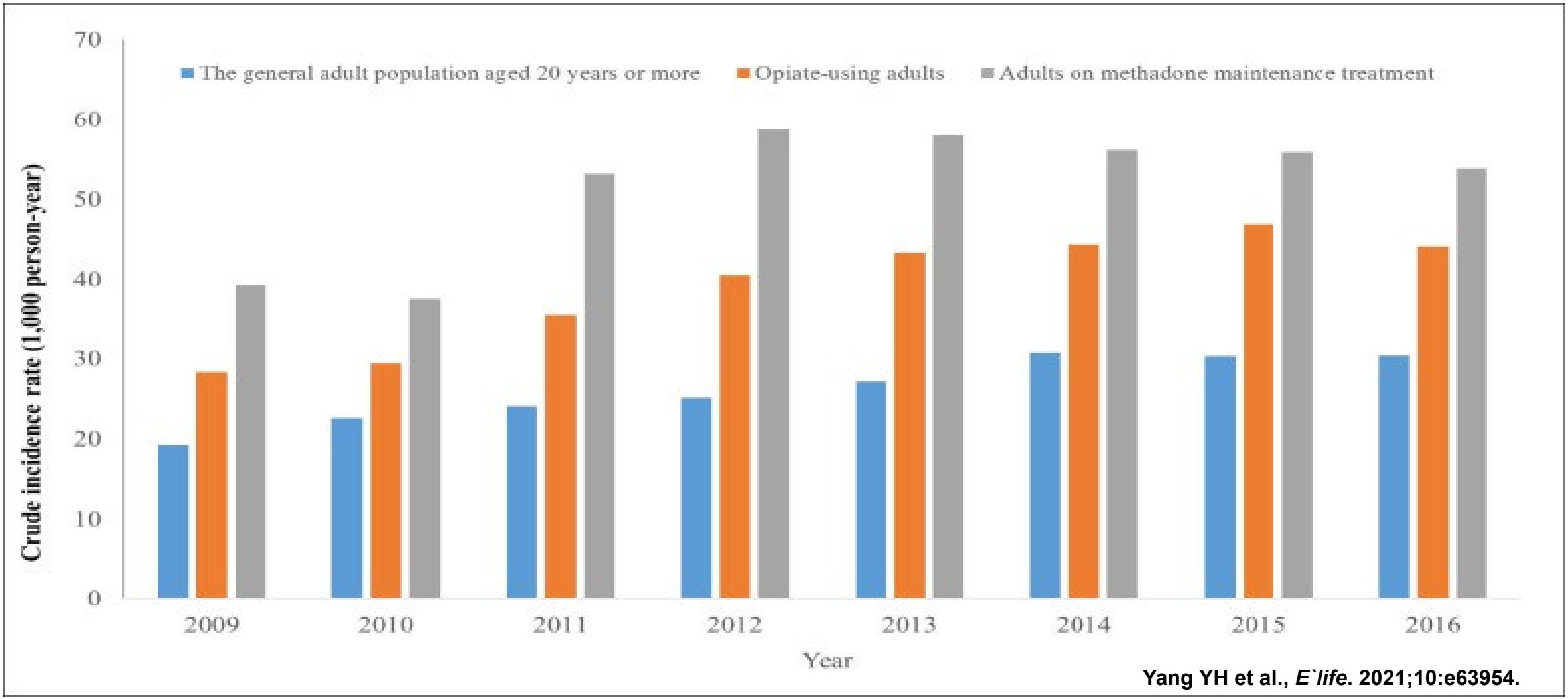
- Cognitive functions in OUD patients treated with methadone were **impaired relative to controls**, but **improved compared to untreated OUD**
- Impairments in cognitive functions in **methadone treated compared to untreated abstinent OUD**
- Improvements in cognitive function with longer methadone **treatment duration**
- Effects may be **dose-dependent**

**Results are confounded by substance use*.

Preclinical studies

- In rodents showed acute and chronic methadone disrupts working memory
- Most effects are not evident after chronic methadone administration due to tolerance

Incidence Rates Of Motor Vehicle Collisions Annually Among The General Adult Population, Adult Opiate Users, and Patients Receiving Methadone Maintenance Treatment (MMT)



Yang YH et al., *E`life*. 2021;10:e63954.

