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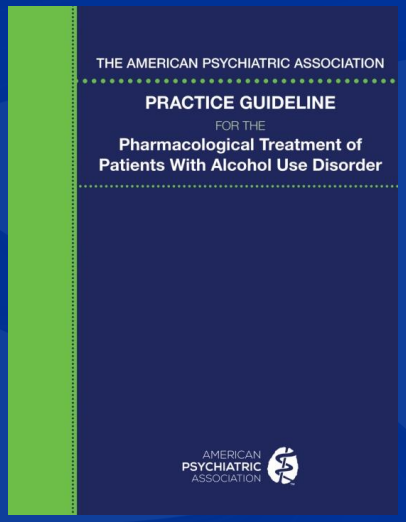
Medical leadership for mind, brain and body.

APA PRACTICE GUIDELINE FOR THE PHARMACOLOGICAL TREATMENT OF PATIENTS WITH ALCOHOL USE DISORDER

December 2017



RATIONALE FOR CHOICE OF TOPIC

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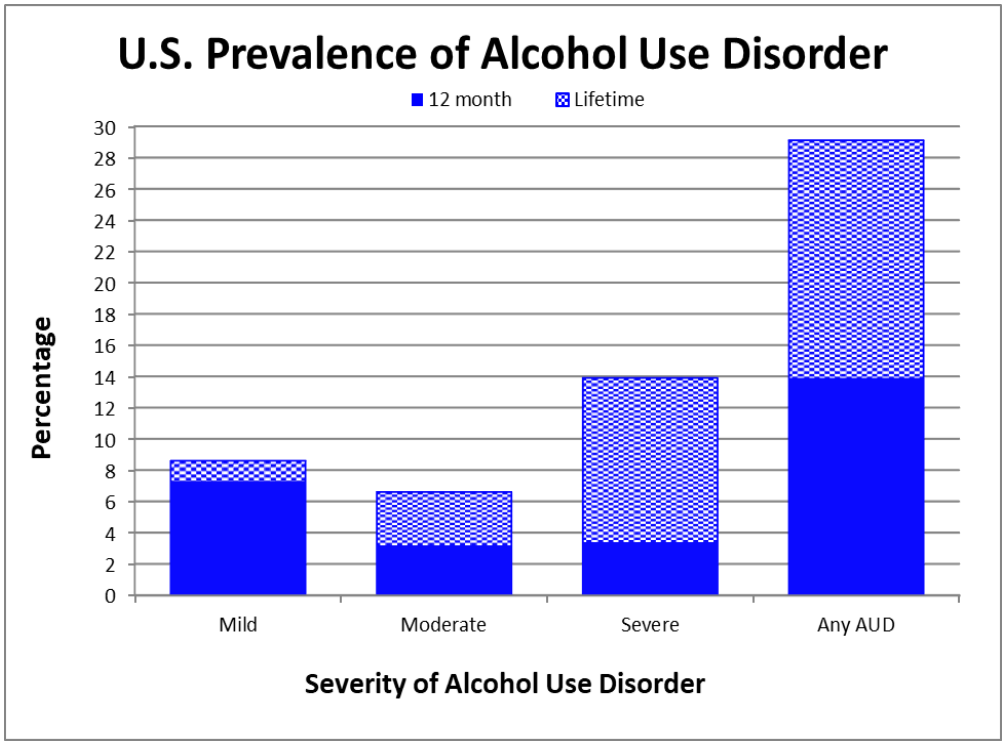
Prevalence:

- Worldwide (Slade et al., 2016)
  - Lifetime 20%
  - 12 month 8.5%
- U.S. (Grant et al. 2015, 2017)
  - Lifetime 29%, with severe alcohol use disorder (AUD) in about half
  - 12 month 13.9 %
  - 12 month rates of AUD increased by ~50% between 2001-2002 and 2012-2013



Based on data from Grant et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry. 2015 Aug;72(8):757-66.

RATIONALE FOR CHOICE OF TOPIC

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AUD affects individuals of all demographic groups (Grant et al. 2015)

- Onset: 18-29 years
- Ethnicity (12 month prevalence):
  - American Indian/Alaska Native 19.2%
  - African American 14.4%
  - White 14%
  - Hispanic 13.6%
  - Asian-American/Pacific Islander 10.6%
- Gender (12 month prevalence):
  - Men 17.6%
  - Women 10.4%

