Applying the ASAM NPG: Ambulatory Withdrawal Management for People Experiencing Homelessness During COVID-19

Brian Hurley, M.D., M.B.A., DFASAM
Director of Addiction Medicine
Los Angeles County Department of Health Services
Assistant Professor of Addiction Medicine
UCLA Department of Family Medicine

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

No disclosures

Addiction During COVID-19

COVID-19 pandemic increases need for addiction treatment:

COVID-19

- Stress, anxiety and isolation
- "Stay-at-Home" orders and border restrictions
- Unemployment, loss of economic opportunity, and poverty

Negative Outcomes

- Increase symptoms of addiction and mental illness
- Reduce drug availability
- Increase symptoms of addiction and mental illness

It is critical that patients have access to treatment during this pandemic.

Rising Overdose Rates

Figure 1a. 12 Month-ending Provisional Counts of Drug Overdose Deaths: United States

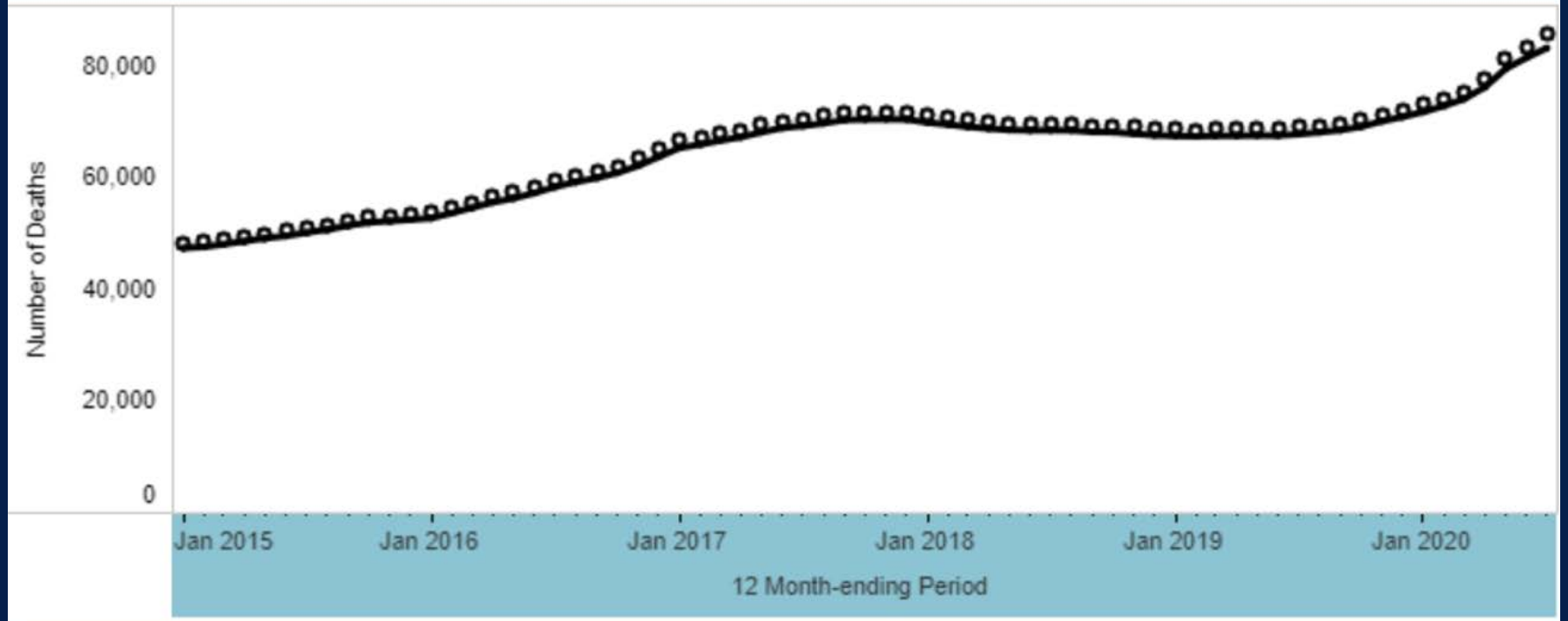


Figure 1b. Percent Change in Predicted 12 Month-ending Count of Drug Overdose Deaths, by Jurisdiction: July 2019 to July 2020

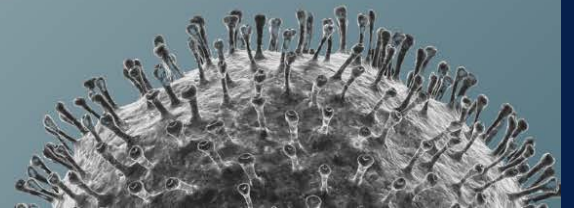
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

COVID-19 Adaptations

Clinicians, treatment programs, and systems of care must pivot during times of disaster from traditional 'best practices' which rely upon usual resource availability, while providing the best care possible under their circumstances for the patients in their community.

NATIONAL ACADEMY of MEDICINE

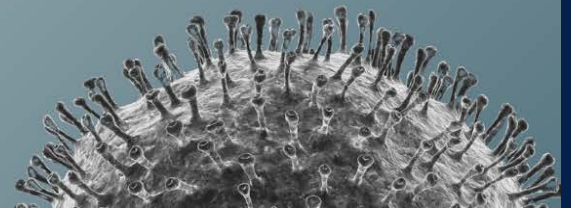
ASAM American Society of Addiction Medicine



COVID-19 Adaptations

Rapid and deep federal guidance, regulatory changes, and payment changes must be implemented within state and local regulatory and payment structures.

There is an urgent/emergent need for clinicians, treatment programs, systems of care to break from silos and collaborate for new systems



Phases of the COVID-19 Pandemic

Early Phase

- **Low population prevalence**
- **Preventing transmission of the virus using physical distancing**
- **Develop protocols for keeping infectious patients /staff in isolation or quarantine**
- **PLAN FOR PHASE 2 !**

Middle Phase

- **Higher population prevalence makes isolating of individuals impractical**
- **Designating entire areas/systems, including community housing, as available to either infectious or non-infectious persons.**

Post-Pandemic

Updated best practices are implemented based upon lessons learned

The ASAM

CLINICAL PRACTICE GUIDELINE ON

Alcohol Withdrawal Management

ASAM American Society of Addiction Medicine

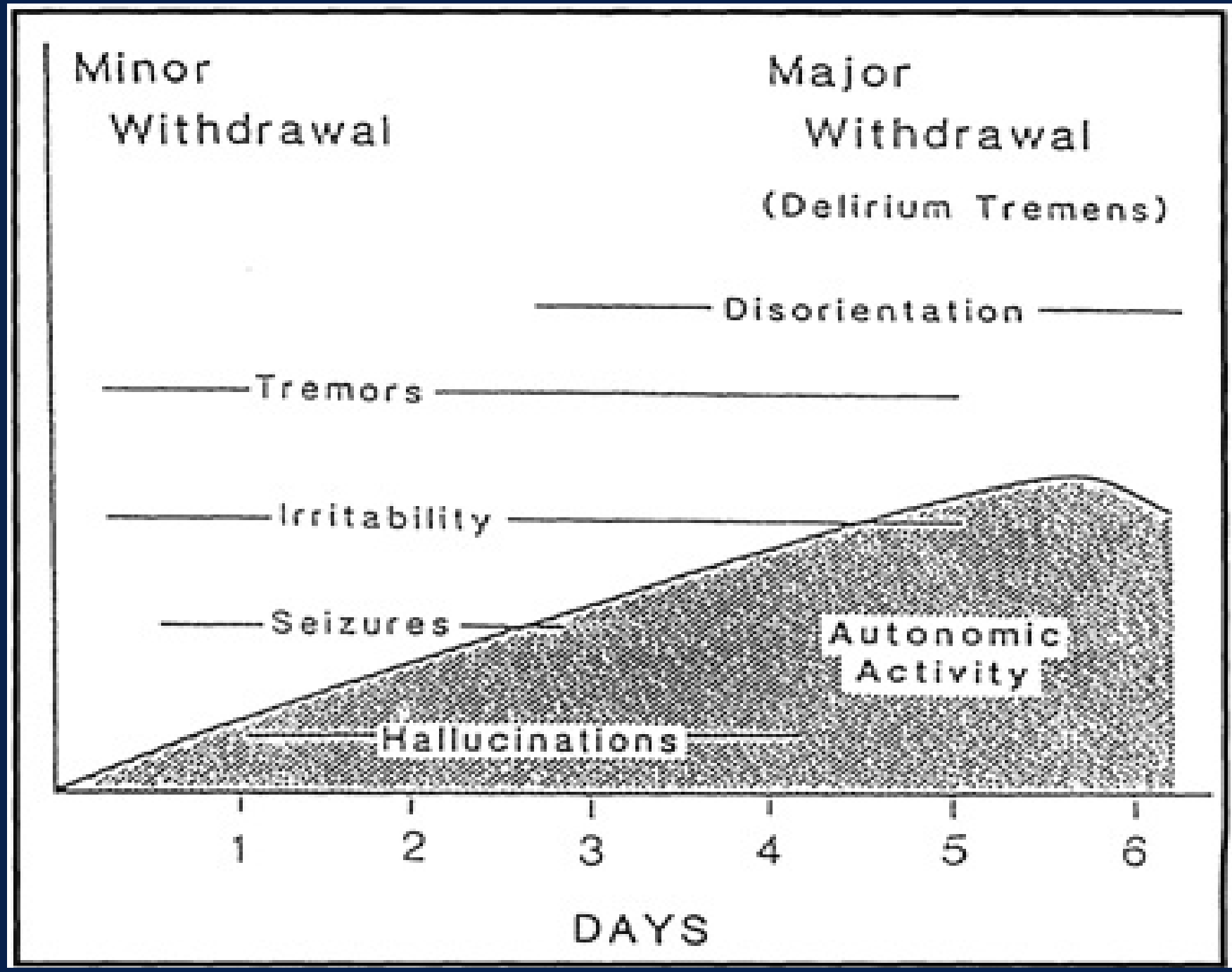
https://www.asam.org/Quality-Science/quality/guideline-on-alcohol-withdrawal-management

