Novel Algorithms for the Prophylaxis and Management of Alcohol Withdrawal Syndromes–Beyond Benzodiazepines

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KEYWORDS

• Alcohol withdrawal • Withdrawal prophylaxis • Benzodiazepines
• Anticonvulsant agents • Alpha-2 agonists • Delirium tremens

KEY POINTS

- Ethanol affects multiple cellular targets and neural networks; and abrupt cessation results in generalized brain hyper excitability, due to unchecked excitation and impaired inhibition.
- In medically ill, hospitalized subjects, most AWS cases (80%) are relatively mild and uncomplicated, requiring only symptomatic management.
- The incidence of complicated AWS among patients admitted to medical or critical care units, severe enough to require pharmacologic treatment, is between 5% and 20%.
- Despite their proven usefulness in the management of complicated AWS, the use of BZDP is fraught with potential complications.
- A systematic literature review revealed that there are pharmacologic alternatives, which are safe and effective in the management of all phases of complicated AWS.

BACKGROUND

Alcohol use disorders (AUDs) are maladaptive patterns of alcohol consumption manifested by symptoms leading to clinically significant impairment or distress.[1] Ethanol is the second most commonly abused psychoactive substance (second to caffeine) and AUD is the most serious drug abuse problem in the United States[2] and worldwide.[3] The lifetime prevalences of *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, alcohol abuse and dependence were 17.8% and 12.5%, respectively; the total lifetime prevalence for any AUD was 30.3%.[4] Alcohol consumption-related problems are the

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Crit Care Clin 33 (2017) 559–599
http://dx.doi.org/10.1016/j.ccc.2017.03.012 **criticalcare.theclinics.com**

third leading cause of death in the United States.[5] An estimated 10% to 33% of patients admitted to the intensive care unit (ICU) have an AUD,[6–8] with a concomitant doubling of mortality.[9–11] AUD increases the need for mechanical ventilation by 49%, whereas a diagnosis of alcohol withdrawal syndrome (AWS) is associated with longer mechanical ventilation.[7] Morbidity and mortality rates are 2 to 4 times higher among chronic alcoholics, due to infections, cardiopulmonary insufficiency, or bleeding disorders[11–17]; and are associated with prolonged ICU stays (P = .0001).[15] The author found that up to 30% of ICU patients require pharmacologic management of complicated AWS.[18]

NEUROBIOLOGICAL EFFECTS OF ALCOHOL

Alcohol has varying effects in the central nervous system (CNS), depending on volume ingested and the chronicity of its use. Ethanol acts on many cellular targets of several neuromodulators within many neural networks in the brain.[19] The abrupt cessation of alcohol results in generalized brain hyperexcitability because receptors previously inhibited by alcohol are no longer inhibited and inhibitory systems are not functioning properly (**Fig. 1**). AWS is mediated by several neurochemical mechanisms: (1) the alcohol-enhanced effect of γ-aminobutyric acid (GABA) inhibitory effect; (2) alcohol-mediated inhibition of N-methyl-D-aspartate (NMDA)-receptors, leading to their upregulation and increased responsiveness to the stimulating effect of glutamate (GLU); and (3) excess availability of norepinephrine (NE) due to desensitization of alpha-2 receptors and conversion from dopamine (DA). The results are the classic clinical symptoms of AWS, including anxiety, irritability, agitation, tremors, and signs of adrenergic excess, as well as, in its extreme forms, withdrawal seizures, and delirium tremens (DT).[17,20–23]

OVERVIEW OF ALCOHOL WITHDRAWAL SYNDROMES

AWS occurs after a period of absolute or, in some cases, relative abstinence from alcohol (ie, as soon as the blood alcohol level decreases significantly in habituated individuals). Therefore, it is possible for patients to experience AWS even with elevated blood alcohol concentration (BAC). Approximately 50% of alcohol-dependent patients develop clinically relevant AWS.[24,25] Moreover, 10% to 30% of patients

