REVIEW ARTICLE

Alcohol Withdrawal in the Surgical Patient: Prevention and Treatment

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Alcohol is the most abused drug worldwide (1). In the United States, the apparent per capita consumption of ethanol from all alcoholic beverage types combined was 2.21 gallons pure ethanol in 1994 (2). In 1996, 109 million Americans aged ≥12 yr had used alcohol in the last month (51% of the population). Approximately 32 million (15% of the population) engaged in binge drinking (five or more drinks on at least one occasion in the last month), and approximately 11 million (5% of the population) were heavy drinkers (drinking five or more drinks per occasion on five or more days in the past 30 days). Traditionally, women have drunk less than men, but the gap is narrowing, especially between young women and men (3). There are 100,000 Americans killed by alcoholism annually, at a cost of $90–$116 billion each year (4).

The risk of being admitted to a hospital due to chronic alcohol misuse increases with the amount consumed daily (5). Chronic alcohol misuse is more common in surgical patients (e.g., up to 43% in otorhinolaryngological departments) than in psychiatric (30%) or neurological (19%) patients (6). Alcohol influences many organ systems and promotes carcinogenesis (1,7–10). More than 50% of patients with carcinomas of the gastrointestinal tract are chronic alcoholics (8). Almost half of all trauma beds are occupied by patients who were injured while under the influence of alcohol (11–14). In addition to the life-threatening complications of alcohol withdrawal syndrome (AWS), the rate of morbidity and mortality due to infections, cardiopulmonary insufficiency, or bleeding disorders is 2 to 4 times greater in chronic alcoholics (10,13–18).

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Natural History, Manifestations, and Clinical Presentation of AWS

The most feared postoperative complication of AWS is the development of an unforeseen delirium tremens. This can develop in chronic alcoholics who are alcohol-dependent according to the *Diagnostic and Statistical Manual of Mental Disorders* (19) or the *International Classification of Diseases* (20) criteria. Alcohol dependence includes physical dependence, tolerance, and compulsive alcohol use that becomes the maingoal directed activity of the subject. At least half of the chronic alcoholics scheduled for surgery or after trauma are alcohol-dependent (14,15). The development of AWS can change a normal postoperative course into a life-threatening situation in which the patient requires intensive care unit (ICU) treatment. In addition to patient risk, the treatment also becomes more complicated and expensive (14,15).

AWS consists of a range of signs and symptoms that typically develop in alcohol-dependent people 6–24 h of their last drink. It may occur unintentionally if abstinence is enforced by illness or injury or other causes (21). The symptoms of AWS were first described by Plinius Major as early as in the first century BC "*. . . . hinc. . . tremulae manus. . . . furiales somni et inquies nocturna*" (22,23). Autonomic hyperactivity appears within hours of the last drink and usually peaks within 24 to 48 h. The most common features are tremulousness, sweating, nausea, vomiting, anxiety, and agitation. Neuronal excitation, which may include epileptiform seizures (frequently grand mal) usually occur within 12–48 h of abstinence. After these prodromi, delirium tremens, which is characterized by auditory and visual hallucinations, confusion, and disorientation, clouding of consciousness, impaired attention, and pronounced autonomic hyperactivity, develops. If left untreated, death by respiratory and cardiovascular collapse may result (21). Despite the well known symptoms, the prevention of AWS is not

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always successful, and the development of AWS is potentially life-threatening.

The Pathophysiology of AWS

Chronic alcohol exposure exerts numerous pharmacological effects by means of interactions with various neurotransmitters and neuromodulators (24). During chronic ethanol administration, compensatory changes can result in an up-regulation of glutamatergic transmission (e.g., by *N*-methyl-D-aspartate [NMDA] or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and a down-regulation of GABAergic functions, restoring equilibrium in the presence of ethanol but resulting in withdrawal hyperactivity in the absence of ethanol (25).

