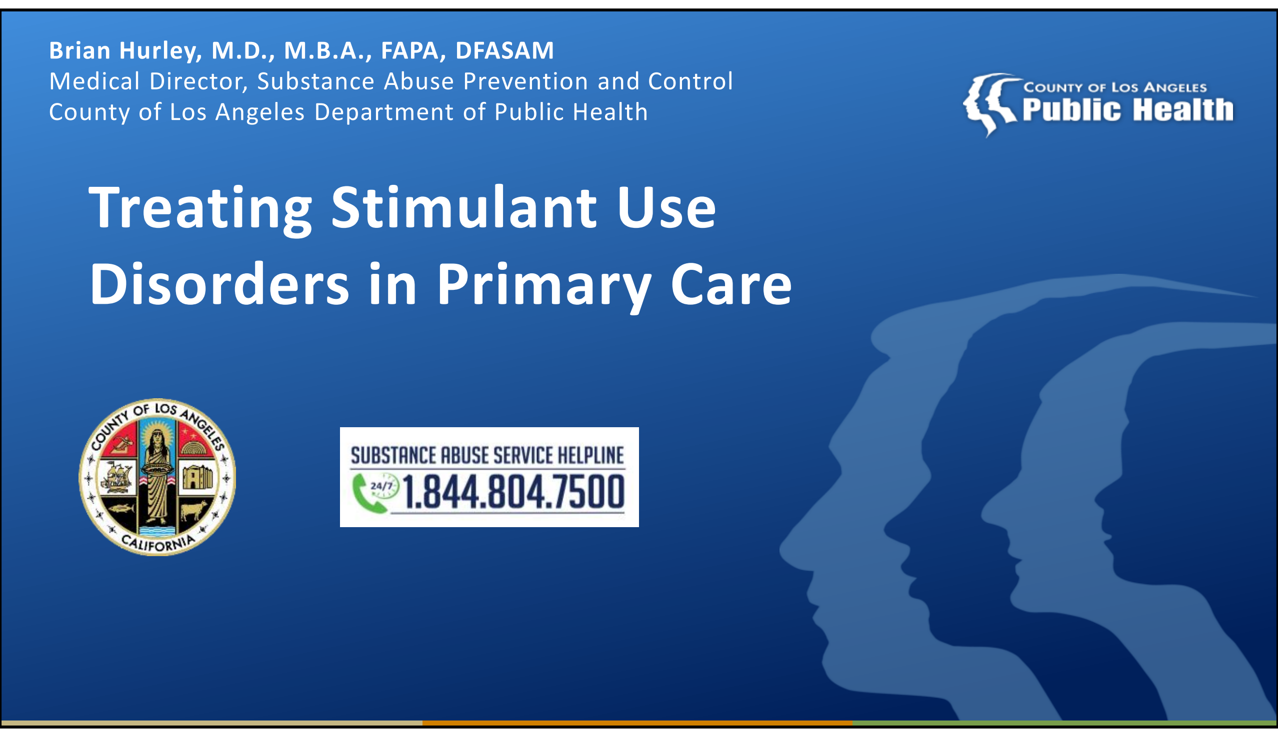
CASE-BASED LEARNING COLLABORATIVE ON STIMULANTS

CME BI-WEEKLY SERIES

CENTER FOR BEHAVIORAL AND ADDICTION MEDICINE

UCLA DEPARTMENT OF FAMILY MEDICINE

1st and 3rd - Fridays at 12pm-1pm PT



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Brian Hurley, M.D., M.B.A., FAPA, DFASAM

No financial conflicts of interests

Brian is the President of the American Society of Addiction Medicine, so comments on topics involving ASAM may be biased towards ASAM

None of the medications discussed today to treat Stimulant Use Disorder are FDA approved for Stimulant Use Disorder

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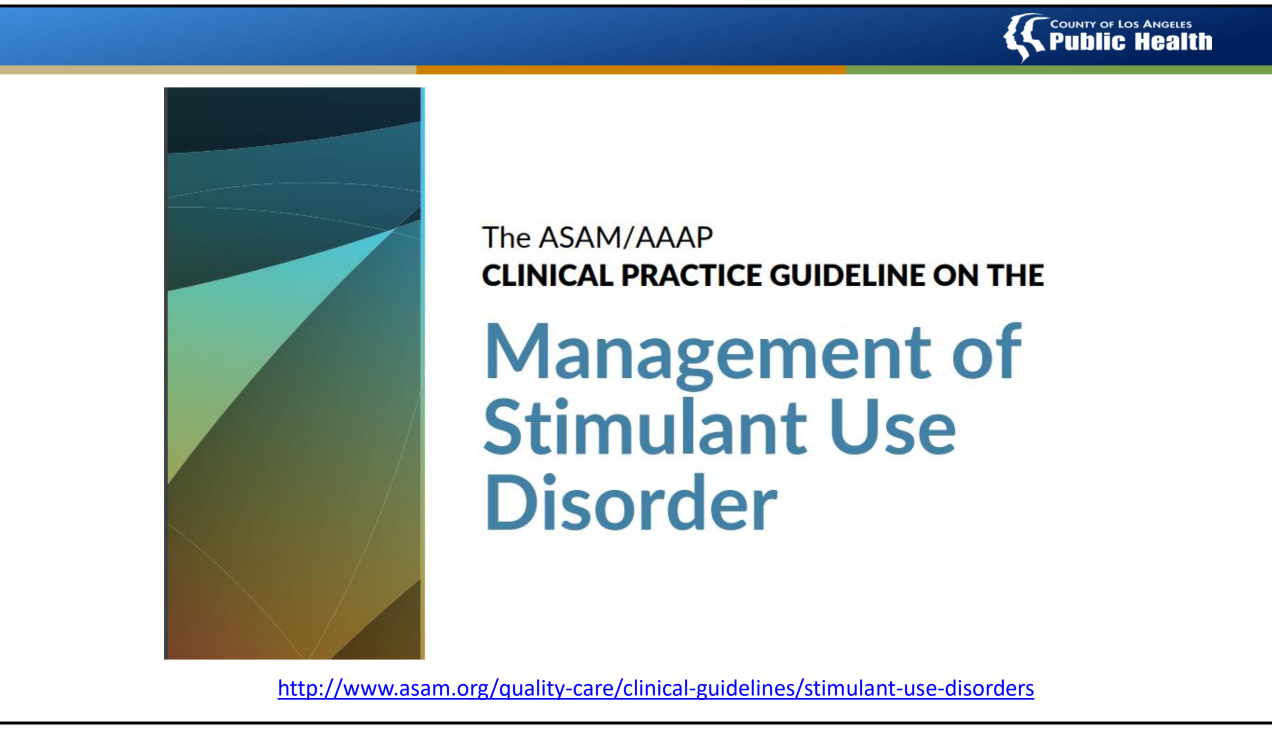