RATIONALE FOR CHOICE OF TOPIC

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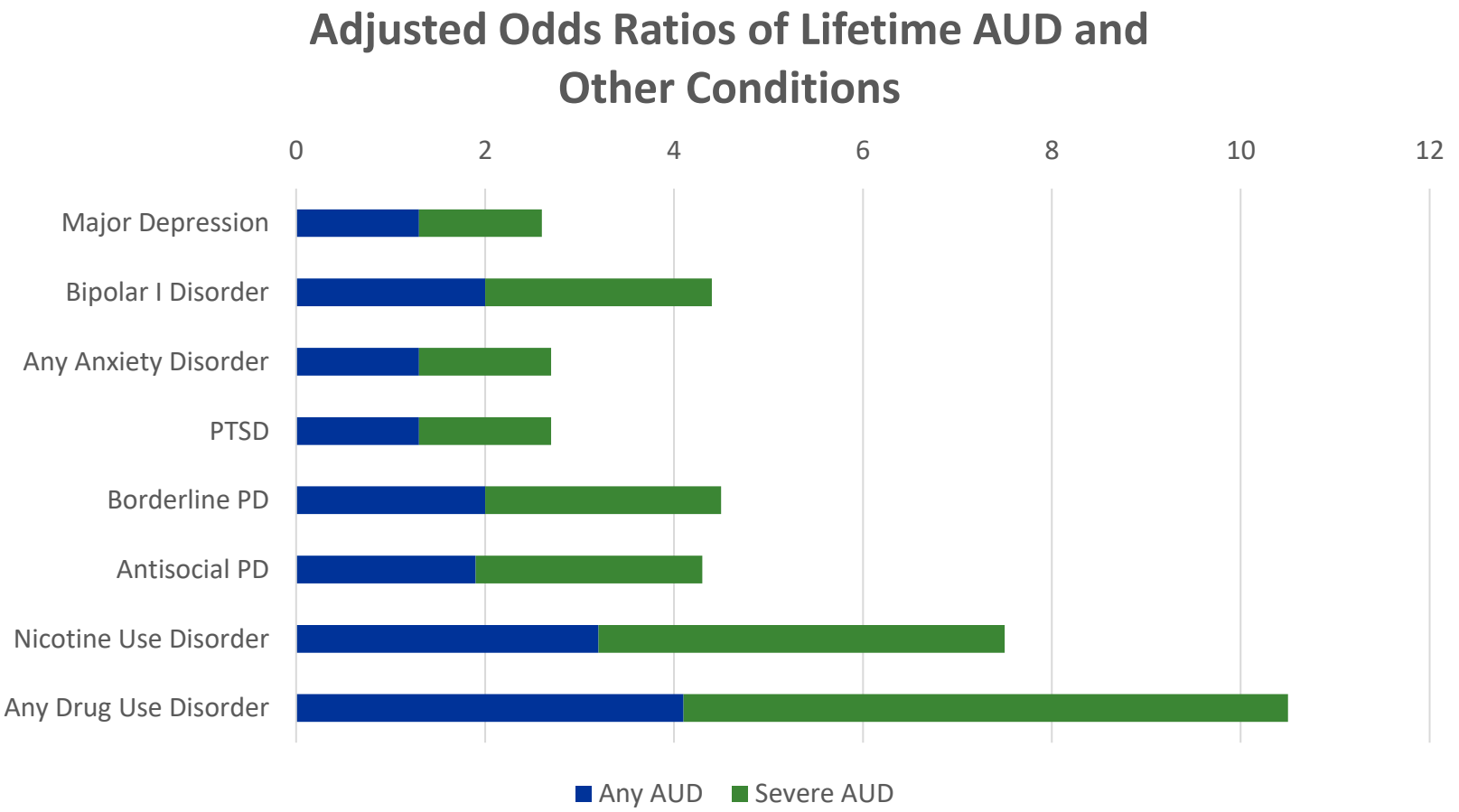
- US spends more than $223.5 billion annually treating AUD and sequelae (Bouchery et al., 2011)
- Globally, AUD associated with substantial burden with premature mortality, disability-adjusted life years, and years lived with disability
- AUD associated with motor vehicle accidents, poor academic performance, increased risk of suicide, increased criminal activity including intimate partner violence, increased risk for overdose death, and increased risk of HIV and other STDs
- AUD often co-occurs with other psychiatric disorders and treatment outcomes can be reduced for both

RATIONALE FOR CHOICE OF TOPIC



Based on data from Grant et al. *JAMA Psychiatry*. Aug;72(8): 757-66, 2015

RATIONALE FOR CHOICE OF TOPIC

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- AUD pharmacotherapy is a topic of increasing interest due to:
  - Burden of AUD in the population
  - Availability of U.S. Food and Drug Administration (FDA)–approved medications for this disorder.
- Despite high prevalence, societal cost, and available treatments, AUD remains undertreated.
  - <1 in 10 with a 12-month AUD diagnosis receive any treatment
  - Even fewer receive evidence-based treatment, e.g., 674,000 prescriptions for FDA approved psychopharmacological treatments were written in 2006 (Mark et al. 2009) vs. an estimated 11 million individuals with AUD (Hasin et al. 2007)
- Treatment received by patients varies based on geography, insurance coverage, and formulary restrictions.