The most widely accepted mechanism of adaptation to chronic ethanol exposure is up-regulation of the cyclic adenosine 3′,5′-monophosphate (cAMP) pathway (26). Whereas acute ethanol exposure stimulates the cAMP pathway in many neurons in the brain, chronic exposure inhibits it, therefore leading to a compensatory up-regulation of the cAMP pathway in certain brain regions (locus coeruleus, nucleus accumbens, ventral tegmental area) (27,28). Up-regulation of the cAMP pathway can represent a form of physiological dependence; on removal of the drug, the up-regulated cAMP pathway can "overshoot" and contribute to features of withdrawal (27–30). Up-regulation of the cAMP pathway interferes with glutamatergic, GABAergic, dopaminergic, serotonergic, and opioidergic actions of the neurons (27–31).

Because of the various neurotransmitter systems affected (32), it is not surprising to find a complex pathophysiology of AWS. The onset and spectrum of the various symptoms result from different transmitter systems, which differ in their vulnerability to the withdrawal of ethanol (Fig. 1). On one hand, there is an increased activity of excitatory mechanisms; on the other hand, there is a decreased function of inhibitory systems (32). Withdrawal also seems to interact with the hypothalamus-pituitary-adrenal axis. An increase in corticotropin-releasing factor (33) and a decrease in β-endorphin (34,35) has been reported after alcohol withdrawal, which has been suggested to predispose patients to relapse to alcohol misuse. Kindling phenomena are reported after repeated withdrawal, i.e., there is evidence for sensitization so that repeated withdrawals become progressively more severe. However, treatment of withdrawal may retard this sensitization process (36,37). Despite long-term abstinence, selective changes such as loss of serotonergic or GABAergic neurotransmission may persist (38).

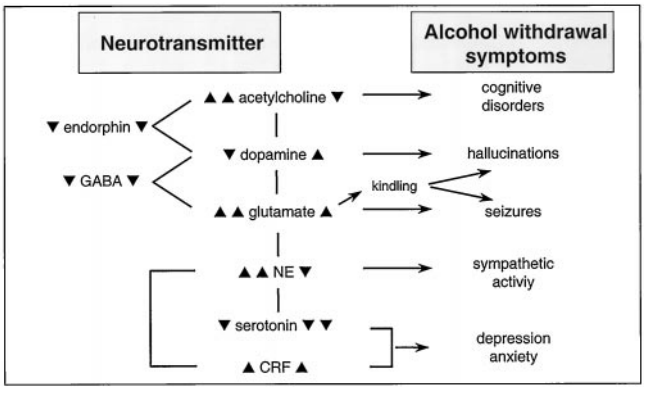

Figure 1. Neurotransmitter imbalance and alcohol withdrawal-related symptoms. NE = norepinephrine, CRF = corticotropin-releasing factor. ▲ = increase, ▼ = decrease.

Differential Diagnosis

The differential diagnosis in ICU patients is often complex. Cognitive disorders and productive-psychotic symptoms such as hallucinations are difficult to recognize in tracheally intubated patients. Most patients in the ICU require prolonged analgesia and sedation. When sedation is reduced, the differential diagnosis includes a broad spectrum of common complications. Before the differential diagnosis of AWS can be established in an agitated ICU patient, common complications, such as bleeding, metabolic, or electrolyte disorders; infection; hypoxia; pain; or focal neurological signs, must be excluded (39). Because of this complex differential diagnosis, adequate therapy may be delayed, and the patient's condition may deteriorate (39).

Incidence and Severity of AWS in Surgical Patients

An Australian study of a representative sample of 2046 patients admitted to a general hospital found 8% of the general population to be at risk of alcohol withdrawal. Of these patients, 8% had seizures or hallucinations during their admission (40). In contrast, a 16% incidence of AWS was found in patients after surgery, and a 31% incidence was found in trauma patients (14,15).