Cognitive and Psychomotor Effects of Buprenorphine

In healthy controls acute buprenorphine impaired performance in some cognitive and psychomotor tests

OUD patients treated with buprenorphine when c**ompared to healthy controls showed impairments** in cognitive and psychomotor performance, but some showed no differences.

- Psychomotor and cognitive functions (attention, reaction time, visual orientation, motor coordination, and vigilance) in OUD patients treated with buprenorphine (long-term) **did not differ from healthy volunteers** based on an RCT

Unclear whether impairments identified by laboratory tests can be extrapolated to performance in the real word.

Comparative Studies Of Methadone, Buprenorphine, and Naltrexone On Cognitive and Psychomotor Effects

- B**uprenorphine had less adverse effects than methadone** on decision-making, attention, verbal memory, reaction times, and other psychomotor measures, but had similar impairments in working memory, executive function, information processing, psychomotor speed, and verbal and non-verbal learning
  - Methadone treated patients were impaired relative to healthy controls in working memory, attention and verbal memory, while buprenorphine patients were impaired only in working memory.
- **OUD patients treated with naltrexone had less impairments than those treated with methadone or buprenorphine** and showed **no differences from controls**.
- OUD patients who transition from buprenorphine to naltrexone improved cognitive function

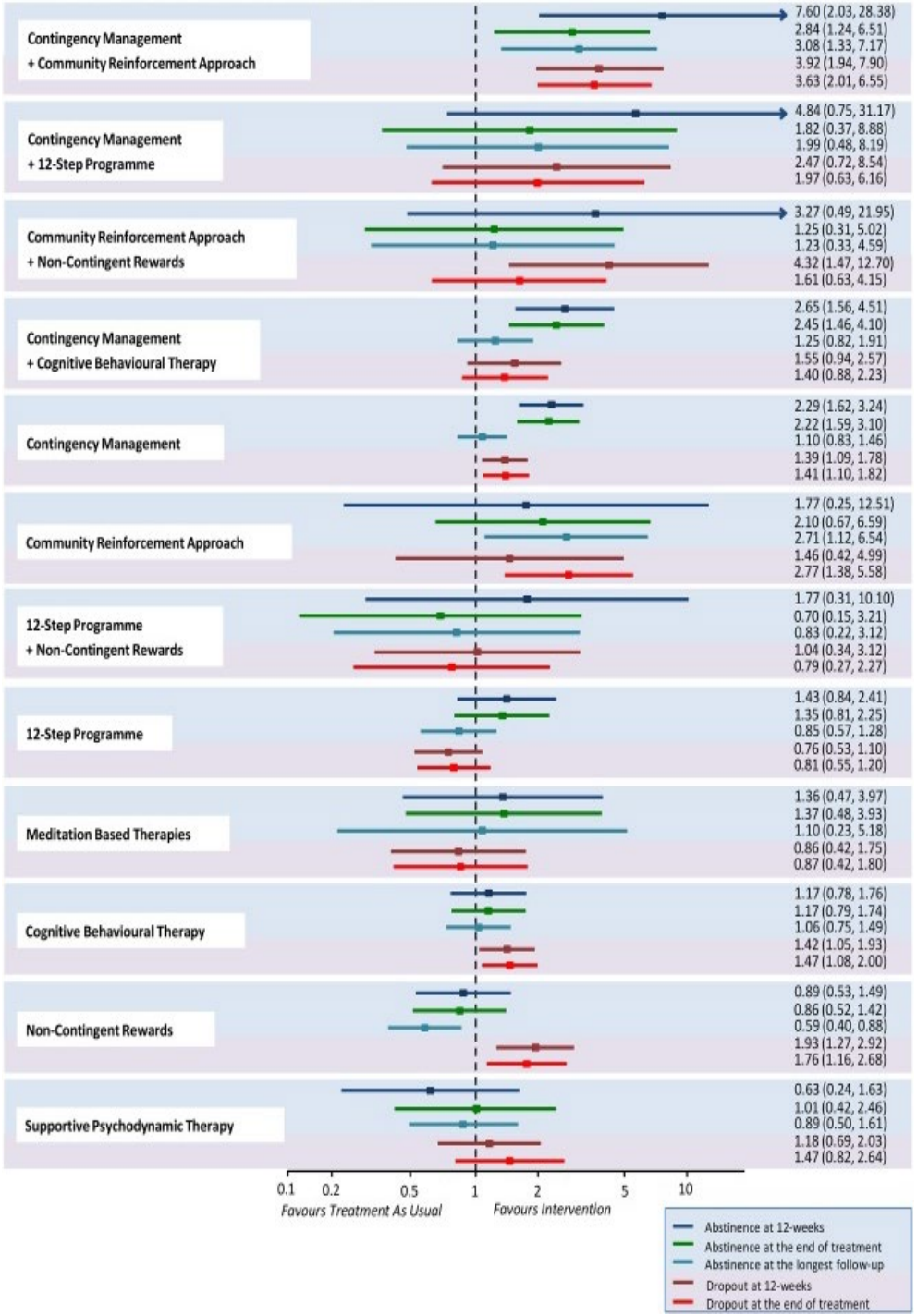
- **Impairments associated with methadone and buprenorphine improve with longer duration of treatment.**
  - Similar levels of performance in buprenorphine and methadone groups compared to healthy controls for most cognitive domains after 8-10 weeks of treatment.