GOAL OF GUIDELINE

- To improve the quality of care and treatment outcomes for patients with alcohol use disorder as defined by DSM-5

- Guidelines are:
  - Assessments of current scientific and clinical information
  - Not inclusive of all proper treatments
  - Not a comprehensive standard of care
  - Not accounting for individual variation
  - Not intended to replace independent clinical judgment

STEPS IN GUIDELINE DEVELOPMENT

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- Systematic review of available evidence (mostly by AHRQ for this guideline with a few additional specialized searches)
- Ratings of risk of bias (for individual studies) and strength of research evidence (overall for specific benefits/harms)
- Generate guideline statements (recommendations or suggestions) based upon the relative balance of benefits and harms of the assessment or intervention
- Modified Delphi approach to achieve group consensus
- External review by stakeholders
- Approval by APA Assembly and Board of Trustees

RATING THE STRENGTH OF RECOMMENDATION AND RESEARCH EVIDENCE

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Strength of recommendation describes the level of confidence that potential benefits of an intervention outweigh potential harms. This level of confidence is informed by available evidence, which includes evidence from clinical trials as well as expert opinion and patient values and preferences.

- A "recommendation" (denoted by the numeral 1 after the guideline statement) indicates confidence that the benefits of an intervention (including a specific assessment) clearly outweigh the harms. The statement would apply to the preponderance of patients and most patients would opt for such an intervention.
- A "suggestion" (denoted by the numeral 2 after the guideline statement) indicates that the benefits still appear to outweigh the harms but the balance of benefits and harms is less clear-cut and different options may be preferable for some patients.

RATING THE STRENGTH OF RECOMMENDATION AND RESEARCH EVIDENCE

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Strength of evidence describes the level of confidence that findings from scientific observation and testing of an intervention reflect a true effect.

- A = High confidence. Further research is very unlikely to change the estimate of effect.
- B = Moderate confidence. Further research may change the estimate of effect and our confidence in it.
- C= Low confidence. Further research is likely to change the estimate of effect and our confidence in it.

Strength of evidence is not the same as the magnitude of the effect as a result of the intervention.

ASSESSMENT & DETERMINATION OF TREATMENT GOALS – ASSESSMENT OF SUBSTANCE USE

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Statement 1: APA *recommends* (1C) that the initial psychiatric evaluation of a patient with suspected alcohol use disorder include assessment of current and past use of tobacco and alcohol as well as any misuse of other substances, including prescribed or over-the-counter medications or supplements.

- Rationale:
  - Establish baseline level and pattern of symptoms to assess later treatment response
  - Develop a treatment plan to reduce symptoms, morbidity, and mortality
- Implementation:
  - Obtain via face-to-face evaluation, review of medical records, and/or history (including from collateral informants)

ASSESSMENT (CONTINUED)

- AUD Symptoms:
  - ❑ Alcohol is often taken in larger amounts or over a longer period than was intended.
  - ❑ There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
  - ❑ A great deal of time is spent in activities to obtain alcohol, use alcohol, or recover from its use.
  - ❑ Craving, or a strong desire or urge to use alcohol.
  - ❑ Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
  - ❑ Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
  - ❑ Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
  - ❑ Recurrent alcohol use in situations in which it is physically hazardous.
  - ❑ Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
  - ❑ Tolerance, as defined by either of the following:
    - ❑A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
    - ❑A markedly diminished effect with continued use of the same amount of alcohol.
  - ❑ Withdrawal, as manifested by either of the following:
    - ❑The characteristic withdrawal syndrome for alcohol.
    - ❑Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relive or avoid withdrawal symptoms.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA, American Psychiatric Publishing, 2013

ASSESSMENT (CONTINUED)

- AUD Severity:
  - Mild: presence of two - three symptoms
  - Moderate: presence of four - five symptoms
  - Severe: presence of six or more symptoms

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA, American Psychiatric Publishing, 2013

ASSESSMENT - USE OF QUANTITATIVE BEHAVIORAL MEASURES

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Statement 2: APA *recommends* (1C) that the initial psychiatric evaluation of a patient with suspected alcohol use disorder include a quantitative behavioral measure to detect the presence of alcohol misuse and assess its severity.

- Rationale:
  - Establish baseline information on alcohol misuse and its severity
  - Help in tracking treatment effects
  - Improve consistency of information obtained
- Implementation:
  - Consider choosing a scale based on patient age, clinical setting, time available for administration, and therapeutic objective
  - Example measures: CAGE, CRAFT, AUDIT, AUDIT-C

ASSESSMENT - QUANTITATIVE BEHAVIORAL MEASURES (CONTINUED)

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- AUDIT-C Questionnaire
  1. How often do you have a drink containing alcohol?
     - [0] Never
     - [1] Monthly or less
     - [2] 2-4 times a month
     - [3] 2-3 times a week
     - [4] 4 or more times a week
  2. How many standard drinks containing alcohol do you have on a typical day?
     - [0] 1 or 2
     - [1] 3 or 4
     - [2] 5 or 6
     - [3] 7 to 9
     - [4] 10 or more
  3. How often do you have six or more drinks on one occasion?
     - [0] Never
     - [1] Less than monthly
     - [2] Monthly
     - [3] Weekly
     - [4] Daily or almost daily

Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA, Ambulatory Care Quality Improvement Project. The AUDIT alcohol consumption questions (AUDIT-C)—an effective brief screening test for problem drinking. Arch Intern Med. 1998;58:1789–1795.

ASSESSMENT - USE OF PHYSIOLOGICAL BIOMARKERS

Statement 3: APA *suggests* (2C) that physiological biomarkers be used to identify persistently elevated levels of alcohol consumption as part of the initial evaluation of patients with alcohol use disorder or in the treatment of individuals who have an indication for ongoing monitoring of their alcohol use.