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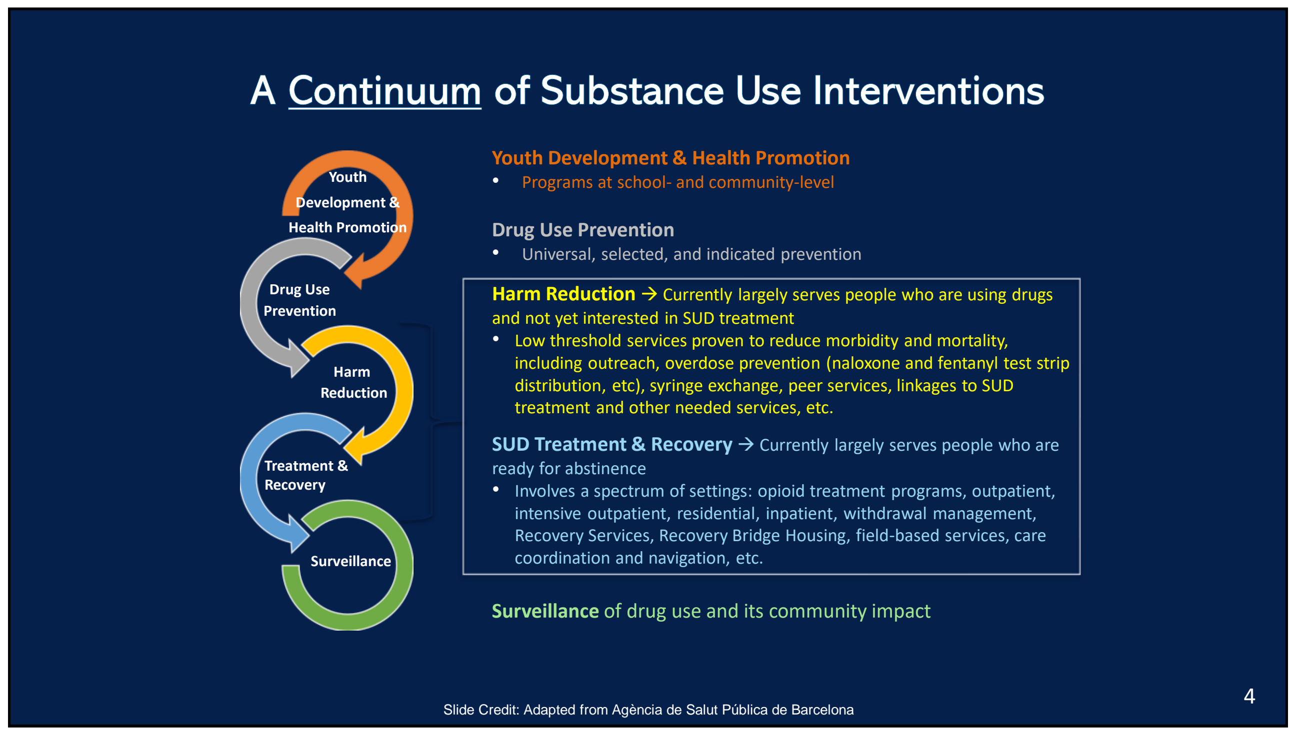

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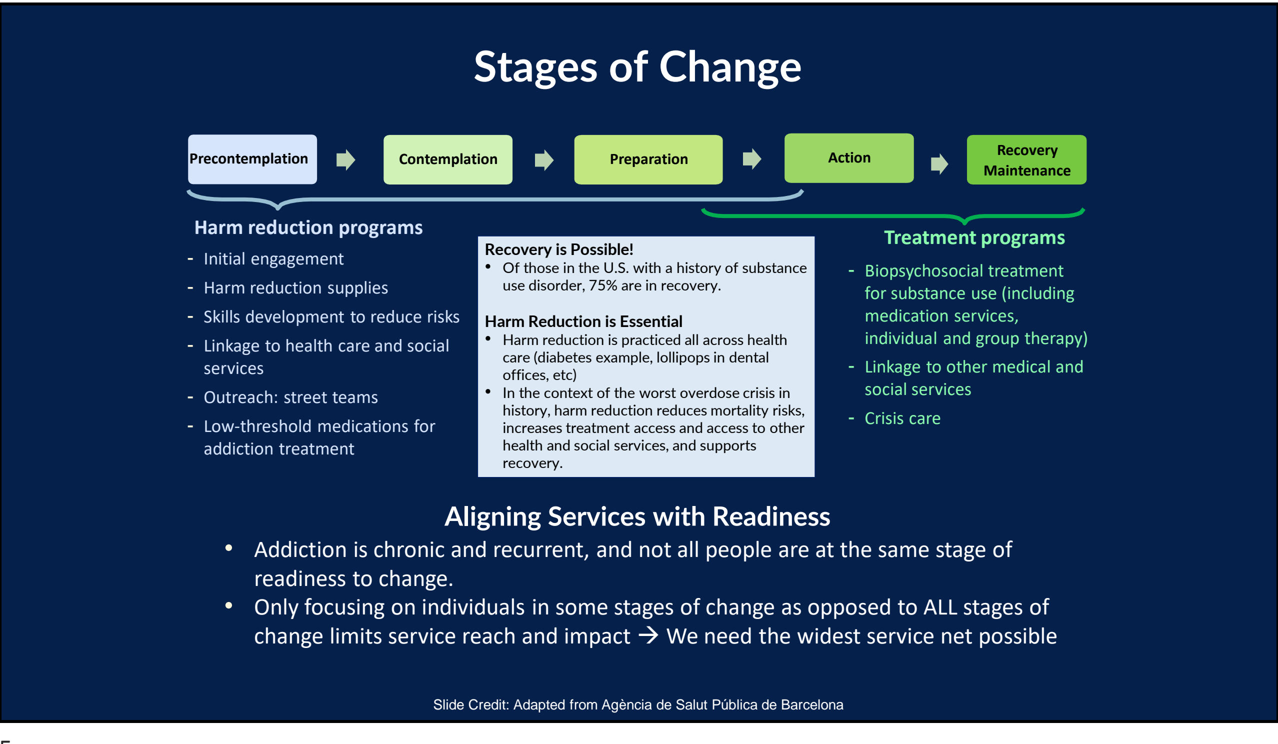

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County of Los Angeles Public Health

Management of Stimulant Use Disorder

Medications

Counseling Support

Interdisciplinary Team

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Primary Care Treatment for Stimulant UD

- Medication Management Visits
- Behavioral Health Visits
- Therapeutic Alliance

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Step-Wise Approach

1. Identify any urgent or emergent biomedical or psychiatric signs or symptoms (including acute intoxication or overdose)
2. Assess risky patterns of stimulant use, routes of administration, and risky sexual behaviors to determine harm reduction services, medical (including PREP/PEP), and counseling needs
3. Assess co-occurring medical and psychiatric conditions
4. Provide appropriate management including harm reduction services (directly or through referral)

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Primary Care for People Who Use Methamphetamine

Health Maintenance

- Infectious disease screening as appropriate for age and for injection and sexual risk behaviors that are often associated with amphetamine-type stimulants
  - HAV, HBV, HCV, HIV, Gon, Chlam, syphillis, TB
- Offer PREP to high risk and likely to adhere
- Vaccines: PPV-23 x1 ages 19-64 and x2 if >65 and never received, tetanus, HAV, HBV
  - if pre-vaccination serological testing is likely to delay vaccine; administer vaccine if high risk
- Screen for depression and anxiety
- Screen for cognitive deficits

California Society of Addiction Medicine (2019). Comprehensive Primary Care Guidelines for Patients who Drink Alcohol and Use Drugs. http://csam-asam.org

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Primary Care for People Who Use Methamphetamine

Monitor for Complications

- General: Weight loss, hygiene and grooming
- Skin: Picking, neurodermatitis; cellulitis/ abscess and other skin/soft tissue infections, esp in PWID
- Intranasal use: rhinitis, mucosal atrophy, rhinorrhea, smell, oronasal fistula, septum perforation
- Oropharyngeal: Teeth grinding and jaw clenching, dentition, earache, headache, facial pain
- Cardiovascular: hypertension, tachycardia, arrhythmia, ischemia, pulmonary HTN, heart failure
- GU: Chronic kidney disease, acute rhabdomyolysis, acute cortical necrosis and necrotizing vasculitis
- Endocrine: Erectile dysfunction
- Neuro: abnormal involuntary movement disorders, rigidity, tremor; stroke, seizure; cognitive impairment (memory, attention)
- Psych: Psychoses, mood disorders (anxiety/depression), ADHD overlap
- Acute sympathomimetic toxidromes with severe hyperthermia causing brain damage, rhabdomyolysis, cardiovascular collapse, and multiple organ failure

California Society of Addiction Medicine (2019). Comprehensive Primary Care Guidelines for Patients who Drink Alcohol and Use Drugs. http://csam-asam.org

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Primary Care for People Who Use Methamphetamine

Drug-Drug Interactions

- CYP2D6 and CYP3A4 inhibitors may increase MA levels
- Antacids: may decrease the excretion of amphetamine
- Concurrent use with sildenafil or other phosphodiesterase inhibitors increase risk of STDs (especially syphilis and HIV) and cardiovascular complications, including death

California Society of Addiction Medicine (2019). Comprehensive Primary Care Guidelines for Patients who Drink Alcohol and Use Drugs. http://csam-asam.org

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Primary Care for People Who Use Methamphetamine

Harm Reduction Guidance

- How might you go about setting a time limit for using before you use?
- Reset your tolerance with sustained periods of non-use
- Plan for a longer duration of action. Smoking produces a long-lasting high: 50% of the drug is removed from the body in 12 hours.