Other treatment factors (like co-treatment with a benzodiazepine) and substance use frequency/history can impact cognitive and psychomotor performance

Behavioral Treatments

- **Cognitive-behavioral therapy (CBT)**, helps patients recognize, avoid, and cope with the situations in which they are most likely to use drugs
- **Motivational interviewing**, makes the most of people's readiness to change their behavior and enter treatment
- **Motivational incentives** (Contingency Management or **CM**), which uses positive reinforcement to encourage abstinence from drugs
- **Community reinforcement approach (CRA),** uses recreational, familial, social, and vocational reinforcers, to make non-drug-using lifestyle more rewarding

Comparative efficacy of behavioral interventions for cocaine and amphetamine addiction: Systematic review and meta-analysis



Only CM and CRA increased the number of abstinent patients at 12 weeks of treatment (OR 7.60) and at the longest follow-up (OR 3.08).

CM and CRA were more efficacious than CBT (OR 2.44), non-contingent rewards (OR 3.31, 95% CI 1.32-8.28, P = 0.010), and 12-step programs (OR 4.07).

CM + CRA had fewer dropouts than other treatments (OR 3.63).

Combination of CRA with CM was superior to CBT alone, CM alone, CM plus CBT, and 12-step programs ($P < 0.001$).

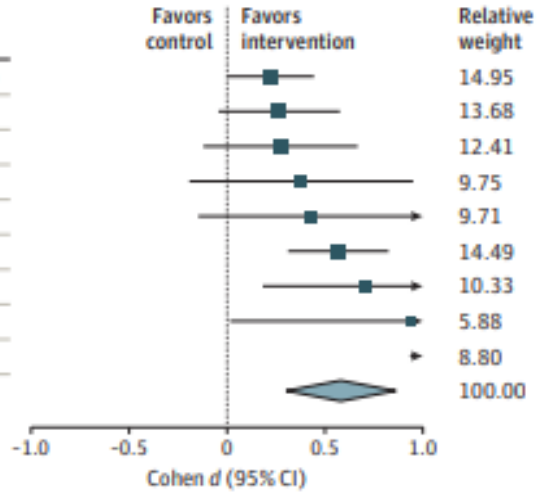
De Crescenzo et al., PLoS Medicine 2018; 15(12): e1002715.

Contingency Management for Patients Receiving Medication for Opioid Use Disorder: A Systematic Review and Meta-analysis

Figure 4. Forest Plots of Treatment Effect Sizes of Contingency Management vs Controls: Abstinence From Illicit Opioid Use and Cigarette Smoking

A Opioid use

Study	Cohen *d* (95% CI)	Relative weight
Hser et al,[60] 2011	0.23 (0.007 to 0.45)	14.95
Jiang et al,[61] 2012	0.27 (-0.04 to 0.58)	13.68
Ling et al,[62] 2013	0.28 (-0.12 to 0.67)	12.41
Jarvis et al,[63] 2019	0.38 (-0.19 to 0.95)	9.75
Robles et al,[64] 2002	0.43 (-0.14 to 1.01)	9.71
Chen et al,[65] 2013	0.57 (0.32 to 0.83)	14.49
Correia et al,[66] 2003	0.71 (0.18 to 1.25)	10.33
McCaul et al,[67] 1984	0.94 (0.02 to 1.87)	5.88
Preston et al,[68] 2000	2.07 (1.42 to 2.71)	8.80
Total (95% CI)	0.58 (0.30 to 0.86)	100.00