- Rationale:
  - Help in determining the initial symptom severity and identifying relapses
  - Detect physiological damage with some of the indirect biomarkers (e.g., AST, ALT, GGT, CDT, MCV)
  - Help to emphasize the medical nature of AUD and potentially reduce stigma
- Implementation:
  - May augment with quantitative behavioral measures and input from collateral informants
  - Can be obtained via various sources (e.g., blood, urine, hair)

ASSESSMENT - BIOMARKERS (CONTINUED)

- Types of Biomarkers
  - Direct biomarkers measure alcohol or alcohol metabolites over a time course of hours (blood ethanol level) to days (urine/hair ethyl glucuronide)
  - Indirect biomarkers typically reflect organ damage or physiologic dysfunction resulting from more chronic, heavy alcohol use

ASSESSMENT - BIOMARKERS (CONTINUED)

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Biomarker	Specimen Type	Direct or Indirect	Time to elevation	Time to normalization after abstinence	Miscellaneous
Ethanol level	Serum	Direct	Minutes to Hours	Depends on amount consumed; usually within hours	
Ethyl glucuronide	Serum/ urine/ hair	Direct	1-3 hours after alcohol ingestion	Urine/hair:2-3 days (urine/hair) 24-48 hours (blood)	Better sensitivity and specificity for active heavy drinking False ⊕: Alcohol containing products False ⊖: UTI

ASSESSMENT - BIOMARKERS (CONTINUED)

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Biomarker	Specimen Type	Direct or Indirect	Time to elevation	Time to normalization after abstinence	Miscellaneous
Ethyl sulfate	Urine (also whole blood or plasma)	Direct	1-3 hours after alcohol ingestion	24-48 hours	Decreased elimination rates with renal disease False ⊕: Alcohol containing products False ⊖: UTI
Phosphatidyl-ethanol (PEth)	Whole blood	Direct	50 grams of alcohol daily for several weeks	2-3 weeks	Nearly 100% sensitivity for heavy alcohol consumption

ASSESSMENT - BIOMARKERS (CONTINUED)

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Biomarker	Specimen Type	Direct or Indirect	Time to elevation	Time to normalization after abstinence	Miscellaneous
Gamma-glutamyl transferase (GGT)	Serum	Indirect	60gm for 3-6 weeks	2-3 weeks	Sensitivity 64% Specificity 72% False ⊕:TCAs, Barbituates, MAOIs, Thiazides, Warfarin, Anabolic Steroids False ⊖:Heavy caffeine intake (>4 cups/day)
%Carbohydrate Deficient Transferrin (%CDT)	Serum	Indirect	1 week	2-4 weeks	Only FDA Approved alcohol biomarker 84% sensitivity; 92% specificity %CDT = CDT/Total Transferrin False ⊕: Increased transferrin (e.g., with ESRD, iron deficiency anemia, menopause, chronic illness False ⊖:Cirrhosis, binge alcohol use, acute blood loss

ASSESSMENT OF CO-OCCURRING CONDITIONS

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Statement 4: APA *recommends* (1C) that patients be assessed for co-occurring conditions (including substance use disorders, other psychiatric disorders, and other medical disorders) that may influence the selection of pharmacotherapy for alcohol use disorder.

- Rationale:
  - Help in identifying co-occurring conditions (e.g., mood or anxiety disorders) that commonly occur with AUD
  - Aid treatment planning and foster provision of integrated care for both AUD and other psychiatric conditions
- Implementation:
  - Assess via face-to-face evaluation, review of medical records, and/or history (including from collateral informants)

DETERMINATION OF INITIAL TREATMENT GOALS

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Statement 5: APA *suggests* (2C) that the initial goals of treatment of alcohol use disorder (e.g., abstinence from alcohol use, reduction or moderation of alcohol use, other elements of harm reduction) be agreed on between the patient and clinician and that this agreement be documented in the medical record.

- Rationale:
  - May improve outcomes by setting explicit drinking goals at baseline
  - Abstinence as a pre-treatment goal has been associated with greater likelihood of achieving abstinence or moderation
  - Strengthen the therapeutic alliance and enhance treatment engagement
- Implementation:
  - Options of treatment goals may be abstinence, reduced alcohol use, or avoiding drinking in high-risk situations
  - Can adjust initial goals based on factors such as treatment responses, history, family input, or education about treatment options and effects

DISCUSSION OF LEGAL OBLIGATIONS

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Statement 6: APA *suggests* (2C) that the initial goals of treatment of alcohol use disorder include discussion of the patient's legal obligations (e.g., abstinence from alcohol use, monitoring of abstinence) and that this discussion be documented in the medical record.

- Rationale:
  - Some patients seek treatment due to court mandate
  - Facilitates treatment planning and sets treatment expectations
  - Documentation promotes accurate communication among those caring for the patient and serves as reminder of initial goals
- Implementation:
  - Discuss whether patient has any legal requirements and document them
  - Discuss reporting requirements with patient, if treatment is mandated

REVIEW OF RISKS TO SELF AND OTHERS

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Statement 7: APA *suggests* (2C) that the initial goals of treatment of alcohol use disorder include discussion of risks to self (e.g., physical health, occupational functioning, legal involvement) and others (e.g., impaired driving) from continued use of alcohol and that this discussion be documented in the medical record.

