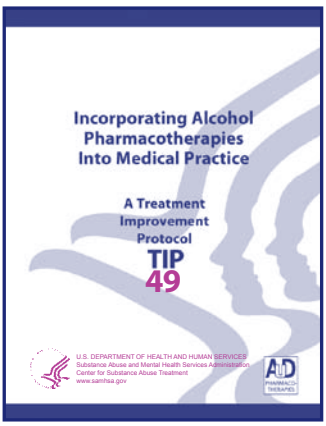
KAP Keys Based on TIP 49
Incorporating Alcohol
Pharmacotherapies Into
Medical Practice

Knowledge Application Program

KAP Keys

For Clinicians

Based on TIP 49
Incorporating Alcohol Pharmacotherapies Into Medical Practice



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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
www.samhsa.gov

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Introduction

KAP Keys were developed to accompany the Treatment Improvement Protocol (TIP) series published by the Center for Substance Abuse Treatment (CSAT), Substance Abuse and Mental Health Services Administration (SAMHSA). These KAP Keys are based entirely on TIP 49 and are designed to meet the needs of the busy clinician for concise, easily accessed how-to information.

Other publications that are relevant to these KAP Keys:

TIP 24: *A Guide to Substance Abuse Services for Primary Care Clinicians* **(SMA) 08-4075**
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat5.chapter.45293

TIP 45: *Detoxification and Substance Abuse Treatment* **(SMA) 08-4131**
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat5.chapter.85279

National Institute on Alcohol Abuse and Alcoholism's (NIAAA's) *Helping Patients Who Drink Too Much: A Clinician's Guide*
http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/guide.pdf

NIAAA's *A Pocket Guide for Alcohol Screening and Brief Intervention*
http://pubs.niaaa.nih.gov/publications/Practitioner/PocketGuide/pocket.pdf

NIAAA's *Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence*
http://pubs.niaaa.nih.gov/publications/combine/Combine%202.pdf

Acamprosate

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Trade name: Campral.

How taken: Two tablets by mouth three times per day, with or without food (a lower dose may be effective with some patients and *must* be used with those with impaired renal function).

How supplied: 333 mg delayed-release, enteric-coated tablets.

Mechanism of action: Not clearly established but is thought to help normalize alcohol-related changes in brain activity, reducing symptoms of postacute (protracted) withdrawal, such as sleep and mood disturbances, that may trigger relapse to drinking.

Drug interactions: No clinically relevant interactions.

Side Effects

Frequency	*Side Effect*
Most common	Diarrhea and drowsiness
Least common	Intestinal cramps, flatulence, nausea, headache, increased or decreased libido, insomnia, anxiety, muscle weakness, itchiness, dizziness

Adverse Reactions and Their Management

Adverse Reaction	*Management*
Suicidal ideation, suicide attempts (very uncommon, but serious)*	Inform patients to contact the prescribing professional immediately Monitor patients for onset or worsening of depression Obtain a psychiatric consult and/or prescribe antidepressant medication as necessary Discontinue acamprosate
Severe and/or persistent diarrhea	Treat with Imodium or Pepto-Bismol Recommend appropriate dietary changes Reduce acamprosate dosage or discontinue use if diarrhea remains intolerable after treatment

*Suicidal ideation is closely linked with substance use disorders, with or without acamprosate use. More information about managing the risk can be found at the National Suicide Prevention Resource Center's Web site (http://www.sprc.org) and at the Suicide Prevention for Physicians Web page (http://suicideandmentalhealthassociationinternational.org/preventionphy.html).

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Contraindications

Condition or Circumstance	***Treatment Recommendation***
Patients who are hypersensitive to acamprosate or its components	Do not prescribe acamprosate
Patients with severe renal impairment (creatinine clearance ≤ 30 mL/min)	Do not prescribe acamprosate

Cautions

Condition or Circumstance	***Treatment Recommendation***
Patients with moderate renal impairment (creatinine clearance 30–50 mL/min)	Reduce dosage to one 333 mg tablet three times per day
Pregnant or nursing women	Avoid using acamprosate unless potential benefits outweigh risks*
Adults ages 65 and older	Perform baseline and frequent renal function tests Has not been evaluated for safety or efficacy in this population
Children or adolescents	Prescribe with caution Has not been evaluated for safety or efficacy in these populations

*Acamprosate is Food and Drug Administration (FDA) pregnancy category C. Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy; but the potential benefits may outweigh the potential risk. It is unknown whether acamprosate is excreted in human milk.

