Treatment Of The Hospitalized Alcohol-Dependent Patient With Alcohol Withdrawal Syndrome

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Citation

Abstract

Alcohol-related disorders remain a significant cause of patient morbidity and mortality. These disorders include alcohol intoxication, withdrawal, abuse, and dependence. While primary care physicians certainly play an important role in managing these conditions, the hospital physician should be equally aware of the acute management of alcohol withdrawal and be prepared to help treat the patient for alcohol abuse and dependence. The objective of this manuscript was to review the contemporary literature regarding treatment of these conditions and distill the knowledge into useful clinical information for a practicing physician. We first addresses alcohol withdrawal syndrome with a discussion of underlying pathophysiology, diagnostic criteria, clinical evaluation, treatment goals, and specific treatment options including pharmacotherapy. To address long-term continuity of care, we include a discussion of alcohol abuse and dependence, specifically addressing clinical assessment and various long-term therapy modalities. With a review of this information, we hope to simplify the management and treatment goals for the internal medicine physician for patients with alcohol-related disorders.

INTRODUCTION

Alcohol-related disorders are a significant cause of patient morbidity and mortality. Alcohol is associated with 50% of homicides, 30% of traffic fatalities, 25% of suicide attempts, 15% of all primary care visits and 8% of emergency department visits. (*1, *2, *3) An estimated 7 to 20 percent of the United States (US) population practices unhealthy alcohol consumption. (*4) Annually, alcohol dependence and abuse account for 100,000 deaths. (*3) While the lifetime prevalence of alcohol dependence was found to be 12.5% during a 2002 US survey, less than one quarter of cases are treated. (*5)

While primary care physicians play a large role in the management of patients with unhealthy alcohol use (*6), inpatient hospitalists and physicians are equally as important in identifying and treating these conditions. Alcohol related problems include, but are not limited to, alcohol withdrawal syndrome (AWS), alcohol intoxication, alcohol abuse, and alcohol dependence. Twenty percent of hospitalized patients meet criteria for diagnosis of alcohol dependence (*7) and as many as two million patients will experience alcohol withdrawal each year (*8). All physicians should also be competent in the diagnosis and management of alcohol withdrawal. One should, however, realize that detoxification and treatment of AWS alone is not sufficient to prevent its

recurrence. Physicians should also prepare patients for long-term treatment of their alcohol abuse and/or dependence. This approach benefits the patient by improving general health, productivity, and quality of life while generating cost-savings. (*9, *10) The goals of this article are to review the inpatient objectives for managing alcohol withdrawal, abuse, and dependence.

CASE REPORT

A 45-year-old male is admitted to the hospital for mild hematemesis and complaints of intermittent abdominal pain. The patient reported being a highly functional business executive and denies any past medical history or medication use. On exam, the patient is afebrile with blood pressure of 137/88 and heart rate of 88 bpm. Mild epigastric tenderness was appreciated on exam.

Esophagogastroduodenoscopy under sedation performed the following morning identified a small friable ulcer in the gastric antrum, confirming the diagnosis of gastric peptic ulcer disease. On the second night of admission, the patient began to experience significant tremors, diaphoresis, and restlessness. The patient's blood pressure and heart rate were found to be 170/98 mmHg and 120 bpm, respectively. Two hours later, the patient became disoriented and reported signs of visual and auditory hallucinations. Further

questioning performed at this time revealed that the patient consumed approximately ten drinks of alcohol three to four times per week. He denied the use of illicit drugs or tobacco. AWS was diagnosed and the patient was treated immediately with lorazepam. Following treatment, the patient's symptoms resolved and vital signs normalized. Management of AWS was continued by administering diazepam in a symptom-triggered dosing regimen as determined by the results of the patient's Clinical Institute Withdrawal Assessment of Alcohol Scale - Revised (CIWA-Ar) score. Given the relation of events and otherwise negative medical workup, the patient's gastric ulceration was thought to be secondary to his alcohol consumption. After three days, the patient was discharged in stable condition.