- Rationale:
  - Facilitates treatment planning and sets treatment expectations
  - Permits education on the value of harm reduction and abstinence
  - Documentation promotes accurate communication among those caring for the patient and serves as reminder of initial goals
- Implementation:
  - Discuss risk of alcohol use with patient and document the discussion

EVIDENCE-BASED TREATMENT PLANNING

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Statement 8: APA *recommends* (1C) that patients with alcohol use disorder have a documented comprehensive and person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments.

- Rationale:
  - Ensures consideration of available non-pharmacological and pharmacological treatment options and identifies the options best suited to the patient's needs
  - Good clinical practice suggests value of a thoughtfully constructed treatment plan (which can be part of a progress note) that targets factors such as acute intoxication or alcohol related medical issues, history and mental status examination, physical examination, etc.

TREATMENT PLANNING (CONTINUED)

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- There are several evidence-based options for non-pharmacological treatment that have minimal harms:
  - Motivational Enhancement Therapy (MET): manualized psychotherapy based on the principles of motivational interviewing; shown to have a small to medium effect size on achieving abstinence
  - Cognitive Behavioral Therapy (CBT): focusing on the relationships between thoughts, feelings, and behaviors; help manage urges and triggers
  - Medical Management (MM): manualized treatment that provides education and strategies to support abstinence and promote medication adherence
  - Community based peer support groups such as Alcoholics Anonymous (AA) and other 12-step programs: helpful in achieving long-term remission but not for replacing formal medical treatment

SELECTION OF A PHARMACOTHERAPY – NALTREXONE AND ACAMPROSATE

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Statement 9: APA *recommends* (1B) that naltrexone or acamprosate be offered to patients with moderate to severe alcohol use disorder who

- **have a goal of reducing alcohol consumption or achieving abstinence,**
- **prefer pharmacotherapy or have not responded to nonpharmacological treatments alone, and**
- **have no contraindications to the use of these medications.**

PHARMACOTHERAPY – NALTREXONE AND ACAMPROSATE (CONTINUED)

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- Rationale:
  - Naltrexone and acamprosate have the best available evidence as pharmacotherapy for patients with AUD
  - These medications showed small benefits overall on alcohol-related outcomes (moderate strength of evidence)
  - Harms for both medications are minimal, particularly compared with the harms of continued alcohol use, when non-pharmacological approaches have not been effective or when patients wish to use one of the medications

COMPARISON OF NALTREXONE AND ACAMPROSATE

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	Naltrexone	Acamprosate
Mechanism of Action	Mu-opioid receptor antagonist	Glutamate receptor modulator
Indication	Alcohol use disorder Opioid use disorder	Alcohol use disorder
Clinical Evidence	Reduced likelihood of return to any and heavy drinking; Fewer drinking days overall; Reduced subjective experience of "craving"	Decreased likelihood of returning to drinking after achieving abstinence; Fewer drinking days
Pre-treatment Workup	Check hepatic function	Measure serum creatinine
Dosing	Oral tablet: 50mg PO daily for most; up to 100mg daily for some 25 mg PO daily then 50mg PO daily for women due to potential GI side effects Intramuscular injection: 380mg IM every four weeks	666mg PO TID

COMPARISON OF NALTREXONE AND ACAMPROSATE (CONTINUED)

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	Naltrexone	Acamprosate
Potential Side Effects	Abdominal pain (11%); Diarrhea (13%); Nausea (29%); Dizziness (13%)	Diarrhea (17%)
Contraindications	None	Contraindication if CrCl <30ml/min Dose reduction if 30< CrCl <50ml/min
Special Considerations	Be cautious when using in patients with acute hepatitis or liver failure Be abstinent from all opioids for 7-14 days prior to taking naltrexone to avoid precipitated opioid withdrawal May be preferable to acamprosate in patients with comorbid alcohol and opioid use disorder	Start treatment as soon as possible after the patient achieves abstinence and continue treatment even if the patient relapses

COMPARISON OF NALTREXONE AND ACAMPROSATE (CONTINUED)

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- A review by the Agency for Healthcare Research and Quality (AHRQ) found no evidence for superiority of one of the medications over the other
- Evidence on combined use of naltrexone and acamprosate is not sufficient to make any recommendation.
- Selection of a medication should be based on factors such as ease of administration, side effects or potential risks, co-occurring conditions, patient history and preferences, etc.
- Specific recommendations are focused on treatment of moderate to severe AUD because individuals with mild AUD are less likely to be included in clinical trials of pharmacotherapies.