#ASAM2021

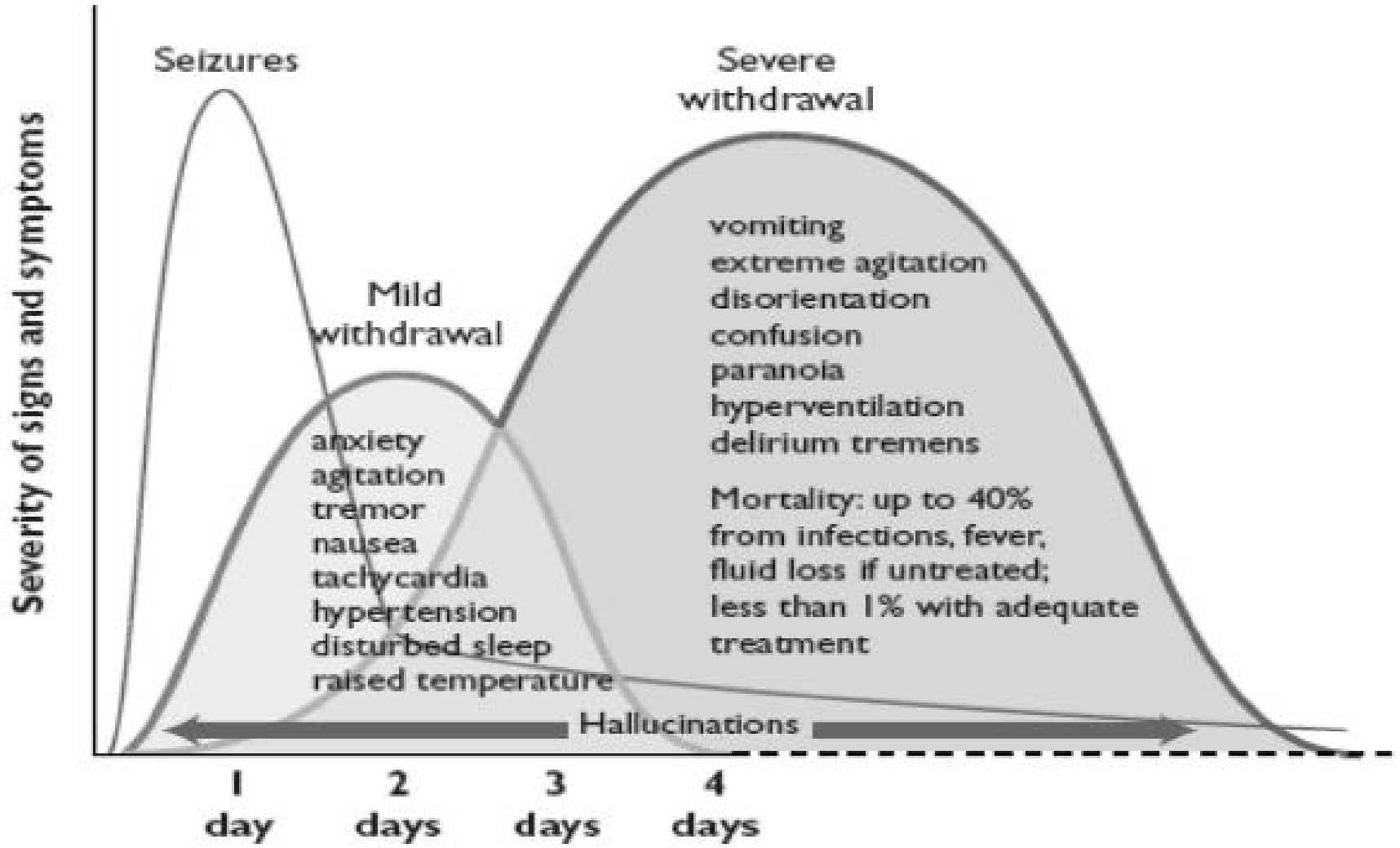
Implementing AWS Management Program

COVID-19 Adjustments in Los Angeles County Department of Health Services

- Rapid deployment of expected practice guidance
- On-Call telephone consultation
- Capacitize field and hotel quarantine / isolation sites for people experiencing homelessness
- Moving routine services to tele-visits, and installation of a telehealth platform


Minor
Withdrawal
Major
Withdrawal
(Delirium Tremens)
Disorientation
Tremors
Irritability
Seizures
Autonomic
Activity
Hallucinations
1
2
3
4
5
6
DAYS

Progress of alcohol withdrawal syndrome



Adapted from Frank L, Pead J. New concepts in drug withdrawal: a resource handbook. © 1995 State of Victoria. Reproduced with permission.

ALCOHOL WITHDRAWAL SEIZURES

- Recurrent detox and prior seizure are risk factors
- Occur 24-48 hrs after abstinence or decreased intake
- Often occur prior to autonomic hyperactivity
- Generalized, single or a few (79% <3, <3% status), over a short time (86%/1st 6 hrs)
- Fever, delirium, focal exam, head trauma, focal or multiple seizures, 1st seizure ever, or status suggest other diagnoses
- CT scanning unhelpful if clinical picture consistent

Victor & Brausch. Epilepsia 1967;8:1
Feussner et al. Ann Int Med 1981;94:519
Lechtenberg 1990

American Society of Addiction Medicine Practice Guidelines

- **Symptom-triggered** (q 1 when CIWA-Ar≥8)
  - Chlordiazepoxide 50-100 mg
  - Diazepam 10-20 mg
  - Lorazepam 2-4 mg
- **Fixed schedule** (q 6 for 4/8 doses + PRN)
  - Chlordiazepoxide 50 mg/25 mg
  - Diazepam 10 mg/5 mg
  - Lorazepam 2 mg/1 mg

Mayo-Smith and ASAM working group JAMA 1997;278:144-51
Saitz and O'Malley Med Clin N A 1997;81:881-907

Benzodiazepines reduce seizures

ANY	1/188 (0.5%)
Placebo	16/201 (8%)

RRR 93%, $p<0.001$

Sereny 1965, Kiam 1969, Zilm 1980, Sellers 1983, Naranjo 1983, summarized in Mayo-Smith MF & ASAM Working Group JAMA 1997;278:144-51

Benzodiazepines reduce delirium

Chlordiazepoxide	3/172 (2%)
Placebo	11/186 (6%)

RRR 71%, p=0.04

Rosenfeld 1961, Sereny 1965, Kaim 1969, Zilm 1980,
summarized in Mayo-Smith MF & ASAM Working Group JAMA 1997;278:144-51