B Cigarette smoking

Study	Cohen *d* (95% CI)	Relative weight
Sigmon et al,[69] 2016	0.46 (-0.04 to 0.96)	37.57
Tuten et al,[70] 2012	0.95 (0.46 to 1.44)	38.27
Dunn et al,[71] 2010	1.03 (0.37 to 1.68)	24.16
Total (95% CI)	0.78 (0.43 to 1.14)	100.00

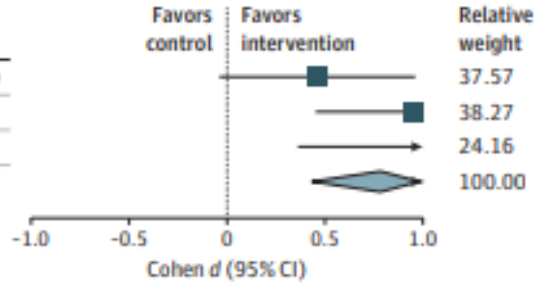
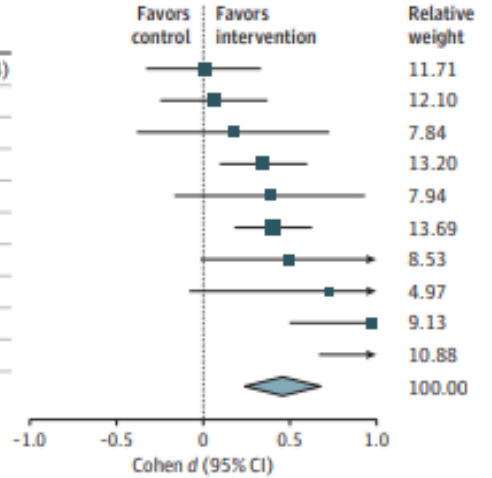


Figure 5. Forest Plots of Treatment Effect Sizes of Contingency Management vs Controls: Therapy Attendance and Medication Adherence

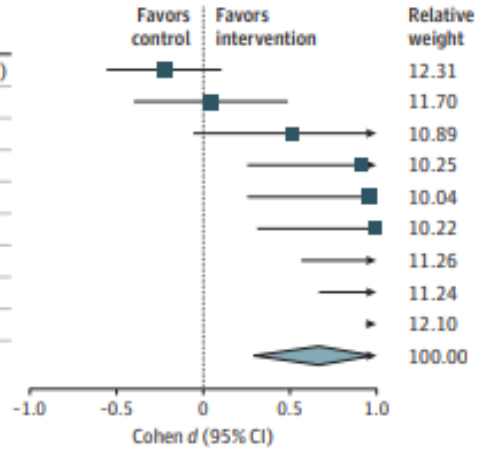
A Therapy attendance

Study	Cohen *d* (95% CI)	Relative weight
Kidorf et al,[72] 2018	0.006 (-0.33 to 0.34)	11.71
Jiang et al,[61] 2012	0.06 (-0.25 to 0.37)	12.10
Rhodes et al,[73] 2003[a]	0.17 (-0.38 to 0.73)	7.84
Chen et al,[65] 2013	0.35 (0.10 to 0.60)	13.20
Rhodes et al,[73] 2003[b]	0.39 (-0.16 to 0.94)	7.94
Hser et al,[60] 2011	0.40 (0.18 to 0.63)	13.69
Rowan-Szal et al,[30] 2005	0.50 (-0.02 to 1.01)	8.53
Jones et al,[74] 2000	0.73 (-0.08 to 1.54)	4.97
Petry et al,[27] 2005	0.97 (0.50 to 1.44)	9.13
Kodorf et al,[75] 2013	1.05 (0.67 to 1.42)	10.88
Total (95% CI)	0.43 (0.22 to 0.65)	100.00



B Medication adherence

Study	Cohen *d* (95% CI)	Relative weight
Kidorf et al,[72] 2018	-0.23 (-0.56 to 0.10)	12.31
Carroll et al,[43] 2001	0.05 (-0.40 to 0.49)	11.70
Carroll et al,[55] 2002	0.52 (-0.05 to 1.09)	10.89
Preston et al,[76] 1999	0.92 (0.25 to 1.59)	10.25
Everly et al,[77] 2011	0.96 (0.26 to 1.66)	10.04
DeFulio et al,[78] 2012	0.99 (0.31 to 1.66)	10.22
Sorensen et al,[79] 2007	1.08 (0.57 to 1.60)	11.26
Dunn et al,[80] 2013	1.19 (0.67 to 1.71)	11.24
Weaver et al,[81] 2014	1.42 (1.04 to 1.79)	12.10
Total (95% CI)	0.75 (0.30 to 1.21)	100.00



