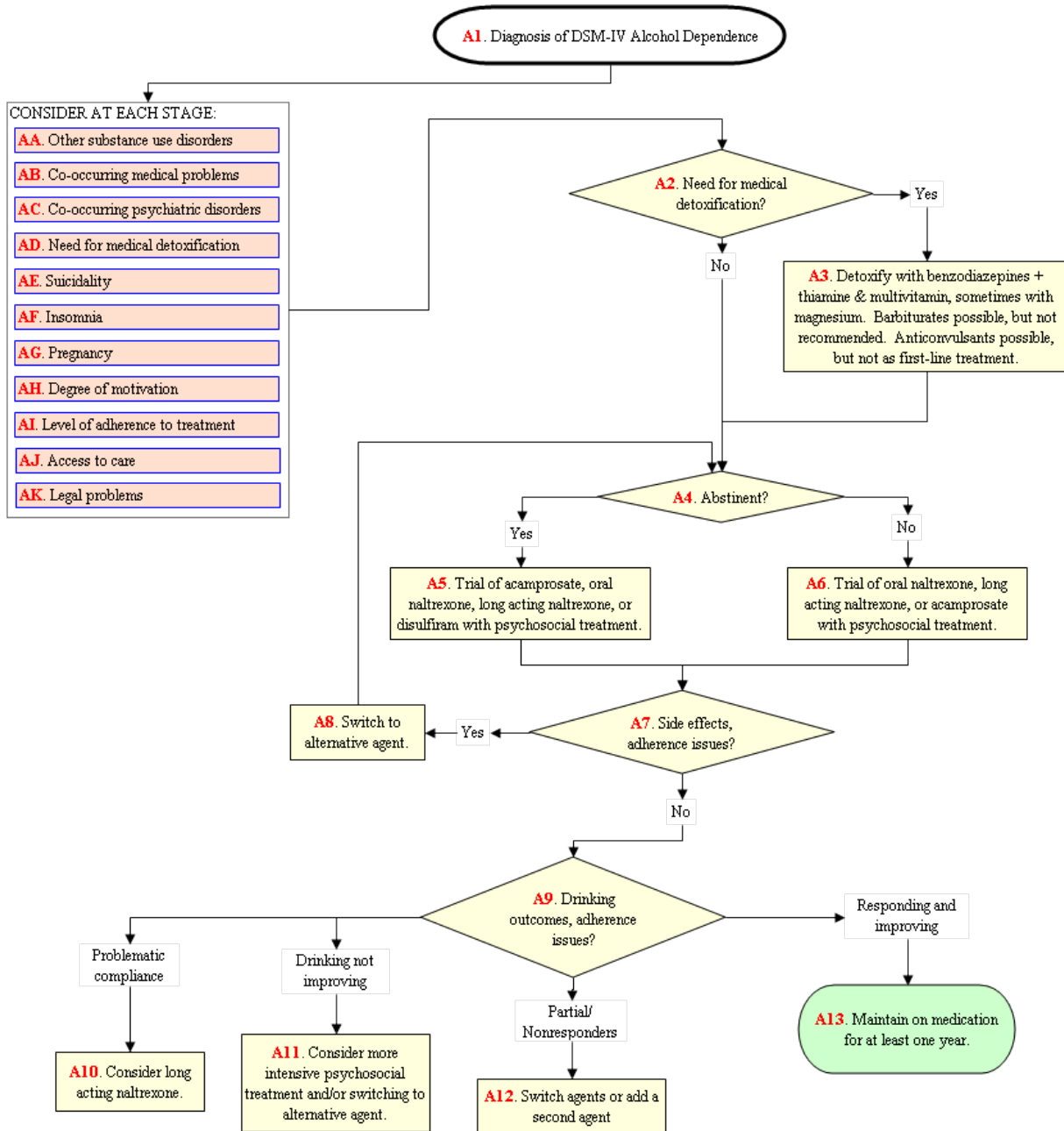


## Alcohol Dependence Medication Treatment Algorithm



**Node A1.** The first task for the clinician is to make a DSM-IV diagnosis of alcohol dependence. At the same time the patient should be assessed with regard to the following considerations. These should be reassessed throughout the treatment.

**Node AA.** Alcohol dependence occurs frequently with other substance use disorders. Therefore, when diagnosing alcohol dependence, it is necessary to ask about use of other substances of abuse. If the patient is dependent on one or more other substances, including nicotine, consult those algorithms as well.