Phenobarbital

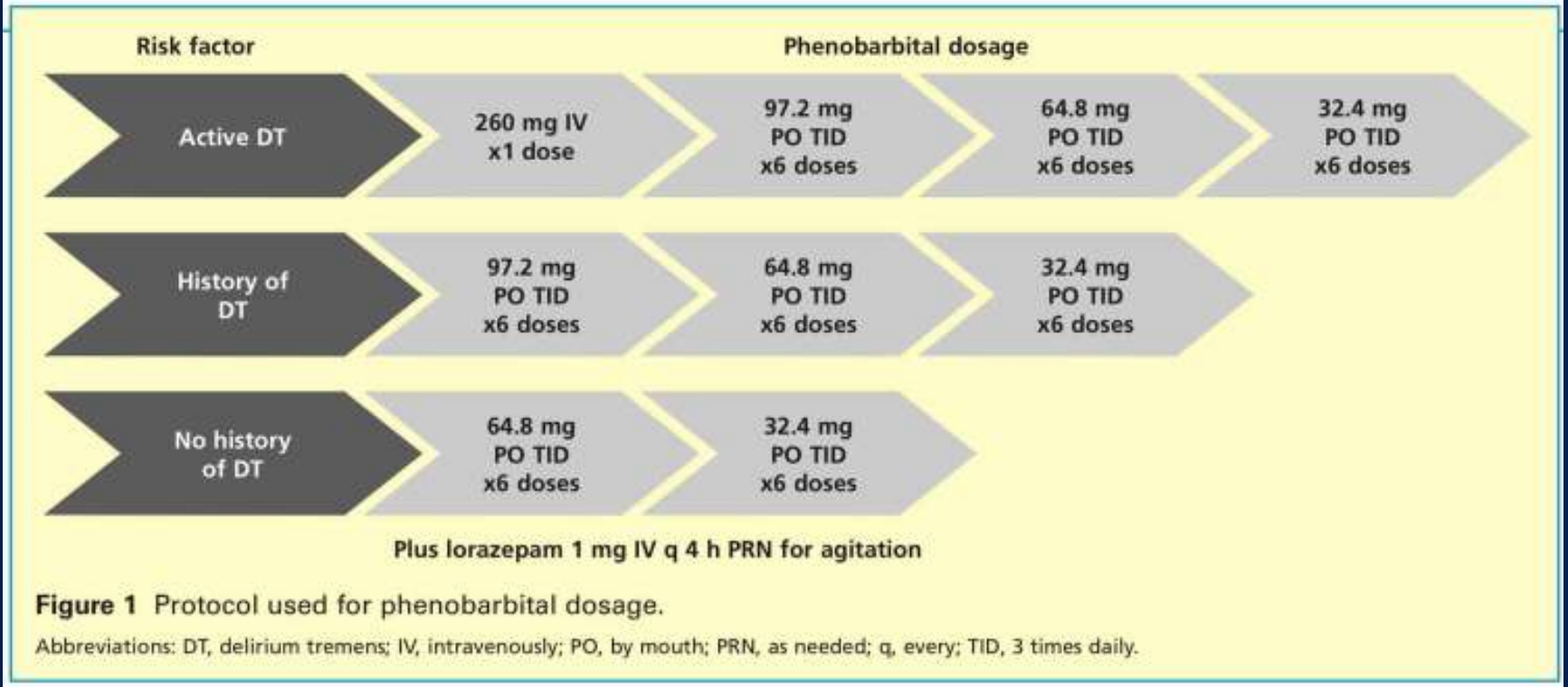


Figure 1 Protocol used for phenobarbital dosage.

Abbreviations: DT, delirium tremens; IV, intravenously; PO, by mouth; PRN, as needed; q, every; TID, 3 times daily.

Tidwell, W. P., Thomas, T. L., Pouliot, J. D., Canonico, A. E., & Webber, A. J. (2018). Treatment of alcohol withdrawal syndrome: phenobarbital vs CIWA-Ar protocol. *American Journal of Critical Care*, *27*(6), 454-460.

Non-Benzodiazepine Anticonvulsants

- Carbamazepine
  - Fixed dose, 800 mg/day tapered over 4, 7, 9, 12 days OR
  - Symptom-triggered dosing at 200mg or 400mg prn (≤1200 mg/day)
- Gabapentin
  - Fixed dose, 300-600mg QID, tapered off in 5-7 days
- Valproate
  - 500mg TID x7d
  - Not great as a monotherapy

Hammond, C. J., Niciu, M. J., Drew, S., & Arias, A. J. (2015). Anticonvulsants for the treatment of alcohol withdrawal syndrome and alcohol use disorders. *CNS drugs*, *29*(4), 293-311.

Non-Benzodiazepine Anticonvulsants

- Oxcarbazepine
  - Fixed dose, 900 mg/day, tapered over 5-6 days
- Pregabalin
  - Flexibly dose to minimize symptoms (between 200 and 450 mg/day) for 7d, followed by a 7d taper
- Levetiracetam
  - Fixed dose, 2000 mg/day, tapered over 6 days
- Topiramate
  - Fixed dose, 25 mg QID x7d
- Zonisamide
  - Flexible dosing starting at 400–600 mg/day and tapered over 21 days to 100–300 mg/day

Hammond, C. J., Niciu, M. J., Drew, S., & Arias, A. J. (2015). Anticonvulsants for the treatment of alcohol withdrawal syndrome and alcohol use disorders. *CNS drugs*, *29*(4), 293-311.

Other Options

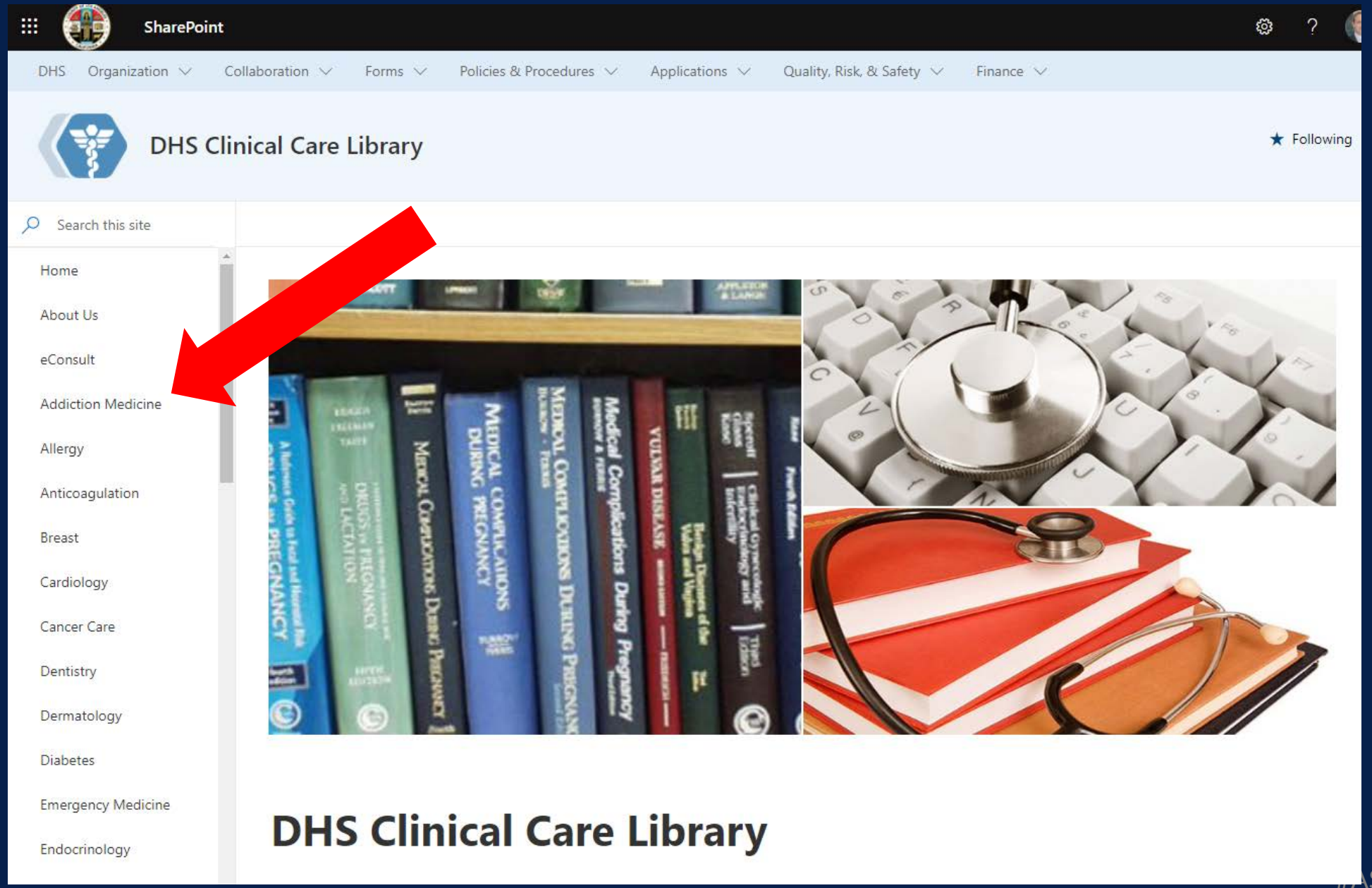
- Baclofen
- Clonidine
- Dexmedetomidate
- Ketamine
- Sodium oxybate

Sachdeva A, Choudhary M, Chandra M. Alcohol Withdrawal Syndrome: Benzodiazepines and Beyond. J Clin Diagn Res. 2015 Sep;9(9):VE01-VE07. doi: 10.7860/JCDR/2015/13407.6538. Epub 2015 Sep 1. PMID: 26500991; PMCID: PMC4606320.
http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/26500991

Benzos vs. Other Anticonvulsants

- Despite their proven usefulness in the management of alcohol withdrawal seizures and delirium tremens, the use of benzodiazepines for alcohol withdrawal in ambulatory settings is fraught with potential complications, which include high risk of the medication being diverted, high risk of benzodiazepines being taken by the patient in ways other than as prescribed, blunted cognition, respiratory and cognitive interactions with other central nervous system depressants such as alcohol, increased alcohol cravings, and psychomotor retardation including ataxia.

Sachdeva A, Choudhary M, Chandra M. Alcohol Withdrawal Syndrome: Benzodiazepines and Beyond. J Clin Diagn Res. 2015 Sep;9(9):VE01-VE07. doi: 10.7860/JCDR/2015/13407.6538. Epub 2015 Sep 1. PMID: 26500991; PMCID: PMC4606320.
http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/26500991


SharePoint
DHS
Organization
Collaboration
Forms
Policies & Procedures
Applications
Quality, Risk, & Safety
Finance
DHS Clinical Care Library
Following
Search this site
Home
About Us
eConsult
Addiction Medicine
Allergy
Anticoagulation
Breast
Cardiology
Cancer Care
Dentistry
Dermatology
Diabetes
Emergency Medicine
Endocrinology
DHS Clinical Care Library

Example of Expected Practice

- Step 1: Diagnose and determine severity of alcohol withdrawal syndrome in patients with clinically significant alcohol consumption where the patient is currently experiencing, or likely to experience, alcohol withdrawal syndrome
  - A formal SAWS or CIWA does not need to be administered or completed prior to offering patients alcohol / sedative withdrawal management if mild to moderate withdrawal is confirmed by the clinical history.
- Indications to refer patients to a higher level of care:
  - History of delirium tremens or withdrawal seizures
  - Acute illness
  - Severe cognitive impairment (acute or chronic) that prevents ability of patient to take medications or follow instructions
  - Inability to take oral medications because of vomiting or swallowing issues
  - Serious psychiatric condition requiring a higher level of care
  - Pregnancy – unless directed by high risk obstetrics team
  - Severe alcohol withdrawal symptoms (SAWS > 16 or CIWA-Ar ≥ 20 if using scales)
- If any of the above are present, refer to a higher level of care as described in Appendix B.

