METHAMPHETAMINE USE DISORDER: A REVIEW OF PHARMACOLOGIC TREATMENT

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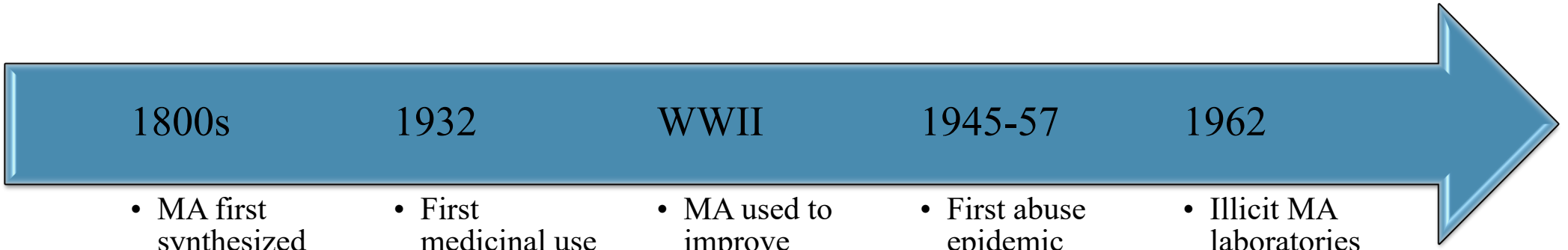
Learning Objectives

1. Compare and contrast pharmacologic agents used in the treatment of methamphetamine use disorder.
2. Identify patients who could benefit from medication therapy.
3. Develop a patient-centered treatment plan considering patient-specific factors such as co-morbidities and socioeconomic parameters.

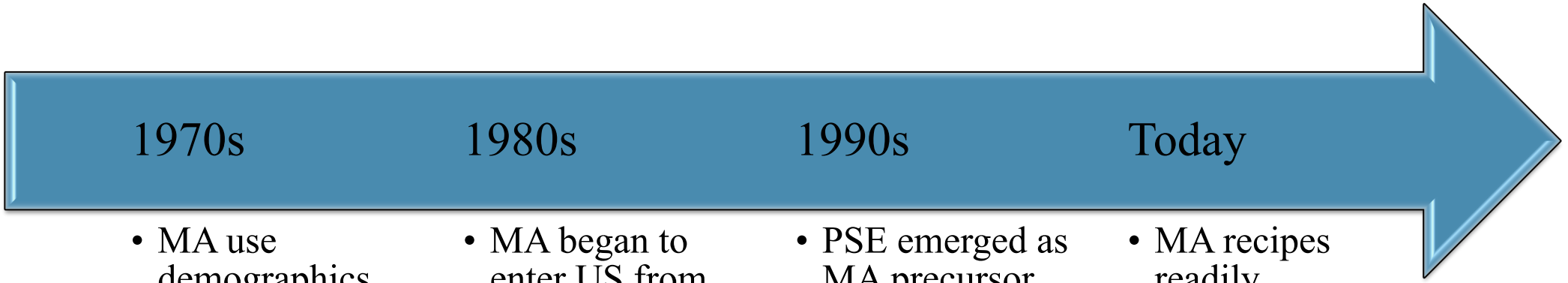
A Look Back



MA: methampethamine

Romanelli F, et al. Pharmacotherapy. 2006

A Look Back



- MA use demographics began to shift towards college students, women, and young professionals
- MA began to enter US from Mexico; distribution in southwest and Midwest US increased
- PSE emerged as MA precursor following regulations of ephedrine
- Comprehensive MA control Act of 1995
- MA recipes readily available on Internet
- WHO describes MA as the second most widely used illicit substance after cannabis

WHO: World Health Organization
PSE: Pseudoephedrine

Romanelli F, et al. Pharmacotherapy. 2006

DSM-5 Behavior Domains of Substance Use Disorders and Accompanying Criterion

Impaired Control	Social Impairment	Risky Use	Pharmacologic Criteria
Using substance in larger amounts or for longer than anticipated	Ongoing substance use resulting in inability to complete obligations	Using substance despite potential for physical harm	Tolerance to substance
Unable to lower or stop use	Ongoing use in spite of problems, both socially and interpersonally, caused by use	Continuing to use substance even though it may be causing mental or physical problems	Withdrawal symptoms following a decrease or cessation of use
A lot of time spent acquiring/using the substance	Withdrawing from activities in life secondary to substance use		
Cravings			

Image from: Palmer. Psychiatric Disorder. ACCP. 2020.

Substance Use Screening

- A 2020 update on screening for unhealthy drug use by the USPSTF recommends asking about substance use in those 18 years of age and older, but only when services are available for diagnosis and treatment following a positive screen
- Several screening tools are available from: https://www.drugabuse.gov/nidamed-medical-health-professionals/screening-tools-resources/chart-screening-tools

Patnode CD, et al. JAMA. 2020.