**Node AB.** Alcohol dependence can cause serious medical problems in many different organ systems, including problems with the liver, central and peripheral nervous system, and heart. Moreover, alcohol-dependent individuals are more prone to accidents, with their medical sequelae, including brain trauma. Medical assessment in this population is necessary, and treatment of comorbid medical problems is required if appropriate. Moreover, since the medications used to treat alcohol dependence have medical warnings or contraindications (e.g., patients with severe liver disease cannot take naltrexone), a medical assessment should be done as part of the process of treating with pharmacotherapy.

**Node AC.** Attempt to establish whether a co-occurring Axis I disorder is independent of the substance use disorder, i.e., is it expected (based on historical data) to persist after several weeks of sobriety. Evidence to support another independent Axis I diagnosis includes a history that the disorder preceded alcohol dependence, that the disorder occurred during prolonged periods of sobriety, or a positive family history of the Axis I diagnosis. For a presumptive independent Axis I disorder, treat the disorder according to standard protocols. There is no good evidence that the presence of alcohol dependence would alter the decision-making process otherwise inherent in choosing one particular psychotropic medication (e.g., an antidepressant) as opposed to another.

**Node AD.** A patient with alcohol dependence should be evaluated to determine if the patient requires medical detoxification. In general, patients at risk are those who are drinking daily or nearly every day. Patients who have been drinking heavily and daily for the longest time are at the greatest risk, although there are no clear rules as to exactly how much one needs to drink, and for how long. People who have been detoxified medically in the past may become physically dependent again in a much shorter time than it took them initially to become physically dependent. Certain standardized assessment instruments, such as the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised version, (Sullivan et al, 1989), can help determine the level of risk of withdrawal.

**Node AE.** Patients with alcohol dependence are at significantly greater risk of suicide than those without this disorder. Interpersonal loss can be a trigger for suicidal risk in this population, more so than in other individuals. An assessment for suicidal risk is thus useful in this population.

**Node AF.** Insomnia is a common complaint in patients with AUDs. Insomnia may precede the development of an AUD and may even be a contributor to its development as the individual uses alcohol as a hypnotic. The neuroadaptational processes associated with AUDs also likely contribute to the development of insomnia and disturbances in the normal sleep cycle. Thus, alcohol-dependent patients have decreased total sleep time, disturbances in REM sleep, and reductions in other sleep stages. Disruption in the sleep cycle has also been shown to be a predictor of relapse. Therefore, treatment of insomnia can be an important clinical issue in dealing with the alcoholic patient.

Of the medications used to treat alcohol dependence, only acamprosate has been shown to have some beneficial effect on sleep (LOE III) (Staner et al., 2006). Clinically, acamprosate should be considered in the approach to managing insomnia in AUDs. The most commonly prescribed hypnotic medications in the general population include benzodiazepines, e.g. temazepam, and GABA-receptor subtype agonists, e.g. zolpidem. These agents do have some abuse potential and can also augment the depressant effects of alcohol. Therefore, most addiction medicine specialists do not recommend treatment with these medications for alcohol-dependent patients. The same precautions pertain to chloral hydrate and other agents that act through the GABA-A/benzodiazepine complex. Other medications that have

been tried include trazodone, gabapentin, mirtazapine, hydroxyzine, and quetiapine. Evidence supporting their efficacy is limited (LOE IV) (Arnedt et al, 2007).

The treatment of anxiety in those with AUDs, particularly after detoxification, is similarly difficult; the use of benzodiazepines, a common treatment for most patients with anxiety, is generally best avoided. Gabapentin, quetiapine, topiramate, and hydroxyzine are commonly prescribed in this situation, but, as with insomnia, the evidence for their efficacy is limited (LOE V). There is some evidence for the efficacy of buspirone in alcohol-dependent patients with ongoing persistent anxiety (Malec et al., 1996) (LOE II).

**Node AG.** None of the medications approved for the treatment of alcohol dependence have been tested in pregnant women, and thus cannot be deemed safe in that population. Each of the approved agents is listed as Pregnancy Category C.

**Node AH.** Patients who have low motivation for change frequently do not return for treatment. Counseling approaches that use motivational interviewing techniques can be tried to enhance willingness for treatment. More intensive psychosocial interventions, including intensive outpatient programs or residential treatment, should be considered to help patients engage in the treatment process.

**Node AI.** Patients who have difficulty taking oral medication for whatever reason should be evaluated to see if long-acting naltrexone is an appropriate option for them.