Example of Expected Practice

- Step 2: Order the following labs at the same time medication (Step 3) is started:
  - Urine drug screen (Urine Drug Toxicology Screen – Expanded)
  - Complete blood count (CBC)
  - Comprehensive metabolic panel (CMP)
- Do not hold medications for the results of these tests unless there is a history of or obvious signs of renal compromise (for gabapentin) or liver compromise (for carbamazepine) where the expected findings would change management. Patients who are found to have profound derangements in laboratory studies should be considered for a higher level of medical care.
- Step 3: Initiate pharmacotherapy for alcohol withdrawal
  - Gabapentin is the first line agent; carbamazepine can be used in patients who experience gabapentin-induced sedation, dizziness, edema, or GI intolerance. Escalate to a higher level of care if the patient has worsening withdrawal symptoms despite gabapentin treatment. Gabapentin is renally cleared so avoid if CrCl is ≤ 30 mL/minute and dose adjusted if CrCl is ≤ 60 mL/min.

Example of Expected Practice

Gabapentin is dosed as 600mg PO TID plus an additional 600mg prn once daily for the first week, followed by a 300mg taper after the first week

Days	Gabapentin Monotherapy (fixed schedule dosing)
1	1,200mg BID plus 1,200mg x1 prn
2-7	600mg TID plus 600mg x1 prn
8	300mg TID
9	300mg BID
10	300mg qHS

How to write the gabapentin prescription:
Rx: Gabapentin 600mg tabs, take as directed, #30, NR
Verbalized or printed instructions for the patient:
Day 1: Take 2 tabs twice daily plus an additional 2 tabs if needed the first day
Days 2-7: Take 1 tab three times daily plus an additional 1 tabs if needed
Day 8: Take ½ tab three times daily
Day 9: Take ½ tab twice daily
Day 10: Take ½ tab once at bedtime

Example of Expected Practice

In patients who do not tolerate gabapentin:

Carbamazepine is dosed 200mg PO QID x 72° followed by a 200mg reduction q72°

Days	Carbamazepine Monotherapy (fixed schedule dosing)
1-3	200mg QID
4-6	200mg TID
7-9	200mg BID
10-11	200mg qHS

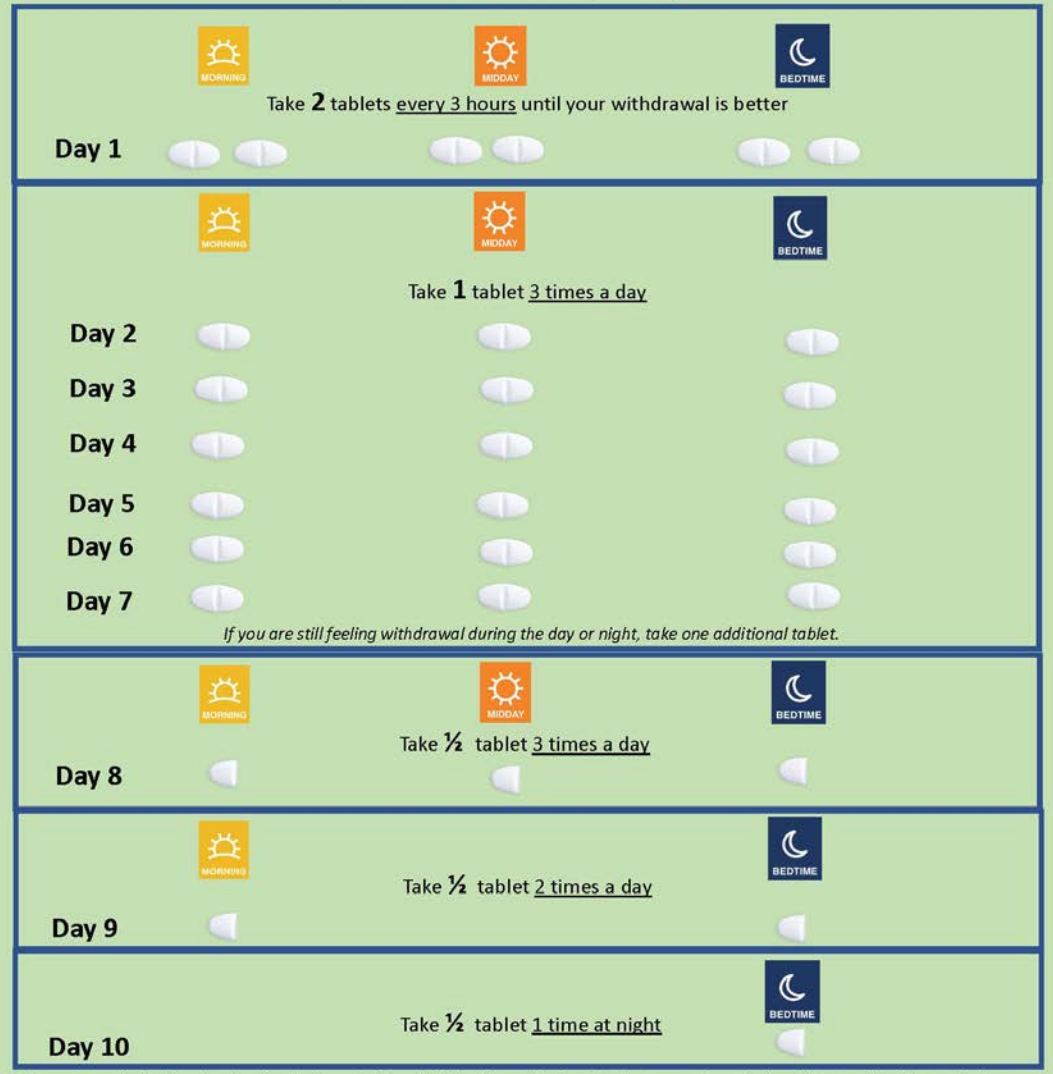
How to write the carbamazepine prescription:
Rx Carbamazepine 200mg tabs, take 1 QID x3d, then 1 TIDx3d, then 1 BID x3d, then 1 qHS x3d, #30, NR
Verbalized or printed instructions for the patient:
Days 1-3: Take 1 four times throughout the day
Days 4-6: Take 1 three times throughout the day
Days 7-9: Take 1 twice a day
Days 10-11: Take 1 at bedtime

Gabapentin 600mg tablets for alcohol / sedative withdrawal

You are being prescribed Gabapentin to help with cravings and withdrawal of alcohol use.

You will receive a supply of 30 tablets. Please notify the staff if you are having any worsening withdrawal and if the dose of medication you are receiving is not working to treat your withdrawal.

HOW to take Gabapentin:



Get emergency medical help if you have signs of an allergic reaction: hives; difficult breathing; swelling of your face, lips, tongue, or throat. Seek medical treatment if you have a serious drug reaction that can affect many parts of your body. Symptoms may include: skin rash, fever, swollen glands, flu-like symptoms, muscle aches, severe weakness, unusual bruising, or yellowing of your skin or eyes. This reaction may occur several weeks after you began using gabapentin.

Sponsored by the National Health Foundation through a Sierra Health Foundation MAT Access Points Project award and developed in partnership with Los Angeles County Department of Health Services, CA Bridge, and the Center for Care Innovation's Addiction Treatment Starts Here program.

Tegretol 200 mg tablets for alcohol / sedative withdrawal

You are being prescribed Tegretol to help with cravings and withdrawal of alcohol use.

You will receive a supply of 30 tablets. Please notify the staff if you are having any worsening withdrawal and if the dose of medication you are receiving is not working to treat your withdrawal.

HOW to take Tegretol:

	MORNING	MIDDAY	EVENING	BEDTIME
Take **1** tablet every 6 hours				
Day 1				
Day 2				
Day 3				
Take **1** tablet 3 times a day				
Day 4			X	
Day 5			X	
Day 6			X	
Take **1** tablet 2 times a day				
Day 7		X	X	
Day 8		X	X	
Day 9		X	X	
Take **1** tablet at bedtime				
Day 10	X	X	X	
Day 11	X	X	X	

Seek medical treatment if you have a serious drug reaction that can affect many parts of your body. Symptoms may include: skin rash, fever, swollen glands, flu-like symptoms, muscle aches, severe weakness, unusual bruising, or yellowing of your skin or eyes. This reaction may occur several weeks after you began using Tegretol. Report any new or worsening symptoms to your doctor, such as: sudden mood or behavior changes, depression, anxiety, insomnia, or if you feel agitated, hostile, restless, irritable, or have thoughts about suicide or hurting yourself.

