# Medication Assisted Treatment for Alcohol Use Disorders

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American College of Physicians
New Mexico Chapter Scientific Meeting
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# Objectives

- Define Alcohol Use Disorders (AUDs)
- Describe the pathogenesis and prevalence of AUDs
- Review the FDA approved medications for the treatment of AUDs
- Summarize other non-FDA approved medications for the treatment of AUDs
- Present a case study on increasing the treatment of alcohol use disorder in the inpatient setting

# Definition of Alcohol Use Disorders (AUDs)

**DSM-5 diagnostic criteria for alcohol use disorder:**

- Recurrent drinking resulting in failure to fulfill role obligations
- Recurrent drinking in hazardous situations
- Continued drinking despite alcohol-related social or interpersonal problems
- Evidence of tolerance
- Evidence of alcohol withdrawal or use of alcohol for relief or avoidance of withdrawal
- Drinking in larger amounts or over longer periods than intended
- Persistent desire or unsuccessful attempts to stop or reduce drinking
- Great deal of time spent obtaining, using, or recovering from alcohol
- Important activities given up or reduced because of drinking
- Continued drinking despite knowledge of physical or psychological problems caused by alcohol
- Alcohol craving

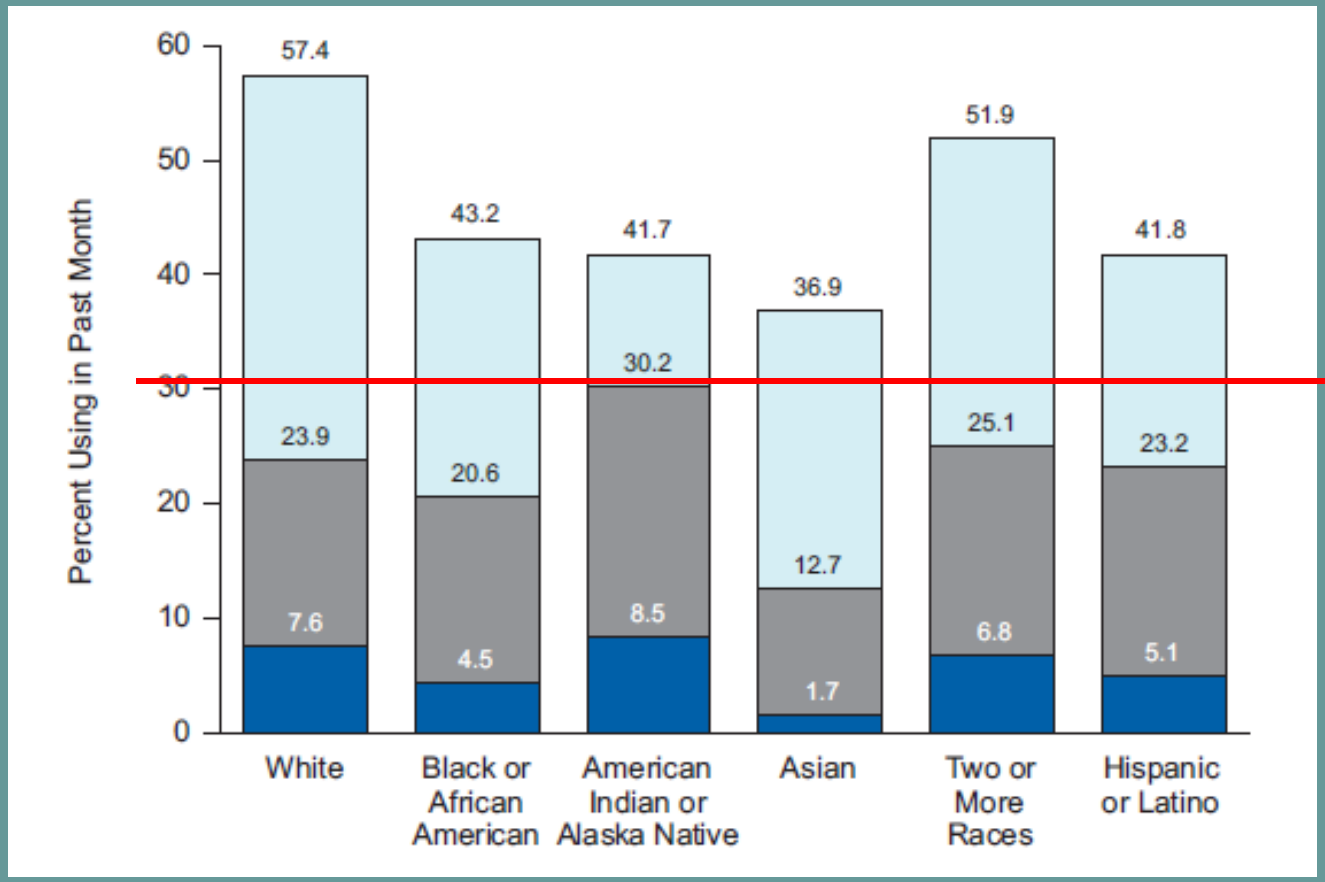
**Disorder severity:**

- Mild: 2-3 symptoms
- Moderate: 4-5 symptoms
- Severe: 6 or more symptoms

# Pathogenesis

- Theories of why some drinkers develop an AUD
  - Positive-affect regulation
  - Negative-affect regulation
  - Pharmacologic vulnerability
- Development of alcohol use disorder is a complex interplay of:
  - Environmental influences
    - family/peer influences, prenatal exposures
  - Personality traits
    - neuroticism, impulsivity, extroversion
  - Genetics (responsible for ~50% of vulnerabilities related to AUDs)
    - Responsiveness to alcohol, personality characteristics, GABA, dopamine, opioid receptors

# Current, Binge, and Heavy Alcohol Use among Persons Aged 12 or Older, by Race/Ethnicity: 2013




**Current**: Any drinks in past 30 days

**Binge**: 5 or more drinks on one occasion

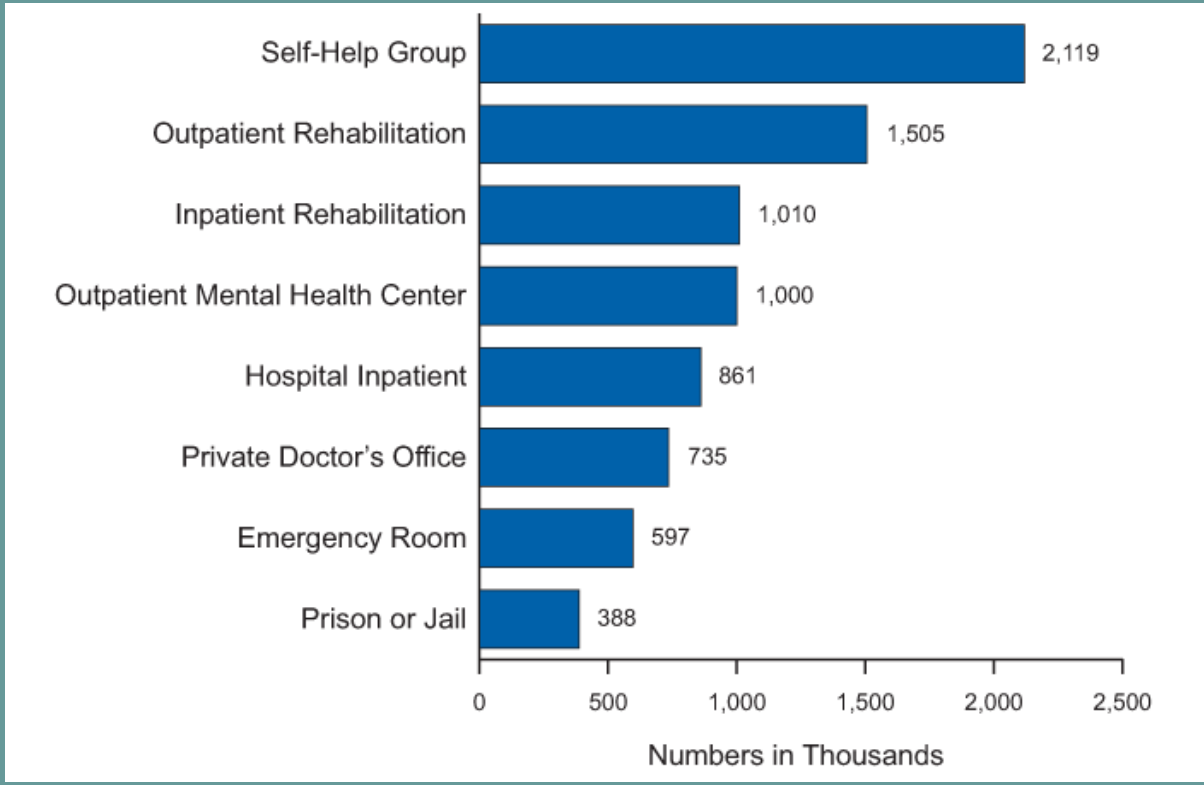
**Heavy**: 5 or more drinks on 5 or more days