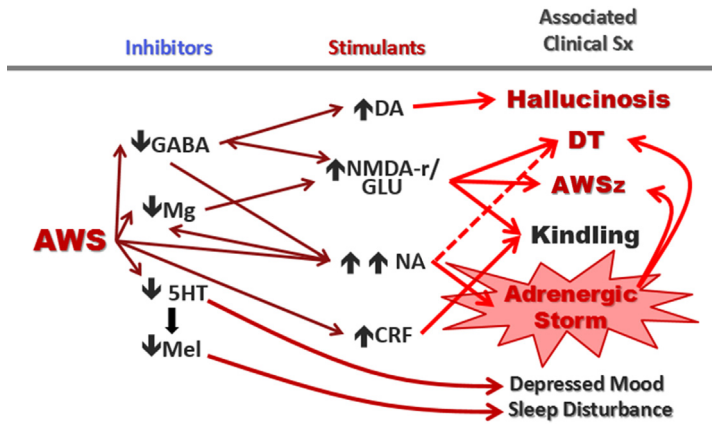

Fig. 1. Summary of neurotransmitter changes associated with AWSs. AWS, alcohol withdrawal syndrome; AWSz, alcohol withdrawal seizures; CRF, corticotropin-releasing factor; DA, dopamine; DT, delirium tremens; GABA, gamma-aminobutyric acid; GLU, glutamate; Mg, magnesium; NA, noradrenaline or norepinephrine; NMDA, N-methyl-D-aspartate receptor.

admitted to the hospital ICU experience AWS[7,8,26,27]; which is associated with increased morbidity and mortality.[28]

Typically, AWS begins within 6 to 24 hours after alcohol cessation or significant reduction of usual consumption, in habituated individuals (**Fig. 2**, **Table 1**).[29]

Uncomplicated withdrawal (so-called shakes) begins on the first day (as early as 12 hours after the last drink), peaking approximately 24 to 36 hours after relative or absolute abstinence. Approximately 80% of alcohol-dependent subjects will experience this and eventually recover without further complications.[30] Tremors, nervousness, irritability, nausea, and vomiting are the earliest and most common signs. In mild cases, withdrawal usually subsides in 5 to 7 days even without treatment. More severe symptoms lasting up to 10 to 14 days include coarse tremors (involving the upper extremities and tongue), anorexia, nausea, vomiting, psychological tension, general malaise, hypertension, autonomic hyperactivity, tachycardia, diaphoresis, orthostatic hypotension, irritability, vivid dreams, and insomnia.[23] Extrapyramidal symptoms may occur during AWS, even in patients not exposed to antipsychotic medications, after several weeks of continuous drinking or after an intensive brief binge episode.[31,32]

Alcohol withdrawal seizures (so-called rum fits) begin on the first day, peaking in approximately 12 to 48 hours (95% occurring in 7–38 hours) after a relative or absolute abstinence from alcohol. Grand mal seizures occur in up to 5% to 15% of patients experiencing AWS. Usually characterized by generalized motor seizures occurring during the course of AWS in the absence of an underlying seizure disorder.[30,33–35] The greater the amount of alcohol consumed, the greater the risk for seizures.[36–38] Approximately one-third of patients who develop AWS-seizures will only experience 1 seizure; whereas two-thirds will have multiple seizures, if untreated. Only a small minority (~3%) will develop status epilepticus; these patients often have an underlying seizure disorder.[30,35,39] Approximately one-third of patients who develop seizures go on to develop alcohol withdrawal delirium, or DTs.

Patients experiencing AWS may experience seizure activity that is not a direct consequence of the withdrawal itself. Alcohol-related seizures are defined as "adult onset seizures that occur in the setting of chronic alcohol dependence."[40] Yet alcohol withdrawal per se is the cause of seizures only in a subgroup of these patients.[40] In fact, approximately 50% of the seizures experienced by alcoholic subjects are a result of concurrent organic causes, such as cerebrovascular accidents, pre-existing epilepsy, toxic or metabolic conditions, structural brain lesions, nontraumatic intracranial lesions