California Society of Addiction Medicine (2019). Comprehensive Primary Care Guidelines for Patients who Drink Alcohol and Use Drugs. http://csam-asam.org

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Psychosocial Treatment for StimUD

Psychosocial approaches to address stimulant use disorder:
- Contingency Management
- Community Reinforcement Approach
- Cognitive Behavioral Therapy
- Matrix Model

Delivery considerations: telehealth, technology, continuing care

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Contingency Management (CM)

- Basic Assumptions of CM
  - Substance use can be reduced using operant conditioning
  - Useful in promoting treatment retention and adherence
  - Incentives for negative urine tests useful in decreasing drug use

Slide Credit: Maxine Stitzer, Ph.D., Johns Hopkins University SOM, ctndisseminationlibrary.org/PPT/485Stitzer.ppt

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Contingency Management (CM)

- Key Concepts
  - Behavior to be modified (e.g. stimulant use) must be objectively measured
  - Behavior to be modified (e.g. urine toxicology tests) must be monitored frequently
  - Reinforcement must be immediate
  - Penalties for unsuccessful behavior (e.g. +UDS) include withholding the reinforcer

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Application of Contingency Management

- Behavioral targets:
  - Counseling attendance
  - Drug use
- Reinforcing consequences:
  - Money (or vouchers)
  - Privileges (e.g. take-home doses)

Slide Credit: Maxine Stitzer, Ph.D., Johns Hopkins University SOM, ctndisseminationlibrary.org/PPT/485Stitzer.ppt

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Fishbowl: Intermittent Reinforcement Schedule

For cost reduction in community health settings

Slide Credit: Maxine Stitzer, Ph.D., Johns Hopkins University SOM, ctndisseminationlibrary.org/PPT/485Stitzer.ppt

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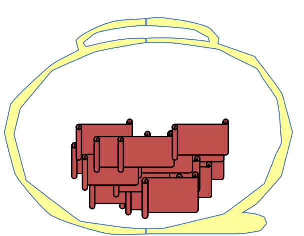
Fishbowl Method

<u>Incentive = draws from a bowl</u>

- Draws earned for each negative urine
- Number of draws can escalate
- Bonus draws can be given for consecutive weeks of abstinence



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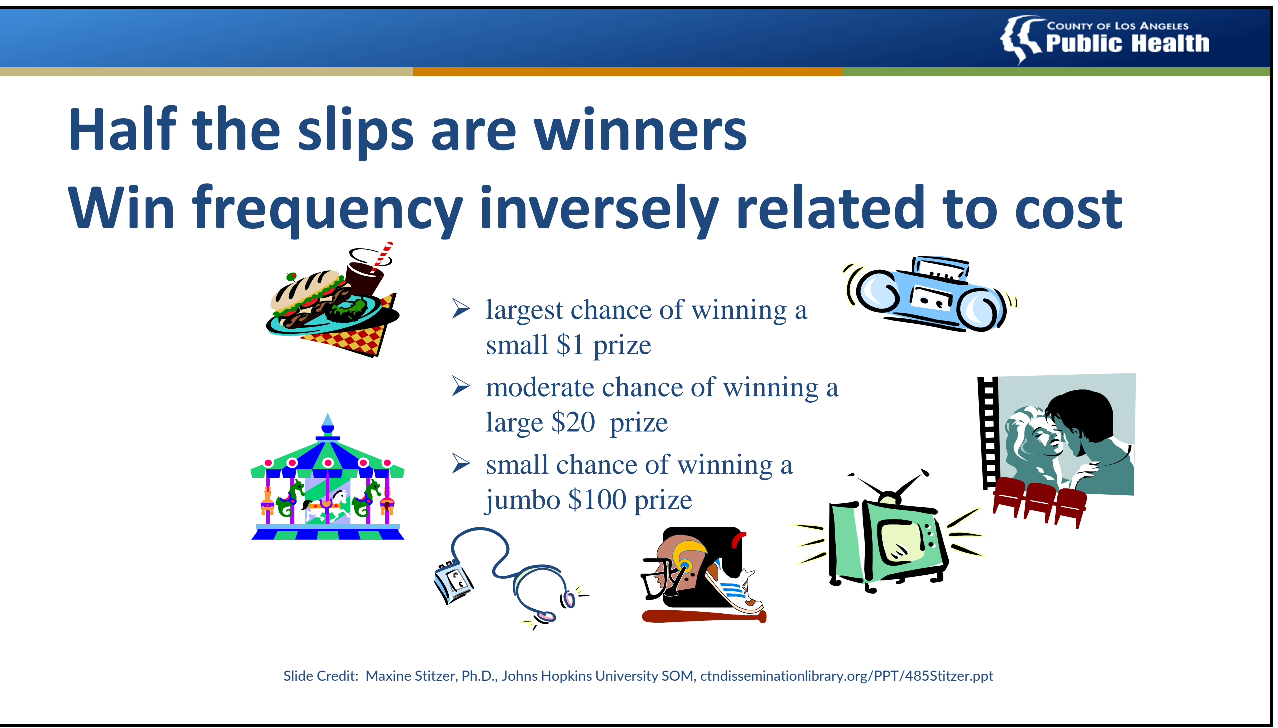

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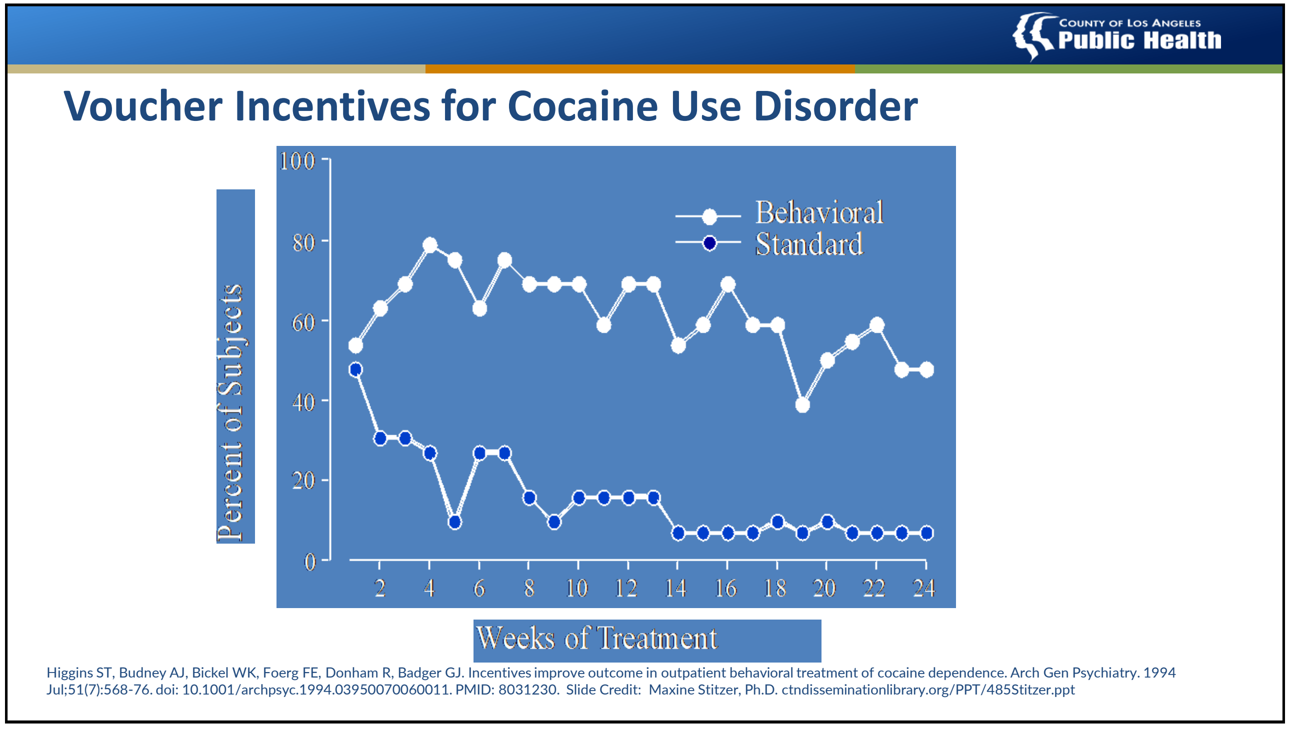