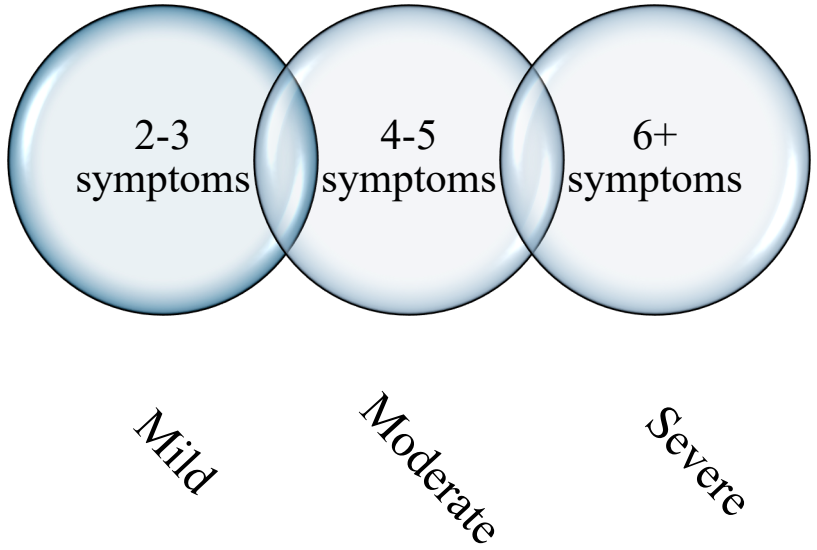
Signs and Symptoms

- Extreme weight loss
- Poor dentition
- Track marks
- Excoriations
- Depressed mood
- Insomnia
- Anxiety
- Paranoia
- Psychosis

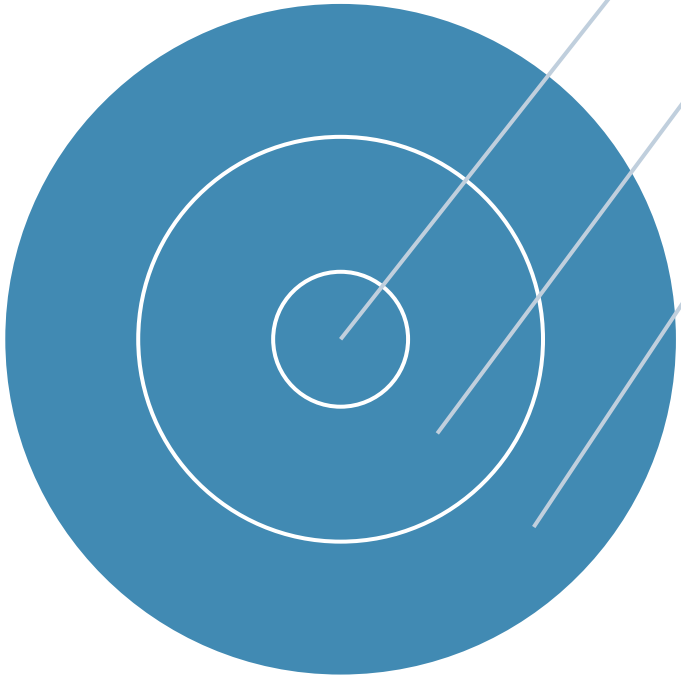
DSM-5 Stimulant Use Disorder

Specifiers

- **Amphetamine-type substance**
- Cocaine
- Other or unspecified stimulant



Scope of Methamphetamine Use Circa 2017



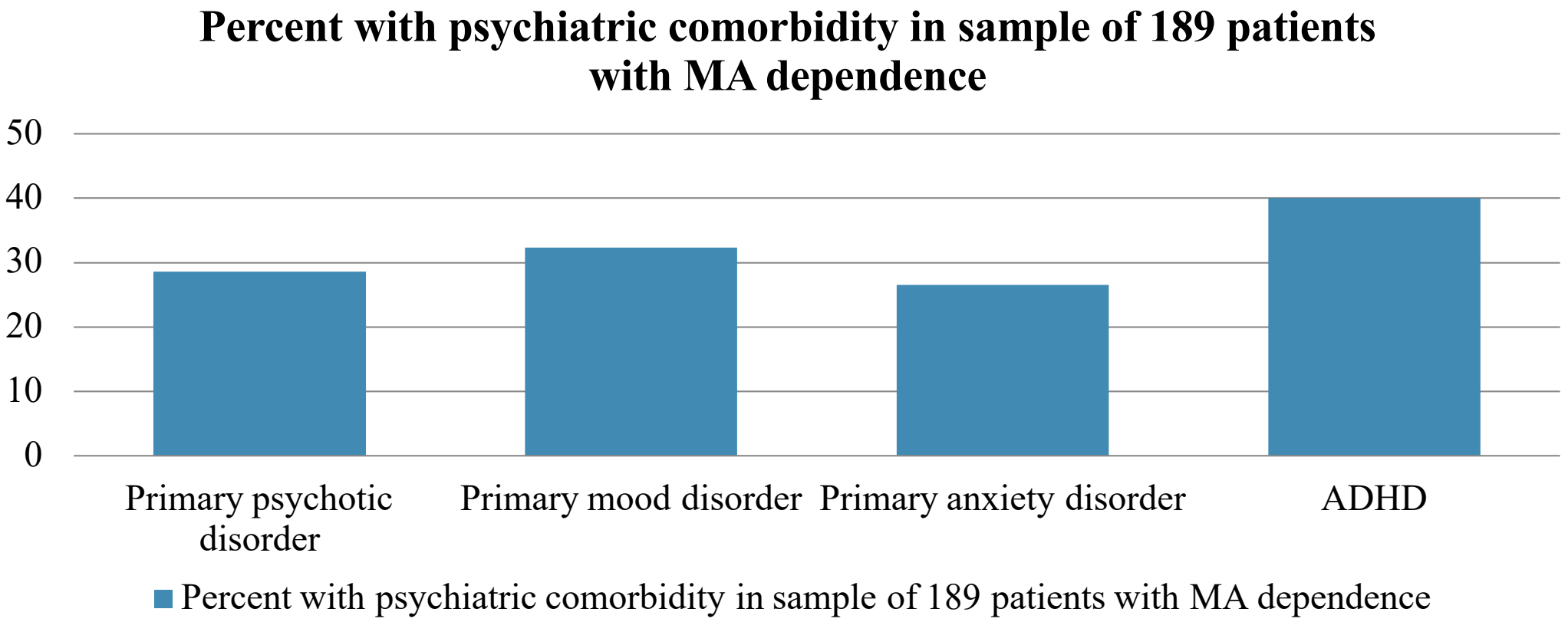
0.3% of population reported using methamphetamine in past month (average age of new users in 2016 was 23.3 years)