The importance of predicting the risk of AWS was clearly illustrated in one of our previous studies (15). Of 121 individuals with chronic alcohol misuse preoperatively, 70 were diagnosed as alcohol-dependent. Two thirds of the latter were identified preoperatively. These patients received prophylactic treatment with flunitrazepam and, as adjunctives, haloperidol and clonidine to treat AWS. Nonetheless, 25% still developed withdrawal symptoms— as measured by the revised Clinical Withdrawal Assessment for Alcohol Scale (Table 1) (41)—although they were significantly

Table 1. Revised Clinical Institute Withdrawal Assessment for Alcohol Scale[a]

Nausea and vomiting (0 = no nausea, no vomiting; 1 = mild nausea without vomiting; 4 = intermittend nausea with dry heaves; 7 = constant nausea, frequent dry heaves, and vomiting)
Tremor (0 = no tremor; 1 = not visible, but can be felt fingertip to fingertip; 4 = moderate, with patient's arms extended; 7 = severe, even with arms not extended)
Paroxysmal sweats (0 = no sweat visible; 1 = barely perceptible sweating, palms moist; 4 = beads of sweat obvious on forehead; 7 = drenching sweat)
Anxiety (0 = no anxiety, at ease; 1 = mildly anxious; 4 = moderately anxious or guarded, so that anxiety is inferred; 7 = equivalent to acute panic states seen in severe delirium or acute schizophrenic reactions)
Agitation (0 = normal activity, 1 = somewhat more than normal activity, 4 = moderately fidgety and restless, 7 = paces back and forth during most of the interview or thrashes about constantly)
Tactile disturbances (0 = none; 1 = very mild itching, pins and needles, burning, or numbness; 2 = mild itching, pins and needles, burning, or numbness; 3 = moderate itching, pins and needles, burning, or numbness; 4 = moderately severe hallucinations; 5 = severe hallucinations; 6 = extremely severe hallucinations; 7 = continuous hallucinations)
Auditory disturbances (0 = not present, 1 = very mild harshness or ability to frighten, 2 = mild harshness or ability to frighten, 3 = moderate harshness or ability to frighten, 4 = moderately severe hallucinations, 5 = severe hallucinations, 6 = extremely severe hallucinations, 7 = continuous hallucinations)
Visual disturbances (0 = not present, 1 = very mild sensitivity, 2 = mild sensitivity, 3 = moderate sensitivity, 4 = moderately severe hallucinations, 5 = severe hallucinations, 6 = extremely severe hallucinations, 7 = continuous hallucinations)
Headache/fullness in head (0 = not present, 1 = very mild, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = very severe, 7 = extremely severe)
Orientation/clouding of sensorium (0 = oriented and can do serial additions, 1 = cannot do serial additions or is uncertain about date, 2 = disoriented as to date by ≤2 calendar days, 3 = disoriented as to date by >2 calendar days, 4 = disoriented as to place and/or person)

Total: 0–67 points.
[a] Modified from Ref. 41.

milder than those of chronic alcoholics who had developed unforeseen AWS (one third of the alcohol-dependent patients). The latter group required prolonged ICU treatment (mean difference 14 days) compared with patients who received prophylactic treatment (15).

Perioperative Assessment

A well performed preoperative assessment can reduce the postoperative risk of AWS (15). With an established diagnosis of alcohol dependence, an adequate prophylaxis can be performed, and AWS can be prevented in up to 75% of patients (15). However, only 1%–24% of surgical patients with a history of chronic alcohol misuse are diagnosed during clinical routines (6,42).

Diagnosis

A precise preoperative assessment should at least include an alcoholism-related questionnaire, along with a routine history and physical examination. In clinical routine, the CAGE (43) is a short, precise, and feasible 4-item questionnaire (Table 2). Patients with a CAGE score >2 are considered chronic alcoholics. Buchsbaum et al. (44) found a good correlation between the CAGE results and the *Diagnostic and Statistical Manual of Mental Disorders* criteria for alcohol dependence (19).