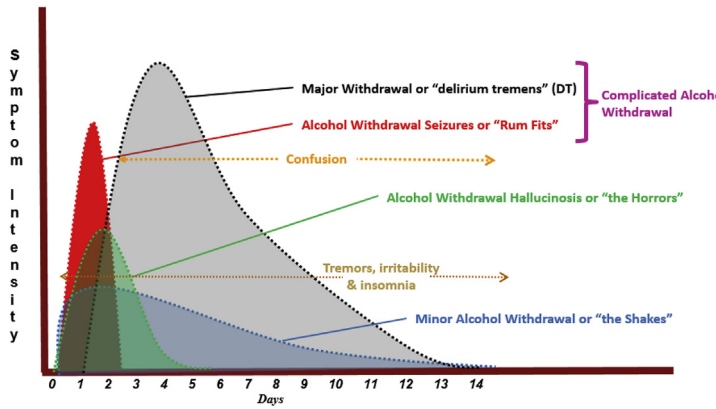

Fig. 2. Timing of alcohol withdrawal syndromes (AWS).

Table 1
Alcohol withdrawal syndromes

AWS	Time to Onset	Incidence	Manifestations
Uncomplicated Withdrawal (The Shakes)	Onset ~12 h, peak 24–36 h	80%	• Mild: tremors, nervousness, irritability, nausea, & vomiting are the earliest and most common signs • More severe symptoms lasting up to 10–14 d include coarse tremors (involving the upper extremities and tongue), anorexia, nausea, vomiting, psychological tension, general malaise, hypertension, autonomic hyperactivity, tachycardia, diaphoresis, orthostatic hypotension, irritability, vivid dreams, and insomnia
Alcohol Withdrawal Seizures (Rum Fits)	Onset ~12 h after cessation, peak 12–48 h	5%–15%	• Seizures are characterized by generalized motor seizures that occur during the course of alcohol withdrawal, usually in the absence of an underlying seizure disorder • The greater the amount of alcohol consumed the greater the risk for seizures • ~1/3 of subjects who develop alcohol withdrawal seizures will only experience 1 seizure, whereas 2/3 will have multiple seizures, often closely spaced, if untreated • Only 3% of cases will develop status epilepticus
Alcoholic Hallucinosis	Onset ~8 h after cessation, peak 24–96 h	As high as 30%	• Incidence seems related to length and amount of alcohol exposure • Usually consist of primarily visual misperceptions and tactile hallucinations • By definition, the sensorium is clear and vital signs are stable, differentiating it from alcohol withdrawal delirium (DTs), yet some signs of early withdrawal may be present
Alcohol Withdrawal Delirium (DTs)	Usually appear 1–3 d after cessation; peak intensity on 4–5th day	~5%	• In most cases (80%) the symptoms of DTs resolve within 72 h, in those that do not, the mortality rate in cases of DTs has been reported between 1% and 15% • When DTs are complicated by medical conditions the mortality rate may increase to 20% • DTs are differentiated from uncomplicated withdrawal by the presence of a profound confusional state (ie, delirium) • Symptoms commonly include confusion, disorientation, fluctuating or clouded consciousness, perceptual disturbances (eg, auditory or visual hallucinations or illusions), agitation, insomnia, fever, and autonomic hyperactivity terror, agitation, and primarily visual (sometimes tactile) hallucinations of insects, small animals, or other perceptual distortions can also occur

(eg, infections, tumors), illicit drug use, and traumatic brain injury (TBI).[41–43] In the case of other causes, the usual signs of AWS (eg, autonomic hyperactivity) may not be present and the patient's BAC is still elevated.[40,44] Focal brain lesions, such as TBI, stroke, and intracranial mass lesions, frequently cause partial rather than generalized seizures.[42,44,45]

Alcoholic hallucinosis begins on the first day (with onset as early as 8 hours after the last drink), peaking approximately 24 to 96 hours after a relative or absolute abstinence from alcohol. The incidence is as high as 30% but related to length and amount of alcohol exposure.[35,46,47] Alcoholic hallucinations usually consist of primarily visual misperceptions and tactile hallucinations (ie, formication).[23,48] Auditory hallucinations can occur but are usually mild, ranging from unformed sounds to accusatory voices, leading to fear and paranoia.[23,49] By definition, the sensorium is clear and vital signs (VS) are stable, differentiating it from DTs; yet some signs of uncomplicated withdrawal may be present. Symptoms resolve in hours to days and their presence have no predictive value regarding the possibility of developing DTs.[49] On rare occasions, hallucinations may persist after all other withdrawal symptoms have resolved.[50]