0.4% of those ≥ 12 years old reported methamphetamine use disorder in 2017

0.6% of population (1.6 million people) reported using methamphetamine in past year

NSDUH 2017. https://www.drugabuse.gov/publications/research-reports/methamphetamine/what-scope-methamphetamine-misuse-in-united-states

Comorbid Psychiatric Conditions



Meredith CW, et al. Harv Rev Psychiatry. 2005.
Salo R, et al. Psychiatry Res. 2011.

Methamphetamine

Street Names	Common Forms	Routes of Administration
• Crank • Chalk • Crystal • Fire • Glass • Go Fast • Ice • Meth • Speed	• White powder • Pieces of glass or shiny bluish rocks (crystal meth)	• PO • Snorted • Smoked • Injected

NIDA. 2019. https://www.drugabuse.gov/drugs-abuse/commonly-abused-drugs-charts#methamphetamine

Methamphetamine Illicit Use

Route(s)	Threshold Dose*	Strong Dose	Duration of Effect	Time to Onset
PO	5mg	40-150mg	3-5 hours	30 minutes
Smoked	5-10mg	50+ mg	3-4 hours	Instantaneous
Injected	5mg	50-100mg	4-8 hours	Nearly instantaneous to 4 minutes
Snorted	5mg	50+ mg	2-4 hours	Nearly instantaneous to 5 minutes

Methamphetamine Pharmacology

- Mechanism of Action: blockade of presynaptic reuptake and displacement of vascular stores of dopamine, norepinephrine, and serotonin → hyper-agonist effect of post-synaptic receptors
- Half-life 12 hours
- Metabolized by CYP2D6
- Overdoses fatal at serum levels ranging from 0.09-41 mg/L (seizures, cerebrovascular hemorrhage)

Romanelli F, et al. Pharmacotherapy. 2006

Methamphetamine Health Effects

Short-Term

- Increased wakefulness and physicality
- Reduction in appetite
- Tachycardia
- Diaphoresis
- Irregular heartbeat

Long-Term

- Anxiety
- Confusion
- Insomnia
- Violence
- Psychosis
- Weight loss
- Dental issues
- Severe itching

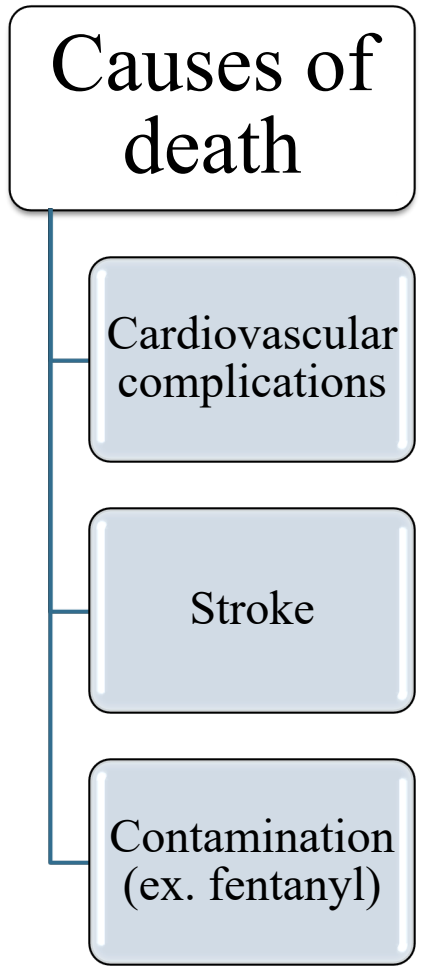
Other

- Premature delivery in pregnancy, low birth weight, heart/brain problems
- Infectious diseases from using shared needles

NIDA. 2019. https://www.drugabuse.gov/drugs-abuse/commonly-abused-drugs-charts#methamphetamine

Methamphetamine Overdose

- Psychostimulant-associated overdose deaths highest in western US (5.3 deaths per 100,000 compared to 1.2 in Northeast)



Methamphetamine Social Cost: Circa 2005

Social Cost	Estimated Dollar Amount (in millions)
Drug treatment	545.5
Health care	351.3
Intangibles/premature death	16,624.9
Productivity	687
Crime and criminal justice	4,209.8
Child endangerment	904.6
Production/environment	61.4
Total	23,384.4

The RAND Corporation, 2009.

Patient Case

- PJ is a 64-year old male presenting to outpatient substance use treatment for methamphetamine use.
- PJ endorses being diagnosed with obstructive sleep apnea approximately 3 years ago. He could not tolerate a CPAP mask due to a history of physical assault by strangulation. His untreated OSA has resulted in excessive daytime sleepiness which led PJ to self-treat with “biker coffee” at the advice of a friend.
- Eventually, PJ noticed he was needing more and more “biker coffee” to get the same effects and began purchasing crystal meth. At first PJ smoked it but progressed to intravenous injection. To avoid crashing, he is using around 1 gram per day.