Bolivar, HA et al., JAMA Psychiatry. 2021;78(10):1092-1102. 2021. Corrected, 2022

12-Step Recovery Programs and Support Groups for Substance Use Disorders

- **Alcoholics Anonymous** (**AA**): international mutual aid fellowship of alcoholics dedicated to abstinence-based recovery from alcoholism through its spiritually-inclined Twelve-Step Program. In 2020 worldwide membership was > two million with 75% in the U.S. and Canada.

- **Narcotics Anonymous (NA):** global, community-based organization founded in 1953. NA is a nonprofit fellowship of men and women for whom drugs are a major problem.

- **Cocaine Anonymous (CA)** is a support group that might help those suffering from cocaine addiction and misuse issues.

- **Marijuana Anonymous (MA)** is best suited for individuals who wish to stop abusing or being addicted to marijuana.

- Other groups including:
  Secular Organizations for Sobriety (SOS) and
  SMART Recovery (Self Management for Addiction Recovery).

Cochrane Review Finds Alcoholics Anonymous and 12-step Facilitation Programs Help People Recover From Alcohol Problems

Included studies by study design, degree of manualization, and theoretical orientation

Study	Design	Degree of manualization	Treatment comparison
Blondell 2001	Non-randomized	Part/non-manualized	Different theoretical orientation
Blondell 2011	RCT	Part/non-manualized	Different theoretical orientation
Bogenschutz 2014	RCT	Part/non-manualized	Different theoretical orientation
Bowen 2014	RCT	Part/non-manualized	Different theoretical orientation
Brooks 2003	Quasi-RCT	Manualized	Different theoretical orientation
Brown 2002	RCT	Manualized	Different theoretical orientation
Davis 2002	RCT	Manualized	Different theoretical orientation
Grant 2017	Non-randomized	Part/non-manualized	TSF variant
Herman 2000	RCT	Part/non-manualized	Different theoretical orientation
Humphreys 1996	Non-randomized & Economic	Part/non-manualized	Different theoretical orientation
Kahler 2004	RCT	Manualized	TSF variant
Kaskutas 2009	Quasi-RCT	Part/non-manualized	TSF variant
Kelly 2017	RCT	Manualized	Different theoretical orientation
Litt 2007	RCT	Manualized	Different theoretical orientation
Litt 2016	RCT	Manualized	Different theoretical orientation
Lydecker 2010	Quasi-RCT	Manualized	Different theoretical orientation
Manning 2012	RCT	Part/non-manualized	TSF variant
MATCH 1997a	RCT	Manualized	Different theoretical orientation
McCrady 1996	RCT	Manualized	Different theoretical orientation
Mundt 2012	Economic	Part/non-manualized	TSF variant
Ouimette 1997	Non-randomized	Part/non-manualized	Different theoretical orientation & TSF variant
Timko 2006	RCT	Manualized	TSF variant
Timko 2011	Quasi-RCT	Manualized	TSF variant
Vederhus 2014	Quasi-RCT	Manualized	TSF variant
Walitzer 2009	RCT	Manualized	Different theoretical orientation & TSF variant
Walitzer 2015	RCT	Manualized	Different theoretical orientation
Zemore 2018	Non-randomized	Part/non-manualized	Different theoretical orientation