For more information on acamprosate, see TIP 49, pages 9–14.

Disulfiram

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Trade name: Antabuse.

How taken: Tablet by mouth once daily (also may be crushed and mixed with water, coffee, tea, milk, soft drink, or fruit juice).

How supplied: 250 or 500 mg tablets.

Mechanism of action: Inhibits aldehyde dehydrogenase, causing a reaction when alcohol is ingested of flushing, sweating, nausea, and tachycardia that is very uncomfortable for the patient. Disulfiram, an alcohol-aversive or alcohol-sensitizing agent, causes an acutely toxic physical reaction that begins 10 to 30 minutes after alcohol is ingested. Intensity varies by personal characteristics and is generally proportional to the amounts of disulfiram and alcohol ingested.

Drug interactions: Metronidazole (Flagyl), medications containing alcohol, oral anticoagulants (e.g., warfarin), oral hypoglycemics, isoniazid, rifampin, benzodiazepines (e.g., chlordiazepoxide [Librium], diazepam), phenytoin (Dilantin), theophylline, tricyclic antidepressants.

Possible Effects of the Disulfiram–Alcohol Aversive Reaction

Body Part	***Moderate Effect***
Skin	Sweating Warmth and flushing, particularly on upper chest and face
Respiratory system	Hyperventilation, respiratory difficulty/ dyspnea
Head, neck, throat	Acetaldehyde breath odor, blurred vision, head and neck throbbing, thirst
Stomach, digestive system	Nausea/vomiting
Chest, heart, circulatory system	Chest pain/palpitations, hypotension, tachycardia
Brain/nervous system	Vertigo, syncope, marked uneasiness, confusion
Other	Weakness

Body Part	***Severe Effect***
Respiratory system	Respiratory depression
Chest, heart, circulatory system	Cardiovascular collapse, arrhythmia Myocardial infarction (in individuals with preexisting coronary artery disease) Acute congestive heart failure (in individuals with preexisting myocardial dysfunction)
Brain/nervous system	Seizures, unconsciousness
Other	Death

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Adverse Reactions

- Optic neuritis
- Peripheral neuritis, polyneuritis, peripheral neuropathy
- Hepatitis, including cholestatic and fulminant hepatitis, as well as hepatic failure; serious disulfiram-induced hepatic injury occurs rarely; the precise etiology is unknown
- Psychosis

Cautions

Condition or Circumstance	*Treatment Recommendation*
Patients with histories of cardiac disease, diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic or acute nephritis, hepatic cirrhosis, or hepatic insufficiency	Use with caution No evidence exists that patients with preexisting liver disease are more likely to suffer severe liver toxicity from disulfiram
Patients with hepatitis C	If baseline transaminase levels are normal or only moderately elevated (< 5 times the upper limit of normal), carefully monitor liver function
Patients receiving or who have recently received metronidazole, paraldehyde, alcohol, or alcohol-containing preparations (e.g., cough syrups, tonics) Patients exposed to ethylene dibromide or its vapors (e.g., in paint, paint thinner, varnish, shellac)	Do not use until substances are out of patient's system
Adults ages 61 and older	May need to decrease dosage
Children and adolescents	Prescribe with caution Has not been evaluated for safety or efficacy in these populations

Patient Instructions

Before using any product that may contain disguised alcohol, such as vinegars, sauces, aftershave lotions, or liniments, patients should apply the product to a small area of skin and wait 1 to 2 hours. Product may be used safely if no redness, itching, or unwanted effects occur.

For more information on disulfiram, see TIP 49, pages 15–26.

Oral Naltrexone

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Trade name: ReVia.

How taken: Tablet by mouth once daily.

How supplied: 50 mg tablets.

Mechanism of action: Not clearly understood; appears to lessen the euphoria associated with alcohol use; may reduce craving.