Acute Treatment

- Laboratory assessments
  - Creatine kinase
  - Rhabdomyolysis
  - HIV/Hepatitis C
- Supportive care
  - Fluids
  - Correct underlying metabolic and electrolyte abnormalities
  - Reduce external stimuli
  - Treat severe agitation with BZDs or antipsychotics

Romanelli F, et al. Pharmacotherapy. 2006

Treatment Outcomes

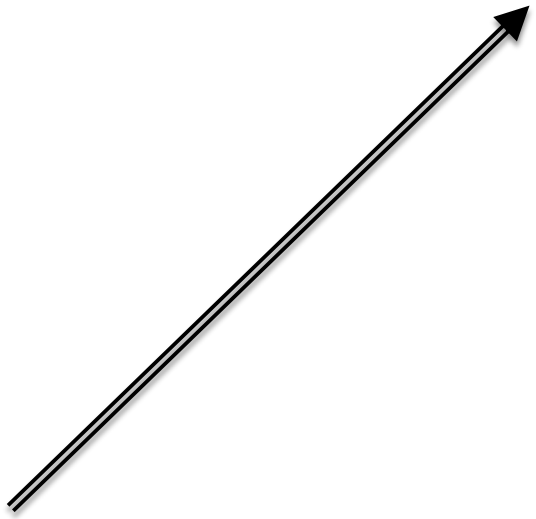
- Ultimate goal: complete cessation → how to get there?
- Patients who use IV have poorer outcomes
  - Decreased treatment engagement
  - More drug use during treatment
  - Lower rates of treatment completion
  - Higher rates of MA use 12 months following treatment

Rawson RA, et al. Am J addict. 2007.

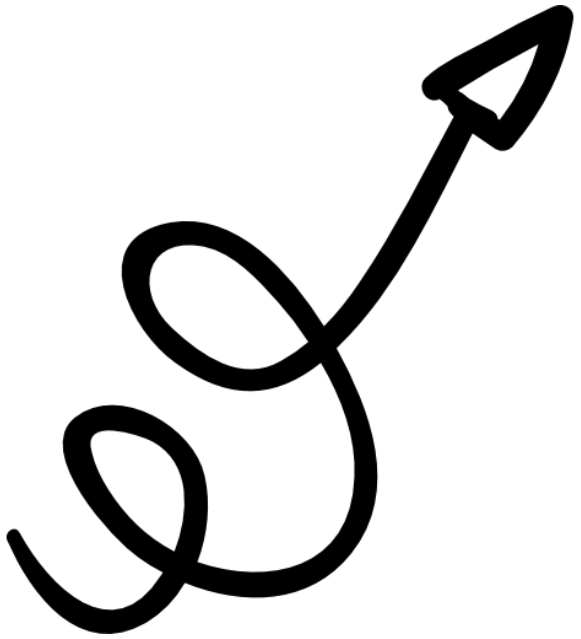
Road to Remission

Growth:

Expectation



Reality



SAMHSA Guidance

Motivational Interviewing

Cognitive Behavioral Therapy

Contingency Management

Community Reinforcement Approach

Available from:
https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP20-06-01-001_508.pdf

Bupropion Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Shoptaw et al.	DB, PC, RCT	N=73 treatment seeking MA dependent adults	Bupropion SR 150mg PO BID versus placebo x 12 weeks	No SS results on MA use (based on UDS) or study retention	Post hoc showed SS effects on MA use for those with lighter MA use (OR = 2.81, 95% CI 1.61-4.93)
Elkashef et al.	DB, PC, RCT	N=152 treatment-seekers with DSM-IV MA dependence	Bupropion SR 150mg PO BID versus placebo x 12 weeks + 30-day follow-up (all received psychotherapy)	No SS results on MA-free weeks.	Subgroup analysis showed SS effects among male patients with lower-level use of MA ($p<0.0001$)

BID: twice daily
SR: sustained release
MA: methamphetamine
SS: statistically significant

DB: double-blind
PC: placebo-controlled
RCT: randomized controlled trial

PO: by mouth
UDS: urine drug screen
OR: odds ratio
CI: confidence interval

Shoptaw S et al. Drug Alcohol Depend. 2008.
Elkashef AM. Neuropsychopharmacology. 2007.

Bupropion Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Anderson et al.	DB, PC, RCT	N=204 adults with MA dependence (low frequency of use ≤ 29 of past 30 days)	Bupropion SR 150mg PO BID versus placebo x 12 weeks (all received 3x weekly psychotherapy)	14% of bupropion group versus 19% of placebo group achieved treatment success (≥ 2 negative UDS in weeks 11 and 12) (p=0.32)	Medication nonadherence was a limitation (47% of bupropion group were adherent per protocol). Number of reported partners declined in both groups
Das et al.	DB, PC, RCT	N=30 adults with MA dependence in MSM	Bupropion 150mg PO daily x 1 week then XL 300mg daily x 11 weeks (all received weekly counseling)	Reductions in UDS similar between groups (p=0.63). Median number of positive urine samples was 5.5/11	Adherence by measured cap openings was 60%

BID: twice daily
SR: sustained release
MA: methamphetamine
DB: double-blind

PC: placebo-controlled
RCT: randomized controlled trial
MSM: men who have sex with men
PO: by mouth

XL: extended release
UDS: urine drug screen

Bhatt M, et al. Systematic Reviews. 2016.