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StimUD Guideline Takeaway

- Contingency management (CM) has demonstrated the best effectiveness in the treatment of StUDs compared to any other intervention studied and represents the current standard of care. CM can be combined with other psychosocial interventions and behavioral therapies, such as community reinforcement approach (CRA) and cognitive behavioral therapy (CBT)

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Motivational Interviewing (MI)

- Evoke change talk from individuals to help resolve ambivalence
- Selectively respond to change talk
- MI does not have a prescribed time period

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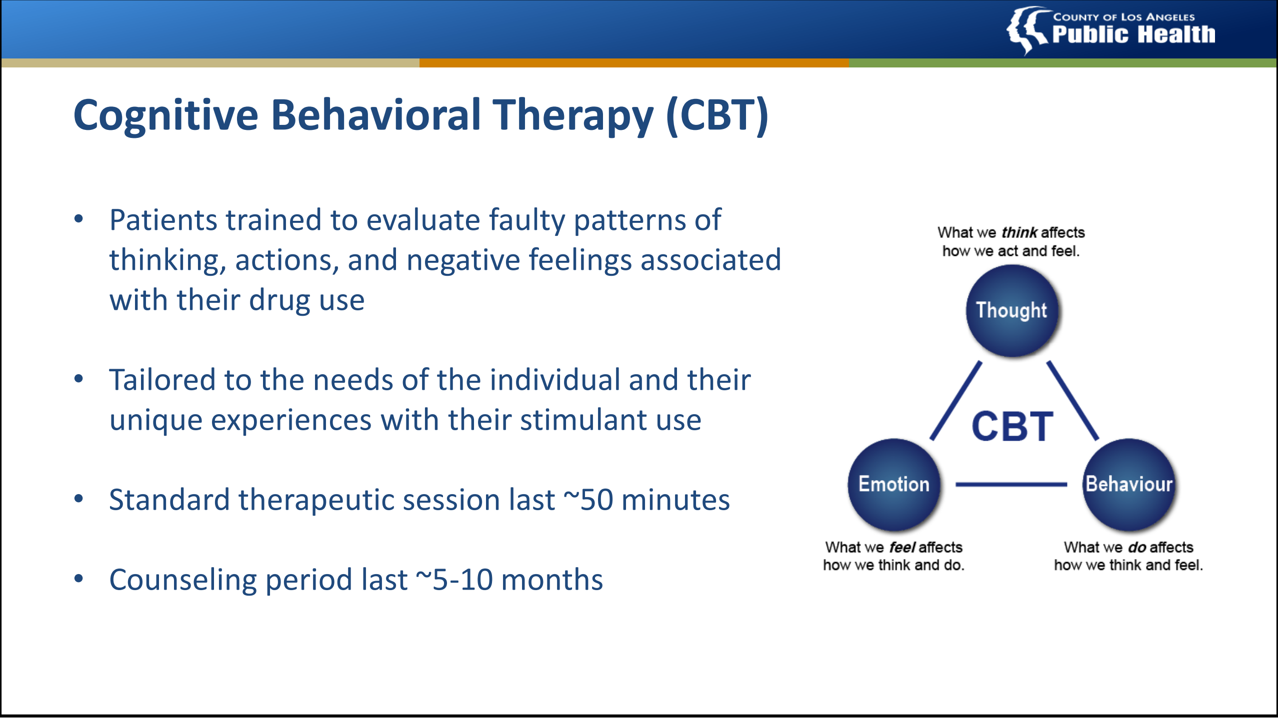

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County of Los Angeles Public Health

Matrix Model

Structured IOP Curriculum

- Early recovery skills groups
- Relapse prevention groups
- Psychoeducation groups
- Social support groups
- Mutual self-help encouragement
- Family education
- Individual counseling
- Urine and breath testing

THE MATRIX MODEL
Intensive Outpatient Alcohol & Drug Treatment Program
Revised and Expanded
Updated to Meet DSM-5 Classifications
THERAPIST'S MANUAL

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Medications for Stimulant Use Disorder (MAT for StimUD)

- Pharmacotherapies, including psychostimulant medications, may be utilized off-label to treat StUD.
- When prescribing controlled medications, clinicians should closely monitor patients and perform regular ongoing assessment of risks and benefits for each patient.
- Psychostimulant medications should only be prescribed to treat StUD by:
  - Physician specialists who are board certified in addiction medicine or addiction psychiatry; and
  - Physicians with commensurate training, competencies, and capacity for close patient monitoring.

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Medications for Methamphetamine Use Disorder

(none are FDA approved for the indication of StimUD)

- ER Naltrexone injection and high dose bupropion
- Mirtazapine (two small studies)
- Bupropion (low-level users who will adhere)
- Topiramate (low-level users)

- Methylphenidate (moderate to high dose in frequent users/those with ADHD)

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Medications for Cocaine Use Disorder

(none are FDA approved for the indication of StimUD)

- Bupropion (works best when combined with CM)
- Topiramate (low-level users)
- Modafinil (if the client does not have alcohol use disorder)

- Combination of Mixed Amphetamine Salts-Extended Release and Topiramate
- Mixed Amphetamine Salts-Extended Release

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ER Naltrexone Injection Plus Bupropion

- Naltrexone extended-release injectable suspension in combination with bupropion XL: Administer naltrexone extended-release injectable suspension 380mg via intramuscular injection **every three weeks** in combination with bupropion XL titrated at bupropion XL 150mg on day 1, 300mg on day 2, and 450mg daily beginning day 3
- Doses can be reduced to alleviate adverse effects; in trial the prescribing clinicians were encouraged to attempt to raise the dose back up to the 450mg daily dose
- 13.6% had a response with naltrexone–bupropion vs 2.5% with placebo
- A response was least three methamphetamine-negative urine samples out of four samples during the end of the two weeks; urine collected twice weekly

Trivedi MH, Walker R, Ling W, Dela Cruz A, Sharma G, Carmody T, Ghitza UE, Wahle A, Kim M, Shores-Wilson K, Sparenborg S, Coffin P, Schmitz J, Wiest K, Bart G, Sonne SC, Wakhlu S, Rush AJ, Nunes EV, Shoptaw S. Bupropion and Naltrexone in Methamphetamine Use Disorder. N Engl J Med. 2021 Jan 14;384(2):140-153. doi: 10.1056/NEJMoa2020214. PMID: 33497547; PMCID: PMC8111570. http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/33497547