Alcohol withdrawal delirium usually appears 1 to 3 days after a relative or absolute abstinence, with a peak intensity on the fourth to fifth day. DTs occurs in approximately 5% of alcoholics.[51] In most cases (80%) the symptoms of DTs resolve within 72 hours.[30] Yet, in those that do not, the mortality rate may be as high as 15%[34,49,52–57]; or up to 20% when complicated by medical conditions. DTs is differentiated from uncomplicated withdrawal by the presence of a profound confusional state (ie, delirium). Symptoms commonly include confusion, disorientation, fluctuating or clouded consciousness, perceptual disturbances (eg, auditory or visual hallucinations or illusions), agitation, insomnia, fever, and autonomic hyperactivity. Terror, agitation, and primarily visual (but tactile hallucinations, formication), and other perceptual distortions can also occur. The confusion and mental status changes can last from a few days to several weeks, even after there has been resolution of the physical withdrawal symptoms. DTs-related deaths are usually the result of medical complications, including infections, cardiac arrhythmias, fluid and electrolyte abnormalities, pyrexia, poor hydration, hypertension, or suicide in response to hallucinations or delusions.

CLINICAL DILEMMA

Studies have shown that in medically ill, hospitalized subjects, most AWS cases are relatively mild and uncomplicated, requiring only symptomatic management (eg, anxiety, tremulousness, insomnia). Usually, the symptoms of uncomplicated AWS do not require medical intervention and disappear within 2 to 7 days. The unnecessary prophylaxis or treatment of patients feared to be at risk or experiencing AWS may lead to several unintended consequences, including sedation, falls, respiratory depression, and delirium.

The incidence of complicated AWS among patients admitted to medical or critical care units, severe enough to require pharmacologic treatment, is between 5% and 20%. When complicated AWS does occur, it is associated with an increased incidence of acute medical and surgical complications; increased ventilator, ICU, and hospital days; increased in-hospital morbidity and mortality; prolonged hospital stay; inflated health care costs; increased burden on nursing and medical staff; and further worsens cognitive functioning among withdrawing subjects.[58]

There is a positive correlation between the severity and duration of DTs symptoms and the occurrence of pneumonia, coronary heart disease, alcohol liver disease, and anemia.[59] The mortality of untreated, complicated AWS is approximately 15% to 20%, compared with 2%, when appropriately treated.

ALCOHOL WITHDRAWAL TREATMENT

The effective management of AWS includes a combination of supportive and pharmacologic measures. Supportive measures include the stabilization and management of comorbid medical problems, assessment and management of concurrent substance intoxication or withdrawal syndrome, and nutritional supplementation.

A recently published Cochrane Review, including 64 studies (n = 4309), evaluated benzodiazepine (BZDP) against placebos, BZDPs against other medications (including other anticonvulsants), and one BZDP against a different BZDP.[60] The data revealed that studies were small, had large heterogeneity, had variable assessment outcomes, and most did not reach statistical significance. Ultimately, the only statistically significant finding was that BZDPs were more effective than placebo for preventing withdrawal seizures; however, they were not shown to be superior to anticonvulsants or other agents. Some studies have suggested that BZDP use itself may be associated with the development of delirium.[61] In fact, others have found that BZDP use (and its amount) was an independent risk factor for the development of delirium.[62–70]

BENZODIAZEPINE-SPARING ALTERNATIVE FOR THE TREATMENT OF ALCOHOL WITHDRAWAL

The effectiveness of BZDP in managing AWS has been covered elsewhere and will not be repeated here.[71] Despite their proven usefulness in the management of complicated AWS, the use of BZDP is fraught with potential complications (**Box 1**). In an