National Survey on Drug Use and Health: Summary of National Findings, 2013. Substance Abuse and Mental Health Services Administration

# Treatment for alcohol use disorders

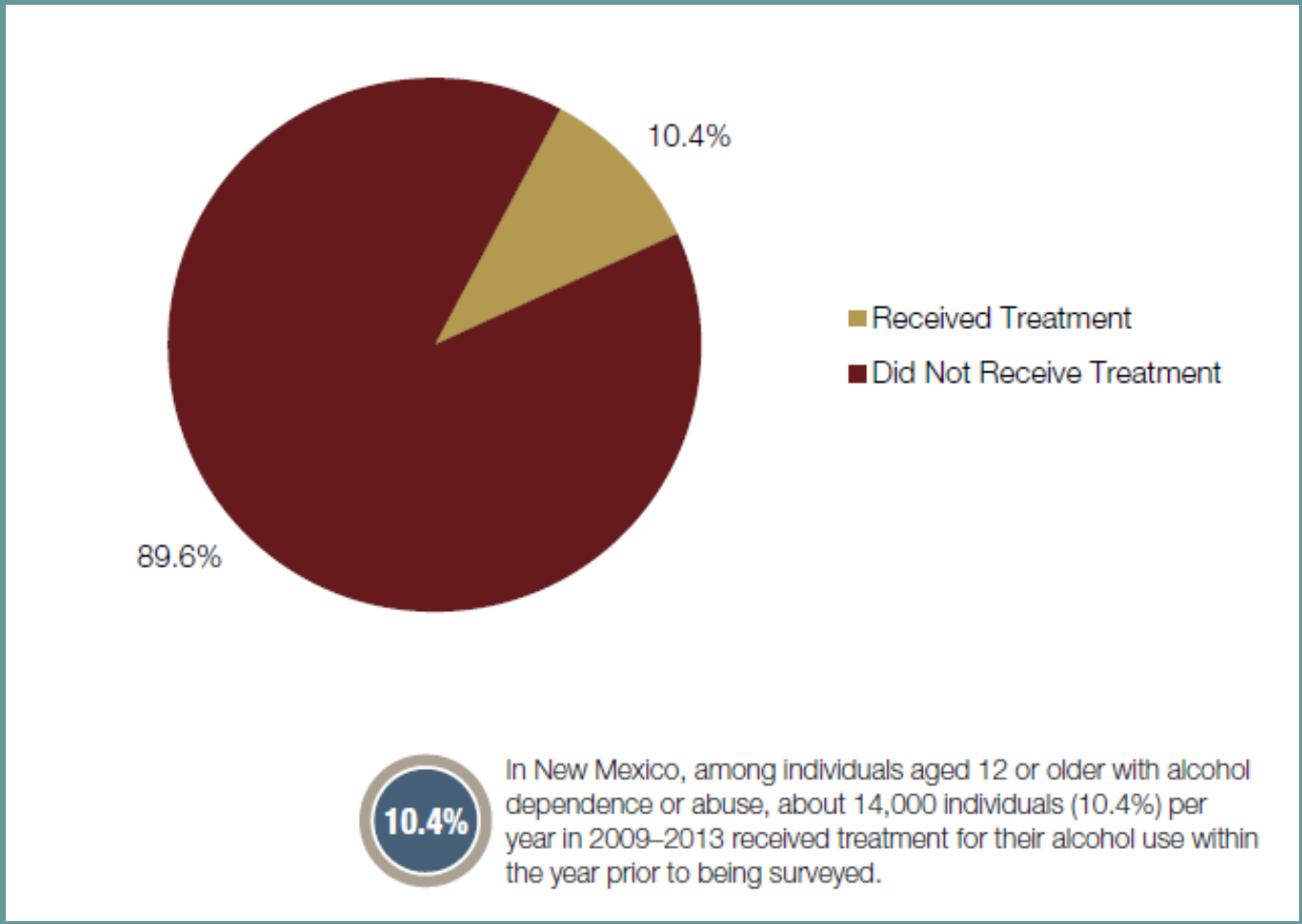
- Of those with an alcohol use disorder, 13.5% (2.4 million/17.8 million) of patients received treatment

Locations where alcohol treatment was received in 2013




National Survey on Drug Use and Health: Summary of National Findings, 2009-2013. Substance Abuse and Mental Health Services Administration.

# Past-Year Alcohol Use Treatment in New Mexico (2009-2013)




National Survey on Drug Use and Health: Summary of National Findings, 2009-2013. Substance Abuse and Mental Health Services Administration.

# Provider Attitudes around Pharmacotherapy

- VA Healthcare System of 194,000 veterans with alcohol use disorder
  - 1.9% were prescribed pharmacotherapy
- Survey of 1388 US physicians on pattern of prescribing
  - 3-13% of physicians use pharmacotherapy for treatment of alcohol dependence
  - Seen in general practitioners, internal medicine physicians, family physicians, VA physicians, and addiction psychiatrists
  - Lack of awareness of medications, lack of knowledge about efficacy, lack of time, and lack of reimbursement sited as main reasons for low use

Petrakis, I. L., Leslie, D., & Rosenheck, R. (2003). Use of naltrexone in the treatment of alcoholism nationally in the Department of Veterans Affairs. *Alcoholism: Clinical and Experimental Research, 27,* 1780–1784.
Mark, T. L., Kranzler, H. R., & Song, X. (2003b). Understanding U.S. addiction physicians' low rate of naltrexone prescription. *Drug and Alcohol Dependency, 71*(3), 219–228.

# Patient Attitudes around Pharmacotherapy

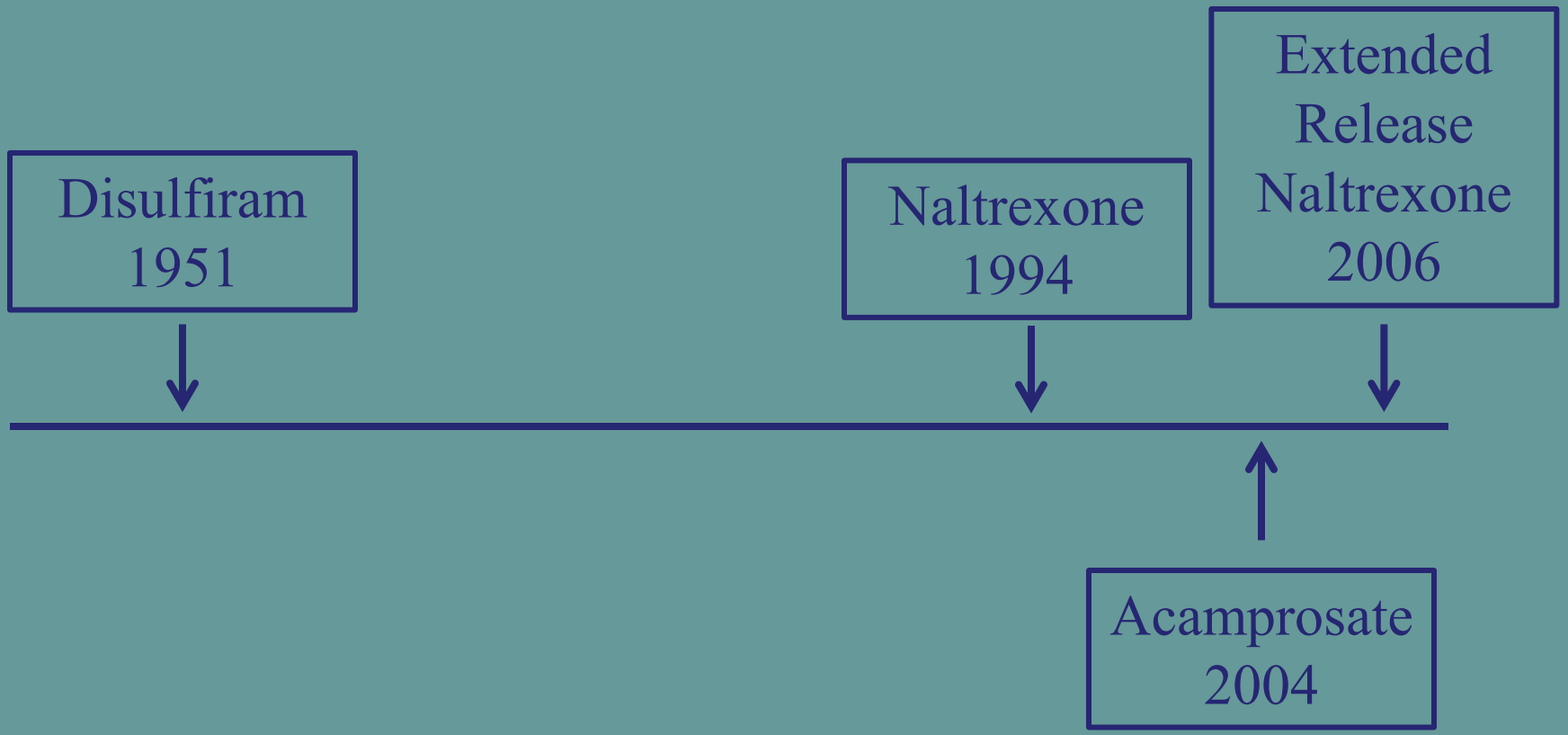
- Survey of hospitalized patients on an internal medicine service in a university public hospital
  - 84% agreed that they needed to stop drinking
  - 66% agreed that they would like to receive an effective medication to help prevent drinking