EFFICACY OF NALTREXONE

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- Oral naltrexone (50mg) compared with placebo

Outcome	# of studies; # of subjects	Risk of bias; design	Summary effect size (95% CI)	NNT	Strength of evidence grade
Return to any drinking	16; 2,347	Medium; RCTs	RD: –0.05 (–0.10 to –0.00)	20	Moderate
Return to heavy drinking	19; 2,875	Medium; RCTs	RD: –0.09 (–0.13 to –0.04)	12	Moderate
Drinking days	15; 1,992	Medium; RCTs	WMD: –5.4 (–7.5 to –3.2)	NA	Moderate
Heavy drinking days	6; 521	Medium; RCTs	WMD: –4.1 (–7.6 to –0.61)	NA	Moderate
Drinks per drinking days	9; 1,018	Medium; RCTs	WMD: –0.49 (–0.92 to –0.06)	NA	Low

Adapted from Jonas DE, Amick HR, Feltner C, et al: Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings. AHRQ Comparative Effectiveness Review No 134. Report No 14-EHC029-EF. Rockville, MD, Agency for Healthcare Research and Quality, May 2014. Available at: www.ncbi.nlm.nih.gov/books/NBK208590/

HARMS OF NALTREXONE

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- Naltrexone compared with placebo

Outcome	# of studies; # of subjects	Risk of bias; design	Summary effect size (95% CI)	Strength of evidence grade
Anxiety	7; 1,461	Medium; RCTs	RD: 0.007 (–0.022 to 0.036)	Low
Diarrhea	11; 2,358	Medium; RCTs	RD: 0.013 (–0.011 to 0.038)	Moderate
Dizziness	13; 2,675	Medium; RCTs	RD: 0.063 (0.036 to 0.089)	Moderate
Headache	17; 3,347	Medium; RCTs	RD: 0.008 (–0.019 to 0.034)	Low
Insomnia	8; 1,637	Medium; RCTs	RD: 0.027 (–0.002 to 0.057)	Low
Nausea	24; 4,655	Medium; RCTs	RD: 0.112 (0.075 to 0.149)	Moderate
Vomiting	9; 2,438	Medium; RCTs	RD: 0.043 (0.023 to 0.062)	Moderate

Adapted from Jonas DE, Amick HR, Feltner C, et al: Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings. AHRQ Comparative Effectiveness Review No 134. Report No 14-EHC029-EF. Rockville, MD, Agency for Healthcare Research and Quality, May 2014. Available at: www.ncbi.nlm.nih.gov/books/NBK208590/

EFFICACY OF ACAMPROSATE

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- Acamprosate compared with placebo

Outcome	# of studies; # of subjects	Risk of bias; design	Summary effect size (95% CI)	NNT	Strength of evidence grade
Return to any drinking	16; 4,847	Medium; RCTs	RD: –0.09 (–0.14 to –0.04)	12	Moderate
Return to heavy drinking	7; 2,496	Low; RCTs	RD: –0.01 (–0.04 to 0.03)	NA	Moderate
Drinking days	13; 4,485	Medium; RCTs	WMD: –8.8 (–12.8 to –4.8)	NA	Moderate
Heavy drinking days	1; 100	Medium; RCT	WMD: –2.6 (–11.4 to 6.2)	NA	Insufficient
Drinks per drinking days	1; 116	Low; RCT	WMD: 0.40 (–1.81 to 2.61)	NA	Insufficient

Adapted from Jonas DE, Amick HR, Feltner C, et al: Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings. AHRQ Comparative Effectiveness Review No 134. Report No 14-EHC029-EF. Rockville, MD, Agency for Healthcare Research and Quality, May 2014. Available at: www.ncbi.nlm.nih.gov/books/NBK208590/

HARMS OF ACAMPROSATE

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- Acamprosate compared with placebo

Outcome	# of studies; # of subjects	Risk of bias; design	Summary effect size (95% CI)	Strength of evidence grade
Diarrhea	12; 3,299	Medium; RCTs	RD: 0.099 (0.030 to 0.168)	Moderate
Dizziness	2; 151	Low to medium; RCTs	RD: 0.08 (–0.22 to 0.38)	Low
Headache	6; 1,074	Medium; RCTs	RD: 0.001 (–0.052 to 0.05)	Low
Insomnia	3; 251	Medium; RCTs	RD: 0.019 (–0.10 to 0.138)	Low
Nausea	7; 1,758	Low to medium; RCTs	RD: 0.006 (–0.012 to 0.023)	Moderate
Vomiting	4; 1,817	Medium; RCTs	RD: 0.024 (0.007 to 0.042)	Moderate

Adapted from Jonas DE, Amick HR, Feltner C, et al: Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings. AHRQ Comparative Effectiveness Review No 134. Report No 14-EHC029-EF. Rockville, MD, Agency for Healthcare Research and Quality, May 2014. Available at: www.ncbi.nlm.nih.gov/books/NBK208590/

SELECTION OF A PHARMACOTHERAPY – DISULFIRAM

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Statement 10: APA *suggests* (2C) that disulfiram be offered to patients with moderate to severe alcohol use disorder who

- **have a goal of achieving abstinence,**
- **prefer disulfiram or are intolerant to or have not responded to naltrexone and acamprosate,**
- **are capable of understanding the risks of alcohol consumption while taking disulfiram, and**
- **have no contraindications to the use of this medication.**

DISULFIRAM (CONTINUED)