Table 2. Recognition of Alcohol Misuse and Strategy in Surgical Patients

Recognition
History and physical examination
Alcoholism-related questionnaire
CAGE[a]
Have you ever felt you should **c**ut down on your drinking?
Have other people **a**nnoyed you by criticizing your drinking?
Have you ever felt **g**uilty about drinking?
Have you ever taken a drink in the morning to steady your nerves or get rid of a hangover (**e**ye opener)?
Laboratory markers: CDT, GGT, and MCV
Strategy
If CAGE ≥ 3 or CAGE ≥ 2 and at least one laboratory marker positive
Preoperative or immediate postoperative prophylaxis required
If CAGE < 2 but two laboratory markers positive
Reevaluation of the patient (history, alcoholism-related questionnaire)
Preoperative or immediate postoperative prophylaxis should be considered

CDT = carbohydrate-deficient transferrin, GGT = γ-glutamyl-transferase, MCV = mean corpuscular volume.
[a] Yes = 1, No = 0; a score ≥3 high risk of alcohol dependence. See Ref. 43.

An alcohol-related history is frequently unobtainable for traumatized patients because of their injuries and subsequent endotracheal intubation. Laboratory tests with sufficient sensitivity and specificity may assist in

the diagnosis and possible prevention of complications (Table 2). Mean corpuscular volume (MCV) and γ-glutamyl-transferase (GGT) are often used, but neither is sufficiently sensitive (MCV 34%–89%, GGT 34%–85%) or specific (MCV 26%–91%, GGT 11%–85%)(45).

A recent biological laboratory marker, carbohydrate-deficient transferrin (CDT), may have a specificity (82%–100%) and a sensitivity (39%–94%) greater than or equal to those of MCV and GGT (45). CDT are isoforms of transferrin (46). A chronic daily intake of >50–80 g of alcohol for longer than a week was reported to increase CDT levels. The half-life of CDT is approximately 2 wk (46), but in ICU patients, it seems to be considerably shorter (47). The sensitivity of CDT in multiple-injury patients decreases from 65% in the emergency room to 35% on admission to the ICU after primary care and surgery (47). Although the reason for this rapid decline has not been fully elucidated, it may be the requirement of blood transfusions (47). Pathologically increased CDT values on admission to the emergency room have been associated with an increased morbidity and a prolonged ICU stay (median difference of 8 days), resulting in extra costs of approximately $12,000 per patient (48). Thus, CDT can be used as a marker to detect patients at risk (48).

It should be emphasized, however, that all biological laboratory markers, whether commercially available or still at the research stage, can detect chronic alcohol use but cannot determine whether the patient is physically dependent (46,47,49–52). Only the former require prophylactic treatment for the potential development of AWS. Nevertheless, chronic alcohol misusers are still at risk of developing other complications, such as infections, cardiovascular complications, and bleeding disorders.(14,15,18)