**Node AJ.** Not all of the medications approved for the treatment of alcohol dependence are readily available for all individuals. For example, the medication may not be available in the formulary of a hospital or managed care plan. This may influence certain prescribing decisions.

**Node AK.** Alcohol-dependent individuals may experience legal problems, and may in fact be seeking treatment as a result of these problems, e.g., driving while intoxicated. This type of external motivating influence can sometimes be helpful in precipitating changes in drinking for this population. Furthermore, court-mandated treatment can be effective.

**Node A2.** The clinician then should determine whether the patient needs medical detoxification. If the answer is yes, proceed to node A3. If no, then proceed to node A4.

**Node A3.** Many patients with alcohol dependence will require medical detoxification before psychosocial and ongoing medication treatment begins. Only a relatively small minority of patients with a diagnosis of alcohol dependence will experience serious alcohol withdrawal problems such as a seizure or alcohol withdrawal delirium, also known as delirium tremens (DTs). However, these can result in significant morbidity and even death, so it is imperative for clinicians to medically detoxify high-risk patients. A number of clinical symptoms and historical antecedents have been identified as predictors of severe alcohol withdrawal problems. These include: an extended history of continuous heavy drinking, in conjunction with co-occurring medical illnesses such as infections, serious burns, and fractures; a prior history of DTs or a withdrawal seizure; evidence of marked autonomic activity including a pulse rate of >120; evidence of severe withdrawal symptoms such as sweating, agitation, tremor, or perceptual changes. The Clinical Institute Withdrawal Assessment-Alcohol Revised (CIWA-Ar) scale is a useful tool to assess alcohol withdrawal; scores > 15 indicate severe withdrawal (Sullivan et al., 1989).

Patients who are not at high risk for serious withdrawal may still benefit from medical detoxification in order to establish an alcohol-free state prior to beginning treatment. However, many patients can achieve sobriety without undergoing medical detoxification.

The medical literature supports the use of benzodiazepines to prevent seizures or DTs (LOE IA) (Mayo-Smith, 1997). Benzodiazepines show efficacy as a class, with little evidence for superiority of one agent over another. Clinicians can choose a benzodiazepine based on attributes, (e.g., short-acting vs. long-acting, metabolized by the liver or not) that may be relevant to the individual patient. Medical detoxification is usually accomplished in 3-5 days, with frequent monitoring. In addition to benzodiazepines, it is important that patients receive thiamine, probably at a dose of  $\geq 200$  mg/d for at least three days. Thiamine may be given intramuscularly because of poor absorption with oral administration after heavy alcohol use (Thomson et al, 2002). Magnesium is sometimes given, particularly if low serum magnesium is present.

Barbiturates, particularly phenobarbital, have been shown to have efficacy for the treatment of serous alcohol withdrawal (LOE III), but their use has not typically been recommended because of their higher risk for respiratory depression.

Several anticonvulsants, including carbamazepine (and oxcarbamazepine), valproate, and gabapentin, have shown benefit in reducing alcohol withdrawal symptoms but efficacy for seizures or DTs has not been demonstrated (Book and Myrick, 2005). Accordingly, these agents should be considered promising, but they are not recommended as the first-line treatment of patients at risk for serious alcohol withdrawal.

**Node A4.** Is the patient abstinent?

The importance of the presence of abstinence relates to two points: 1) there is evidence that acamprosate appears to work best in patients who have achieved some degree of abstinence prior to treatment [LOE V]. The exact duration of abstinence is not well established and in the product label the indication is for "...maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation." There have been some positive trials with acamprosate in patients started during detoxification (Gual and Leheret, 2001). 2) Patients who might benefit from disulfiram need to be abstinent from alcohol for at least 24 hours or until no alcohol is detected in their system prior to starting medication.

**Node A5.** Yes, the patient is abstinent: There are four medications approved by the FDA for the treatment of alcohol dependence: acamprosate, naltrexone (oral and long-acting injectable), and disulfiram. Both acamprosate and naltrexone have been widely studied, with both having primarily positive outcomes, albeit with modest effect sizes (Kranzler and Van Kirk, 2001; Srisurapanont and Jarusuraisin, 2002; Bouza et al, 2004). Although studies in the U.S. have generally favored naltrexone over acamprosate (Anton et al, 2006), both medications have demonstrated positive results in numerous (but not all) trials.