Three weeks later, the patient presented to the emergency department with active symptoms of alcohol withdrawal. Blood alcohol level was 53 and urine toxicology was negative. AWS was diagnosed and the patient was treated in a similar manner. Again his symptoms resolved with administration of diazepam following symptom-triggered dosing regimen as determined by CIWA-Ar scores. Further questioning of the patient's history of alcohol consumption led to the diagnosis of alcohol dependence. Standard interventions were performed for symptomatic relief as needed on a daily basis while the patient was hospitalized. Long-term treatment plans were discussed with the patient and he was amenable to the treatment strategy for his alcohol dependence. Prior to discharge, outpatient follow-up with a twelve-step facilitation program and plans to initiate treatment with naltrexone were coordinated with the help of social and psychiatric services.

DISCUSSION

ALCOHOL WITHDRAWAL SYNDROME

Each year, two million patients experience symptoms of AWS. (*8) As a result, all physicians and medical staff should have an understanding of the pathophysiology, diagnosis, evaluation, and treatment of this condition.

PATHOPHYSIOLOGY

Alcohol enhances the activation of GABA on inhibitory type A gamma-aminobutyric acid (GABA-A) receptors and inhibits excitatory N-methyl-d-aspartate (NMDA) and non-NMDA glutamate receptors in the brain leading to overall decreased central nervous system (CNS) excitability. (*11) As CNS tolerance develops from prolonged or repetitive exposure to alcohol, the brain adapts by up-regulating glutamate receptors and down-regulating GABA-A

receptors. In the absence of alcohol, this combination of neurobiological events results in a new homeostatic state of CNS hyper-excitability that can manifest as anxiety, agitation, tremors, irritability, seizures and delirium tremens (DT). Repeated detoxifications also result in long-term neuronal changes often referred to as "kindling." Kindling is the establishment of stable neurobehavioral alterations secondary to repeated electrophysiologic stimulation. Neuronal kindling is hypothesized to increase alcohol craving (*12) and worsen subsequent episodes of AWS (*13).

DIAGNOSIS

The Diagnostic and Statistical Manual of Mental Disorders IV, Text Revision (DSM-IV) defines criteria for diagnosis of AWS (Table 1). (*14) AWS can occur upon cessation or reduction in alcohol consumption and may appear while the patient has a measurable alcohol level. Symptoms are associated with CNS hyper-excitability and can vary from mild manifestations such as anxiety and tremors, to fatal conditions such as delirium tremens. (*13) Symptoms can begin as early as a few hours after cessation or reduction in alcohol consumption or appear several days afterwards (Table 2). Often, symptoms develop after patients are hospitalized for other reasons. In general, severity of withdrawal symptoms is correlated with amount and duration of alcohol consumption. (*13) Approximately 7% of patients with AWS develop alcoholic hallucinations, 5-10% develop withdrawal seizures, and 5% develop alcohol withdrawal delirium better known as delirium tremens (DT). (*15)

Figure 1

Table 1

DSM-IV Criteria for Alcohol Withdrawal	
A.	Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B.	Two (or more) of the following, developing within several hours to a few days after criterion A:
1.	Autonomic hyperactivity
2.	Increased hand tremor
3.	Insomnia
4.	Nausea or vomiting
5.	Transient visual, tactile, or auditory hallucinations or illusions
6.	Psychomotor agitation
7.	Anxiety
8.	Grand mal seizures
C.	The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D.	The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

Ref #14: Adopted from: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Publishing Inc; 2000.

Figure 2

Table 2

Symptoms and Time Course for Alcohol Withdrawal Syndrome	
6 to 12 hours	Minor withdrawal symptoms: insomnia, tremulousness, mild anxiety, gastrointestinal upset, headache, diaphoresis, palpitations, anorexia
12 to 24 hours*	Alcoholic Hallucinations: auditory, visual, or tactile; normal sensorium
24 to 48 hours†	Withdrawal Seizures: Generalized tonic-clonic seizures
48 to 72 hours‡	Alcohol Withdrawal Delirium/Delirium Tremens: hallucinations (visual), disorientation, tachycardia, hypertension, low-grade fever, agitation, diaphoresis

* - Symptoms generally resolve within 48 hours.
† - Symptoms reported as early as two hours after cessation
‡ - Symptoms peak at five days

Ref #13: Bayard M, McIntyre J, Hill K, et al. Alcohol withdrawal syndrome. Am Fam Physician 2004; 69:1443– 50.