Intraoperative Management

Chronic alcohol intake may produce either enhanced or reduced sensitivity to anesthetics. Oxidation of ethanol by means of the alcohol dehydrogenase pathway produces acetaldehyde, which is converted to acetate; both reactions reduce nicotinamide adenine dinucleotide (NAD) to NADH. Excess NADH causes a number of metabolic disorders, including hyperlactacidemia. NADH also opposes gluconeogenesis (thereby favoring hypoglycemia), increases α-glycerophosphate levels, and inhibits the Krebs cycle and fatty-acid oxidation (1). Cytochrome P-450 2E1 (CYP2E1) is the major ethanol-oxidizing enzyme of the nonalcohol dehydrogenase metabolic pathway in the liver (1). Long-term consumption of ethanol induces the microsomal ethanol-oxidizing system (1). The induction of this oxidizing system contributes to the metabolic tolerance of ethanol in alcoholics and also affects the metabolism of other drugs. When volunteers consumed alcohol over several weeks, the clearance of meprobamate, pentobarbital, propanolol, antipyrine, tolbutamide, warfarin, diazepam, and rifamycin from the blood was increased for a number of days or weeks (1). The most important clinical feature of CYP2E1 is its extraordinary capacity to convert many foreign substances into highly toxic metabolites. These drugs include anesthetics (e.g., enflurane), commonly used medications (e.g., isoniazid and phenylbutazone), and over-the-counter analgesics (e.g., acetaminophen), all of which are substrates for or inducers of CYP2E1 (1,53). The perianesthetic plasma fluoride kinetics subsequent to sevoflurane anesthesia have also been associated with CYP2E1 activity (54). Therefore, renal function should be assessed before and after sevoflurane anesthesia in chronic alcoholics (54). In contrast to the long-term consumption of ethanol, which induces the hepatic metabolism of drugs, short-term consumption inhibits their metabolism because of the direct competition for CYP2E1 (1). Methadone exemplifies this dual interaction: 50% of methadone users are also alcohol abusers. Whereas long-term consumption of ethanol increases the hepatic microsomal metabolism of methadone, short-term consumption inhibits microsomal demethylation of methadone and increases its concentrations in the brain and liver. The combined intake of ethanol and tranquilizers or barbiturates may also dangerously increase drug levels. In view of the opposite effects of immediate and long-term alcohol consumption, it is difficult to predict the net effect of concomitant alcohol and anesthetic use in a given long-term alcohol consumer. It varies with the amounts used, the relative affinity of alcohol and the other drugs for the microsomal detoxification process, and the severity of the underlying liver injury, which may offset the enzyme induction (1).

Prevention of AWS

In contrast to the psychiatric patient admitted for ethanol detoxification (55), surgical patients can usually undergo prophylactic treatment (Table 3) (56). Whereas withholding prophylaxis from alcohol-dependent patients increases postoperative complications and the duration of ICU treatment, prophylactic treatment is actually required in ICU settings (Table 4) (15). A study showed that in 72% of the 672 surgical departments involved, prophylactic treatment was administered, based mostly on a combination of benzodiazepines, chlormethiazole, haloperidol, clonidine, or ethanol (56). In a randomized (but unblinded) study of alcohol-dependent patients after surgery and ICU admission, we assessed the efficacy of four different prophylactic regimens (benzodiazepine and haloperidol versus benzodiazepine and clonidine versus chlormethiazole and haloperidol versus ethanol) (57). We found a significant variation in the dosages required to prophylactically treat AWS (Table 4). The different regimens were not significantly different with respect to the duration of ICU treatment, but the incidence of tracheobronchitis was significantly increased in

Table 3. Treatment of Alcohol Misuse in Surgical Ward Patients

- Prophylaxis
  - First-line treatment: benzodizepines—diazepam 2.5–10 mg, lorazepam 0.5–2 mg, or chlordiazepoxide 5–25 mg every 6 h
    - Alternative to benzodiazepines: chlormethiazole (enteral 0.25–1 g every 6 h; contraindication: pulmonary infection) or ethanol (0.5–1 $g \cdot kg^{-1} \cdot d^{-1}$ enteral or 0.5 $g \cdot kg^{-1} \cdot d^{-1}$ IV; contraindication: infection, congestive heart failure, CIWA-Ar Score >15)
  - Monitor patient every 4 h by means of CIWA-Ar to maintain score <10 for 24 h
- Therapy
  - Establish diagnosis and severity of alcohol withdrawal syndrome
    - Use validated measure such as CIWA-Ar Score
    - Perform differential diagnosis (the diagnosis of alcohol withdrawal syndrome must only be established if other differential diagnoses are excluded: e.g., I WATCH DEATH); monitor vital signs and obtain laboratory results (heart rate, blood pressure, temperature, sodium, potassium, magnesium, blood sugar, arterial blood gas analysis, WBC, Hb, Hct)
  - If CIWA-Ar Score >20, transfer patient to critical/intensive care unit and start therapy; if 10 < CIWA-Ar Score ≤ 20, watch patient until symptoms are controlled
  - Start with benzodiazepine (alternative: chlormethiazole, ethanol)
    - Symptom-triggered regimen: administer one of the following benzodiazepines every hour when CIWA-Ar Score >10—titrate diazepam 10–40 mg, lorazepam 1–8 mg, or chlordiazepoxide 50–100 mg; repeat CIWA-Ar 1 h after every dose to assess need for further medication
    - Fixed-schedule regimen: administer one of the following benzodiazepines—diazepam 10–20 mg every 6 h for four doses, then 5–10 mg every 6 h for eight doses; lorazepam 2–4 mg every 6 h for four doses, then 1–2 mg every 6 h for eight doses; chlordiazepoxide 50–100 mg every 6 h for four doses, then 25–50 mg every 6 h for eight doses
  - Provide additional medication as needed when symptoms occur (e.g., in case of autonomic signs, use clonidine or β-blockers; in case of hallucinations, use haloperidol)
  - Monitor patient every 4 h by means of CIWA-Ar until score has been <10 for 24 h