Acamprosate (Efficacy LOE IA) (Kranzler and Van Kirk, 2001; Srisurapanont and Jarusuraisin, 2002; Bouza et al, 2004). The following issues should be considered when prescribing this medication: it should be avoided in patients with renal failure, and the dose should be reduced for individuals with renal insufficiency. Since acamprosate can cause diarrhea, one should consider the potential impact on patients with disorders associated with diarrhea. Acamprosate requires taking 2 pills (666 mg) t.i.d., which is a challenge to adherence. The FDA label notes increased "...events of a suicidal nature..." with acamprosate compared to placebo; patients with suicidal behavior/ideation should thus be monitored.

Oral naltrexone (Efficacy LOE IA) (Kranzler and Van Kirk, 2001; Srisurapanont and Jarusuraisin, 2002; Bouza et al, 2004) is an opioid antagonist medication, and is thus contraindicated in patients receiving opiate medications for any medical reason, as well as being contraindicated in patients with opioid dependence currently using opioids, unless they are detoxified from the opioids first. patients who intermittently abuse opiates require caution and education about naltrexone/opiate interactions; moderate to severe elevation of liver function tests is a relative contraindication, although there is no clear agreement in the field as to exactly the level of elevation that would preclude the use of naltrexone. Dose is 50 mg po daily, although many clinicians start at a lower dose (e.g., 25 mg a day) initially to avoid

side effects. Nausea and vomiting are the most common side effects that may lead to poor adherence or discontinuation of the medication. Recent evidence suggests that those with the Asn40Asp functional polymorphism of the mu-opioid receptor gene may respond particularly well to naltrexone (Oslin et al, 2003; Anton et al, 2008).

Long-acting injectable naltrexone (Efficacy LOE II) (Garbutt et al, 2005) is administered via a monthly injection of 380 mg intramuscularly in the buttock. Patients with adherence problems may thus be particularly likely to benefit from this formulation of naltrexone. Like oral naltrexone, the injectable form is contraindicated in patients taking opiates for any reason, medically prescribed or otherwise. The same warnings described above for oral naltrexone in conjunction with active opiate use hold true for injectable naltrexone. As with oral naltrexone, moderate to severe elevation of liver function tests is a relative contraindication, although there is no clear agreement in the field as to exactly the level of elevation that would preclude the use of either form of naltrexone.

Disulfiram (Efficacy LOE II for drinking frequency) (Garbutt et al, 1999) interferes with the action of the enzyme aldehyde dehydrogenase, leading to a buildup of acetaldehyde and thus a serious toxic reaction if the patient consumes beverage alcohol or is exposed to alcohol in disguised forms, e.g., in alcohol-containing cough syrup. Unfortunately, as with a number of other medications prescribed for substance use disorders, adherence to disulfiram is frequently a problem, and supervised use, e.g., by involving a spouse or personnel in a treatment program, significantly enhances adherence. The dose in the United States is ordinarily 125-500 mg/day. Rare episodes of severe hepatotoxicity may occur, which have occasionally been fatal; monitoring of liver function should be done both before prescribing disulfiram and during treatment. Significant liver dysfunction is a relative contraindication, although clinical experts do not agree on the exact degree of liver function test elevation that would lead them to not prescribe disulfiram.

Choosing among agents: The choice among agents is not straightforward except under specific circumstances: if there is significant liver dysfunction, one would choose acamprosate over naltrexone or disulfiram. In the case of severe renal disease, acamprosate is contraindicated. Disulfiram should not be chosen in an individual who is either unwilling or unable to take enough care to avoid alcohol in either beverage or disguised form. Otherwise, there are few head-to-head comparisons of these agents. While some research (e.g., Anton et al., 2006) suggests the superiority of naltrexone over acamprosate, either agent is a reasonable choice for an alcohol-dependent patient.

The importance of medication adherence: One of the primary reasons for lack of efficacy among medications for any chronic disease, including alcohol dependence, is poor medication adherence. Indeed, studies of disulfiram and naltrexone have shown that adherence is a major determinant of treatment outcome. Medication adherence can be increased in a number of different ways. First, the physician should ask about adherence and barriers to adherence (which can range from reluctance to accept the diagnosis of alcohol dependence to poor memory). Helping the patient to resolve difficulties in adherence can be critical. Simple prescribing regimens may also be helpful in increasing adherence. One may also consider long-acting injectable naltrexone for individuals who are having problems adhering to oral medications. Finally, engaging family members or significant others in the process can improve adherence, e.g., by having a family member observe the patient taking medication. All of these strategies have been found to improve adherence and thus outcome in alcohol-dependent individuals.