Stewart, S. H., & Connors, G. J. (2007). Interest in pharmacotherapy and primary care alcoholism treatment among medically hospitalized, alcohol dependent patients. *Journal of Addictive Diseases, 26*(2), 63–69.

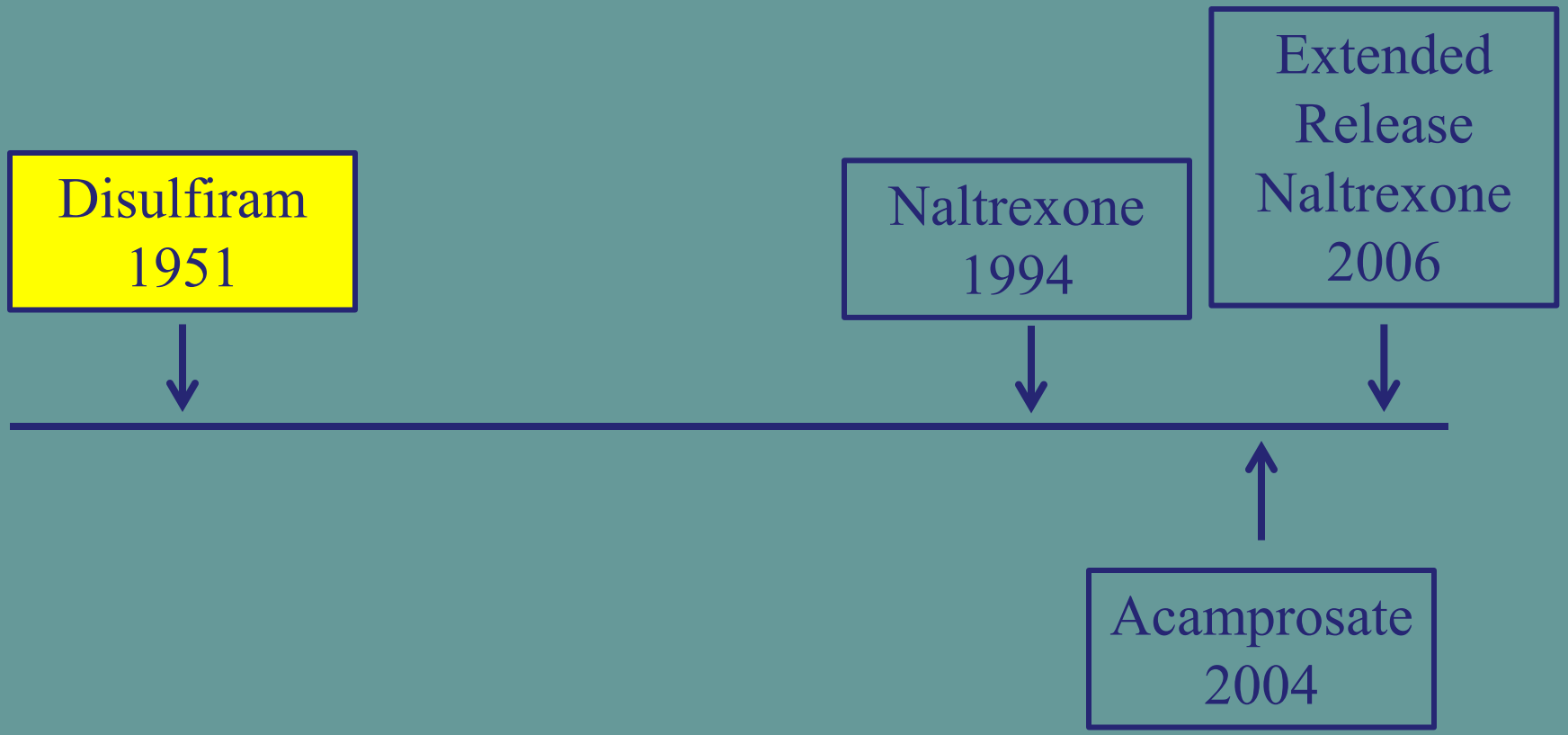
# Wouldn’t it be great if there was something that could help…

- Lengthen periods of abstinence
- Prevent a lapse from becoming a full-blown relapse
- Relieve symptoms of protracted withdrawal
- Allow brain cells to readapt to a normal nonalcoholic state, helping patients stabilize, think more clearly, strengthen coping mechanisms, and increase motivational readiness for change
- Support the effects of psychosocial treatment and sustain the gains of intervention

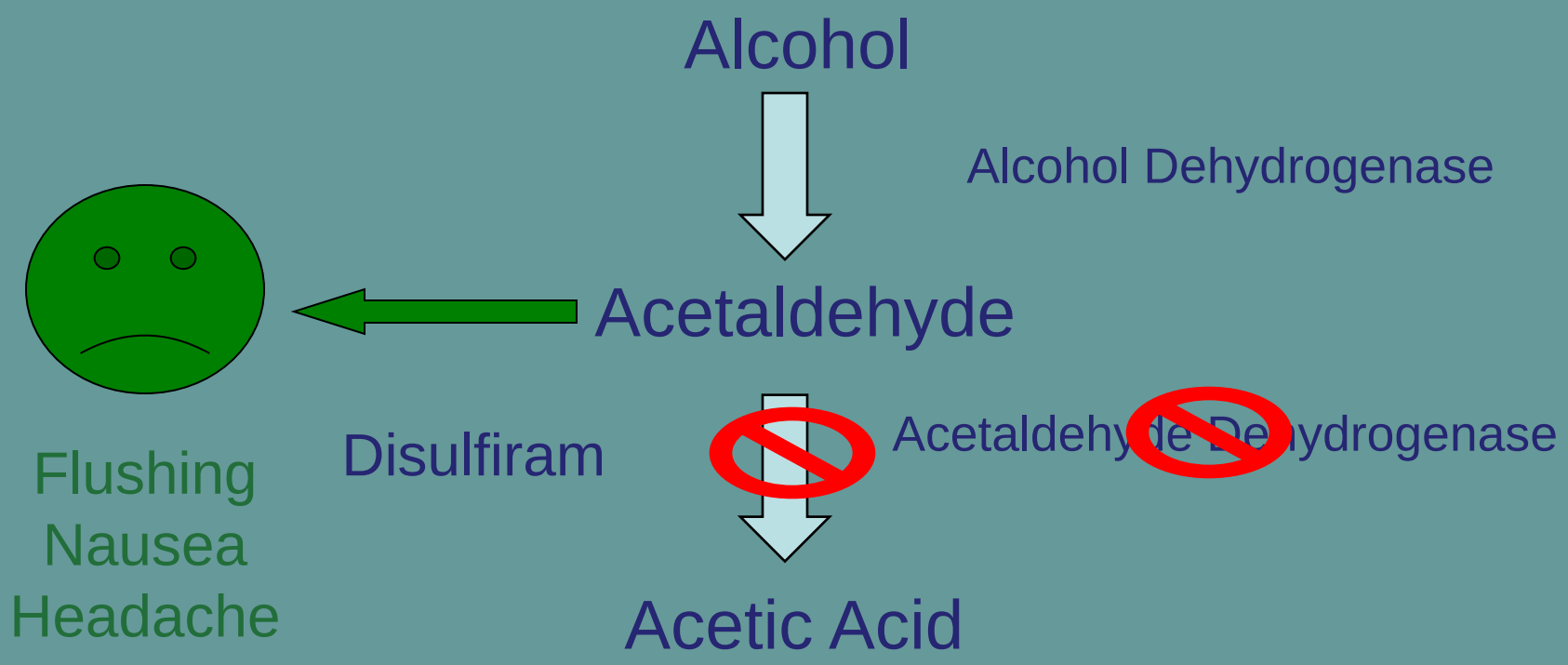
# FDA Approved Medications for the Treatment of Alcohol Dependence