Withdrawal seizures are more common in patients with a history of multiple episodes of AWS (*13). They are typically grand-mal type and may occur several times daily after alcohol cessation. Alternate causes should be sought if focality is identified. An effort to identify DT is critical as this condition carries a 1 to 5% mortality rate. (*16) Alcoholic hallucinosis consists primarily of visual, auditory, or tactile hallucinations and can be differentiated from DT by the absence of sensorium clouding, disorientation, and fluctuating awareness. Risk factors associated with the development of DT include old age, history of DT or withdrawal seizures, presence of severe withdrawal symptoms on presentation, current acute medical illness, history of heavy daily alcohol use, and decreased hepatic metabolism. (*13)

Withdrawal from benzodiazepines and barbiturates and intoxication of amphetamines, cocaine, or anticholinergic drugs can lead to increased sympathetic drive and mental status changes which can mimic AWS. CNS infection, trauma, and thyrotoxicosis can also present similarly to AWS. These conditions should be ruled out before solidifying a diagnosis of AWS.

EVALUATION

The Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) is the most commonly used validated method of quantifying severity of AWS (Figure 1). (*17, *18). The CIWA-Ar can also be used to monitor the progress of patients and determine treatment plans for AWS. (*17, *18, *19, *20) The CIWA-Ar is a cumulative rating of ten AWS symptoms each scored on a scale of 0 to 7 or 0 to 4. Trained staff can reliably conduct this assessment in less than one minute. A CIWA-Ar score below 8 indicates mild AWS; a score between 8 and 15 signifies moderate AWS; a score above 15 constitutes severe withdrawal and a higher risk for the development of DT. The categories of AWS are associated with treatment recommendations, with patients demonstrating moderate or severe AWS requiring treatment with benzodiazepine (discussed below). While the CIWA-Ar

is a helpful tool, clinicians and medical staff should realize that symptoms listed are not specific to AWS. Co-morbid medical (e.g. hyperthyroid) or psychiatric (e.g. psychosis) illness and medications (e.g. ꞵ blockers) can falsely elevate or decrease CIWA-Ar scores and therefore interfere with proper treatment if not accounted for by the evaluator.

Figure 3

Figure 1: The Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar)

Ref #17: Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). Br J Addict 1989;84:1353-7.

TREATMENT
GOALS OF DETOXIFICATION

There are three goals of drug and alcohol detoxification as described by the American Society of Addiction Medicine (ASAM): 1) "To provide a safe withdrawal from the drug[s] of dependence and enable the patient to become drug-free" 2) "To provide a withdrawal that is humane and thus protects the patient's dignity" and 3) "To prepare the patient for ongoing treatment of his or her dependence on alcohol or other drugs." (*16)

BASICS OF CARE

All patients who are admitted for acute withdrawal (seizures, DT's) or other comorbidities related to unhealthy alcohol consumption should be evaluated and treated following a standardized protocol. Basic laboratory tests such as complete blood counts, blood alcohol level, urine drug screen, transaminases, bilirubin, albumin, coagulation tests, and electrolyte levels should be performed on admission. Particular attention should be paid to potassium, bicarbonate, magnesium and phosphate, as these electrolytes are commonly decreased in chronic alcohol use secondary to emesis, volume depletion, and malnutrition.

Patients should be treated with thiamine, folate and multivitamins. Hypomagnesia may predispose patients to seizures (in addition to cardiac arrhythmias). While supplementation with magnesium is appropriate if hypomagnesia is present, routine administration of magnesium has not been proven to improve AWS. (*21) Intravenous fluids are indicated in patients with excessive fluid losses (*13). If glucose-containing fluids are necessary, it is suggested they be administered after thiamine to prevent precipitation of Wernicke's encephalopathy. (*13, *22) Patients at risk for AWS can benefit from placement in quiet environments with reduced light and limited interactions with others. (*23) Based on risk factors for specific populations (e.g. indigent populations) and comorbid medical issues, tuberculosis testing and administration of appropriate vaccines can be performed as well.

TREATMENT SETTING

In the majority of patients with mild to moderate withdrawal symptoms, outpatient detoxification is appropriate, assuming the patient is motivated and has a supportive home environment. This method has been proven to be effective, safe and less costly than inpatient treatment. (*8, *24, *25, *26) If outpatient treatment is undertaken, only small quantities of medication should be prescribed following a fixed-dosing regimen (described in greater detail below) and close monitoring of the patient by another individual should be confirmed.