Box 1
Potential problems with the use of benzodiazepines for alcohol withdrawal

- BZDPs represent the standard of care for the treatment of alcohol withdrawal and have been shown to prevent alcohol withdrawal seizures and DTs.[71]
- Yet there are potential problems with their use in the management of AWS.
  1. BZDPs have abuse liability (eg, iatrogenic BZDP dependence); concurrent alcohol or BZDP use 29% to 76%. (Ciraulo and colleagues, 1988)[224] This is problematic in an outpatient setting or when trying to discharge home a patient on moderate or high doses.
  2. BZDPs blunt cognition might hamper early attempts at rehabilitation and counseling.[75]
  3. BZDPs have significant interactions with alcohol, opioids, and other CNS depressants. If taken together, there can be additive respiratory depression and cognitive impairment.
  4. There are preclinical and clinical studies suggesting that BZDP use may increase craving, early relapse to alcohol use, and increased alcohol consumption.[91] (Poulos and Zack, 2004)
  5. The risk of developing BZDP-induced delirium is increased.[75]
  6. There is risk of psychomotor retardation, cognitive blunting, ataxia, and poor balance, and decreased mobility.
  7. Anxiolytic and hypnotic drugs, such as BZDPs and Z drugs (zaleplon, zolpidem, and zopiclone) were associated with significantly increased risk of mortality over a 7-year period, after adjusting for a range of potential confounders. (Weich and colleagues BMJ 2014)[232]
  8. There is increased compensatory up-regulation of NMDA and kainite-Rs and Ca^{2+} channels.
  9. Thalamic gating function is disrupted.
  10. There is increased risk of developing BZDP-induced delirium.[69]
  11. It can interfere with central cholinergic function muscarinic transmission at the level of the basal forebrain and hippocampus (ie, cause a centrally mediated acetylcholine deficient state).
  12. New evidence suggests that BZDP use may be associated with an increased risk of dementia. (de Gage and colleagues BMJ 2012)[222] and (de Gage and colleagues BMJ 2014)[223]
  13. It can interfere with physiologic sleep patterns (eg, decreased slow wave sleep and REM periods duration, REM latency, and REM deprivation).

attempt to avoid the extremes of undersedation or oversedation, and some of their side effects, the author decided to search for pharmacologic agents effective in the management of AWS beyond conventional BZDP-based protocols.

The author found that the available data support the use, safety, and efficacy of various alternatives to BZDP agents that, rather than substituting for ethanol, actually addressed the underlying pathophysiological derangements that underlie alcohol dependence and withdrawal syndromes. A systematic review of the literature revealed that pharmacologic alternatives to BZDPs were classified into one of 3 groups: non–BZDP-GABA-ergic agents; anticonvulsant agents, usually with glutamatergic or Calcium^{2+} (Ca^{2+}) channel modulator activity; and alpha-2 adrenergic (AAG) agonists.

Other γ-Aminobutyric Acid-ergic Agents

Propofol is a short-acting, lipophilic intravenous general anesthetic.[72] Although structurally distinct from other agents, its clinical action and effects on cerebral activity and intracranial dynamics are similar to short-acting barbiturates.[73] Propofol causes global CNS depression, presumably through direct activation of the $GABA_A$ receptor-chloride ionophore complex (increasing chloride conductance)[74] and by inhibiting the NMDA subtype of GLU receptor, possibly through an allosteric modulation of channel gating,[75] which may explain its effectiveness in treating status epilepticus and DTs.[76–78] There are 6 case reports on propofol's effectiveness in treating AWS in cases of nonresponsive to conventional therapy.[79–81] Its rapid onset and short half-life make it easy to titrate but may also create problems, especially when abruptly discontinued (ie, withdrawal). Common side effects include hypotension, bradycardia, and respiratory depression. Other significant side effects include decreased cerebral metabolism, propofol-induced hypertriglyceridemia (which has been causally associated with pancreatitis) and tachyphylaxis, and propofol infusion syndrome.[82–85] Of note, propofol has no US Food and Drug Administration (FDA) approval for the prophylaxis or treatment of AWS.