# FDA Approved Medications for the Treatment of Alcohol Dependence



# Disulfiram: Mechanism of Action



# Disulfiram: Evidence

- Review of all 18 RCTs with disulfiram under direct supervision
  - 17 of 18 showed improved abstinence, treatment retention and/or proportion of days of alcohol consumption
- Most comprehensive review of literature covering 1937-2005 concluded that supervised disulfiram is effective treatment for alcohol dependence
  - Disulfiram similar to placebo when not under close supervision

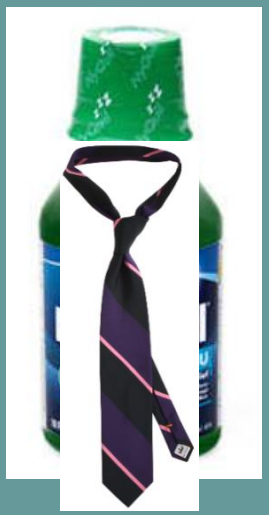
Brewer, C., Meyers, R. J., & Johnsen, J. (2000). Does disulfiram help to prevent relapse in alcohol abuse? *CNS Drugs, 14*(5), 329–341.
Suh, J. J., Pettinati, H. M., Kampman, K. M., & O'Brien, C. P. (2006). The status of disulfiram: A half of a century later. *Journal of Clinical Psychopharmacology, 26*(3),290–302.

# When to Use Disulfiram?

- Use in motivated patients with good supervision to increase adherence (court ordered, inpatient rehab, strong support system)
- Use as adjunct to other medications
- Use to support abstinence if attending events that involve alcohol (ie weddings, holidays)
- May not be a viable option in primary care settings given limited ongoing supervision
- Contraindications: Cardiovascular or cerebrovascular disease
- Monitoring: Baseline LFTs, q1-3 month monitoring

# Disulfiram: Patient Information

- Take 250mg/day, if no effect with alcohol, can increase to 500mg/day
- Avoid alcohol at least 12 hours prior to initiation and at least 2 weeks after last dose
- Avoid disguised forms of alcohol
- Mild side effects: headache, fatigue, allergic dermatitis
- Rare but serious side effects: neuropathy, hepatitis, severe disulfiram reactions



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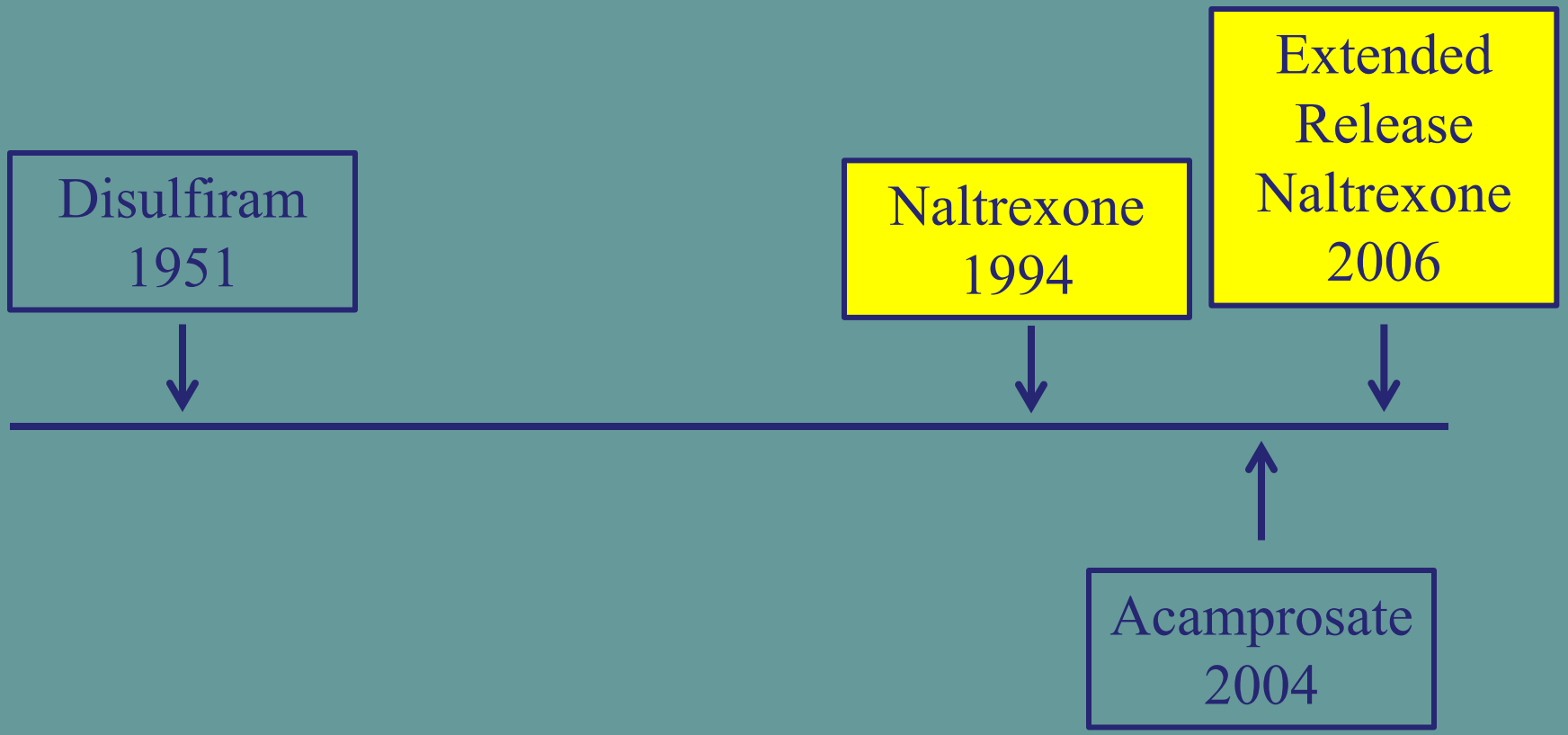
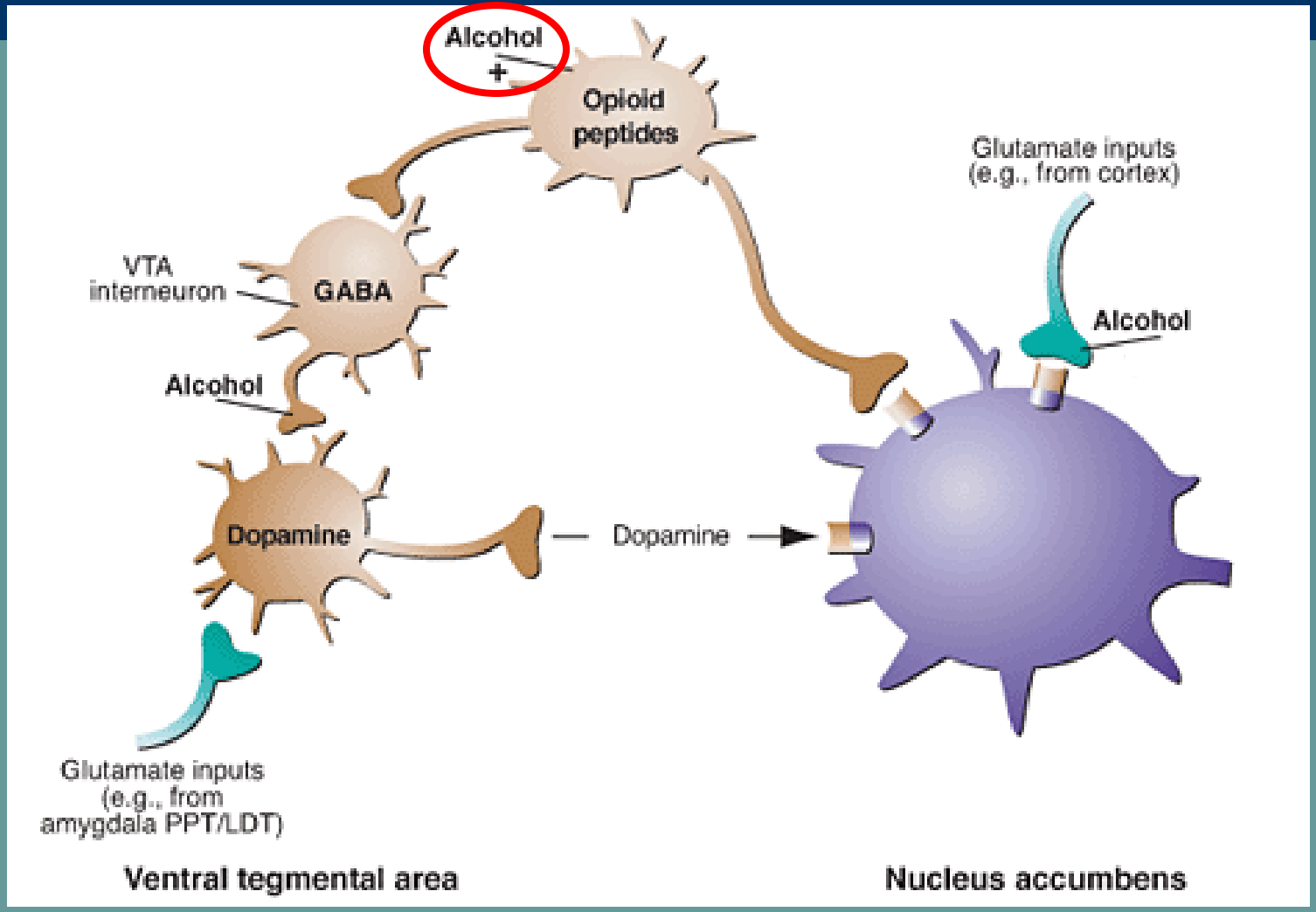