Bupropion Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Heinzerling et al. 2013	DB, PC, RCT	N=19 adolescents with MA abuse or dependence (low frequency use ≤ 18 days out of past 30); all received counseling	Bupropion SR 150mg PO BID versus placebo x 8 weeks	Average of twice weekly MA-free UDS in bupropion group =5 compared to placebo =8.9 (p=0.043)	A female was hospitalized for suicidal ideation following resumption of MA use
Heinzerling et al. 2014	DB, PC, RCT	N=30 adults with MA dependence (low frequency use ≤ 29 days out of past 30); all received counseling	Bupropion 150mg PO daily x 1 week then BID x 16 weeks versus placebo	Abstinence not SS between groups at weeks 11 and 12 (bupropion 12/41, placebo 6/43, p=0.087)	In bupropion group patients with higher adherence (54%) abstinence was high (7/13 compared to 5/28)

BID: twice daily
SR: sustained release
MA: methamphetamine
SS: statistically significant

DB: double-blind
PC: placebo-controlled
RCT: randomized controlled trial
PO: by mouth

UDS: urine drug screen

Bhatt M, et al. Systematic Reviews. 2016.

Modafinil Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Anderson et al.	DB, PC, RCT	N=210 adults with MA dependence	Modafinil PO 200 or 400mg once daily versus placebo x 16 weeks. All patients received group psychotherapy and contingency management	No SS results on MA non-use days or weeks (0=0.53) at week 12	Secondary results ad-hoc showed longer max duration of abstinence in higher modafinil adherence group (23 vs. 10 days)
Heinzerling et al.	DB, PC, RCT	N=71 adults with MA dependence	Modafinil PO 200mg x 3 days then 400mg daily x 14 weeks versus placebo	OR of MA-free urine 0.78 (95% CI 0.39-1.56) for modafinil	No difference between retention, depressive symptoms, or MA cravings
Shearer et al.	DB, PC, RCT	N=80 adults with MA regular use ≥ 2-3 days/week	Modafinil 200mg PO daily x 22 weeks versus placebo	No SS difference in positive weekly UDS (p=0.07)	Treatment retention and adherence similar between groups; outcomes better for patients in counseling

MA: methamphetamine
SS: statistically significant
DB: double-blind
UDS: urine drug screen
PC: placebo-controlled
RCT: randomized controlled trial
PO: by mouth
OR: odds ratio
CI: confidence interval

Bhatt M, et al. Systematic Reviews. 2016.

Dextroamphetamine Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Galloway et al.	PC, DB, RCT	N=60 adults with MA dependence (all received 8 psychotherapy sessions)	d-AMP PO 60mg Day 1 then 30mg BID x 8 weeks versus placebo	d-AMP 2.9 ± 4.3 out of 16 MA negative UDS compared to placebo at 3.2 ± 5.0 (p=0.894)	Withdrawal and cravings lower in d-AMP group ($p < 0.05$)
Longo et al.	PC, DB, RCT	N=49 adults with MA dependence	d-AMP 20mg PO daily starting dose; titrated by 10mg daily until stable or max of 110mg/day (titrated over 2 weeks). Trial lasted 12 weeks	Both groups had significant decrease in hair MA concentrations ($p<0.0001$)	Treatment retention higher in d-AMP group (86.3 days versus placebo 48.6 days =0.014). Degree of MA dependence lower in d-AMP group

MA: methamphetamine
DB: double-blind
UDS: urine drug screen
PC: placebo-controlled

RCT: randomized controlled trial
PO: by mouth
d-AMP: dextroamphetamine
BID: twice daily

Bhatt M, et al. Systematic Reviews. 2016.

Dextroamphetamine Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Shearer et al.	Open-label, PC, RCT	N=41 adults with amphetamine dependence (treatment-seeking)	d-AMP 20mg PO daily; titrated by 5mg/day to max of 60mg (reduced to max of 40mg weeks 10-12) + weekly counseling sessions x 12 weeks	(+) UDS and self-reported amphetamine use did not differ between groups at 6 or 12 weeks	6 participants on methadone maintenance treatment; d-AMP group more likely to attend counseling sessions

MA: methamphetamine
DB: double-blind
UDS: urine drug screen
PC: placebo-controlled

RCT: randomized controlled trial
PO: by mouth
d-AMP: dextroamphetamine

Bhatt M, et al. Systematic Reviews. 2016.

Leeds Dependence Questionnaire

- Lead in: In answering this questionnaire: think about the last week; think about your main substance or substance groups (please specify); tick the answer that's most appropriate to you
  1. Do you find yourself thinking about when you will next be able to have another drink or take drugs?
  2. Is drinking or taking drugs more important than anything else you might do during the day?
  3. Do you feel your need for drink or drugs is too strong to control?
  4. Do you plan your day around getting and taking drink or drugs?
  5. Do you drink or take drugs in a particular way in order to increase the effect it gives you?

Raistric D, et al. Addiction. 1994.

Leeds Dependence Questionnaire

- Lead in: In answering this questionnaire: think about the last week; think about your main substance or substance groups (please specify); tick the answer that's most appropriate to you

6. Do you take drink or drugs morning, afternoon and evening?
7. Do you feel you have to carry on drinking or taking drugs once you have started?
8. Is it getting the effect you want more important than the particular drink or drug you use?
9. Do you want to take more drink or drugs when the effect starts to wear off?
10. Do you find it difficult to cope with life without drink or drugs?

Raistric D, et al. Addiction. 1994.