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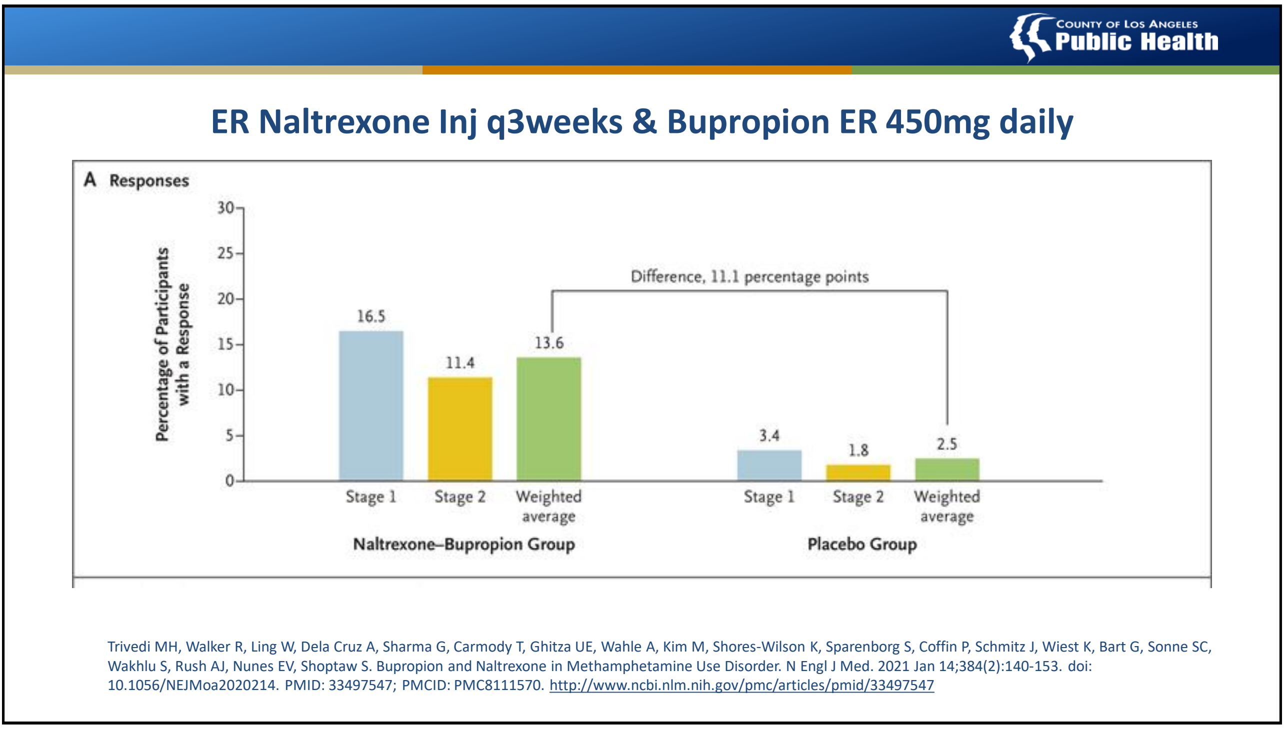

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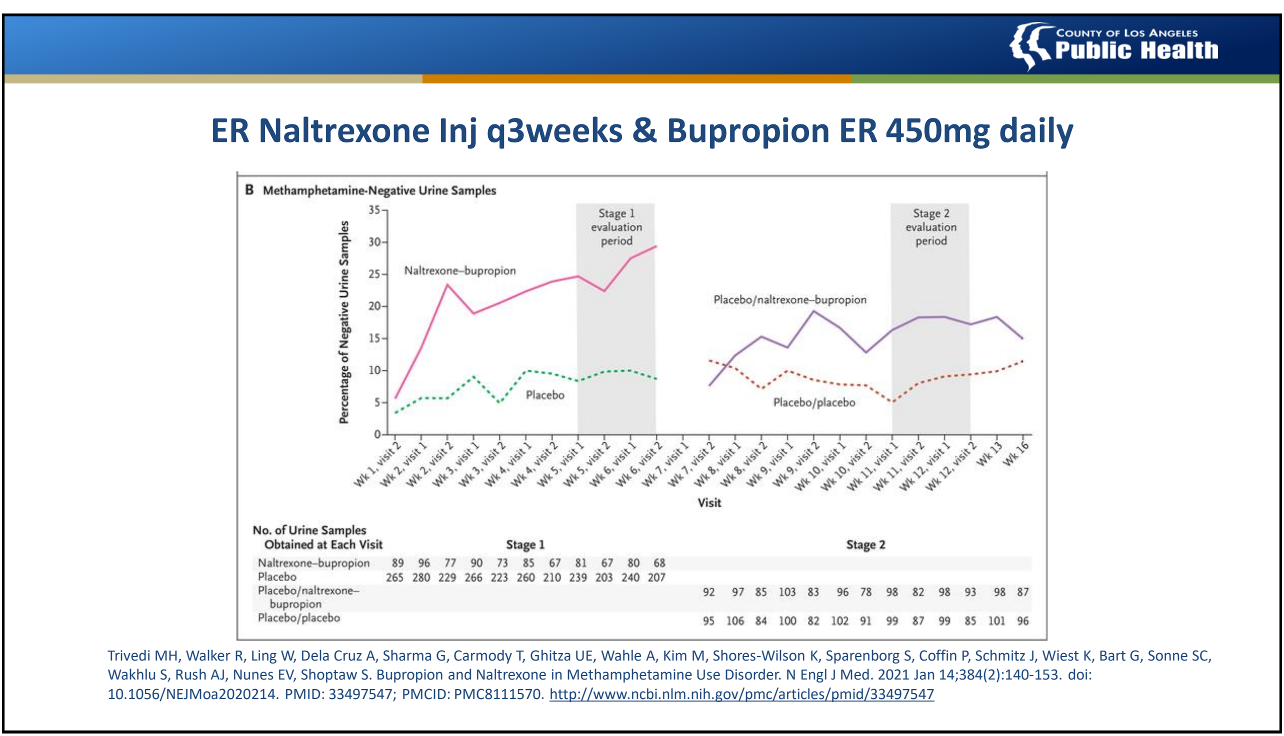

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Mirtazapine for Methamphetamine UD

- Mirtazapine: Start mirtazapine at 15 mg at bedtime and increase to 30 mg at bedtime after 3-7 days
- Promising findings from two trials among MSM in San Francisco
- Response was despite inconsistent adherence (28.1% at 14 weeks assessed by medication monitoring / 38.8% by self-report)
- NNT: 14 fewer individuals will test positive for methamphetamine at 12-weeks per 100 individuals receiving mirtazapine compared to placebo
- No impact vs. placebo on treatment retention

Naji L, Dennis B, Rosic T, Wiercioch W, Paul J, Worster A, Thabane L, Samaan Z. Mirtazapine for the treatment of amphetamine and methamphetamine use disorder: A systematic review and meta-analysis. Drug Alcohol Depend. 2022 Mar 1;232:109295. doi: 10.1016/j.drugalcdep.2022.109295. Epub 2022 Jan 11. PMID: 35066460. http://pubmed.ncbi.nlm.nih.gov/35066460

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Mirtazapine for Methamphetamine UD

Odds of continued methamphetamine use via toxicology testing

Study or Subgroup	Mirtazapine Events	Mirtazapine Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Coffin et al 2019	25	38	32	41	76.8%	0.84 [0.64, 1.12]
Colfax et al 2011	12	27	17	27	23.2%	0.71 [0.42, 1.18]
Total (95% CI)		**65**		**68**	**100.0%**	**0.81 [0.63, 1.03]**
Total events	37		49			

Heterogeneity: $Chi^2 = 0.36$, df = 1 (P = 0.55); $I^2 = 0\%$
Test for overall effect: Z = 1.69 (P = 0.09)

Risk Ratio
IV, Fixed, 95% CI
0.2 0.5 1 2 5
Favours mirtazapine Favours placebo

Naji L, Dennis B, Rosic T, Wiercioch W, Paul J, Worster A, Thabane L, Samaan Z. Mirtazapine for the treatment of amphetamine and methamphetamine use disorder: A systematic review and meta-analysis. Drug Alcohol Depend. 2022 Mar 1;232:109295. doi: 10.1016/j.drugalcdep.2022.109295. Epub 2022 Jan 11. PMID: 35066460. http://pubmed.ncbi.nlm.nih.gov/35066460