CIWA-Ar = Clinical Institute Withdrawal Assessment for Alcohol Scale; I WATCH DEATH = infections, acute metabolic, trauma, central nervous system pathology, hypoxia, deficiencies, endocrinopathies, acute vascular, toxins/drugs, heavy metals; WBC = leukocyte count; Hb = hemoglobin; Hct = hematocrit. Prophylaxis and therapy modified from Ref. 55.

the chlormethiazole/haloperidol group due to bronchial hypersecretion (67% vs 25%–44% in the other groups) (57). According to recently published evidence-based practice guidelines (55), ethyl alcohol is not recommended for the prevention of withdrawal symptoms because only uncontrolled trials have been performed (58–61). In our own randomized but unblinded study, ethanol was as efficient as the other pharmacological drugs in preventing AWS (57). Moreover, *in vitro* studies have shown that small-dose ethanol may be immunoprotective (62). Based on these considerations, current prophylactic regimens are summarized in Table 3 for surgical ward patients and in Table 4 for surgical ICU patients.

Therapy of AWS

Evidence-Based Guidelines

Although there has been extensive research on pharmacological interventions aimed at ameliorating withdrawal, the studies are widely dispersed in the medical literature, involve few subjects, and are often of uncertain methodological quality. Recommendations from authoritative sources vary widely, with recommendations for drugs that have never been tested in clinical trials or for approaches that result in the administration of unnecessary medication (23,55). Most studies have failed to use an international scale to quantify AWS (41,55). In certain studies, even the differentiation among autonomic signs, hallucinations, and the delirious state is missing (23,55). In many studies, there are too few patients to detect differences among different regimens (23,55).

Notwithstanding, the following evidence-based practice guidelines were developed for nonsurgical patients (55). Benzodiazepines are suitable drugs for alcohol withdrawal. The choice among different drugs should be guided by duration of action, rapidity of onset, and cost. Because withdrawal severity varies greatly and the amount of medication needed to control symptoms can also vary significantly, AWS cannot be adequately treated by a fixed standardized dose for all patients. Treatment should allow for a degree of individualization so that patients can receive large amounts of medication rapidly if needed (55,63). Individual treatment should be based on withdrawal severity as measured by withdrawal scales, comorbid illness, and history of withdrawal seizures. Trials comparing different benzodiazepines have demonstrated that all seem similarly effective in reducing signs and symptoms. There is some evidence that longer-acting drugs such as diazepam may be more effective in preventing seizures (55). There are few data on the comparative efficacy of benzodiazepines in reducing delirium (55). Pharmacological and clinical experience suggests that longer-acting benzodiazepines

Table 4. Intravenous treatment for Alcohol Withdrawal Syndrome in Surgical Intensive Care Patients

Prophylaxis
Start with benzodiazepine (alternative: chlormethiazole, ethanol) and add additional medication such as clonidine or haloperidol
Monitor patient every hour by means of CIWA-Ar to maintain score <10 for 24 h
Therapy
Start with benzodiazepine, add additional medication such as haloperidol or clonidine
Titrate medication immediately to decrease CIWA score <10, then monitor patient every hour by means of CIWA-Ar until score has been <10 for 24 h
Control electrolytes very closely (cave potassium and magnesium!)