Relative indications for inpatient detoxification include a history of severe withdrawal symptoms, seizures, DT, multiple previous detoxifications, co-morbid psychiatric or medical illnesses, and lack of a reliable support network. (*23)

PHARMACOTHERAPY

Prompt pharmacological treatment is indicated in all cases of AWS, as nontreatment or undertreatment can be fatal. (*27, *28) Benzodiazepines are safe, effective and the preferred treatment for AWS. (*7) Benzodiazepines are cross-tolerant with alcohol and modulate anxiolysis by stimulating GABA-A receptors. (*29) They are proven to reduce withdrawal severity and incidence of both seizures and DT. (*7, *30, *31, *32, *33) All subclasses of benzodiazepines appear to be equally effective in treating AWS (*7). Therefore, choosing a benzodiazepine depends on selection of preferred pharmacokinetic properties in relation to the patient being treated. (*34) Longer acting benzodiazepines such as diazepam and chlordiazepoxide are most often preferred because they allow for easy tapering (*35), have lower potential for abuse (*7) than short acting benzodiazepines, and cause fewer rebounds and withdrawal seizures upon discontinuation. Short acting agents such as lorazepam or oxazepam do not undergo hepatic metabolism like most long acting benzodiazepines and are more appropriate for patients with significantly decreased liver function. (*36) Short acting agents also avoid the risk of excessive sedation caused by longer acting agents and may be beneficial in the elderly or cognitively impaired. (*37)

Two regimens, fixed-scheduled and symptom-triggered, are commonly employed for benzodiazepine dosing AWS. In fixed-scheduled regimens, medication doses are administered at specific intervals and additional doses are given as needed. In symptom-triggered regimens, medications are dosed based upon the patient's current manifestations of symptoms, which can be evaluated by the CIWA-Ar. (*38)

A symptom-triggered regimen is preferred in most cases of AWS because it results in the administration of less total medication and shorter duration of treatment. (*39, *40) This regimen may also reduce the risk of undermedicating or overmedicating a patient since dosing is based upon withdrawal symptoms. (*41) The efficacy of symptom-triggered regimens, however, depends on the validity of patient assessment. Consequently, a fixed-dose regimen may be preferred if CIWA-Ar scores cannot be accurately performed (i.e. lack of training, outpatient care setting, co-morbid medical or psychiatric illnesses or use of medications that may affect COWA-Ar measurements. (*7)

Institutional variations in symptom-triggered regimens often create confusion regarding the standard of care when using

the symptom-triggered regimens but guidelines from the ASAM are available. As described earlier, the CIWA-Ar is a well-validated method of assessing severity of AWS using a cumulative rating of ten AWS symptoms. (*7) In general, CIWA-Ar scores below 8 should be treated with supportive care; CIWA-Ar scores between 8 and 15 require treatment with benzodiazepines in addition to supportive care (institutional dependent; e.g. diazepam 10-20 mg q1hour, lorazepam 2-4 mg q1h); CIWA-Ar scores above 15 require hourly monitoring for respiratory failure in addition to pharmacotherapy and supportive care.

Several medications can be used as adjunctive treatments of AWS including haloperidol, atenolol, clonidine and phenytoin. Haloperidol is often used for managing severe agitation and hallucinations; this drug can, however, reduce the seizure threshold. (*13) Atenolol, a -blocker, improves vital signs more rapidly and provides better craving control than benzodiazepines alone. (*42) Atenolol should be considered in patients with coronary artery disease, who may not be able to tolerate the strain that sympathetic withdrawal symptoms can place on the cardiovascular system. (*23). Clonidine has also been shown to improve the autonomic symptoms of withdrawal. (*7) Although phenytoin does not treat withdrawal seizures and does not need to be routinely started, it is an appropriate to continue it as an adjunct in patients who have an underlying seizure disorder. (*13)

Anticonvulsants have been proposed as an alternative to benzodiazepines because of their low abuse potential, minimal effect on cognition, and ability to reduce kindling. (*43, *44) One randomized control trial demonstrated the effectiveness of carbamazepine as an alternative to benzodiazepines in the treatment of mild to moderate AWS. (*45) No statistically significant benefit was demonstrated during systemic review of carbamazepine, however; benzodiazepines remain the mainstay of treatment.