- Rationale:
  - Randomized open-label studies showed a moderate benefit compared with no disulfiram and other medications (low strength of evidence)
  - Serious adverse events were few although rates of overall adverse events were significantly greater with disulfiram than with control conditions
  - Benefits were judged as outweighing harms with appropriate patient selection and given the known risks of continued alcohol use

DISULFIRAM (CONTINUED)

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	Disulfiram
Mechanism of Action	Inhibitor of aldehyde dehydrogenase When the patient consumes alcohol while taking disulfiram, the accumulation of acetaldehyde causes a physical response such as tachycardia, flushing, headache, nausea, and vomiting
Indication	Alcohol use disorder
Clinical Evidence	Increased likelihood of achieving abstinence in patients for whom this is their goal
Pre-treatment Workup	ECG, physical exam, hepatic function
Dosing	First dose 12 hours after the last drink; 500mg PO each morning for 1-2 weeks, then 250mg PO each morning

DISULFIRAM (CONTINUED)

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	Disulfiram
Potential Side Effects	Elevations in hepatic enzymes (common) Potentially fatal acute hepatotoxicity (rare) Neuropathy and increased blood pressure
Contraindications	Recent myocardial infarction or coronary artery disease History of a seizure disorder
Special Considerations	Only for those seeking abstinence from alcohol Instruct not to consume alcohol within 12-24 hours of taking disulfiram Recommend involving a family or roommate as an observer of daily medication adherence Physical reaction can be precipitated by alcohol containing products (e.g., cold medicine, mouthwashes) and certain medications (e.g., sertraline oral concentrate, metronidazole, ritonavir)

SELECTION OF A PHARMACOTHERAPY – TOPIRAMATE AND GABAPENTIN

AMERICAN PSYCHIATRIC ASSOCIATION

Statement 11: APA *suggests* (2C) that topiramate or gabapentin be offered to patients with moderate to severe alcohol use disorder who

- **have a goal of reducing alcohol consumption or achieving abstinence,**
- **prefer topiramate or gabapentin or are intolerant to or have not responded to naltrexone and acamprosate, and**
- **have no contraindications to the use of these medications.**

TOPIRAMATE AND GABAPENTIN (CONTINUED)

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- Rationale:
  - There is less available evidence on benefits and harms of topiramate and gabapentin compared to naltrexone and acamprosate
  - Topiramate and gabapentin showed moderate benefits on alcohol related outcomes (moderate and low strength of research evidence, respectively)
- Implementation:
  - These medications are typically used after trying naltrexone and acamprosate but may be used earlier based on patient preference

TOPIRAMATE AND GABAPENTIN (CONTINUED)

AMERICAN PSYCHIATRIC ASSOCIATION

	Topiramate	Gabapentin
Clinical Evidence	Reduction in drinks per drinking day; Reduction in percentage of heavy or any drinking days; Reduction in the subjective experience of "craving"	Increased likelihood of abstinence from drinking and abstinence from heavy drinking
Dosing	Between 200-300mg daily	900-1800mg daily
Potential Side Effects	Short-term memory (3-12%); Dizziness (4-25%); Paresthesias and GI; Less commonly, metabolic acidosis and nephrolithiasis	Dose-dependent sedation (21%)
Contraindications	Renal impairment	Severe renal impairment

RECOMMENDATION AGAINST THE USE OF ANTIDEPRESSANTS

AMERICAN PSYCHIATRIC ASSOCIATION

Statement 12: APA *recommends* (1B) that antidepressant medications not be used for treatment of alcohol use disorder unless there is evidence of a co-occurring disorder for which an antidepressant is an indicated treatment.

- Rationale:
  - Evidence reported minimal efficacy with antidepressants for individuals with AUD and no co-occurring conditions; outcomes worsened in some studies
- Implementation:
  - Carefully consider differential diagnoses during evaluation; mood or anxiety symptoms can be associated with alcohol use or withdrawal and need not indicate the presence of a mood or anxiety disorder
  - Can be combined with other AUD medications if an antidepressant is indicated for a co-occurring disorder

RECOMMENDATION AGAINST THE USE OF BENZODIAZEPINES

Statement 13: APA *recommends* (1C) that in individuals with alcohol use disorder, benzodiazepines not be used unless treating acute alcohol withdrawal or unless a co-occurring disorder exists for which a benzodiazepine is an indicated treatment.

- Rationale:
  - No evidence for benzodiazepine use in the primary treatment of AUD, except for alcohol detoxification or alcohol withdrawal
  - No evidence for the use of other sedative-hypnotics in patients with AUD
  - Harms of benzodiazepine use in combination with alcohol use include: increased risk for sedation, behavioral impairment, respiratory depression, and (in severe cases) death

RECOMMENDATION AGAINST THE USE OF MEDS IN PREGNANT OR BREASTFEEDING WOMEN

AMERICAN PSYCHIATRIC ASSOCIATION

Statement 14: APA *recommends* (1C) that for pregnant or breastfeeding women with alcohol use disorder, pharmacological treatments not be used unless treating acute alcohol withdrawal with benzodiazepines or unless a co-occurring disorder exists that warrants pharmacological treatment.