	Prophylactics[a]	Therapeutics[b]
Flunitrazepam		
Bolus (mg)	1.0 (0.5–2.0)	4.0 (0.5–16.0)
Infusion rate ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	6 (1–61)	19 (2–290)
Chlormethiazole		
Bolus (mg)	150 (25–500)	375 (45–500)
Infusion rate ($mg \cdot kg^{-1} \cdot h^{-1}$)	2.5 (0.6–8.9)	8.2 (1.5–12.0)
Haloperidol		
Bolus (mg)	10 (5–20)	20 (10–40)
Infusion rate ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	29 (9–99)	53 (5–355)
Clonidine		
Bolus (mg)	0.15 (0.075–0.30)	0.30 (0.15–1.20)
Infusion rate ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	0.83 (0.07–3.39)	0.88 (0.14–4.69)
Ethanol		
Bolus (g)	3 (2–4)	Obsolete
Infusion rate ($mg \cdot kg^{-1} \cdot h^{-1}$)	48 (12–157)	

CIWA-Ar = Clinical Institute Withdrawal Assessment for Alcohol Scale.
[a] Modified from Ref. 57.
[b] Modified from Ref. 69.

can pose a risk of excess sedation in selected groups, including the elderly and those with marked liver disease (55). Longer-acting benzodiazepines, however, contribute to an overall smoother withdrawal course with less breakthrough or rebound symptoms (55). Certain benzodiazepines have a higher liability for abuse, and the cost of these drugs varies considerably (55). β-adrenergic blockers, clonidine, and neuroleptic drugs may be used as adjunctive therapy but are not recommended as monotherapy (55). To prevent Wernicke's encephalopathy, thiamine may be administered to all patients with alcohol dependence at the initial examination (55).

These guidelines have limited applicability to surgical and ICU patients because, in these situations, withdrawal severity not only varies greatly, but is usually increased. In addition, the amount of medication needed to control symptoms may be increased in individual patients by up to 100-fold compared with psychiatric patients admitted for ethanol detoxification (Tables 3 and 4) (39,55,64–67). Of 672 centers performing therapy for AWS in surgical patients, 64% use drug combinations (56,67). The reasons for the discrepancies in the dose and number of detoxifying drugs in surgical and ICU patients are poorly understood. Transmitter imbalances (e.g., in endorphin and noradrenergic systems) may be more pronounced because of trauma, pain, and stress (68). We investigated the three most popular current regimens for AWS (benzodiazepine/haloperidol, benzodiazepine/clonidine, and chlormethiazole/haloperidol) in ICU patients after trauma (Table 4) (69). The intercurrent complications, but not the duration of ICU treatment, differed among the groups. The incidence of pneumonia was increased in the chlormethiazole/haloperidol group (68% vs 40% in the flunitrazepam/clonidine group and 53% in the flunitrazepam/haloperidol group), whereas cardiac complications were significantly increased in the flunitrazepam/clonidine group (59% vs 17% in the flunitrazepam/haloperidol group and 18% in the chlormethiazole/haloperidol group) (69). The major side effects of chlormethiazole are bronchial hypersecretion and respiratory depression; therefore, many patients require mechanical ventilation (39). Clonidine and haloperidol may lead to QT-interval prolongation, which may induce life-threatening arrhythmias (39,56,65,70). Clonidine may not be the drug of choice for patients with increased intracranial pressure because α_2-agonists can decrease cerebral blood flow and increase cerebral vascular resistance (71,72). This was also found in experimental settings after hypoxia and may lead to insufficient cerebral tissue oxygenation (73).