Methylphenidate Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Ling et al.	DB, PC, RCT	N=49 adults with MA dependence	MPH 18mg PO daily x 1 week then 36mg daily x 1 week then 56mg daily for weeks 3-10	No SS difference in self-reported days of MA use during last 30 days of active phase (10 weeks) (p=0.22)	MPH group had fewer self-reported days of MA use from baseline through 10 weeks (p=0.05)
Rezaei et al.	DB, PC, RCT	N=56 adults with MA dependence	MPH 18mg PO daily x 1 week then 36mg daily x 1 week then 54mg daily for 8 weeks (10 weeks total)	MA cravings were lower compared to placebo (p=0.03) – clinical significance??	MPH group had less MA positive UDS compared to placebo at week 10 (p=0.03). Numbers estimated from graph: 19% MPH versus 36% placebo
Miles et al.	Parallel group, DB, PC, RCT	N=78 with amphetamine or MA dependence (ages 16-65)	MPH 18mg titrated to max of 54mg PO daily over two weeks and continued x 20 weeks (daily administration)	No SS difference in % of positive UDS (95% CI 0.83-1.08)	More MPH participants remained in treatment (p < 0.05)

MA: methamphetamine
DB: double-blind
UDS: urine drug screen
PC: placebo-controlled
RCT: randomized controlled trial
PO: by mouth
MPH: methylphenidate
SS: statistical significance

Bhatt M, et al. Systematic Reviews. 2016.

Methylphenidate Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Tiihonen et al.	Active comparator, PC, RCT	N=53 adults with amphetamine dependence (IV use)	Aripiprazole 15mg PO daily versus MPH 18mg PO daily x 1 week then 35mg daily x 1 week then 54mg daily thereafter versus placebo (all for 20 weeks)	Aripiprazole group more likely to have AMP positive UDS compared to placebo (OR=3.77, 95% CI 1.55-9.18); MPH group less likely (OR=0.46, 95% CI 0.26-0.81)	None positive for MA at baseline (only amphetamines). MPH reached SS at 18 weeks
Solhi et al.	Active comparator, RCT	N=86 adults with MA dependence	Risperidone 1mg PO daily x 1 week then 2mg daily x 3 weeks versus MPH 10mg daily x 2 weeks then 7.5mg daily x 1 week then 5mg daily x 1 week	Cravings per week higher in MPH group (19.6±12.45) versus risperidone group (6.31±8.31) (p=0.002)	Risperidone also more effective for lowering frequency/intensity of psychiatric, neurologic, cardiac, and somatic symptoms following MA cessation

MA: methamphetamine
UDS: urine drug screen
PC: placebo-controlled
AMP: amphetamine

SS: statistical significance
RCT: randomized controlled trial
PO: by mouth

MPH: methylphenidate
IV: intravenous

Tiihonen J, et al. Am J Psychiatry. 2007.
Solhi J, et al. Saudi Pharm J. 2014.

Antipsychotic Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Coffin et al.	DB, PC, RCT	N=90 sexually-active adults with MA dependence	Aripiprazole PO daily (5mg x 1 week then 10mg x 1 week then 20mg thereafter) versus placebo x 12 weeks (all received weekly 30-minute counseling)	43% reduction in positive UDS in aripiprazole group compared to 38% in placebo (p=0.41)	Overall adherence 42% with no differences between groups
Sulaiman et al.	DB, PC, RCT	N=37 adults with MA dependence and history of psychosis	Aripiprazole 5-10mg daily versus placebo for 8 weeks	No difference in abstinence; aripiprazole group in treatment longer (48.7 days versus 37.1 days)	Psychosis reduced in aripiprazole arm

MA: methamphetamine
DB: double-blind
UDS: urine drug screen
PC: placebo-controlled

RCT: randomized controlled trial
PO: by mouth

Coffin PO, et al. Addiction. 2013.
Sulaiman AH, et al. Int J Psychiatry Clin Pract. 2013.

Antipsychotic Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Meredith et al.	Open label	N=34 with MA dependence	7-day run-in with PO risperidone followed by 25mg LAI q 2 weeks x 4 injections (PO overlap for 3 weeks) + weekly counseling	Days of use/week dropped from 4.1 to 1.0 (95% CI 0.6-1.4) while on LAI	High dropout rate (19 out of initial 53 participants)
Meredith et al.	Open label	N=11 in treatment seeking adults with MA dependence	Risperidone x 4 weeks	Days of MA use per month decreased from 13.0 to mean of 0.125	Average dose 3.6mg/day

MA: methamphetamine
PO: by mouth
LAI: long-acting injectable
CI: confidence interval

Meredith CW, et al. J Addict Med. 2009.
Meredith CW, et al. J Psychoactive Drugs. 2007.

Antidepressant Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Shoptaw et al.	PC, DB, RCT	N=229 treatment-seeking patients with MA abuse or dependence (all received psychosocial group therapy)	Four groups of sertraline + CM; sertraline; placebo + CM; placebo (sertraline dosed 50mg PO BID) x 12 weeks	Survival analysis exhibited fewer participants in sertraline group that were retained in treatment. No change in MA use for any group	Post hoc of UDS showed sertraline group had more positive UDS ($p<0.05$)

PC: placebo-controlled
DB: double-blind
MA: methamphetamine
RCT: randomized controlled trial

CM: contingency management
BID: twice daily
PO: by mouth
UDS: urine drug screen

Shoptaw S, et al. Drug Alcohol Dependence. 2006.

Mirtazapine Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Coffin et al.	DB, PC, RCT	N=120 transgender women and cisgender/transgender men who reported having sex with men and had MA use disorder	Mirtazapine 15mg PO daily x week 1 then 30mg x 23 weeks versus placebo; all received weekly 30-minute counseling	(+) UDS 63% at week 24 in mirtazapine arm compared to 74% in placebo group (RR=0.75, 95% CI 0.56-1.00)	Adherence ~38%; no changes in symptoms or risky sexual behaviors at week 12* although lower at week 24
Colfax, et al.	PC, DB, RCT	N=60 MSM, MA dependence	Mirtazapine 30mg versus placebo x 12 weeks (all received weekly 30-minute counseling)	Mirtazapine arm had 40% reduction in positive UDS at week 12 (NNT to achieve negative UDS =4)	Adherence ~48%. Also decreased high-risk sexual behaviors

DB: double-blind
PC: placebo-controlled
RCT: randomized controlled trial
MA: methamphetamine
MSM: men who have sex with men

PO: by mouth
UDS: urine drug screen
RR: risk ratio
NNT: number needed to treat

Coffin PO, et al. JAMA Psychiatry. 2019.
Colfax GN, et al. Arch Gen Psychiatry. 2011.