Sponsored by the National Health Foundation through a Sierra Health Foundation MAT Access Points Project award and developed in partnership with Los Angeles County Department of Health Services, CA Bridge, and the Center for Care Innovation's Addiction Treatment Starts Here program

Core Components of Addiction Treatment

*Medications

*Counseling

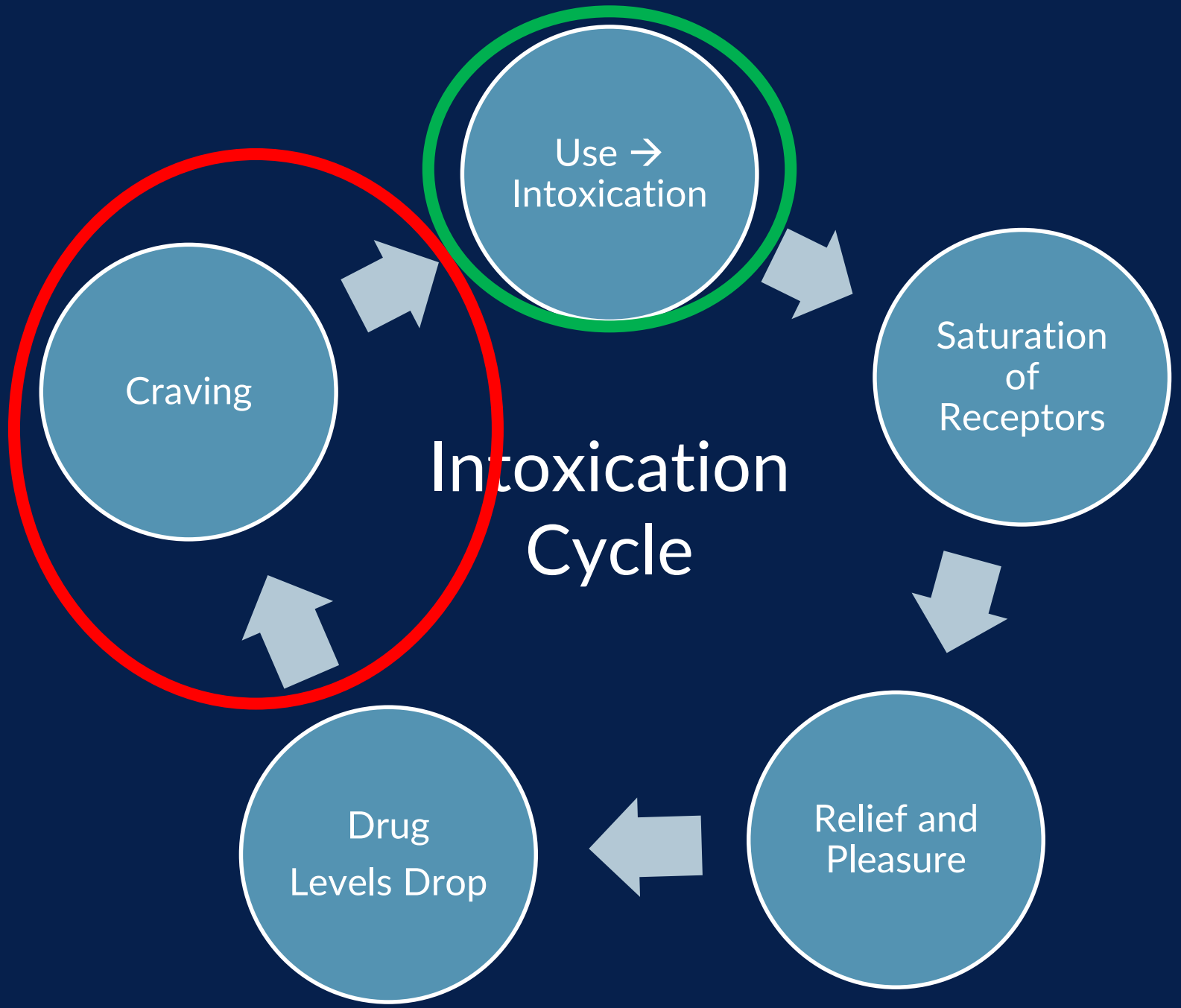
*Support

*When appropriate

Source: http://www.samhsa.gov/treatment

Medications for Addiction Treatment (MAT)

- Opioids
  - Methadone
  - Buprenorphine
  - Naltrexone
  - Naloxone* (not a maintenance medication)
- Alcohol
  - Disulfiram
  - Naltrexone
  - Acamprosate
- Tobacco
  - Nicotine
  - Bupropion
  - Varenicline
- Others
  - No FDA-approved medications (yet)


Use → Intoxication
Saturation of Receptors
Relief and Pleasure
Drug Levels Drop
Craving
Intoxication Cycle

Effectiveness: Alcohol

Acamprosate

- NNT: 12 to avoid return to drinking

Disulfiram

- No association with changes in drinking, but fewer drinking days in subset of pts

Oral Naltrexone

- NNT: 20 to avoid return to drinking, 12 to avoid heavy drinking

Naltrexone (LAI)

- NNT: 12 to avoid return to drinking

Johnson, B. A. (2007). Naltrexone long-acting formulation in the treatment of alcohol dependence. *Therapeutics and clinical risk management*, *3*(5), 741.

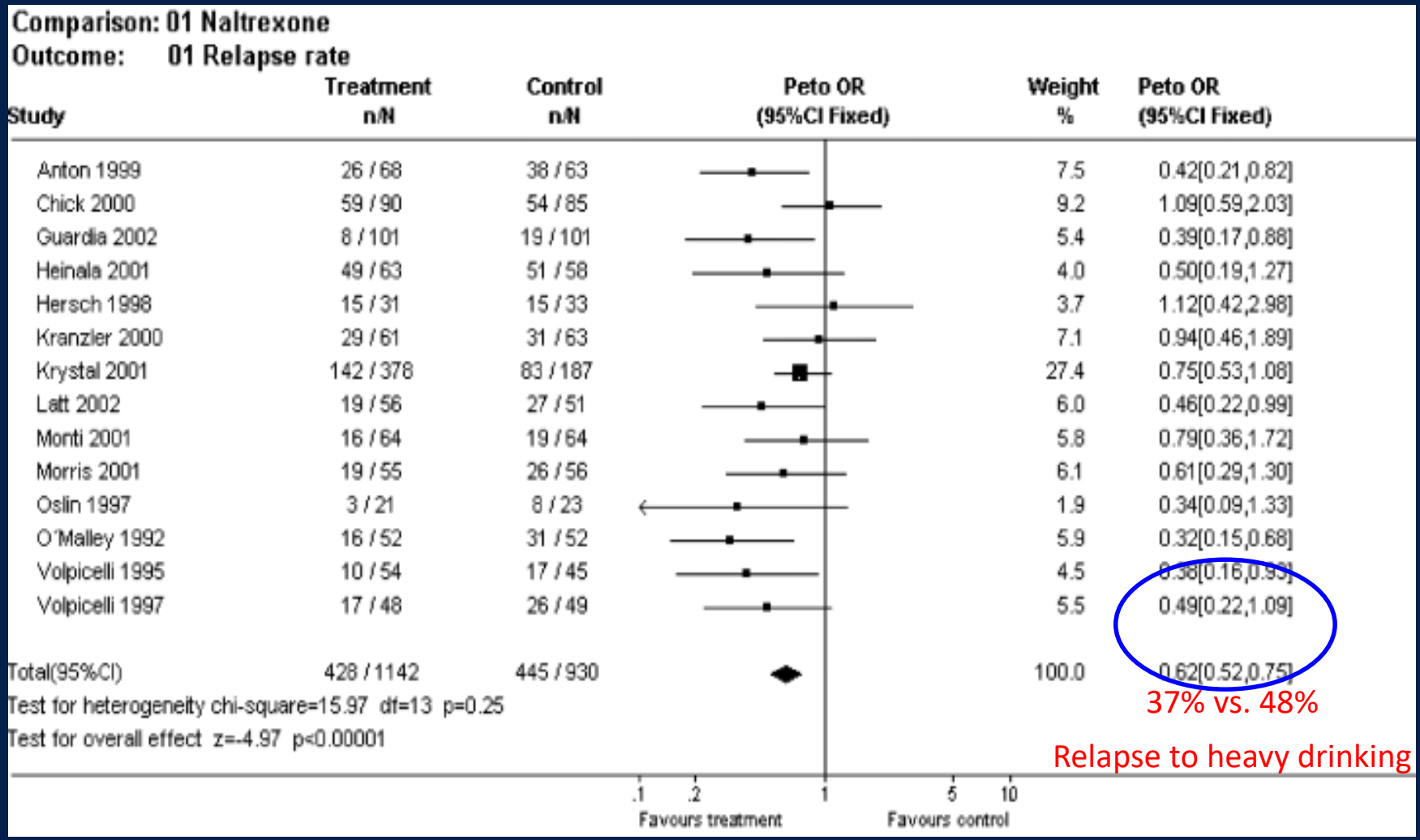
Jonas, D. E., Amick, H. R., Feltner, C., Bobashev, G., Thomas, K., Wines, R., ... & Garbutt, J. C. (2014). Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *Jama*, *311*(18), 1889-1900.

Off-Label Rx for AUD

- Topiramate
  - Known teratogen
  - Start 25mg qHS, titrate to 300mg / day (in split dosing) if pt tolerates (many don't tolerate >150mg daily)
- Gabapentin
  - 300-600mg TID used in maintenance protocols
- Baclofen
  - 30 mg/day has mixed results
- Ondansetron
  - Watch QTc
  - 4mg BID to 8mg BID

Kim, Y., Hack, L. M., Ahn, E. S., & Kim, J. (2018). Practical outpatient pharmacotherapy for alcohol use disorder. *Drugs in Context*, *7*.