Drug Interactions

Medication	*Effect*
Cough/cold medications	May decrease benefit if medication contains an opioid
Antidiarrheal medications	May block benefit if medication contains an opioid
Opioid analgesics	May require greater amount of opioid analgesic than usual and may result in deeper and more prolonged respiratory depression than if the patient were not taking naltrexone
Thioridazine	May result in lethargy and drowsiness
Yohimbine	May result in anxiety and increased pulse rate and blood pressure
Nonsteroidal anti-inflammatory drugs (NSAIDs)	May result in liver enzyme elevations in combination with regular use of very high doses of naltrexone (200–250 mg/day); this effect has not been observed in the recommended therapeutic dose range of naltrexone (50–100 mg)

Dosage Schedule

Schedule	*Dosage*
Initial dosage for most patients	50 mg/day in a single tablet
Initial dosage for patients at risk of adverse events (e.g., young patients, those with short abstinence)	12.5 mg/day to 25 mg/day for 1 to 2 weeks Gradually increased to 50 mg/day
Average maintenance dosage	50 mg/day

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Side Effects

Frequency	*Side Effect*
Most common	Nausea, vomiting, headache, dizziness, fatigue, nervousness, anxiety, somnolence
Least common	Diarrhea, constipation, stomach pains, cramps; chest pain; joint/muscle pain; difficulty sleeping; excessive thirst, loss of appetite; rash, sweating; increased tears; mild depression; delayed ejaculation

Adverse Reactions and Their Management

Reaction	*Management*
Nausea	Suggest that patient take naltrexone with complex carbohydrates (e.g., bread) rather than on an empty stomach Suggest that patient take a tablespoon of simethicone (e.g., Gas-X, Mylicon) or bismuth subsalicylate (e.g., Pepto-Bismol) Reduce dose or stop for 3 or 4 days and restart at lower dose
Liver toxicity	Discontinue naltrexone
Precipitated opioid withdrawal	Discontinue naltrexone Provide supportive treatments (i.e., hydration, antispasmodic and antidiarrheal medications) until opioid withdrawal symptoms resolve Give an α-2-agonist such as clonidine to alleviate symptoms; watch for side effects of clonidine (e.g., dizziness, hypotension, fatigue, headache)
Naltrexone overdose	Treat symptomatically under close supervision Contact poison control center for most recent information

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Oral Naltrexone

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Contraindications

The patient should have an alternative medication if he or she:

- Is using illicit opioids
- Is taking buprenorphine (Suboxone or Subutex) or methadone
- Is undergoing opioid withdrawal
- Is experiencing acute hepatitis or liver failure
- Will need opioid analgesics within 7 days
- Is sensitive to naltrexone, to structurally similar compounds (e.g., naloxone, nalmefene), or to any inactive ingredients in the tablet

Cautions

Condition or Circumstance	***Treatment Recommendation***
Patients with moderate to severe renal impairment	Carefully monitor (naltrexone is eliminated through the kidneys)
Patients with active liver disease	Monitor liver function frequently
Patients with serum aminotransferase levels > 5 times the upper limit of normal	Generally avoid, unless potential benefits outweigh risks
Pregnant and nursing women and women of childbearing age	Do not prescribe during pregnancy and nursing unless potential benefits outweigh risks* Caution that effects on fetus are unknown Encourage use of effective birth control method
Patients with chronic pain or acute or recurring need for opioid analgesics	Have patients abstain from naltrexone for at least 3 days (conservatively, 7 days) before initiating opioid analgesics

*Oral naltrexone is FDA pregnancy category C. Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy; but the potential benefits may outweigh the potential risk. It is unknown whether oral naltrexone is excreted in human milk.

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Oral Naltrexone Black-Box Warning

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses.

Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only fivefold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses.

Patients should be warned of the risk of hepatic injury and advised to stop the use of naltrexone and seek medical attention if they experience symptoms of acute hepatitis.

For more information on oral naltrexone, see TIP 49, pages 27–35.

Extended-Release Injectable Naltrexone

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Trade name: Vivitrol.

How taken: Intramuscular injection once every 4 weeks.

How supplied: Single-use carton containing 380 mg vial of Vivitrol microspheres, 4 mL vial of diluent, 5 mL syringe, 20-gauge ½-inch needle, and two 20-gauge 1½-inch needles.