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Topiramate for Stimulant UD

- Topiramate: Start 25 mg qHS and titrate up in 25 to 50mg increments as tolerated over a month until the patient is taking either 100mg BID or 200mg at bedtime, or until the patient's maximum tolerated dose is reached. [Do not neglect to provide contraceptive treatments to patients with childbearing potential who are prescribed topiramate]
- More participants randomized to topiramate reduced their methamphetamine use compared with placebo; not statistically significant different in cessation of methamphetamine
- Topiramate was associated with extending cocaine abstinence

Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. CNS Drugs. 2020 Apr;34(4):337-365. doi: 10.1007/s40263-020-00711-x. PMID: 32185696; PMCID: PMC7125061. http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/32185696
Singh M, Keer D, Klimas J, Wood E, Werb D. Topiramate for cocaine dependence: a systematic review and meta-analysis of randomized controlled trials. Addiction. 2016 Aug;111(8):1337-46. doi: 10.1111/add.13328. Epub 2016 Apr 1. PMID: 26826006. http://pubmed.ncbi.nlm.nih.gov/26826006

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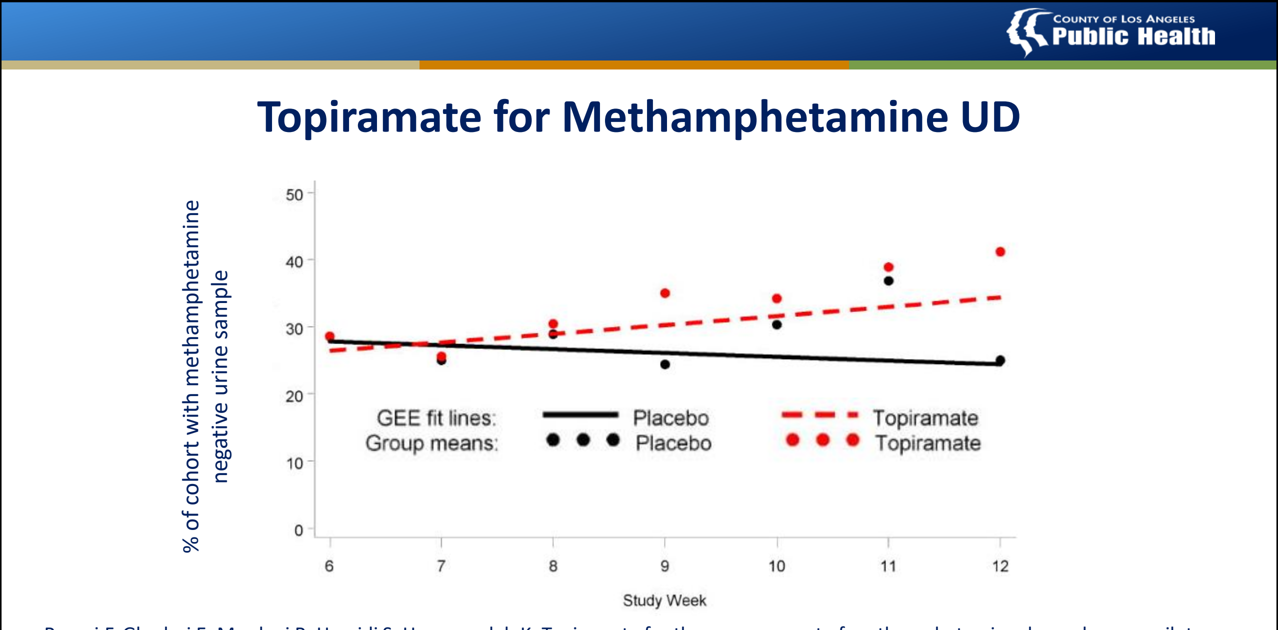
Topiramate for Methamphetamine UD



Rezaei F, Ghaderi E, Mardani R, Hamidi S, Hassanzadeh K. Topiramate for the management of methamphetamine dependence: a pilot randomized, double-blind, placebo-controlled trial. Fundam Clin Pharmacol. 2016 Jun;30(3):282-9. doi: 10.1111/fcp.12178. Epub 2016 Mar 4. PMID: 26751259. http://pubmed.ncbi.nlm.nih.gov/26751259

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Topiramate for Cocaine UD

b) Continuous Abstinence

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Kampman et al. 2004	10	20	5	20	50.2%	2.00 [0.83, 4.81]
Kampman et al. 2013	17	83	6	87	49.8%	2.97 [1.23, 7.17]
Total (95% CI)		**103**		**107**	**100.0%**	**2.43 [1.31, 4.53]**
Total events	27		11			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.40$, df = 1 (P = 0.53); $I^2 = 0\%$
Test for overall effect: Z = 2.81 (P = 0.005)

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours Control Favours Experimental

Singh M, Keer D, Klimas J, Wood E, Werb D. Topiramate for cocaine dependence: a systematic review and meta-analysis of randomized controlled trials. Addiction. 2016 Aug;111(8):1337-46. doi: 10.1111/add.13328. Epub 2016 Apr 1. PMID: 26826006. http://pubmed.ncbi.nlm.nih.gov/26826006

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Modafinil for Cocaine Use Disorder

- Modafinil: start modafinil 100mg daily
- Worked best in cocaine users that did not have alcohol use disorder

Study name	Risk ratio	Lower limit	Upper limit	p-Value	Total	Relative weight
Karila (2016)	0.103	0.015	0.706	0.021	27	4.47
Schmitz (2012)	0.667	0.248	1.791	0.421	36	12.27
Dackis (2012) A	0.854	0.149	4.880	0.859	102	5.28
Anderson A (2009)	1.148	0.432	3.050	0.782	105	12.44
Anderson B (2009)	1.148	0.432	3.050	0.782	105	12.44
Dackis (2005)	1.541	0.774	3.068	0.219	62	18.12
Morgan (2016)	1.929	0.928	4.006	0.078	57	17.14
Dackis (2012) B	2.171	0.485	9.715	0.310	108	6.76
Kampmann (2015a)	2.750	0.943	8.022	0.064	94	11.07
Overall	1.259	0.813	1.949	0.302	696	

Risk ratio and 95% CI
Favours MOD Favours PBO
10 5 2 1 0.5 0.2 0.1

Sangroula D, Motiwala F, Wagle B, Shah VC, Hagi K, Lippmann S. Modafinil Treatment of Cocaine Dependence: A Systematic Review and Meta-Analysis. Subst Use Misuse. 2017 Aug 24;52(10):1292-1306. doi: 10.1080/10826084.2016.1276597. Epub 2017 Mar 28. PMID: 28350194. http://pubmed.ncbi.nlm.nih.gov/28350194

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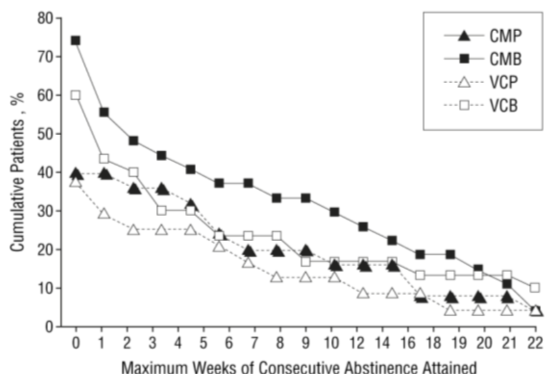
Bupropion for Cocaine Use Disorder

- Modafinil: start bupropion 75mg daily, titrate to 300mg daily
- Worked best when combined with contingency management



Weeks of consecutive abstinence from cocaine. The average maximum numbers of consecutive weeks of cocaine abstinence were 3.04 for voucher control and placebo (VCP), 4.28 for contingency management and placebo (CMP), 4.9 for voucher control and bupropion hydrochloride (VCB), and 6.74 for contingency management and bupropion (CMB). The hierarchical linear modeling MIXPREG analysis (see legend to Figure 4) results indicate the following: CMB vs VCP: P<.001; CMB vs CMP: P<.001; CMB vs VCB: P = .004; VCP vs CMP: P = .02; VCP vs VCB: P<.001; and CMP vs VCB: P = .29.