Antiepileptic Drugs

Antiepileptic drugs (AEDs) with GABA-ergic and GLU-Ca^{2+} channel modulator activity may be used. The routine use of AEDs, such as phenytoin, in cases of AWS is not recommended. A meta-analysis of randomized, placebo-controlled trials for the secondary prevention of AWS-seizures showed phenytoin was ineffective.[42]

Yet new promising data on the use of other anticonvulsants for the prophylaxis and treatment of ASW is emerging, including evidence for carbamazepine (CBZ), valproic acid (VPA), gabapentin (GAB), pregabalin, tiagabine, and vigabatrin. The mechanism by which these other agents exert their positive effects on the prevention and management of AWS is likely associated with their effects on GLU and Ca channels (**Table 2**). Of note, none of the anticonvulsant agents discussed here have FDA approval for the prophylaxis or treatment of AWS.

Carbamazepine

CBZ has effects on various types of channel receptors, including sodium (Na), Ca, and potassium (K), as well as neurotransmitter receptor systems, including adenosine, serotonin (5HT), DA, GLU, cyclic adenosine monophosphate (cAMP), and peripheral BZDP receptors.[86] Mechanisms of action include (1) its ability to stabilize the Na channels, reducing firing frequency[87–89]; (2) its potentiation of GABA receptors[90]; and (3) its inhibition of GLU release, likely contributing to its anticonvulsant properties.[86] CBZ has been in use in Europe for the treatment of AWS for more than 25 years.[91]

Table 2
Glutamate and calcium channel modulators

Drug	T ½	Product Availability	Bioavailability	Metabolism	Protein Binding	Mechanism Action
CBZ	25 h	po	~100%	Hepatic	55%	• Stabilizes neuronal membranes • Inhibits voltage-sensitive Na+ channels and/or Ca+ channels→ ↓ cortical GLU release • Ca channel blockers • Excitatory amino acid antagonists
VPA	9–16 h	po or intravenous (IV)	90%	Hepatic conjugation	90%	• GABA transaminase inhibitor → ↑ GABA • Inhibits voltage-sensitive Na+ channels→ ↓ cortical GLU release • ↓ Release of the epileptogenic amino acid, γ-hydroxybutyrate (GHB)
GAB	5–7 h	po	60%	None Renal excretion	<3%	• Voltage-gated Ca+ channel blockade → ↓ cortical GLU release • NMDA antagonism • Activation of spinal alpha-2 adrenergic receptors • Attenuation of Na+-dependent action potential
Vigabatrin	5–8 h	po	50%	None Significant renal excretion	~0%	• Block the reuptake of GABA & inhibits the catabolism of GABA→↑GABA concentrations, no receptor agonist • Inhibition of voltage-sensitive Na+ channels
Tiagabine	7–9 h	po	90%	Hepatic, various Cytochromes P450 (CYP): CYP3A, CYP1A2, CYP2D6, or CYP2C19	96%	• Block the reuptake of GABA →↑GABA concentrations, no receptor agonist • Inhibition of voltage-sensitive Na+ channels

Abbreviation: T ½, half-life.

CBZ is superior to placebo[92] and non-BZDP hypnotic agents, such as clomethiazole[93] and barbiturates,[94] in suppressing all aspects of AWS. Nine randomized, controlled studies (n = 800) have demonstrated the effectiveness of CBZ in alcohol detoxification, compared with BZDP (**Table 3**).[91,93–105]

CBZ-treated subjects had an overall better response to treatment (ie, were calmer, less irritable, and less dysphoric)[92,96]; experienced superior and faster relief of symptoms, including anxiety, fear, and hallucinations[96,106]; had shortened duration of DTs[94,99,107]; and decreased incidence of AWS-seizures.[99,101,106,107] CBZ was found particularly useful in outpatient detoxification because it enabled the alcoholic to return to work more quickly[92,108] and had greater efficacy than BZDP in preventing post-treatment relapses to drinking.[91] Data suggest CBZ may be useful in the treatment of alcohol dependence and the reduction of cravings and recidivism.[91,109–111] Furthermore, it has a strong antikindling effect and lacks any misuse potential.[108]