The acute management of DT in the inpatient setting utilizes many of the same medications used in AWS. In the United States, benzodiazepines have been established as the medication of choice for the prevention and treatment of DT. They have been proven to be safe and effective in preventing complications of DT. Additionally, haloperidol may be used as an adjunctive treatment with benzodiazepines to treat psychiatric symptoms of DT, including anxiousness, hallucinations, and combativeness. Phenobarbital has a theoretical benefit due to similar underlying mechanism as benzodiazepines, though literature has shown application of phenobarbital leads to negative outcomes such as respiratory depression and coma more often than benzodiazepines and thus should be administered only in a controlled ICU setting as intubation may become necessary. Propafol has also been shown to be a useful agent for treating refractory DT in the intubated patient, particularly in the inpatient setting. Finally, anti-adrenergics, beta blockers, and clonidine may help treat autonomic hyperactivity symptoms, but do not treat delirium. Carbemazepine has been shown to be effective in treating early AWS, though it has not been proven efficacious in treating DT. (*47)

PSYCHOTHERAPY

Psychotherapy complements medical treatment in attaining successful outcomes. (*48) Physicians should be familiar with and capable of scheduling outpatient treatment for all methods of psychotherapy. Additionally, they should be able to perform brief interventional psychotherapy confidently as this can be completed while the patient is hospitalized for withdrawal. The National Institute for Alcohol Abuse and Alcoholism (NIAAA) has developed an outline of brief intervention components and goals. (*49) In general, a brief intervention includes an initial counseling session of ten to fifteen minutes to assess alcohol use, and a session to provide feedback, advice, and goal-setting. Follow-up by office visit or phone conversation is also encouraged. (*4) A meta-analysis of brief intervention demonstrated a mean reduction of four drinks of alcohol per week with significant results achieved in men but not women. (*50)

ALCOHOL ABUSE AND DEPENDENCE

Twenty percent of all hospitalized patients meet criteria for diagnosis of alcohol dependence (*7), and a significantly greater percent of patients suffering from AWS are alcohol dependent. Treatment of withdrawal alone does not address underlying alcohol addiction and does not produce long-term abstinence. Untreated alcohol dependence leads to repeated withdrawal episodes that can further worsen alcohol dependence. (*51) On the other hand, treatment of alcohol dependence benefits both the patient and society by improving general health, productivity, and generating cost savings. (*9, *10) Therefore, treatment of alcohol withdrawal should be followed by assessment and treatment of alcohol dependence; the ASAM delegates this as the third goal of detoxification. (*16)

ASSESSMENT

All patients presenting with alcohol-related complaints should be assessed for alcohol abuse and dependence. Physicians should begin by assessing the patient's history

for evidence of alcohol-related problems. The quantity of alcoholic intake, history of alcohol use, time since last drink, presence of co-morbid medical or psychiatric conditions, previous alcohol withdrawals, and abuse of other agents should be elicited from the patient. The NIAAA defines at risk drinking as greater than 14 drinks per week or four drinks per occasion for men and greater than seven drinks per week or three drinks per occasion for women. (*52) A standard drink is defined as 0.5 ounces (oz) of alcohol, which is equivalent to 12 oz of beer, 5 oz of wine and 1.5 oz of 80-proof distilled spirit. (*82)

Specific tools and criteria are available to accurately identify and diagnose alcohol abuse and dependence. The CAGE questionnaire is one of many screening tools that can be used in primary care, hospitalized and pre-operative settings to identify alcohol addiction. (*53, *54) Patients are given a point for each of four screening questions (Table 3) that they identify with. A score of 2 or greater suggests that a more detailed assessment with alcohol use is warranted. (*53).

Figure 4

Table 3

CAGE Questionnaire
Have you ever felt you should Cut down on your drinking?
Have other people Annoyed you by criticizing your drinking?
Have you ever felt Guilty about drinking?
Have you ever taken a drink in the morning to calm your nerves or get rid of a hangover (Eye opener)?

Ref #53: Ewing JA. Detecting alcoholism. the CAGE questionnaire. JAMA 1984;252:1905 –7.

Other screening tools that have been utilized include the Michigan Alcoholism Screening Test (MAST), a modified short MAST (sMAST), Alcohol Use Disorders Identification Test (AUDIT), and several others. The CAGE, MAST, and sMAST are the most widely used, with the MAST being more sensitive than CAGE, except in elderly patients, where CAGE may be more effective. Overall the CAGE, MAST, and sMAST perform comparably (*81). Multiple other screening modalities exist with differing sensitivities and specificities based on different patient populations.