Varenicline Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Briones et al.	DB, PC, RCT	N=52 treatment-seeking adults with MA dependence	Varenicline 1mg PO BID versus placebo – both with CBT x 9 weeks	No difference between varenicline (15%, 4/27) and placebo (20%, 5/25) for EOTA or TES (p=0.9)	Treatment condition did not affect relapse; greater reduction in smoking in varenicline group (difference of 18 cigarettes at 9 weeks)

MA: methamphetamine
DB: double-blind
PC: placebo-controlled
RCT: randomized controlled trial
PO: by mouth

BID: twice daily
CBT: cognitive behavioral therapy
EOTA: end of treatment abstinence
TES: treatment effectiveness score

Briones M, et al. Drug Alcohol Depend. 2018.

Gabapentin Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Heinzerling et al.	PC, DB, RCT, active comparator	N=88 treatment-seeking participants with MA dependence	Randomized to gabapentin 800mg PO TID versus baclofen 20mg TID versus placebo x 16 weeks (all received 3x weekly counseling)	No differences in MA use	Post hoc analyses indicated high baclofen adherence increased MA free UDS to a greater degree than gabapentin

PC: placebo-controlled
DB: double-blind
RCT: randomized controlled trial
MA: methamphetamine

TID: three times daily
UDS: urine drug screen
PO: by mouth

Heinzerling KG, et al. Drug Alcohol Depend. 2006.

Topiramate Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Elkashef et al.	DB, PC, RCT	N=140 participants with MA dependence	Topiramate (initial dose 50mg/day, increased to target 200mg/day weeks 6-12) versus placebo x 13 weeks (all received weekly brief compliance enhancement treatment)	No difference in MA abstinence; 64.2% in topiramate versus 42.3% (p=0.03) in placebo achieved ≥ 25% reduction of MA use in weeks 6-12	May be effective in patients who have already reached MA abstinence
Rezaei et al.	DB, PC, RCT	N=57 with MA dependence	Topiramate (initial dose 50mg/day, increased to 200mg/day) versus placebo x 10 weeks	Difference in UDS + for MA only significant at week 6 (0% topiramate versus 25% placebo, p=0.01); both groups 0% at week 10	100% medication adherence; topiramate group had lower drug use severity and drug need

DB: double-blind
PC: placebo-controlled
RCT: randomized controlled trial

MA: methamphetamine
UDS: urine drug screen
PO: by mouth

Elkashef A, et al. Addiction. 2012.
Rezaei F, et al. Fundam Clin Pharmacol. 2016.

Naltrexone Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Coffin et al.	DB, PC, RCT	N=100 sexually-active, MA use, MSM	XR-NTX 380mg LAI versus placebo x 12 weeks (3 injections)	No reduction in MA use or sexually risky behaviors	> 90% adherence
Jayaram-Lindström et al.	DB, PC, RCT	N=80 with AMP dependence	Naltrexone 50mg PO daily versus placebo x 12 weeks (all received 2x weekly 'relapse prevention therapy')	Mean % of negative UDS 79.7% (naltrexone) versus 64.1% (placebo)	Only 16% of samples had high concentration of MA
Kohno et al.	DB, PC, RCT	N=37 treatment-seeking individuals with MA dependence	XR-NTX 380mg LAI versus placebo x 4 weeks (1 injection)	Mean days of use/month decreased from 5.06 to 1.56 (XR-NTX) and 3.56 to 2.74 (placebo)	Had to be right-handed?? Cravings scores decreased to similar levels in both groups

DB: double-blind
PC: placebo-controlled
RCT: randomized controlled trial
MA: methamphetamine
MSM: men who have sex with men
AMP: amphetamine
XR-NTX: naltrexone extended-release
LAI: long-acting injectable
UDS: urine drug screen
PO: by mouth

Coffin PO, et al. Addiction. 2018.
Jayaram-Lindström N, et al. Am J Psychiatry. 2008.
Kohno M, et al. Drug Alcohol Depend. 2018.

Naltrexone Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Grant et al.	DB, PC, RCT	N=31 with MA dependence (non-treatment seeking)	Naltrexone + NAC (titrated to 200mg PO naltrexone + 2400mg/day PO NAC during by final 2 weeks) versus placebo x 8 weeks	No difference in Penn Craving Scale total scores (-43.6% versus -37.7%)	No difference in self-reported MA use or UDS results
Trivedi et al.	DB, PC, RCT	Stage 1) N=403 Stage 2) N=225 Treatment-seeking individuals with moderate to severe stimulant use disorder (MA type)	1) XR-NTX (380mg LAI q 3 weeks) + bupropion PO 450mg/day versus placebo x 6 weeks 2) Non-responders randomized to same groups for additional 6 weeks	1) Response* 16.5% versus 3.4% 2) Response 11.4% versus 1.8% *Defined as ≥ 3 MA-negative UDS out of 4 during weeks 5-6 or 11-12	Overall weighted difference in treatment effect ~11%

DB: double-blind
PC: placebo-controlled
RCT: randomized controlled trial
MA: methamphetamine

NAC: n-acetylcysteine
LAI: long-acting injectable
XR-NTX: naltrexone extended-release
PO: by mouth

UDS: urine drug screen

Grant JE, et al. Eur Neuropsychopharmacol. 2010.
Trivedi MH, et al. N Engl J Med. 2021.