Efficacy of Oral Naltrexone



37% vs. 48%

Relapse to heavy drinking

Bouza C et al. Addiction 2004;99:811

Project Combine

Table 5. Drinking Outcomes Through End of Treatment

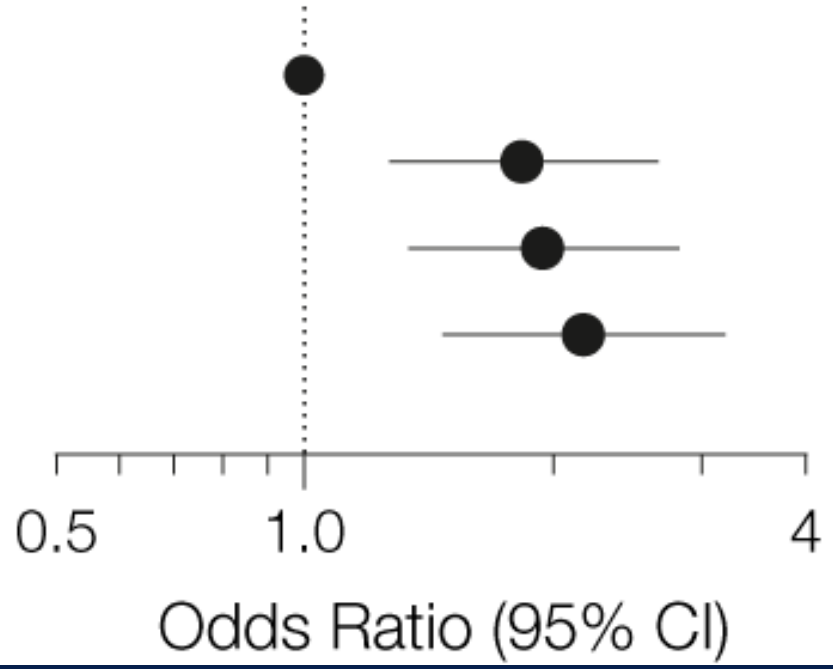
Drinking Outcomes*	No. (N = 1383)†	Medical Management (No CBI)				CBI + Medical Management				CBI Only
		Placebo (n = 153)	Naltrexone (n = 154)	Acamprosate (n = 152)	Naltrexone + Acamprosate (n = 148)	Placebo (n = 156)	Naltrexone (n = 155)	Acamprosate (n = 151)	Naltrexone + Acamprosate (n = 157)	No Pills (n = 157)
Percent days abstinent, mean (SD)‡	1376	73.8 (25.98)	80.0 (26.06)	75.6 (26.01)	80.5 (25.91)	79.8 (25.94)	75.9 (26.02)	78.2 (25.93)	77.6 (25.94)	66.6 (27.14)
Return to heavy drinking, No. events (%)§	1383	115 (75.2)	104 (67.5)	108 (71.1)	96 (64.9)	111 (71.2)	103 (66.5)	103 (68.2)	116 (73.9)	124 (79.0)
Good clinical outcome, No. events (%)‖	1294	71 (58.2)	87 (73.7)	79 (60.8)	91 (78.4)	92 (71.3)	99 (74.4)	93 (74.4)	97 (73.5)	80 (60.6)

Abbreviation: CBI, combined behavioral intervention.
*All drinking measures are adjusted for baseline drinking.
†A total of 1383 patients were randomly assigned. Other numbers represent all patients who have data available for analysis.
‡Percent days abstinent is computed monthly for the treatment period. At least 5 days of data per month were required to compute percent days abstinent; otherwise, it was considered missing.
§A heavy drinking day is defined as ≥4 drinks/d for women and ≥5 drinks/d for men.
‖See "Methods" section for definition.

Anton, R. F., O'Malley, S. S., Ciraulo, D. A., Cisler, R. A., Couper, D., Donovan, D. M., ... & Longabaugh, R. (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *Jama*, *295*(17), 2003-2017.

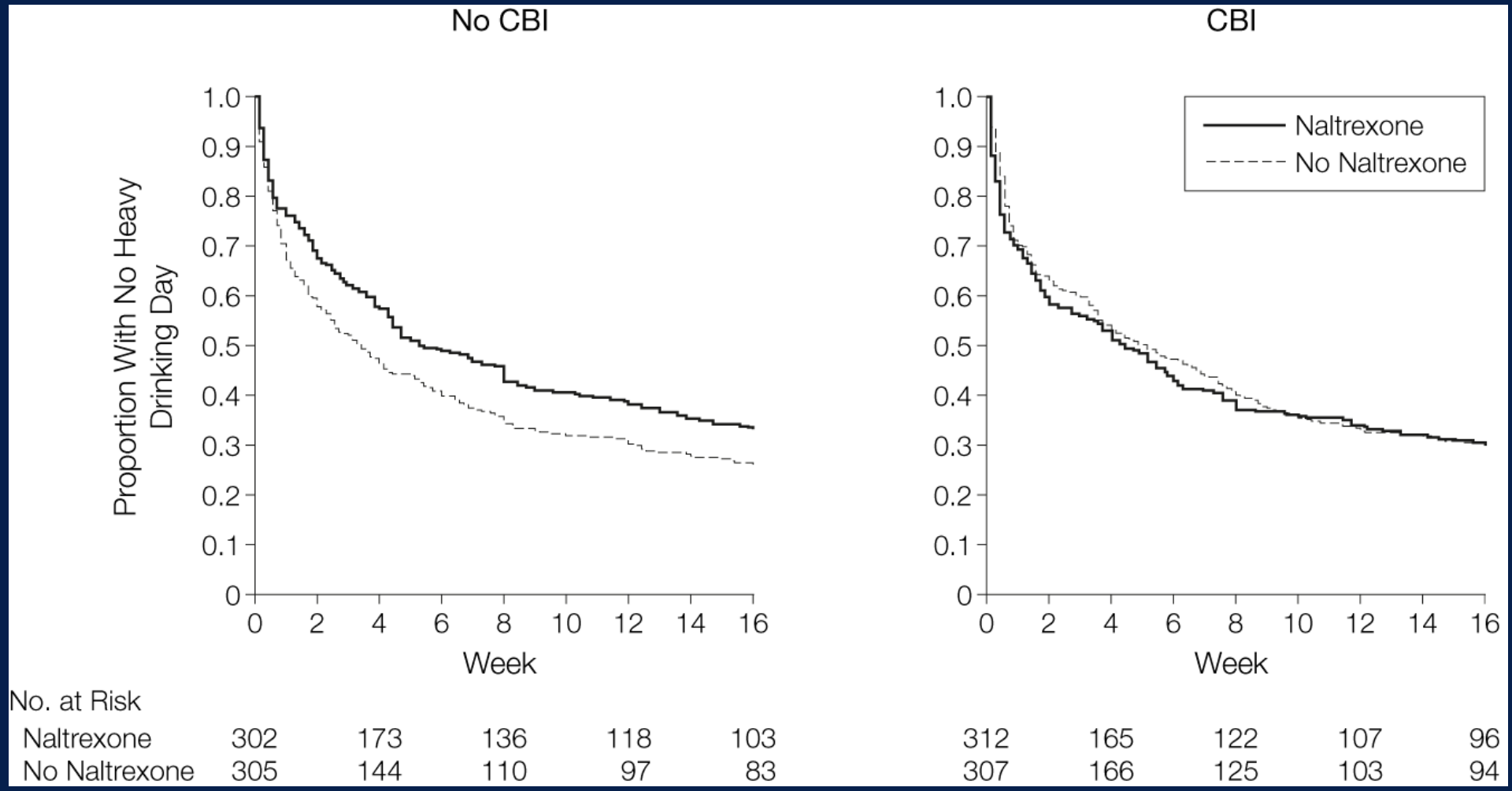
Project Combine

Treatment	Odds Ratio (95% CI)
Placebo Naltrexone/No CBI	1.00
Placebo Naltrexone/CBI	1.82 (1.26-2.65)
Naltrexone/CBI	1.93 (1.33-2.80)
Naltrexone/No CBI	2.16 (1.46-3.20)



Anton, R. F., O'Malley, S. S., Ciraulo, D. A., Cisler, R. A., Couper, D., Donovan, D. M., ... & Longabaugh, R. (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *Jama*, *295*(17), 2003-2017.

Project Combine



Anton, R. F., O'Malley, S. S., Ciraulo, D. A., Cisler, R. A., Couper, D., Donovan, D. M., ... & Longabaugh, R. (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *Jama*, *295*(17), 2003-2017.

Example of Expected Practice

- Step 4: Treat alcohol use disorder in accordance with the DHS Alcohol Use Disorder Treatment EP. Treat alcohol use disorder concurrently with medications for withdrawal management.
- Step 5: When to Refer to specialty SUD Services
  - Interested patients should be referred to an addiction counselor or social worker, or directly to the LA County Substance Use Disorder Helpline, in parallel with offering outpatient medication management services.

Health Services
LOS ANGELES COUNTY

Naltrexone

One Pill
A Day

Help reduce alcohol cravings
Cut down on how much alcohol you are drinking

HOW to take Naltrexone

Before getting started:

1. Tell staff if you have a history of liver problems like cirrhosis, swelling of your stomach, or yellowing of your eyes.