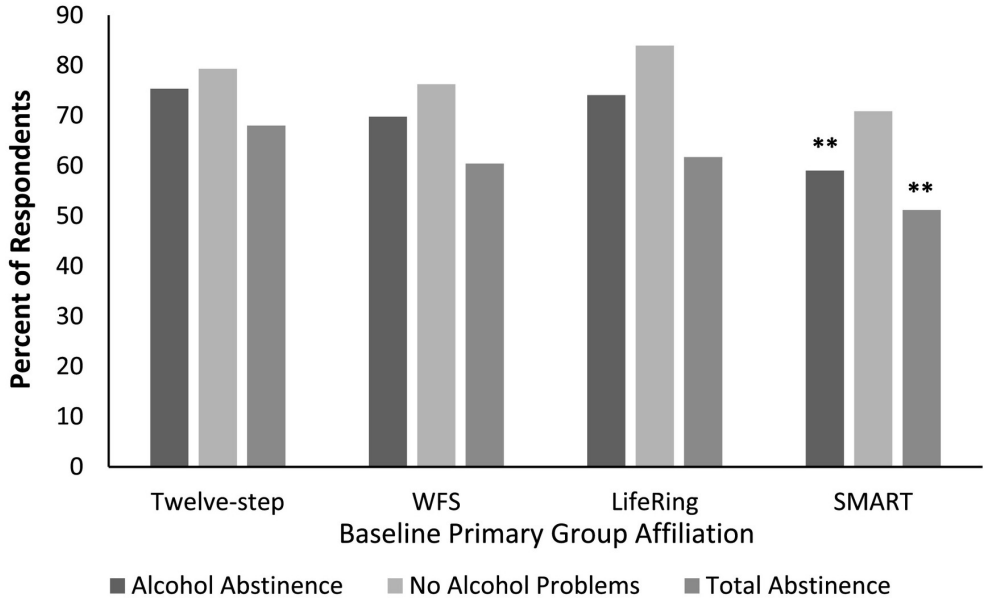
- High Certainty Evidence That Clinically Delivered and Manualized TSF Programs Designed To Increase AA Participation **Can Lead To Higher Rates Of Continuous Abstinence Over Months and Year**.
- AA/TSF may perform as well as other clinical interventions for **drinking intensity outcomes**; however, these results are based on low certainty evidence.
- Substantial healthcare cost savings can be obtained when treatment programs systematically link people with AUD to AA using TSF strategies.

Kelly et al., Cochrane Database of Systematic Reviews 2020, CD012880. 2022.

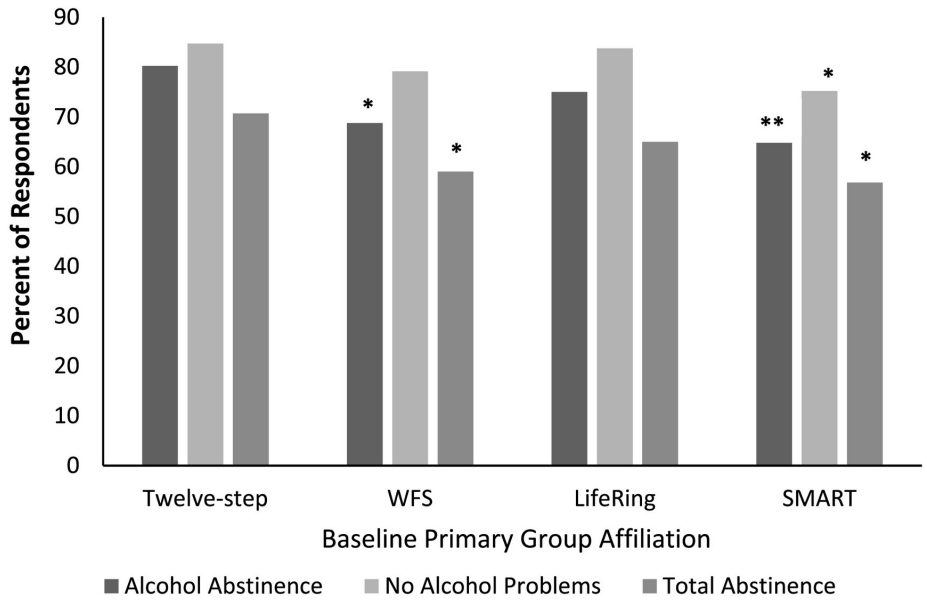
Comparison of Peer Support Groups for AUD

- Extremely limited evidence on mutual help alternatives.
- Data tentatively suggest that **Women For Sobriety, LifeRing, and SMART are as effective as 12-step groups for those with AUD.**
- An optimal care plan may involve **facilitating involvement in a broad array of mutual help groups** and supporting abstinence motivation.