# Naltrexone: Mechanism of Action



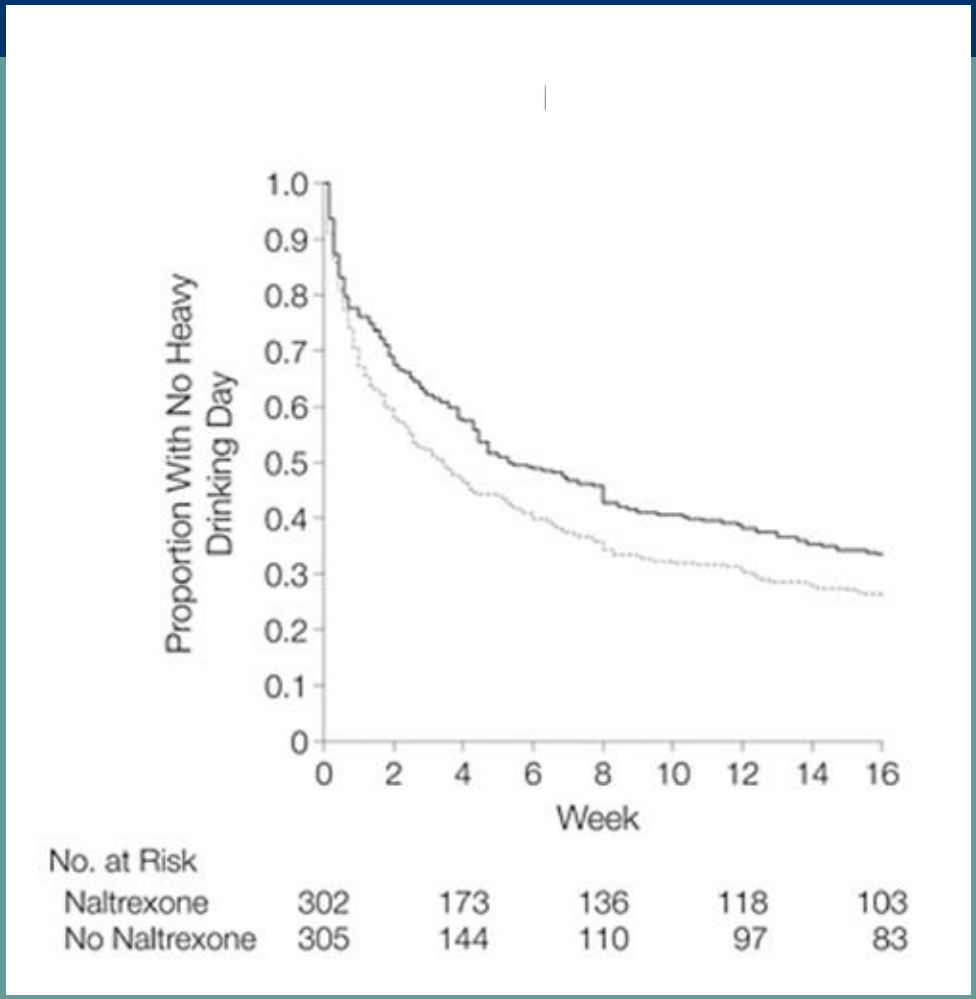

Nicholas, W. Neurobiology of Alcohol Dependence. NIAAA 2007.

# Naltrexone: Evidence Timeline

- 1992: First two randomized control trials confirming efficacy in reducing frequency and severity of relapse to drinking
- 1994: FDA approved for the treatment of alcohol dependence
- 1998: Treatment Improvement Protocol published on the use of naltrexone in alcohol dependence by Health and Human Services
- 2006: Multi-center COMBINE study has proven usefulness of naltrexone in the primary care setting (JAMA)
  - Largest RCT to date, 11 academic sites in the US, N=1383
  - All received sessions with primary care provider: Initial 45 minute session, then 15 minutes sessions q2-4 weeks
  - Randomized to:
    - Naltrexone or Placebo group
    - With or without combined behavioral intervention = Twenty 50 minute sessions with behavioral health specialist

Anton, R. F., O'Malley, S. S., et al., COMBINE Study Research Group. (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study, A randomized controlled trial. *JAMA, 295*(17), 2003–2017.

# Rate of No Heavy Drinking

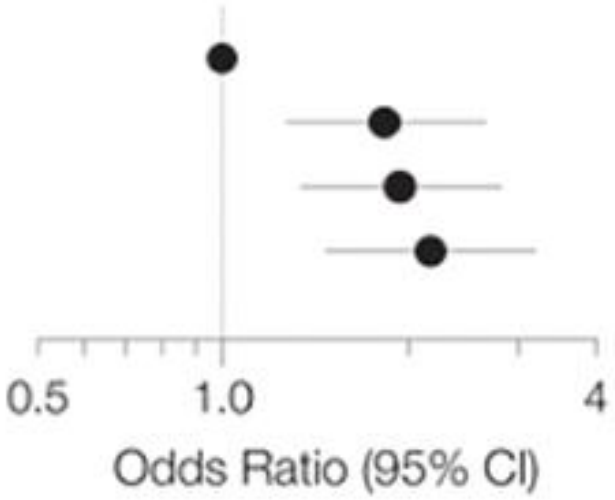



Anton RF. Combined pharmacotherapy and behavioral interventions for alcohol dependence: the COMBINE study. JAMA 2006; 295:2003-17.

# Odds Ratios for Good Composite Clinical Outcome at End of Treatment

"Good clinical outcome" :
Abstinence or moderate drinking without problems
(Women: <11d/wk and <3d/day, Men: <14d/wk or <4d/day)

| 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 RF. Combined pharmacotherapy and behavioral interventions for alcohol dependence: the COMBINE study. JAMA 2006; 295:2003-17.

# Naltrexone: Evidence Timeline (continued)

- 2008: Review of Naltrexone for the Management of Alcohol Dependence (NEJM)
- 2008: Cochrane Review published which evaluated 27 randomized control trials from 1992-2001 in N. America, Europe, Asia, Australia, N = 3048
  - Short term (16 week) treatment of naltrexone decreased the chance of alcohol relapses by 36% (NNT = 7). NTX can lower the risk of withdrawal in alcohol dependent patients by 28% (NNT = 13)
  - Treatment up to 1 year gave no benefit for relapse prevention, but decreased overall alcohol consumption and diminished cravings

# Number Needed to Treat (NNT) for Common Medical Problems


Dickerson, L. Prevention of Recurrent Ischemic Stroke. Am Fam Physician. 2007 Aug 1;76(3):382-388.

Sanmagunathan, P. Aspirin for primary prevention of coronary heart disease. Heart. 2001 Mar; 85(3): 265-271.

Wang, W. Effects of proton-pump inhibitors on functional dyspepsia. Clin Gastroenterol Hepatol. 2007 Feb; 5(2): 178-85.