2. Do not take Naltrexone if you have taken any narcotic pain pills like heroin, fentanyl, Subutex, Suboxone, methadone or tramadol in the past week.

Instructions:

Take **1** 50mg tablet each day.
Follow-up with your medical provider in 2 to 4 weeks to discuss how naltrexone is working.

If you have stomach aches or headache:

Take **½** tablet each day for **3 days** and then **1** full tablet each day after.

Please notify the staff if you are having any worsening withdrawal and if the dose of medication you are receiving is not working to treat your withdrawal.

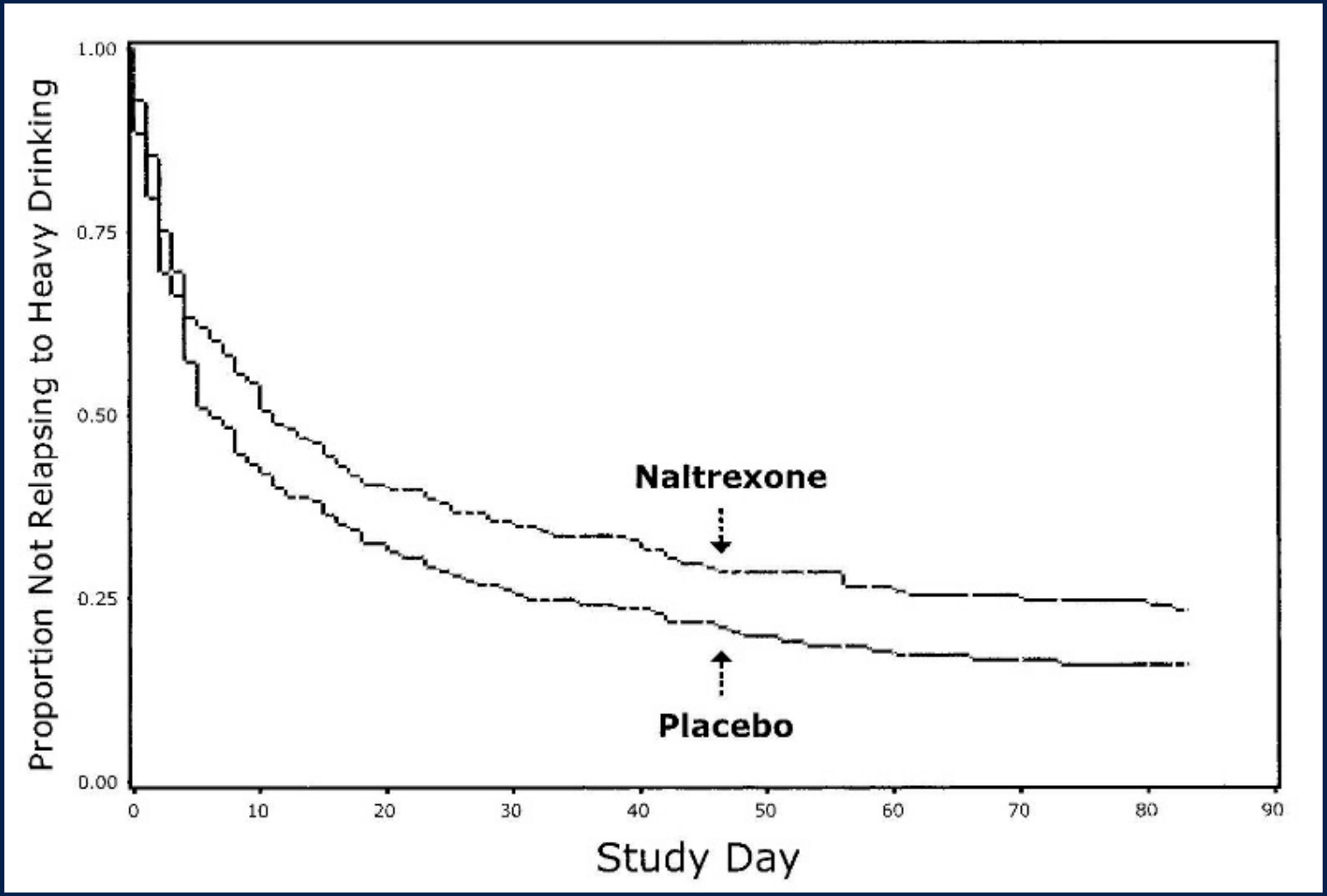
Sponsored by the National Health Foundation through a Sierra Health Foundation MAT Access Points Project award and developed in partnership with Los Angeles County Department of Health Services, CA Bridge, and the Center for Care Innovation's Addiction Treatment Starts Here program.

Naltrexone Long Acting Injection

- 380mg IM dose of naltrexone
- Injected as a suspension with microspheres that elute naltrexone over ~28 days
- Gluteal injection

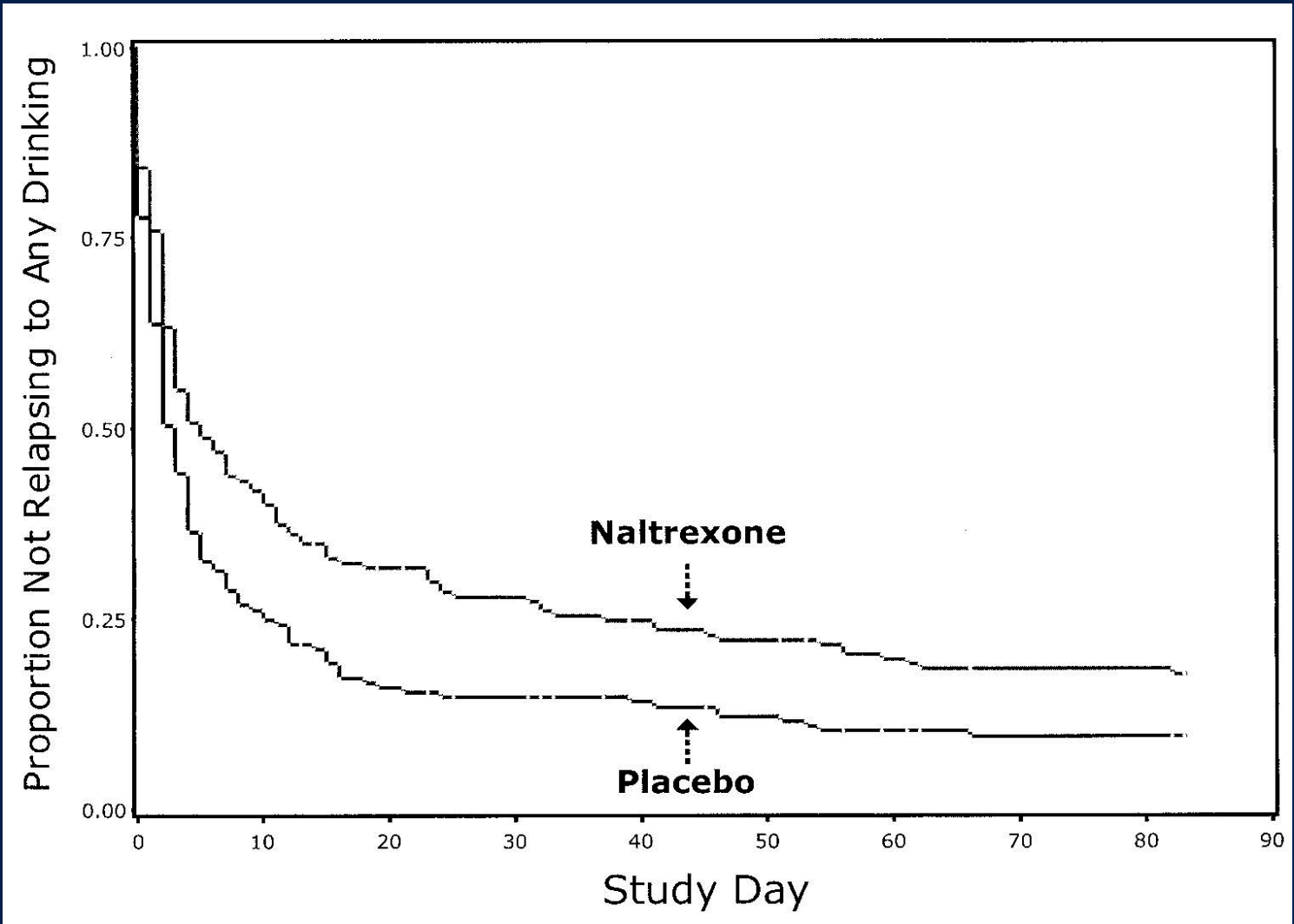
https://www.youtube.com/watch?v=IZBaDCIWSwg