- Rationale:
  - There is limited data regarding the use of AUD medications and risks to a fetus or infant, but the use of topiramate was associated with an increased risk of malformation in pregnant women
  - Studies with pregnant animals reported a moderate risk for naltrexone use, a high risk for acamprosate use, and possible risks for gabapentin and topiramate use
  - Limited data showed potential for toxicity with disulfiram, naltrexone, and topiramate during breastfeeding
- Implementation:
  - For women who become pregnant while taking a medication to treat AUD, an individualized decision should be made based on the risk of continuing or stopping the medication after discussion with the patient, her obstetrician, and, if applicable, her partner .

ACAMPROSATE IN SEVERE RENAL IMPAIRMENT

AMERICAN PSYCHIATRIC ASSOCIATION

Statement 15: APA *recommends* (1C) that acamprosate not be used by patients who have severe renal impairment.

- Rationale:
  - Because of the excretion of acamprosate through the kidneys, patients with severe renal impairment could experience toxicity from excessive drug levels
  - Although the strength of research evidence is low and based on a single pharmacokinetic study, the statement was influenced by the FDA recommendation, the availability of other effective medications, and the clinician and patient's preference to avoid toxicities from the medication use

ACAMPROSATE IN MILD TO MODERATE RENAL IMPAIRMENT

Statement 16: APA *recommends* (1C) that for individuals with mild to moderate renal impairment, acamprosate not be used as a first-line treatment and, if used, the dose of acamprosate be reduced compared with recommended doses in individuals with normal renal function.

- Rationale:
  - A single pharmacokinetic study showed linear increases in acamprosate levels with reductions in CrCl; the FDA added package insert information about reducing acamprosate doses with moderate renal impairment
- Implementation:
  - Avoid first-line use of acamprosate in patients with mild to moderate renal impairment
  - Monitor for evidence of toxicity if acamprosate is used in such patients

NALTREXONE IN ACUTE HEPATITIS OR HEPATIC FAILURE

Statement 17: APA *recommends* (1C) that naltrexone not be used by patients who have acute hepatitis or hepatic failure.

- Rationale:
  - Evidence for naltrexone-associated hepatotoxicity is relatively weak, yet some data reported elevated hepatic enzymes levels or other signs of hepatocellular injury with naltrexone
  - In individuals who are already experiencing significant liver damage such as acute hepatitis or hepatic failure, it is preferable to avoid further hepatic compromise.

NALTREXONE WITH CONCOMITANT OPIOID USE

AMERICAN PSYCHIATRIC ASSOCIATION

Statement 18: APA *recommends* (1C) that naltrexone not be used as a treatment for alcohol use disorder by individuals who use opioids or who have an anticipated need for opioids.

- Rationale:
  - Because naltrexone is an opioid receptor antagonist, using it with opioids will precipitate withdrawal
- Implementation:
  - Do not use naltrexone unless an individual has been abstinent from opioids for 7-14 days
  - Avoid using naltrexone in patients who may need opioid medications in the near future

AUD AND CO-OCCURRING OPIOID USE DISORDER

AMERICAN PSYCHIATRIC ASSOCIATION

Statement 19: APA *recommends* (1C) that in patients with alcohol use disorder and co-occurring opioid use disorder, naltrexone be prescribed to individuals who

- **wish to abstain from opioid use and either abstain from or reduce alcohol use and**
- **are able to abstain from opioid use for a clinically appropriate time prior to naltrexone initiation.**

- Rationale:
  - Naltrexone showed benefits in treating AUD and some evidence reported efficacy in patients with opioid use disorder, especially with long-acting injectable naltrexone
- Implementation:
  - Abstain from opioids for 7-14 days before naltrexone use

CONSIDERATIONS IN MEDICATION SELECTION

- Does the patient have a stated preference for a specific medication? Are there specific side effects that the patient wishes to avoid?
- Does the patient have a stated goal of abstinence from drinking or reduced drinking?
  - Abstinence from alcohol is essential with disulfiram.
- Does the patient have co-occurring physical or psychiatric conditions that would influence medication tolerability or potential side effects?
  - Naltrexone treated patients must abstain from opioids before starting treatment
  - Naltrexone is not recommended if acute hepatitis or hepatic failure is present
  - Disulfiram can be associated with increases in hepatic enzymes and rarely with fatal acute hepatotoxicity
  - If a patient has renal impairment, use acamprosate, topiramate, and gabapentin cautiously or avoid use (depending on renal function)

ADDITIONAL RESOURCES

AMERICAN PSYCHIATRIC ASSOCIATION

- Full guideline text available for free:

https://psychiatryonline.org/doi/book/10.1176/appi.books.9781615371969

- To purchase a hard copy of the guideline:

https://www.appi.org/American_Psychiatric_Association_Practice_Guideline_for_the_Pharmacological_Treatment_of_Patients_With_Alcohol_Use_Disorder

- CME course (half price for residents):

http://apapsy.ch/aud-guideline

In this interactive online course, the case of a patient with AUD is presented with examples of how the guideline recommendations would be integrated into practice.

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