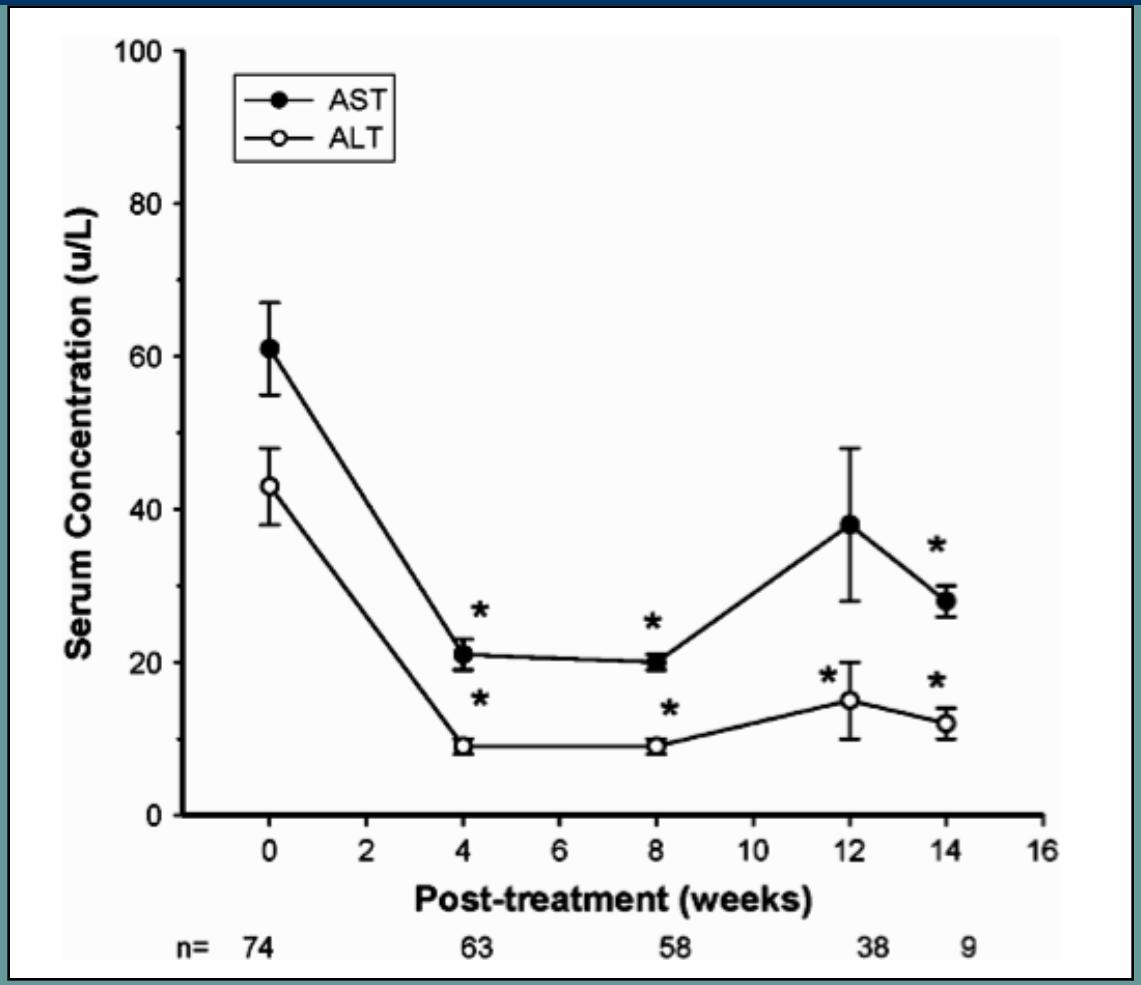
Cochrane Briefs: Effectiveness of Antidepressants Compared with Placebo for Depression in Primary Care. Am Fam Physician. 2010 Jul 1: 81(1).

# When to Use Naltrexone?

- First line treatment (unless severe liver disease or opioid use)
- Decreases cravings, enhances ability to abstain from drinking, reduces heaving drinking
- Contraindications: severe liver disease (AST, ALT or GGT > 6xULN), acute or chronic opioid use
- Monitoring: baseline LFTs, then q1-3months (Black Box Warning for hepatocellular injury at doses >300mg/day)

# Liver Safety of Naltrexone

- 74 alcohol dependent patients given 50mg/day for 12 weeks




Yen, M.H., et al. Study of hepatotoxicity of naltrexone in the treatment of alcoholism. 2006; 38:117-120.

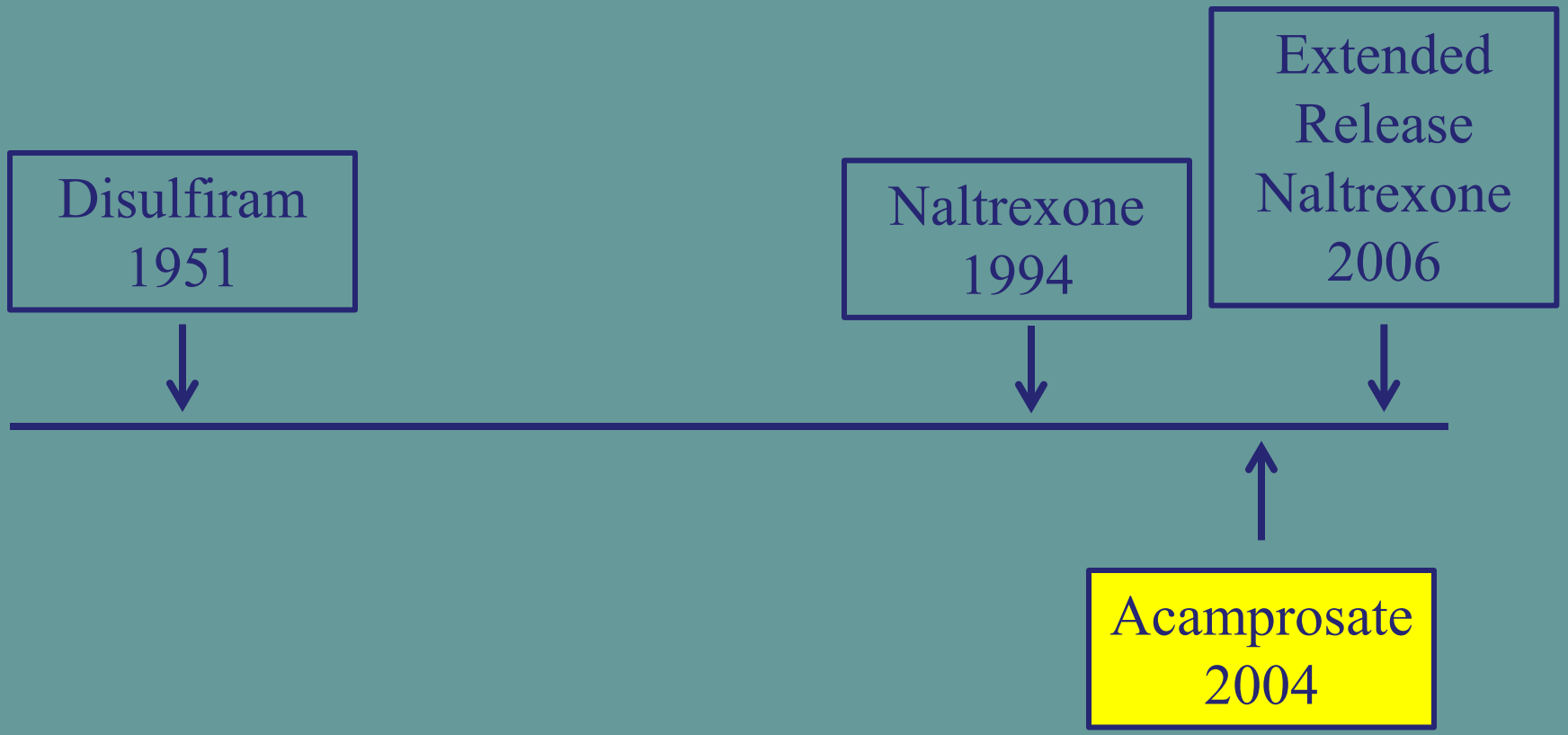
# Naltrexone: Patient Information

- Take 25mg per day for 1 week, then 50mg daily
- Best to abstain from alcohol for 3 days, but safe to use in supervised withdrawal or concomitant alcohol use
- Mild side effects: headache, nausea
- Severe side effects:  None at recommended doses