**Node A6.** No, the patient is not abstinent: Oral naltrexone (issues: side-effects may be more pronounced if patient is in early withdrawal; contraindicated in patients receiving opiate medications for any medical reason; contraindicated in patients with opiate dependence currently using opiates; patients who intermittently abuse opiates require caution and education about naltrexone/opiate interactions; significant liver dysfunction is a relative contraindication, although clinical experts do not agree on the exact degree of liver function test elevation that would lead them to not prescribe naltrexone).

Long-acting injectable naltrexone (issues: clinical trial data indicate can be given safely one day after alcohol is consumed; a once-monthly injection, patients with adherence problems may benefit; contraindicated in patients

receiving opiate medications for any medical reason; contraindicated in patients with opiate dependence currently using opiates; patients who intermittently abuse opiates require caution and education about naltrexone/opiate interactions; acute hepatitis is a relative contraindication)

Acamprosate (most positive studies have been in patients who have established at least 5 or more days of abstinence. Not contraindicated in the actively drinking population but less evidence of efficacy in this population.)

When choosing among agents, see the discussion above for individuals who are abstinent.

**Node A7.** Evaluate for side effects and adherence within the first 1-2 weeks.

**Node A8.** If side effects are problematic and reduce willingness to take medication, switch to alternate agent.

**Node A9.** Evaluate for drinking outcomes and adherence in the first month.

**Node A10.** If adherence remains problematic, consider another agent, including long-acting naltrexone.

**Node A11.** If drinking behavior is not improving, assess whether more intense psychosocial treatment is required and consider switching to an alternate agent.

**Node A12.** Approach to Partial/Nonresponders. Switch medications or add a second medication

Patients who do poorly on one agent should be tried on another agent unless there is a contraindication. For patients who have been treated with all of the FDA-approved medications for alcohol dependence and have not experienced improvement, one could consider either adding a second agent (see below) or, in some cases, treating with a medication that is not FDA-approved, but for which there is evidence of potential benefit. At this time, topiramate is one medication that fits this description (see below) (Johnson et al, 2007). It should be noted that in some cases, it is not necessary to, in fact, try all of the FDA-approved medications before trying either combination treatment or a medication such as topiramate. In some instances, a patient may be unable (e.g., because of liver dysfunction, allergy, or concomitant opioid therapy) or unwilling (e.g., in the case of disulfiram or injectable naltrexone) to take one of the FDA-approved medications. In such circumstances, the other options described above can be considered. However, it is recommended that medications that are approved by the FDA for the treatment of alcohol dependence be tried first.

Adding a second agent (combination therapy): The evidence for combination therapy is mixed. One small to moderate sized randomized trial in Europe found evidence for statistical superiority of acamprosate + naltrexone over acamprosate but not over naltrexone (LOE III) (Kiefer et al, 2003). A large trial in the U.S. did not find evidence for superiority of the combination of acamprosate + naltrexone over naltrexone or acamprosate. In this trial, a main effect was found for naltrexone but not for acamprosate (LOE II) (Anton et al, 2006). Other trials have examined other combinations, e.g. acamprosate + disulfiram, using a variety of trial designs, but the overall evidence for or against efficacy of a particular combination is not persuasive.

**Node A13.** In patients who are responding and improving, continue medication management for at least 6-12 months (LOE V). Controlled trials comparing varying lengths of maintenance treatment are lacking. The recommendation to continue treatment for 6-12 months is based on the opinions of clinical investigators with experience with these medications.

## **The Context of Treatment for Alcohol Dependence**

Alcohol dependence and alcohol abuse are common problems, with combined lifetime prevalence rates for men in the 20% range and for women in the 10% range. The economic and health care consequences of alcohol use disorders (AUDs) and misuse are large. Alcohol-related problems cost the U.S. on the order of \$200 billion/year and contribute to nearly 100,000 deaths/year. Despite the high prevalence of AUDs, it has been estimated that only about 25% of individuals with an AUD ever receive treatment. Furthermore, of those individuals who receive treatment, only about 10% receive a medication for their AUD. The reasons for the low treatment rates are many, and include the unwillingness of patients to seek treatment, the reluctance of physicians to ask patients about alcohol problems, and financial coverage issues.

Efforts to increase physician awareness about the prevalence and consequences of AUDs have been ongoing in medical schools and professional societies for some time. Simple questionnaires such as the CAGE and the AUDIT-C have been developed to help physicians screen for alcohol problems. The third question of the AUDIT, "How often do you have 5 or more drinks on one occasion?" has been suggested as a single screening question that physicians could use, as any positive answer for the past year indicates a high likelihood of unhealthy alcohol use and provides an impetus for further inquiry.