Differentiating alcohol abuse from dependency is confusing to some clinicians. In general, abuse refers to misuse of alcohol that leads to impaired functioning, while dependence refers to an inability to control alcohol use for either physical or psychological reasons. Strict criteria for diagnosis of alcohol abuse (Table 4) and alcohol dependence (Table 5) are defined in DSM-IV. (*14) A diagnosis of alcohol dependence supercedes the diagnosis of alcohol abuse.

Figure 5

Table 4

DSM-IV Criteria for Alcohol Abuse:	
A.	A maladaptive pattern of alcohol abuse leading to clinically significant impairment or distress, as manifested by one or more of the following, occurring within a 12-month period:
1.	Recurrent alcohol use resulting in failure to fulfill major role obligations at work, school, or home.
2.	Recurrent alcohol use in situations in which it is physically hazardous.
3.	Recurrent alcohol-related legal problems.
4.	Continued alcohol use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the alcohol.
B.	These symptoms must never have met the criteria for alcohol dependence.

Ref #14: Adopted from: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Publishing Inc; 2000.

Figure 6

Table 5

DSM-IV Criteria for Alcohol Dependence:	
A.	A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three or more of the following seven criteria, occurring at any time in the same 12-month period:
1.	Tolerance, as defined by either of the following:
a	A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
b	Markedly diminished effect with continued use of the same amount of alcohol.
2.	Withdrawal, as defined by either of the following:
a	The characteristic withdrawal syndrome for alcohol.
b	Alcohol is taken to relieve or avoid withdrawal symptoms.
3.	Alcohol is often taken in larger amounts or over a longer period than was intended.
4.	There is a persistent desire or there are unsuccessful efforts to cut down or control alcohol use.
5.	A great deal of time is spent in activities necessary to obtain alcohol, use alcohol or recover from its effects.
6.	Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
7.	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 the alcohol

Ref #14: Adopted from: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Publishing Inc; 2000.

TREATMENT

Once a diagnosis of alcohol abuse or dependence has been made and the patient is amenable to treatment, the physician should treat the patient for co-morbid medical and psychiatric illnesses, refer the patient to an appropriate addiction therapy program, and discuss the pharmacotherapy options. These decisions can be made in consultation with addiction and psychiatry specialists. While most treatments are completed as outpatient, the physician or member of the medical staff should initiate them before discharge. Though brief intervention is helpful in patients with alcohol abuse (*55), more intensive treatment is needed to address alcohol dependence. Other psychological pharmacological treatments are available and complement each other in attaining successful outcomes in these patients. (*48)

The COMBINE study is the largest randomized trial comparing placebo, behavioral therapy, drug treatment with naltrexone or acamprosate, a combination of these methods, and no intervention for treatment of alcohol dependence. (*56) Results of this study demonstrated that naltrexone is as effective as behavioral therapy in achieving a high number of days of abstinence from alcohol, but was no more effective when combined with behavioral therapy. Acamprosate alone or combined with naltrexone or Cognitive Behavioral Therapy were all more effective than

non-treatment, but not placebo. At one-year follow-up, effects of all treatments were absent with the exception of naltrexone, which demonstrated a reduction in relapse to heavy drinking days. This indicates that alcohol abuse can be managed in the primary care setting with naltrexone or behavioral therapy. All physicians should be familiar with the methods described in this study. These methods are briefly discussed below.

BEHAVIORAL THERAPY

Cognitive Behavioral Therapy (CBT), Twelve Step Facilitation programs such as Alcoholics Anonymous (AA), and Motivational Enhancement Therapy (MET) are the main psychotherapy methods used in treating alcohol dependence. CBT is a structured, goal-directed intervention that aims to help patients identify how their thoughts contribute to maladaptive drinking behaviors. The goal is to develop new and healthy behaviors to control one's thoughts. Though CBT is proven to be effective alone in the treatment of alcohol dependence, controversy exists regarding whether CBT is synergistic with drug treatment. (*57, *56).