*Bivariate associations between baseline primary group affiliation and **6-month outcomes** (N = 503).*



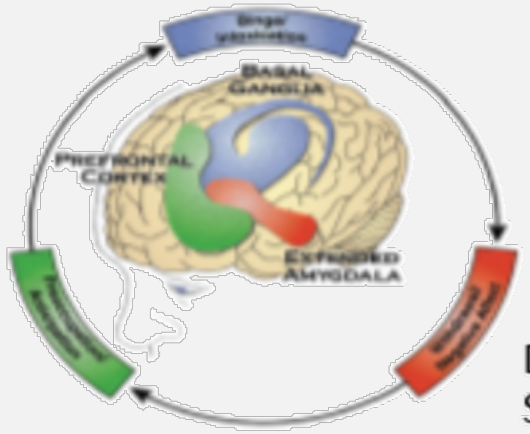
*Bivariate associations between baseline primary group affiliation and **12-month outcomes** (N = 503).*



Zemore et al., JSAT, 2018

Neuromodulation: SUD Treatment

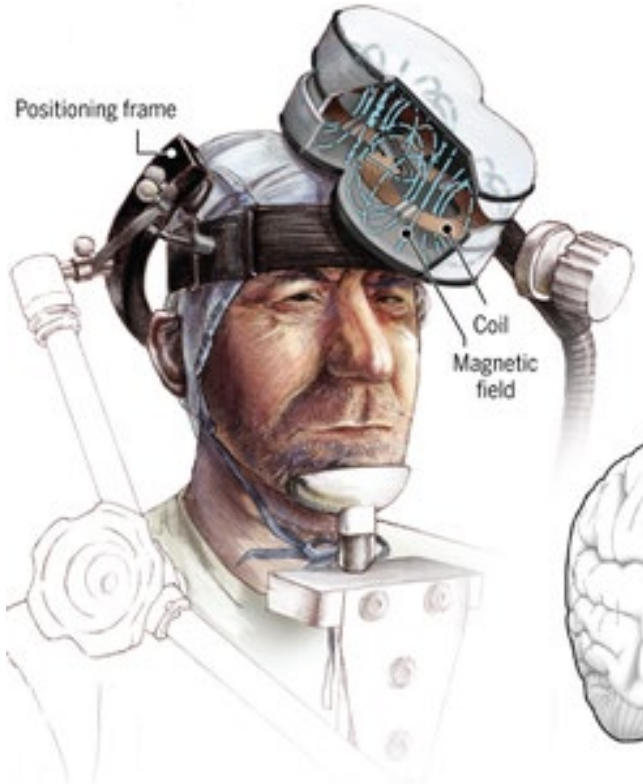
Neuromodulation Techniques



Transcranial Magnetic Stimulation (TMS)

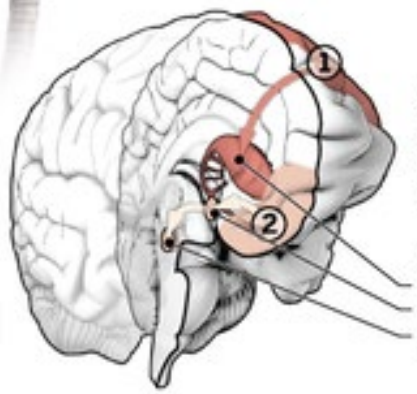
Deep Brain Stimulation (DBS)

Transcranial Direct Current Stimulation (tDCS)



Magnetic medicine

Electric pulses in a coil held near the scalp induce a changing magnetic field that creates electric currents in the cortex. Changing the frequency and pattern of magnetic pulses delivered to the cortex can either increase or decrease neuronal firing. Multiple stimulation strategies are being used to battle cocaine addiction.

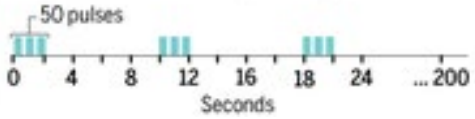


Cortex
1 Dorsolateral prefrontal cortex
2 Ventromedial prefrontal cortex

Midbrain
Caudate nucleus
Nucleus accumbens
Ventral tegmental area

"Cold" (executive control) circuit

In one form of transcranial magnetic stimulation, pulses are delivered many times per second, on and off, for a few minutes. This "intermittent theta burst" stimulation of the dorsolateral prefrontal cortex may propagate to the midbrain (arrows, left) and strengthen the "cold" (right, dark pink) circuit that overrides drug-seeking impulses.



"Hot" (craving and reward) circuit

Continuous theta burst stimulation applied to the ventromedial prefrontal cortex is thought to inhibit the neurons of the "hot" (light pink) circuit that connects to the midbrain's nucleus accumbens and ventral tegmental area. It is abnormally active when people addicted to cocaine are exposed to cues such as white powder.