Poling J, Oliveto A, Petry N, Sofuoglu M, Gonsai K, Gonzalez G, Martell B, Kosten TR. Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. Arch Gen Psychiatry. 2006 Feb;63(2):219-28. doi: 10.1001/archpsyc.63.2.219. PMID: 16461866. http://pubmed.ncbi.nlm.nih.gov/16461866

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Insufficient Evidence For…

Intervention Type	Intervention
Technology-based interventions	Text messaging interventions for StUD
Technology-based interventions	Noninvasive brain stimulation for StUD
Alternative interventions	Exercise as standalone or add-on treatment for StUD
Alternative interventions	Auricular acupuncture for ATS use disorder
Pharmacotherapy	Topiramate and mixed amphetamine salts for ATS use disorder
Pharmacotherapy	Bupropion and naltrexone for cocaine use disorder
Pharmacotherapy	Modafinil for ATS use disorder
Pharmacotherapy	Mirtazapine for cocaine use disorder
Pharmacotherapy	Disulfiram
Pharmacotherapy	Naltrexone
Pharmacotherapy	Naltrexone and N-acetylcysteine

ATS, amphetamine-type stimulants; StUD, stimulant use disorder

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Case #1: 23yo Cisgender Man Using Methamphetamine, Nicotine, Cannabis

- Mr. Brown is a **23 year-old** HIV-negative male smokes methamphetamine in 2-3 day binges two to four times a month and his methamphetamine use is typically concurrent with group sexual activity, and he is sexually active with both men and women. He is prescribed PREP which he takes consistently. He reports no history of chronic medical conditions or taking non-PREP medications. During his methamphetamine binge episodes, he typically does not sleep. After these episodes, he sleeps for over twenty hours and feels depressive symptoms including deflated self-attitude. He vapes 5mg of nicotine daily (a 20mg pod lasts four days) and smokes cannabis daily. He denies consuming alcohol, using opioids, and denies any other substance use.
- He's not ready to stop using methamphetamine, vaping, or using cannabis.

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Case #2: 32yo Cisgender Woman Using Methamphetamine

- Ms. Green is a **32 year-old** HIV-negative cisgender woman who recently became homeless after the end of a relationship. She began using methamphetamine to maintain alternateness overnight in the encampment where she has been staying. She was brought in by ambulance to a local hospital with symptoms of acute agitation; EMS brought her into the emergency room after she became behaviorally disruptive at her encampment. On interview in the emergency department, she reported feeling as though everyone in her encampment was plotting against her and began feeling the sensation of insects crawling underneath her skin. She usually experiences these symptoms when she uses methamphetamine, but they resolve within a day of stopping methamphetamine use.
- Urine labs obtained in the emergency room were positive for amphetamines and positive for human chorionic gonadotropin (hCG).

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Case #3: 42yo Transgender Woman Using Methamphetamine, Cocaine, and Alcohol

- Ms. Black is a **42 year-old** HIV positive transgender woman who works as an interstate truck driver. During long-haul drives, she will use methamphetamine to maintain alertness overnight. During days off she binge drinks alcohol typically two days each week and uses cocaine with alcohol typically twice a month. She arranges her use to avoids using cocaine or methamphetamine the three days prior to scheduled drug checked required by her employer
- She takes efavirenz / emtricitabine / tenofovir, spironolactone, and 17-beta estradiol daily. She takes no other medications.
- She has begun experiencing palpitations during these drives so presents to the clinic 'for a heart check.' She is open to changing her substance use if her substance use might be causing health problems.

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County of Los Angeles
Public Health

Discussion

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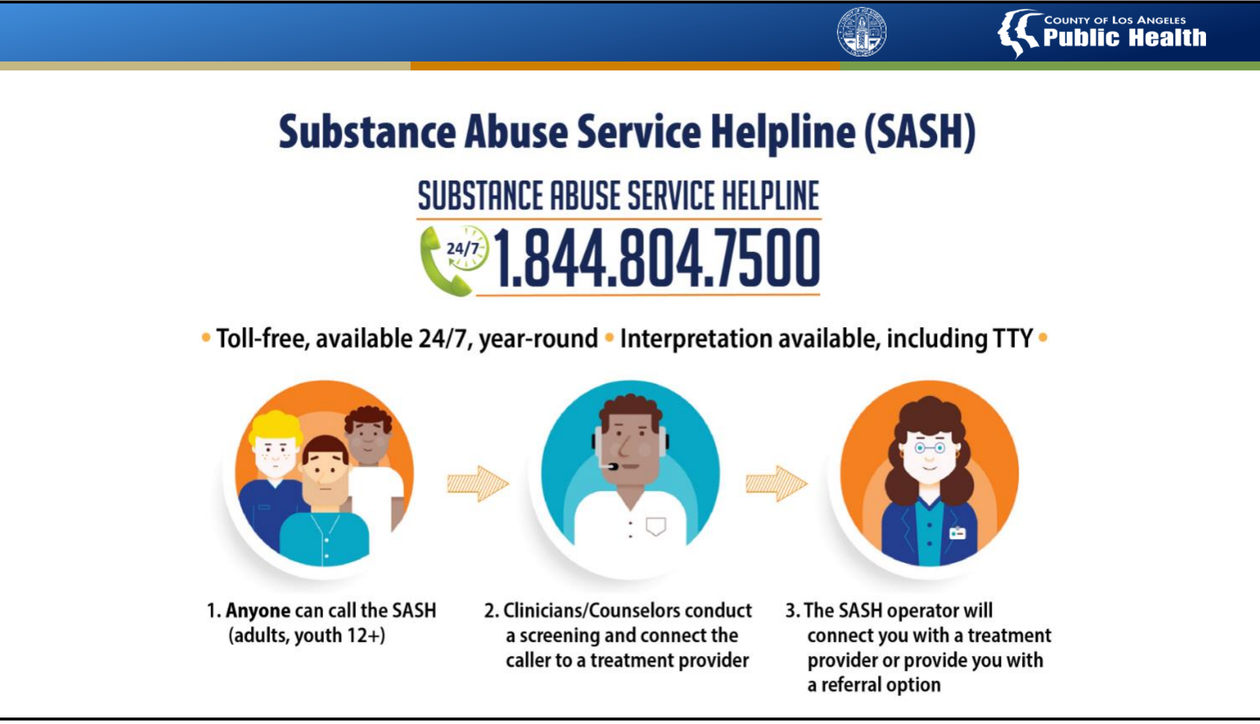