Mechanism of action: Same as oral naltrexone.

Drug interactions: Presumed same as oral naltrexone; clinical drug interaction studies have not been performed.

Side Effects

- Injection-site reactions (sometimes severe)
- Nausea/vomiting
- Headache
- Dizziness
- Fatigue
- Back pain
- Upper abdominal pain
- Decreased appetite
- Joint pain; muscle aches or cramps

Serious Adverse Reactions, Contraindications, and Cautions

Category	*Description*
Serious adverse reactions	Same as oral naltrexone Inadvertent subcutaneous injection may cause a severe injection-site reaction Depression Rare events include allergic pneumonia and suicidal ideation and behavior
Contraindications	Same as oral naltrexone Inadequate muscle mass for deep intramuscular injection Body mass that precludes deep intramuscular injection Rash or infection at injection site History of sensitivity to polylactide glycolide, carboxymethylcellulose, or any components of the diluent
Cautions	Same as oral naltrexone, plus hemophilia, coagulation disorders, or other bleeding problems Thrombocytopenia Recent opioid dependence

For more information on extended-release injectable naltrexone, see TIP 49, pages 37–44.

Naltrexone blocks the effect of opioid analgesics. Typical doses of narcotic analgesics (e.g., codeine, morphine, oxycodone, hydrocodone) may not be effective. When opioids must be used, it is possible to reverse the naltrexone blockade using higher than usual doses of opioids. However, because of the potential for opioid-induced respiratory depression, reversal of naltrexone blockade should be done only in medical settings that can provide respiratory support.

Naltrexone does not block the effects of aspirin, acetaminophen, or NSAIDs, including ibuprofen and naproxen sodium. It does not block the effects of local anesthetics such as lidocaine or general (nonopioid) anesthetics. (If patients taking naltrexone require opioid pain medication, a rapidly acting opioid analgesic is recommended to minimize the duration of respiratory depression. Patients should be monitored closely.)

Extended-Release Injectable Naltrexone

Pain management for patients using injectable naltrexone can be more complicated than that for oral naltrexone because the medication is long acting. The package insert states:

> In an emergency situation in patients receiving Vivitrol, a suggested plan for pain management is regional analgesia, conscious sedation with a benzodiazepine, and use of non-opioid analgesics or general anesthesia.
>
> In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged.
>
> A rapidly acting opioid analgesic which minimizes the duration of respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of the patient. Non-receptor mediated actions may occur and should be expected (e.g., facial swelling, itching, generalized erythema, or bronchoconstriction), presumably due to histamine release.
>
> Irrespective of the drug chosen to reverse Vivitrol blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

Useful Laboratory Tests

- Breath or blood alcohol tests
- Urine toxicology
- Gamma glutamyltransferase (GGT)
- Liver function tests, including serum aspartate aminotransferase (AST)
- Complete blood count
- Vitamin deficiency test
- Renal function tests: Standard panel for urea (blood urea nitrogen), electrolytes, and serum creatinine
- Pregnancy test (women of childbearing age)

Elements of Patient Education

- Information about alcohol dependence as a chronic medical disorder
- Description of what to expect in recovery, including symptoms of postacute withdrawal
- List of the possible benefits of a particular medication
- Information about the medication itself:
  - How and when to take it and the importance of adhering to the regimen
  - When the medication will become fully effective
  - Possible common side effects and their expected duration
  - Under what conditions the patient should immediately call the provider
  - Any cautions regarding daily activities
  - Medication interactions
- Explanation of the importance for women of childbearing age to use an effective birth control method
- Information about what to do if the patient starts drinking after a period of abstinence
- Description of the importance of concurrent psychosocial treatment and mutual- or self-help programs
- Followup plans

For more information on patient management, see TIP 49, pages 45–61.

Ordering Information

TIP 49

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Three Ways to Obtain Free Copies of All TIP Products

1. Call SAMHSA's Health Information Network (SHIN) at **1-877-SAMHSA-7 (1-877-726-4727)** (English and Español).
2. Visit SHIN's Web site at **http://www.samhsa.gov/shin**.
3. Access products online at **http://www.kap.samhsa.gov**.

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