Naltrexone Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Mooney, et al.	Open-label pilot	Stage 1) N=20 Stage 2) N=29 Individuals with severe stimulant use disorder (MA type)	1 and 2) XR-NTX (380mg LAI at weeks 1 and 5) + bupropion 150mg PO days 1-2, 300mg days 3-4, 450mg day 5 x 8 weeks then taper off	All 49 included in efficacy analyses: 11/49 (22%) were responders (6/8 MA-negative UDS)	Smartphones recorded home bupropion administration. Response rates were not affected by adherence

MA: methamphetamine
XR-NTX: naltrexone extended-release
LAI: long-acting injectable

PO: by mouth
UDS: urine drug screen

Mooney LJ, et al. J Addict Med. 2016.

Other Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Salehi et al.	DB, PC, RCT	N=40 men with MA dependence	BUP SL (2mg increased to 6mg/day within 1 week) versus placebo x 16 weeks; followed by self-help groups q 2 weeks x 3 months for all	More negative UDS in BUP ($p<0.05$) at all weeks except 3 and 28	Rebound in MA cravings after BUP discontinuation but small decrease still present compared to placebo

MA: methamphetamine
DB: double-blind
UDS: urine drug screen
PC: placebo-controlled

RCT: randomized controlled trial
SL: sublingual
BUP: buprenorphine

Salehi M, et al. J Clin Psychopharmacol. 2015.

Other Pharmacologic Treatment

Trial	Type	Patients	Intervention	Primary Outcome	Other
Mousavi et al	DB, PC, crossover RCT	N=23 treatment-seeking individuals with MA dependence	A: NAC PO 600mg/day x one week then 1200mg/day x 3 weeks B: placebo 3 days of washout and groups switched (all received weekly 60-minute counseling)	Cravings at end of first 4 weeks: A: 3.38 versus B: 5.96 Second 4 weeks: A: 4.57 versus B: 3.2 P=0.029 for period effect	Utilized Cocaine Craving Questionnaire-Brief for primary outcome
Rabiey et al	DB, PC, RCT	N=86 treatment-seeking individuals with MA dependence on methadone maintenance	Atomoxetine PO 40mg/day versus placebo x 8 weeks	Negative UDS higher in atomoxetine group only at week 8 (56% versus 26%, p=0.007)	Depression, anxiety, and stress decreased in both groups; more pronounced for atomoxetine at week 8

MA: methamphetamine
DB: double-blind
PC: placebo-controlled

UDS: urine drug screen
RCT: randomized controlled trial
PO: by mouth

Mousavi SG, et al. Arch Iran Med. 2015.
Rabiey A, et al. Arch Iran Med. 2019.

Cocaine Craving Questionnaire-Brief

The following questions scored on a scale from STRONGLY AGREE : : : : : : : STRONG DISAGREE

- I want cocaine so bad I can almost taste it
- I have an urge for cocaine
- I am going to use cocaine as soon as possible
- I think that I could resist using “coke” now
- I crave “coke” right now
- All I want to use now is cocaine
- I have no desire for cocaine right now
- Using cocaine now would make things seem just perfect
- I will use cocaine as soon as I get the chance
- Nothing would be better than using “coke” right now

Sussner BD, et al. Drug Alcohol Depend. 2006.

Literature Limitations

- Dissimilar outcomes
- MA use heterogeneity
- Limited generalizability based on study populations
- Attrition
- Differences in outcomes
  - Often omitting functional outcomes

Things to Consider

- Methamphetamine use patterns
- Motivations and triggers
- Underlying ADHD
- Comorbid conditions
- Other substance use
- Harm reduction strategies

Most Promising Agents

Drug	Noted Outcome(s)
MPH	Daily low MA use may have better outcomes
dAMP	More likely to attend counseling
Bupropion	Lower MA use may have better outcomes; males responded better than females
Mirtazapine	30-40% reduction in MA use (when used with counseling); may decrease high-risk sexual behaviors
Topiramate	Functional level improved
Naltrexone	?? PO results promising but LAI trials negative

Think about comorbidities:

Drug	Comorbidities that could also benefit
MPH	Depression, ADHD, narcolepsy
dAMP	
Bupropion	Depression, anxiety, ADHD, tobacco use
Mirtazapine	Depression, anxiety, poor appetite
Topiramate	Migraines, seizures, binge eating disorder, antipsychotic-induced weight gain, alcohol use disorder
Naltrexone	Alcohol use disorder, opioid use disorder

Who is most likely to have good outcomes?

- High medication adherence
- Males
- Low MA use
- Abstinence early in treatment

Patient Case

- PJ is a 64-year old male presenting to outpatient substance use treatment for methamphetamine use.
- PJ endorses being diagnosed with obstructive sleep apnea approximately 3 years ago. He could not tolerate a CPAP mask due to a history of physical assault by strangulation. His untreated OSA has resulted in excessive daytime sleepiness which led PJ to self-treat with “biker coffee” at the advice of a friend.
- Eventually, PJ noticed he was needing more and more “biker coffee” to get the same effects and began purchasing crystal meth. At first PJ smoked it but progressed to intravenous injection. To avoid crashing, he is using around 1 gram per day.

Patient Case: PJ

- Will need to undergo MA withdrawal → supportive care
- Presence of dysphoria versus depression
- Support system?
- Nonpharmacologic support
- Treatment of OSA
- Comorbidities → pharmacologic intervention?
- Patient-centered

METHAMPHETAMINE USE DISORDER: A REVIEW OF PHARMACOLOGIC TREATMENT

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