The cornerstone of treatment of AUDs has traditionally been psychosocial, and psychosocial interventions remain a key component of treatment. In fact, psychosocial interventions are effective for many patients. Psychosocial interventions provided by professionals that have evidence to support their efficacy include brief interventions, motivational interviewing, cognitive-behavioral relapse prevention, behavioral marital therapy and others. In addition to professional treatment, Alcoholics Anonymous, a mutual-help group, represents an important resource for patients, as it does not require financial resources, has a long tradition of success for many alcoholics, and provides access to a community with a focus on sobriety. Physicians should discuss A.A. with their patients and encourage them to try it. Some individuals do not engage with A.A. and there are alternative self-help programs including Smart Recovery and Women for Sobriety. No "one size fits all" psychosocial intervention has been identified.

A few basic concepts are useful in counseling patients with an AUD and helping them move towards sobriety or less destructive alcohol use. First, clinicians should avoid being judgmental and approach the management of an AUD as they would other chronic illnesses such as diabetes or hypertension. It is important to note that many patients enter treatment as a result of external pressure, often as a result of an intervention by a family member or employer, or because of legal trouble. Interventions by family members or employers can be a critical factor in helping initiate treatment, particularly when there is sufficient leverage to motivate the alcohol-dependent individual to seek treatment. Building up internal motivation then becomes an important component of ongoing treatment; purely confrontational methods have generally been shown to not be effective and may drive the patient away from treatment. Even brief interventions of 15-30 minutes by a physician have been shown to reduce both harmful alcohol use and health care costs. A key goal of initial conversations should be to enhance the patient's motivation to change and let the patient know it can be done. Second, patients should be evaluated for risk of serious alcohol withdrawal. Patients who are physically dependent on alcohol can experience serious and even life-threatening withdrawal. Patients at high risk for serious withdrawal should be medically detoxified from alcohol and this is most commonly done in an inpatient setting. Detoxification is often necessary to get the patient ready to engage in treatment. Third, stay engaged with the patient through the ups and downs of their alcoholism. Many patients do not achieve long-term sobriety until they have had years of treatment. Some patients may never achieve long-term sobriety. Sobriety is the best outcome for the alcohol dependent patient but physicians can help patients and society by reducing harmful alcohol use. This "harm reduction" approach is an appropriate outcome particularly when the patient is not ready for sobriety.

Medications are tools that should be complemented by some form of psychosocial intervention. It is unlikely that medication alone will be sufficient to treat patients with AUDs. However, the intensity of the required psychosocial

intervention is frequently not clear at the beginning of treatment. A common rule of clinical care is that as patients fail lower levels of care they need to be referred to higher levels of care, e.g., outpatient treatment, intensive outpatient treatment (e.g., two or more evenings a week), day treatment (e.g., every day or evening), short-term residential treatment, and finally long-term residential treatment.

### **Non-FDA Approved Medications**

Topiramate (LOE II): Topiramate has been reported to reduce heavy drinking and enhance abstinent days at a target dose of 300 mg/d (Johnson et al, 2000, 2007). Efficacy has recently been demonstrated in a multicenter trial among patients who were actively drinking heavily (though not requiring medical detoxification) at the start of the study (Johnson et al., 2007).

Ondansetron (LOE II): Ondansetron has been reported to increase abstinent days and reduce drinks/drinking day in one single-site study (Johnson et al, 2000). Efficacy has yet to be demonstrated in a multicenter trial.

Baclofen (LOE III): Baclofen has been reported to enhance abstinence and reduce alcohol use in alcoholic patients without serious liver disease (Addolorato et al, 2002) and in alcoholic patients with cirrhosis (Addolorato et al, 2007). Efficacy has not yet been demonstrated in a multicenter trial.

Selective Serotonin Reuptake Inhibitors (SSRIs): SSRIs have shown benefit in AUD patients with co-occurring depression (Cornelius et al, 1997). Preliminary work has suggested that sertraline is beneficial for alcohol dependent patients with a less severe subtype of alcohol dependence (Type A alcoholic) (Pettinati et al, 2000).

Other Agents: A number of other medications are in the process of investigation for the treatment of AUDs including dopamine agonists/antagonists, CRF1 receptor antagonists, NPY1 receptor antagonists, varenicline (a nicotinic receptor partial agonist), quetiapine, and cannabinoid receptor antagonists. Clinical data on these agents is either lacking or still too premature to identify whether they have any efficacy for AUDs.

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