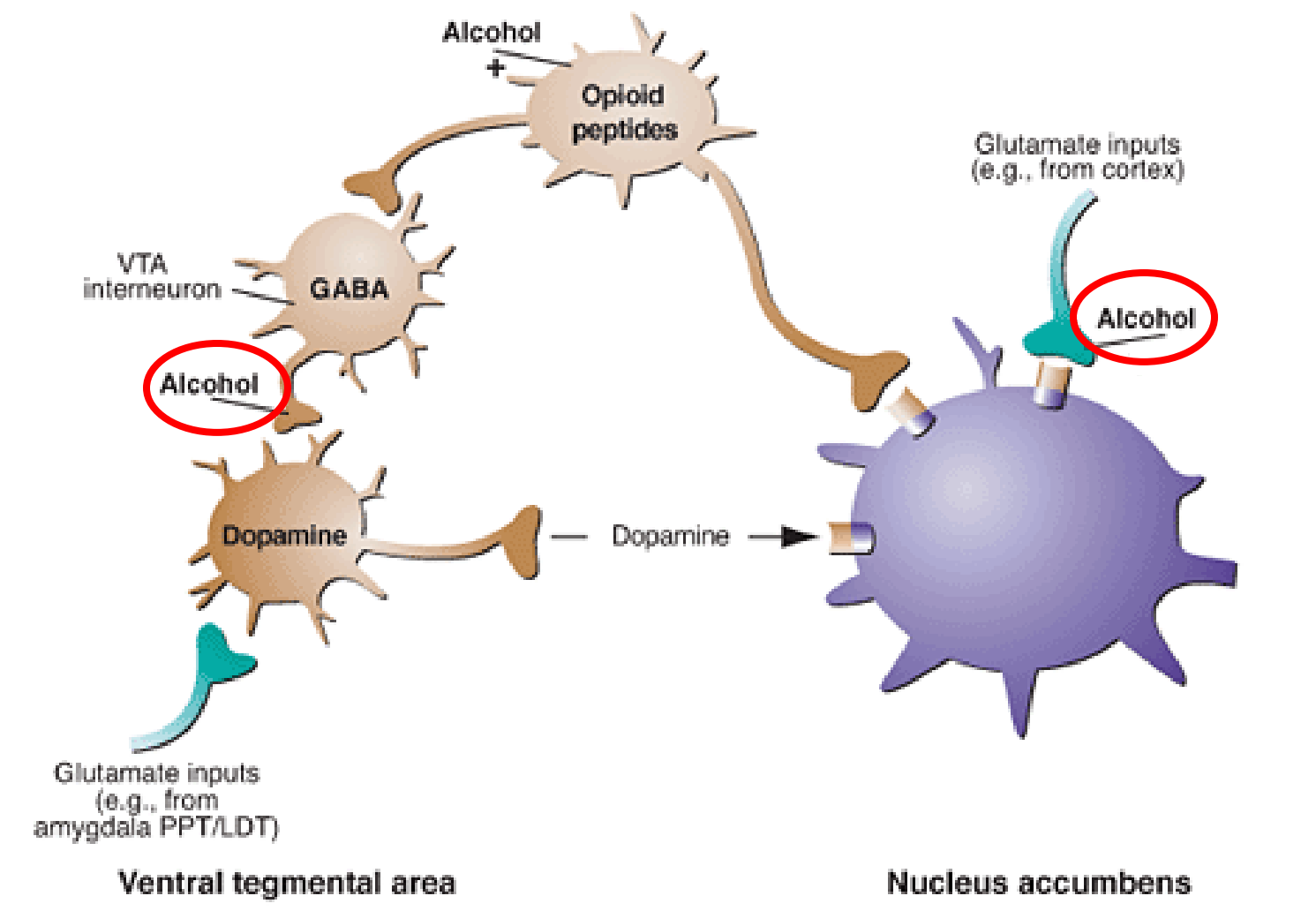
# Extended Release Naltrexone

- 380mg IM injection every 4 weeks
- Does not go through first pass liver metabolism
- Indicated for patients who have not responded to other treatments, in particular those who have trouble with adherence (ie poor memory, mental illness)
- RCTs show effectiveness in decreasing heavy drinking
  - No definitive head to head trials between oral and extended release naltrexone
- Cost prohibitive

# FDA Approved Medications for the Treatment of Alcohol Dependence



# Acamprosate: Mechanism of Action




Nicholas, W. Neurobiology of Alcohol Dependence. NIAAA 2007.

# Acamprosate: Evidence

- 17 RCTs in 12 countries with 5000 patients measuring 3 months to over a year
  - 14 of 17 showed increased abstinence, time to first drink and decreased LFT levels
  - Combined abstinence rate at the end of treatment was 35% in acamprosate versus 21% in placebo groups
  - Of 3 studies that failed, only 2 month treatment period was used
- Large US RCT COMBINE in 2006 did not show evidence of efficacy for acamprosate
  - Outcomes only measured for 4 months

# When to Use Acamprosate?

- First line treatment if there is a contraindication to naltrexone, second line if partial or no response to naltrexone
- Indicated to reduce drinking days, increase complete abstinence and time to relapse
- Safe in liver disease, no medication interactions, no abuse potential
- Contraindications: CrCl <30, suicidality (1.4% vs 0.5% suicidal ideation, no difference in completion 0.1% overall)
- Monitoring: Baseline renal function

# Acamprosate: Patient Information

- Take two 333mg tablets three times per day
- Best to abstain from alcohol for 3 days, but safe to use in supervised withdrawal or concomitant alcohol use
- Continue taking medication if a slip or relapse occurs
- Mild side effects: diarrhea
- Rare but serious side effects: suicidality

# Other drugs for the treatment of Alcohol Use Disorders
## (Non-FDA Approved)

- Topiramate:
  - Mechanism: Glutamate antagonist and GABA inhibitor
  - Efficacy: Meta-analysis (JAMA 2014) showed decreased alcohol consumption compared to placebo
  - Dose: 50mg daily -150mg BID
- Gabapentin
  - Mechanism: GABA regulation
  - Efficacy: Insufficient sample size to assert efficacy, some concern for abuse potential in patients with a SUD
  - Dose: 900-1800mg/day

Jonas DE. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014 May;311(18):1889-900.

# Other drugs for the treatment of Alcohol Use Disorders
(Non-FDA Approved)

- Baclofen
  - Mechanism: GABA regulation
  - Efficacy: mixed results
  - Dose: 30mg/day
- SSRI
  - Mechanism: Serotonin regulation
  - Efficacy: May only be effective in treating alcohol dependence in patients who have comorbid mental health disorders
- Ondansetron
  - Mechanism: Serotonin regulation
  - Efficacy: May be selectively effective in patients with early onset subtype of alcohol dependence or those with a specific genetic variant of the serotonin transporter (5-HTT) gene.

# Medication and Psychosocial Treatment

- Review of clinical trials on interactions of pharmacotherapy and psychosocial treatment
  - Adding medication to psychosocial therapy improves outcomes
  - Interventions ranging from brief medical management to intensive psychotherapy have all been show to be produce positive outcomes

Weiss, R. D., & Kueppenbender, K. D. (2006). Combining psychosocial treatment with pharmacotherapy for alcohol dependence. *Journal of Clinical Psychopharmacology, 26*(Suppl 1), S37–S42.

# Summary of Medically Assisted Treatment for Alcohol Dependence

- Naltrexone
  - First line therapy (unless severe liver disease or opioid use)
- Acamprosate
  - First line if contraindication to naltrexone
  - Second line if partial or no response to other meds
- Disulfiram
  - Must be motivated with close supervision
  - Use as adjunct therapy to other meds
  - Use to support abstinence if attending events that involve alcohol

# An Inpatient Treatment and Discharge Planning Protocol for Alcohol Dependence

Wei, J. Defries, T. et al. J Gen Intern Med, Mar 2015.

San Francisco General Hospital
Discharge Planning and Information Sheet
For Patients with Alcohol Dependence

1. Patient Name:

*Question A: Does the patient have moderate to severe liver damage as evidence by AST/ALT >150, or INR >2?*

☐ NO ☐ YES

*Question B: Is the patient dependent on opioids (including Methadone) OR has he/she used short acting opioids (ie oxycodone, hydromorphone, hydrocodone) within the past 3 days?*

☐ NO ☐ YES

**□ Patient IS a candidate for naltrexone: (check all that apply)**

- □ Patient started on naltrexone as an inpatient
- □ Outpatient prescription given for naltrexone
- □ Prescription NOT given for naltrexone because _____

□ An appointment was made with the Treatment Access Program (415 503 4730) for follow up and/or refills on naltrexone

**□ Patient is NOT a candidate for naltrexone**

□ Referred to Treatment Access Program (TAP) and/or appointment given for Treatment Access Program (TAP)

□ Primary care provider was updated regarding inpatient discussion around treatment of alcohol dependence

□ An appointment was made with the Treatment Access Program (415 503 4730) for follow up and/or refills on naltrexone