To prevent the recurrence of withdrawal symptoms and secondary withdrawal from drugs, it is essential to

gradually reduce the therapy (69,73). A more symptom-oriented approach may decrease the medication requirement and the duration of treatment. The benefits of a symptom-triggered therapy with chlordiazepoxide have been shown in in-patient detoxification (63), but this requires extensive staff training. When no such training is available, an acceptable alternative is the use of fixed-schedule therapy, with the provision of additional medication when symptoms are not controlled (55). Because haloperidol or clonidine decreases seizure thresholds, the administration of a benzodiazepine (alternatively chlormethiazole) should be considered for every patient (39,55,69). A summary concentrating on the evaluation of treatment is given in the guidelines developed by the Plinius Major Society (23).

New and Experimental Therapies

Although pharmacological inhibitors of the NMDA transmitter system or anti-sense oligonucleotide-induced reduction of nitric oxide (NO) synthase produce beneficial effects (74), NMDA antagonists (including phencyclidine) have reinforcing and synergistic effects with drugs of abuse (74), which suggests that chronic co-administration of NMDA receptor antagonists could make certain drugs more addictive. In addition, such compounds (e.g., ketamine, a noncompetitive antagonist of the NMDA receptor) may have deleterious effects due to a reduced seizure threshold (75). The only indication for ketamine would be obstructive lung disease in patients with AWS pretreated with benzodiazepines and with no signs of autonomic hyperactivity. As adjunctive therapy, the dose is 0.4–1.0 $mg \cdot kg^{-1} \cdot h^{-1}$ IV

Drugs that act on GABA receptors or that modulate GABA function, such as benzodiazepines and γ-hydroxybutyric acid (76–78), are also abused (73,79). γ-Hydroxybutyric acid is a potent growth hormone releaser used by bodybuilders and athletes. Propofol acts on a subunit of the GABA receptor ionophore complex (75). The outstanding characteristic of propofol is its rapid penetration into the central nervous system and its rapid elimination kinetics (75). It can be used as an additive to reduce AWS symptoms overnight and leave the patient more alert during daytime. It can also be useful in refractory delirium tremens (80).

Special Considerations

Ethanol consumption alters neuroendocrine and immune functions in both adults and the fetus. In animal studies, abnormal hypothalamic-pituitary-adrenal axis functions have been linked to the development of inflammation and infection (81). Surgery or trauma adds to the ethanol-induced immune suppression (82), possibly by down-regulating T-cell–mediated responses, delayed type hypersensitivity, interleukin (IL)-2 expression, initial tumor necrosis factor (TNF) and interferon production, and cytolytic activity (82–84). We found significantly decreased levels of the proinflammatory cytokines TNF-α, IL-1, IL-6, and IL-8 in septic shock patients with a history of chronic alcohol use compared with those in nonalcoholics (85). More extensive research concerning the actions of alcohol on the neuroendocrine-immune axis should lead to the development of therapies aimed at alleviating aberrant immune system functions in these patients (81).

Summary

In the literature on AWS, there is repeated emphasis on performing a thorough preanesthesia assessment in patients with suspected chronic alcohol use. Because these patients are difficult to diagnose and to treat in surgical settings if complications arise, a multimodal approach is highly recommended (86). Ideally, AWS should be prevented by adequate prophylaxis. If AWS develops after surgery or trauma, immediate therapy is required. The symptoms of AWS can be controlled using the combination of a benzodiazepine (in Europe, also chlormethiazole) with haloperidol or clonidine. The drug regimens must be individualized and symptom-oriented to treat hallucinations and autonomic signs. Dosages are generally larger than those in detoxification units. Other approaches to modulate the neuroendocrine-immune axis in patients with an increased risk of postoperative infectious complications look promising but await controlled trials.

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