Twelve Step facilitations programs such as Alcoholics Anonymous (AA) are familiar to most physicians. AA seeks to help patients with alcohol addiction through voluntary fellowship and a spiritual basis for recovery. In addition to wider availability, AA is beneficial for patients because it is more cost-effective (*58) and equally efficacious (*59) as other outpatient treatment options. In patients who are uncomfortable with the spiritually-based approach employed by AA, alternative treatment groups are available. There is, however, insufficient data to determine the effectiveness of these programs.

MET involves patient-centered, non-confrontational counseling aimed at resolving ambivalence about behavioral changes that contribute to alcohol abuse and dependence. (*60, *61) MET has equivalent three year outcomes when compared to CBT and 12 step facilitation programs. (*62)

PHARMACOTHERAPY

Pharmacotherapy is of proven benefit (*63) and can reduce relapse in patients who have been treated for alcohol dependence (*64, *65). Thus far, naltrexone, acamprosate and disulfiram are approved for treatment of alcohol dependence in the US. (*70)

Naltrexone is an opioid receptor antagonist that reduces craving for alcohol by inhibiting the actions of endogenous opioids responsible for producing the pleasurable effects of

drinking. (*53, *66) Prior to publication of the COMBINE trial, naltrexone was proven to reduce relapse and number of drinking days (*66) and increase participation in behavioral therapy. (*67, *68). While previous trials suggested that naltrexone should only be used as an adjunct to behavioral therapy (*48) because of their proposed synergistic effect (*69), the randomized COMBINE demonstrated that naltrexone can be used without behavioral therapy. (*56)

Treatment with naltrexone is not completely benign. Relapse is common after the drug is discontinued (*58), and naltrexone can induce opioid withdrawal in opioid users. Naltrexone can also cause hepatocellular damage and is contraindicated in patients with liver failure or acute hepatitis, both of which are common in persons with alcohol dependence. Furthermore, most of the studies described above had short-term follow up periods. The long-term efficacy of naltrexone is relative weak and controversial (*70, *71, *56) Long-acting intramuscular depots of naltrexone have been developed to increase compliance (*72) and newer opioid antagonist such as nalmefene with more favorable side effect profiles are currently being investigated. (*73)

Acamprosate is a structural analog of gamma-aminobutyric acid that decreases excitatory glutamergic neurotransmission. Prior to publication of the COMBINE trial, multiple studies demonstrated to the effectiveness of acamprosate in maintaining abstinence from alcohol (*74), leading to its approval for use in 2004. However, after the publication of the COMBINE trial, the effectiveness of acamprosate has largely been associated with the placebo effect. (*56)

Disulfiram is an inhibitor of aldehyde dehydrogenase and is used as aversive therapy for maintenance of abstinence. Patients who consume alcohol while taking disulfiram experience symptoms such as hypotension, nausea, vomiting, flushing, headache, and palpitations that can be severe enough to cause convulsions or death. (*75) Disulfiram may reduce drinking days in dependent patients (*65) but the results are controversial (*76, *77) Given its hazardous side effects, patients must be cognizant of the consequences of alcohol consumption while on disulfiram and must champion its use. (*78) Even under these circumstances, disulfiram is rarely used in the US.

Other drugs that have shown promise for the treatment of alcoholism are still under investigation. Baclofen, topiramate, ondansetron have all been studied and found to

be helpful, however, sufficient clinical data is not yet available presently to recommend their use.

PATIENT FOLLOW-UP

Once abstinence from alcohol is achieved, it is important for physicians to monitor for and treat relapse as well as other co-morbidities associated with alcohol use. (*79) Physicians should be supportive of patients and encourage them to participate in treatment groups. Physicians should understand that a minority of patients with alcohol dependence may eventually be able to consume alcohol safely. (*80)

CONCLUSION

Alcohol-related disorders are a significant cause of morbidity for patients. With proper understanding of the pathophysiology, diagnosis, evaluation, and treatment of AWS, this condition can be managed well while minimizing complications for a hospitalized patient with AWS. Physicians should, however, understand that treatment of AWS in the acute setting should be followed by assessment and initial treatment for underlying alcohol abuse and dependence. In the transition from the hospital setting to outpatient, it is important for the physician to facilitate patient follow-up with appropriate behavioral therapy and initiate proper pharmacotherapy as needed. This transition requires actively engaged and dedicated physicians to manage patients effectively for their alcohol abuse and dependence long-term.

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