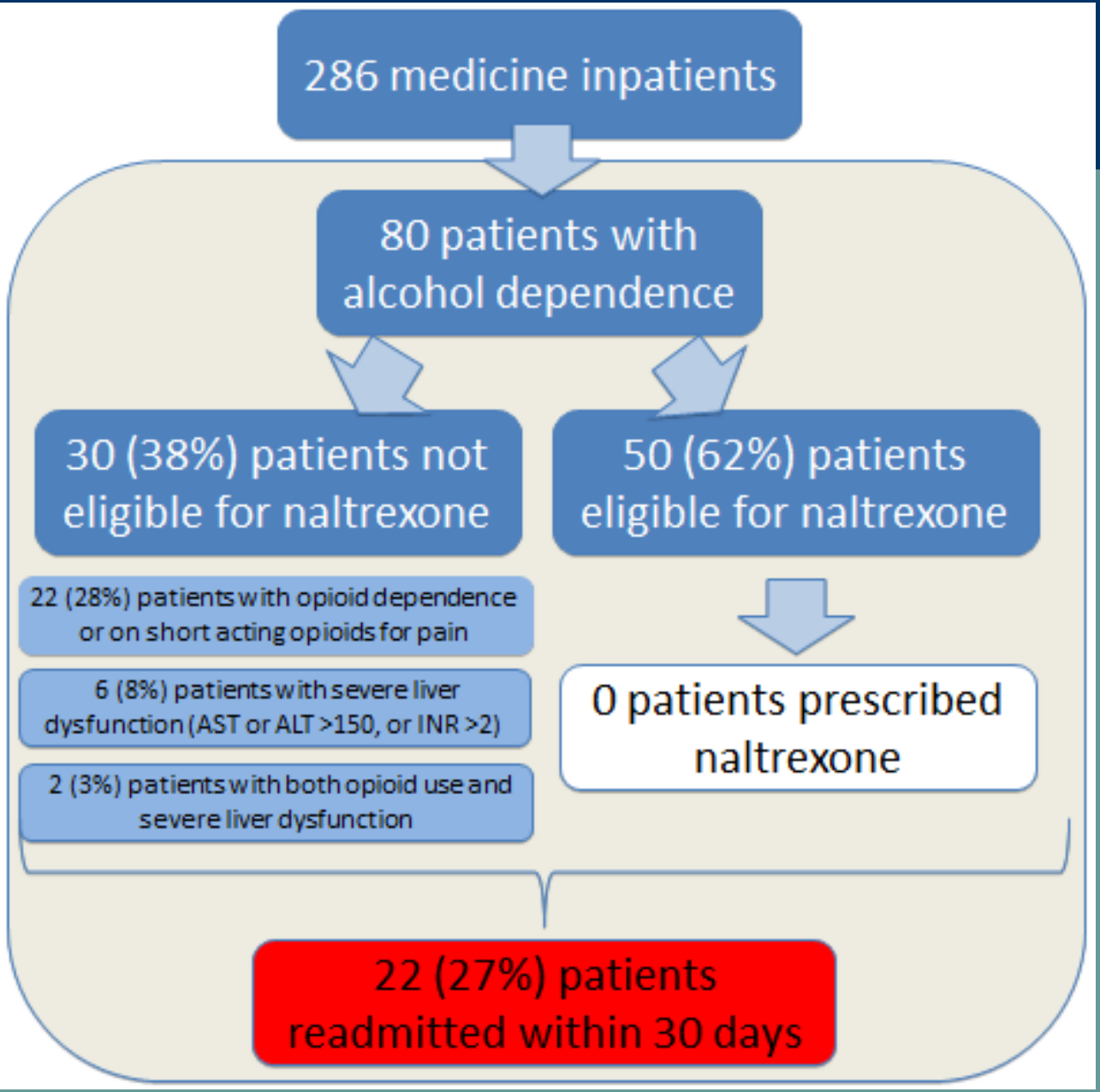
# Results

**Pre Intervention**

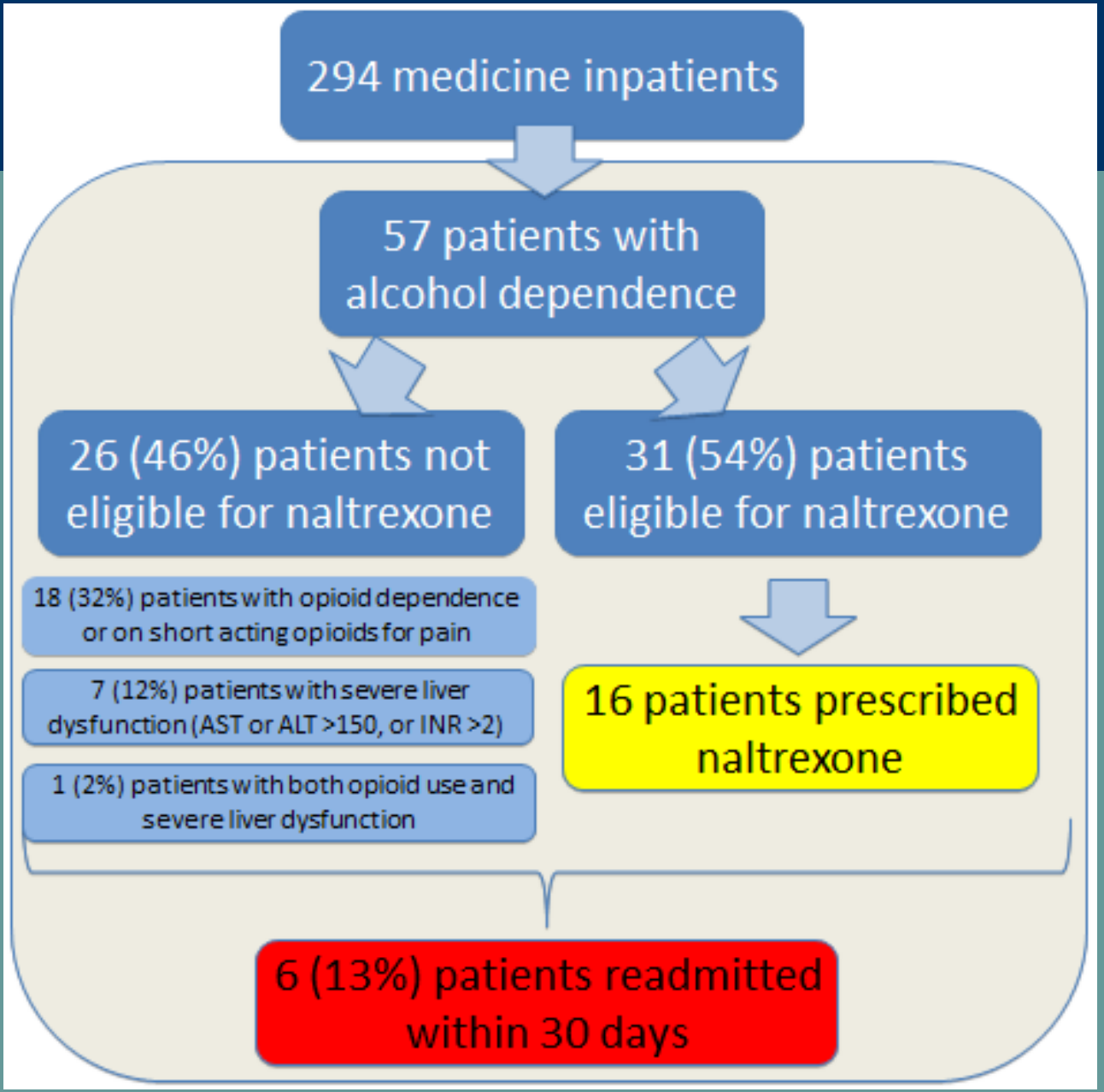
**June 2011**

**Chart Review**

**Pre Intervention**
**June 2011**
**Chart Review**



**Post Intervention March 2012 Chart Review**



# Lessons Learned

- Over 50% of SFGH patients are eligible for naltrexone:
  - Contraindicated in opioid use (~30%) and severe liver dysfunction (~10%)
- Through the use of a discharge planning tool:
  - Rates of prescription for naltrexone increased from 0% to 52%.
  - 30 day readmission rates decreased from 27% to 13%.
- With a discharge planning tool, residents are able to screen for alcohol dependence, assess naltrexone eligibility, prescribe medication and refer for outpatient management during an inpatient hospitalization

*“He's been sober since his hospitalization with you guys. He looks great and is feeling well and is very happy about being sober. It's still a day at a time process for him to stay sober, but having you guys care so much made an impact on him. Sometimes it feels like we're fighting an uphill battle taking care of alcohol withdrawal patients, so I wanted to make sure you know that the extra effort you took in caring for him seems to have paid off.”*

- UCSF Internal Medicine R3