Naltrexone LAI and Alcohol



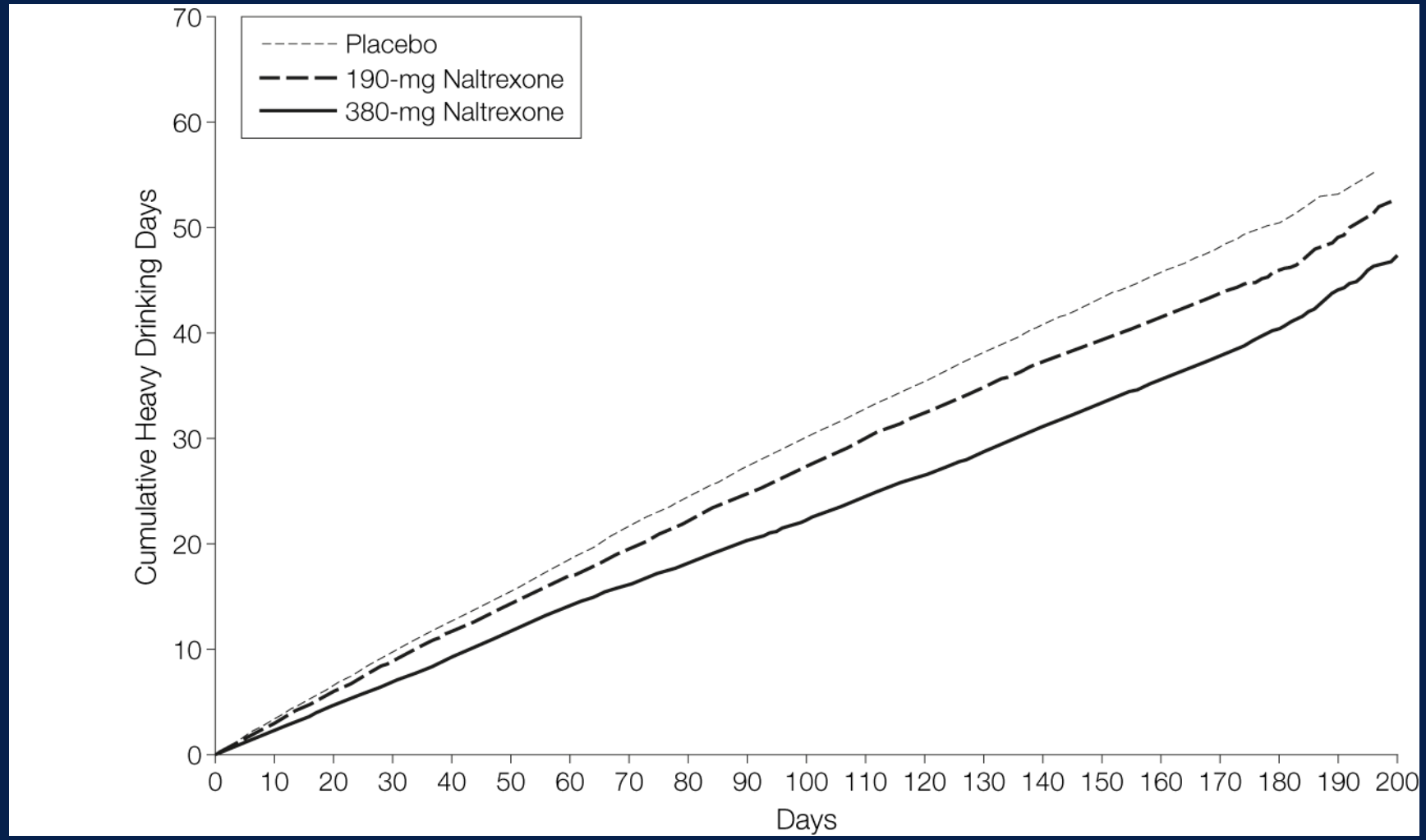
Kranzler, H. R., Wesson, D. R., & Billot, L. (2004). Naltrexone Depot for Treatment of Alcohol Dependence: A Multicenter, Randomized, Placebo-Controlled Clinical Trial. *Alcoholism: Clinical and Experimental Research*, *28*(7), 1051-1059.

Naltrexone LAI and Alcohol



Kranzler, H. R., Wesson, D. R., & Billot, L. (2004). Naltrexone Depot for Treatment of Alcohol Dependence: A Multicenter, Randomized, Placebo-Controlled Clinical Trial. *Alcoholism: Clinical and Experimental Research*, *28*(7), 1051-1059.

Naltrexone LAI and Alcohol: fewer heavy drinking days



Garbutt, J. C., Kranzler, H. R., O'Malley, S. S., Gastfriend, D. R., Pettinati, H. M., Silverman, B. L., ... & Vivitrex Study Group. (2005). Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *Jama*, *293*(13), 1617-1625.

Contraindications to Naltrexone Long Acting Injection

- Patients receiving opioid analgesics
- Patients with active physiologic opioid dependence
- Patients in acute opioid withdrawal
- Any individual who has failed the naloxone challenge test or has a positive urine screen for opioids
- Patients who have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent

Ambulatory Care Network
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Medications for Addiction Treatment (MAT) Consultation

Support Available 7 days per week

- *MAT can be started in any setting. Safe via telehealth. Save lives, improve health and social functioning.*
- *DHS on-call providers help you start MAT for patients with alcohol and/or opioid use disorder.*
- *Patients benefit, even if not yet ready to quit drinking/using opioids.*
- *Reminder: offer Narcan/Naloxone in high risk settings*

MAT Consult Line:
(213) 288-9090

Health Services
LOS ANGELES COUNTY

5/11/2021

Sponsored by National Health Foundation for MAT Access Points Project, in partnership with Los Angeles County and CA Bridge

Questions / Feedback

bhurley@ucla.edu

References

1. Centers for Disease Control. NVSS Vital Statistics Rapid Release Provisional Drug Overdose Death Counts. http://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm - accessed 3/14/2021

2. Wong J, Saver B, Scanlan JM, Gianutsos LP, Bhakta Y, Walsh J, ... & Rudolf V. (2020). The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management. J Addict Med. 2020 May/Jun;14(3S Suppl 1):1-72. doi: 10.1097/ADM.0000000000000668. Erratum in: J Addict Med. 2020 Sep/Oct;14(5):e280. PMID: 32511109.

3. Victor M, Brausch C. The role of abstinence in the genesis of alcoholic epilepsy. Epilepsia. 1967 Mar;8(1):1-20. doi: 10.1111/j.1528-1157.1967.tb03815.x. PMID: 4961509.

4. Feussner JR, Linfors EW, Blessing CL, Starmer CF. Computed tomography brain scanning in alcohol withdrawal seizures. Value of the neurologic examination. Ann Intern Med. 1981 Apr;94(4 pt 1):519-22. doi: 10.7326/0003-4819-94-4-519. PMID: 7212510.

5. Lechtenberg R, Worner TM. Seizure risk with recurrent alcohol detoxification. Arch Neurol. 1990 May;47(5):535-8. doi: 10.1001/archneur.1990.00530050055012. PMID: 2334301.

6. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA. 1997 Jul 9;278(2):144-51. doi: 10.1001/jama.278.2.144. PMID: 9214531.

References

7. Saitz R, O'Malley SS. Pharmacotherapies for alcohol abuse. Withdrawal and treatment. Med Clin North Am. 1997 Jul;81(4):881-907. doi: 10.1016/s0025-7125(05)70554-x. PMID: 9222259.

8. Tidwell WP, Thomas TL, Pouliot JD, Canonico AE, Webber AJ. Treatment of Alcohol Withdrawal Syndrome: Phenobarbital vs CIWA-Ar Protocol. Am J Crit Care. 2018 Nov;27(6):454-460. doi: 10.4037/ajcc2018745. PMID: 30385536.

9. Hammond CJ, Niciu MJ, Drew S, Arias AJ. Anticonvulsants for the treatment of alcohol withdrawal syndrome and alcohol use disorders. CNS Drugs. 2015 Apr;29(4):293-311. doi: 10.1007/s40263-015-0240-4. PMID: 25895020; PMCID: PMC5759952.

10. Sachdeva A, Choudhary M, Chandra M. Alcohol Withdrawal Syndrome: Benzodiazepines and Beyond. J Clin Diagn Res. 2015 Sep;9(9):VE01-VE07. doi: 10.7860/JCDR/2015/13407.6538. Epub 2015 Sep 1. PMID: 26500991; PMCID: PMC4606320.

11. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014 May 14;311(18):1889-900. doi: 10.1001/jama.2014.3628. PMID: 24825644.

References

12. Kim Y, Hack LM, Ahn ES, Kim J. Practical outpatient pharmacotherapy for alcohol use disorder. Drugs Context. 2018 Feb 7;7:212308. doi: 10.7573/dic.212308. PMID: 29445407; PMCID: PMC5804871.

13. Bouza C, Angeles M, Muñoz A, Amate JM. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. Addiction. 2004 Jul;99(7):811-28. doi: 10.1111/j.1360-0443.2004.00763.x. Erratum in: Addiction. 2005 Apr;100(4):573. Magro, Angeles [corrected to Angeles, Magro]. PMID: 15200577.

14. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift R, Weiss RD, Williams LD, Zweben A; COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006 May 3;295(17):2003-17. doi: 10.1001/jama.295.17.2003. PMID: 16670409.

15. Kranzler HR, Wesson DR, Billot L; DrugAbuse Sciences Naltrexone Depot Study Group. Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. Alcohol Clin Exp Res. 2004 Jul;28(7):1051-9. doi: 10.1097/01.alc.0000130804.08397.29. PMID: 15252291.

16. Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, Loewy JW, Ehrich EW; Vivitrex Study Group. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. JAMA. 2005 Apr 6;293(13):1617-25. doi: 10.1001/jama.293.13.1617. Erratum in: JAMA. 2005 Apr 27;293(16):1978. Erratum in: JAMA. 2005 Jun 15:293(23):2864. PMID: 15811981.