Wadman, Science 2017.

THANK YOU!

Duration of Treatment With OUD Medication

Patients can take medication for OUD on a short-term or long-term basis. However, patients who discontinue OUD medication generally return to illicit opioid use. Why is this so, even when discontinuation occurs slowly and carefully? Because the more severe form of OUD (i.e., addiction) is more than physical dependence. Addiction changes the reward circuitry of the brain, affecting cognition, emotions, and behavior. Providers and their patients should base decisions about discontinuing OUD medication on knowledge of the evidence base for the use of these medications, individualized assessments, and an individualized treatment plan they collaboratively develop and agree upon. Arbitrary time limits on the duration of treatment with OUD medication are inadvisable.

Maintenance Treatment

The best results occur when a patient receives medication for as long as it provides a benefit. This approach is often called "maintenance treatment."[67,68] Once stabilized on OUD medication, many patients stop using illicit opioids completely. Others continue to use for some time, but less frequently and in smaller amounts, which reduces their risk of morbidity and overdose death.

OUD medication gives people the time and ability to make necessary life changes associated with long-term remission and recovery (e.g., changing the people, places, and things connected with their drug use), and to do so more safely. Maintenance treatment also minimizes cravings and withdrawal symptoms. And it lets people better manage other aspects of their life, such as parenting, attending school, or working.

Medication Taper

After some time, patients may want to stop opioid agonist therapy for OUD through gradually tapering doses of the medication. Their outcomes will vary based on factors such as the length of their treatment, abstinence from illicit drugs, financial and social stability, and motivation to discontinue medication.[69] Longitudinal studies show that most patients who try to stop methadone treatment relapse during or after completing the taper.[70,71] For example, in a large, population-based retrospective study, only 13 percent of patients who tapered from methadone had successful outcomes (no treatment reentry, death, or opioid-related hospitalization within 18 months after taper).[72] A clinical trial of XR-NTX versus treatment without medication also found increased risk of returning to illicit opioid use after discontinuing medication.[73] **Adding psychosocial treatments to taper regimens may not signifcantly improve outcomes compared with remaining on medication.** One study randomly assigned participants to methadone maintenance or to 6 months of methadone treatment with a dose taper plus intensive psychosocial treatment. The maintenance group had more days in treatment and lower rates of heroin use and HIV risk behavior at 12-month follow-up.[74] Patients wishing to taper their opioid agonist medication should be offered psychosocial and recovery support

Medically Supervised Withdrawal

Medically supervised withdrawal is a process in which providers offer methadone or buprenorphine on a short-term basis to reduce physical withdrawal signs and symptoms. Formerly called detoxification, this process gradually decreases the dose until the medication is discontinued, typically over a period of days or weeks. Studies show that most patients with OUD who undergo medically supervised withdrawal will start using opioids again and won't continue in recommended care.[75, 76, 77, 78, 79, 80, 81, 82, 83] Psychosocial treatment strategies, such as contingency management, can reduce dropout from medically supervised withdrawal, opioid use during withdrawal, and opioid use following completion of withdrawal.[84] Medically supervised withdrawal is necessary for patients starting naltrexone, which requires at least 7 days without short-acting opioids and 10 to 14 days without long-acting opioids.

Patients who complete medically supervised withdrawal are at risk of opioid overdose.

Effects Of Methadone and Buprenorphine On Driving Performance

- Acute buprenorphine or methadone in healthy volunteers impaired driving task performance
- OUD patients given acute methadone or buprenorphine performed similarly to controls in a driving test, except for decision making and reaction time.
- OUD individuals receiving long-term treatment with methadone, buprenorphine, or heroin, compared to healthy controls on tests of driving ability reported no differences between treatment groups in visual perception or tracking; but the heroin group performed worse under stress conditions and monotony; and the buprenorphine group performed better in decision making and reaction tests.
- OUD patients treated with Buprenorphine compared to Methadone performed better in a driving performance task; but both groups performed worse than controls.
- In a simulated driving task, there were no differences in driving performance between OUD patients treated for 3 months with methadone or buprenorphine and healthy controls.
- Reports that individuals treated with methadone or buprenorphine are at increased risk for being responsible for road traffic crashes, particularly during the first 90 days of treatment.
- *However, these associations are complex and influenced by a number of factors*.