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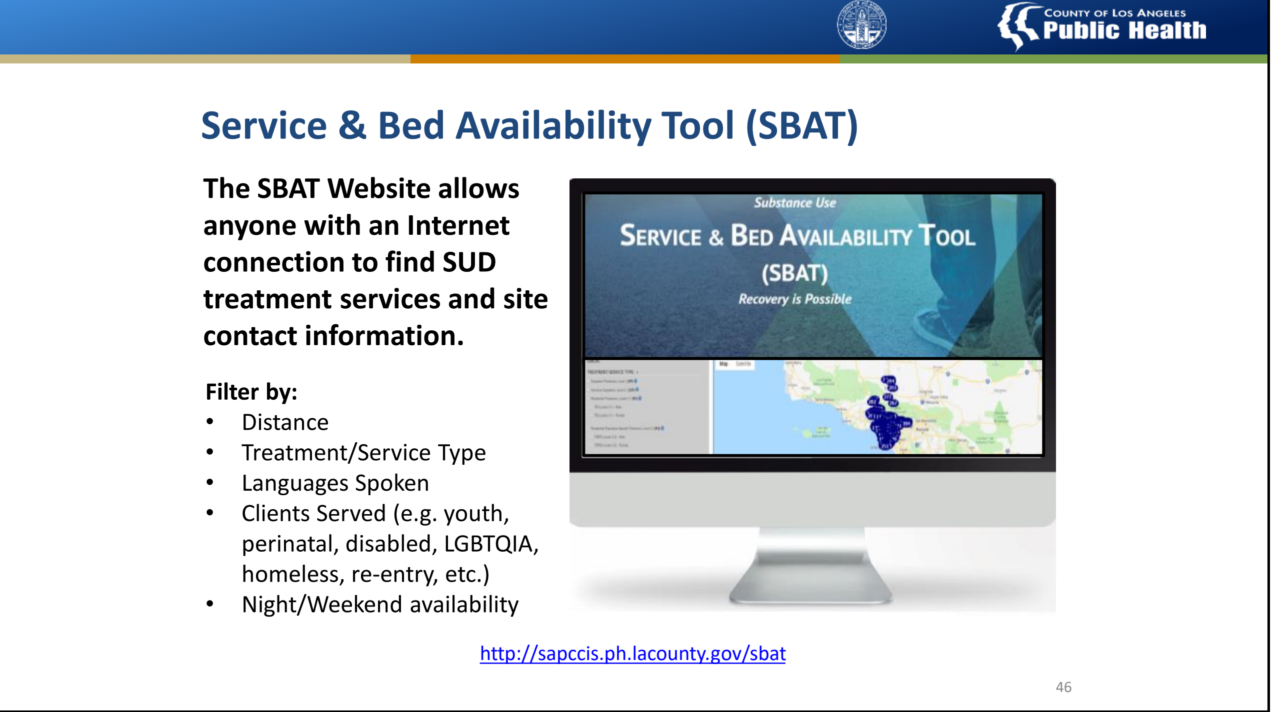

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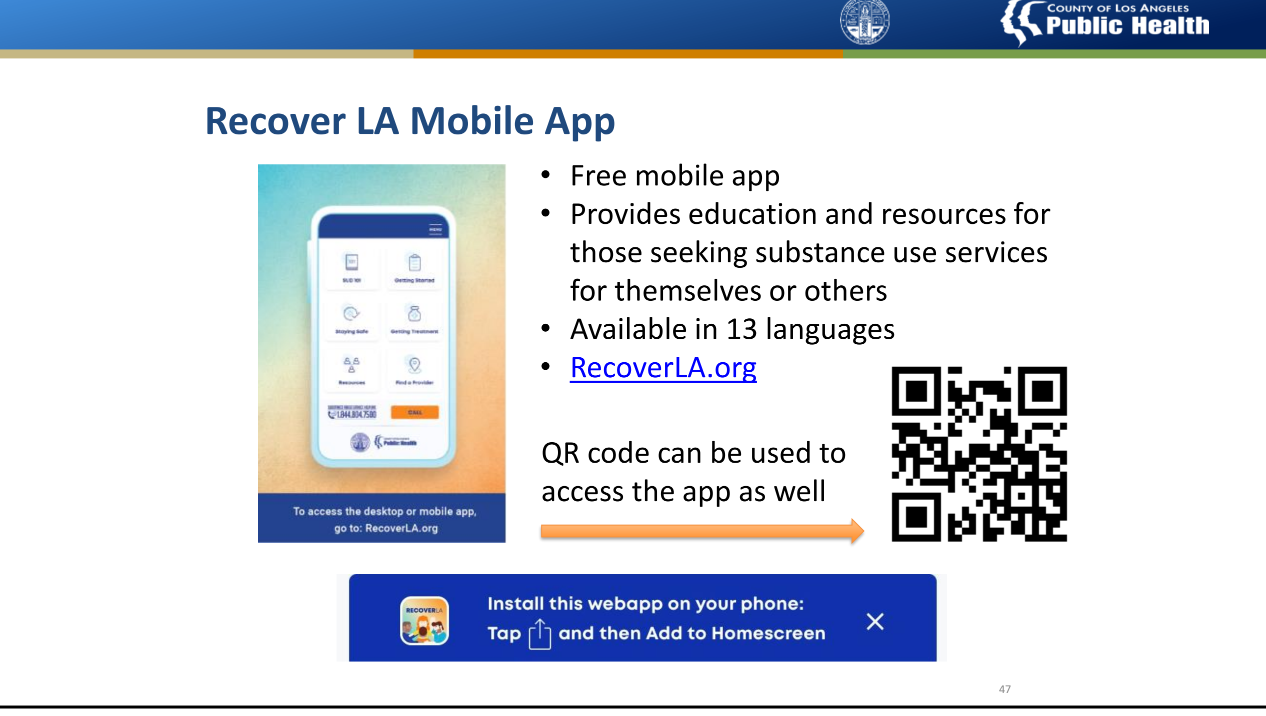

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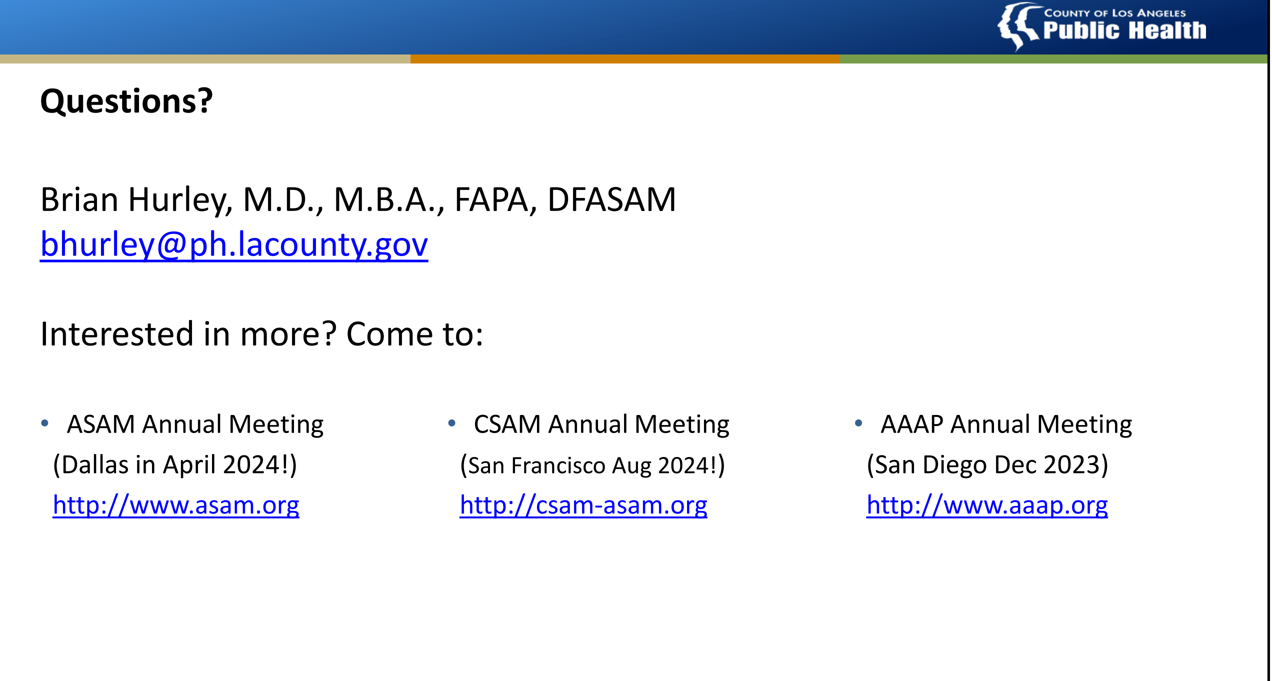

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