CBZ is well-tolerated, rapidly absorbed after oral administration, and its metabolism is largely unaffected by liver damage.[112,113] There were no significant cardiovascular or hepatotoxic effects noted, and no adverse interactions when used with ethanol.[114] Reports suggest that CBZ improves sleep without rapid eye movement (REM)-suppression.[106]

Potential side effects include pruritus without rash (18.9%),[91] followed by dizziness, ataxia, headache, somnolence, dry mouth, orthostatic hypotension, vertigo, nausea, and vomiting (in up to 10% of patients).[115] A major concern is the risk of agranulocytosis or aplastic anemia, both potentially lethal conditions, occurring in less than 0.01%.[116] This was not reported in any of the studies cited.

Oxcarbazepine

An analogue of CBZ, oxcarbazepine (OXC) reduces high-voltage–dependent Ca channels of striatal and cortical neurons, thus reducing NMDA glutamatergic transmission associated with alcohol withdrawal states.[117] Unlike CBZ, oxazepam (OXA) is not associated with significant neurologic side effects or blood dyscrasias and is only a weak inducer of the P450 system.[118] Studies have shown OXC has comparable effects to CBZ in the treatment of AWS,[119–122] reducing both AWS symptoms and alcohol craving score, suggesting a role in relapse prevention.[123–126]

Valproic acid

VPA has effects at various types of channel receptors (eg, Na+, Ca+, K+) and neurotransmitter receptor systems (eg, GABA, GLU, 5HT, DA).[127] Mechanisms of action include increase in the turnover of GABA, inhibition of the NMDA subtype of GLU receptors, and the reduction of γ-hydroxybutyrate (GHB).[127]

Six randomized, controlled studies (n = 900 subjects) have demonstrated the effectiveness of VPA in alcohol detoxification when compared with BZDPs (**Table 4**).[98,128–137] Compared with placebo, VPA-treated subjects experienced faster symptom resolution, required less adjunct medication, and experienced fewer seizures (5 in placebo vs none in VPA).[98,128,131] Compared with BZDP, VPA-treated subjects experienced better resolution of AWS symptoms ($P \leq .01$) and required less rescue medication.[130,132] Compared with CBZ, VPA-treated subjects reported faster symptom resolution, shorter course of AWS, fewer ICU transfers, a more favorable side-effect profile, and fewer withdrawal seizures.[133]

VPA's tolerability and safety are similar to that of CBZ.[127] The most significant adverse effects include teratogenic potential, thrombocytopenia, and idiosyncratic liver toxicity.[127] Compared with other AEDs, VPA causes fewer neurologic adverse effects and fewer skin rashes.[127]

Table 3
Glutamate and calcium channel modulators: carbamazepine

Study	Population	Intervention	AWS Definition	Outcome
Bjorkqvist et al,[95] 1976; DBPCRCT	O/P ETOH Rehabilitation settings-multicenter trial, N = 105	Placebo (PBO) vs CBZ: 800 mg d 1–2 600 mg d 3–4 400 mg d 5–6 200 mg d 7	Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar)	• CBZ proved superior to PBO ◦ Greater change in the total symptom score in the CBZ group than in the PBO ◦ Subjects' ability to return to work improved significantly faster on CBZ
Ritola et al,[93] 1981 DB-BD	Male inpatients, N = 68	Chlormethiazole (CMT) vs CBZ: 400 mg d 0 800 mg d 1–2 600 mg d 3–4 400 mg d 5–6	—	• 70% good to excellent results, both groups • CBZ improvement all areas, except depression • Fewer dropouts in CBZ group
Agricola et al,[96] 1982; DBRCT	University Med Center Substance Abuse I/P Unit, N = 60	CBZ 600 mg vs tiapride 600 mg	CIWA-Ar	• Both drugs were effective in the treatment of AWS ◦ No significant difference was found with respect to total symptoms, score, and visual analog scale assessment • CBZ gave faster relief of symptoms and a superior response on anxiety, fear, & hallucinations • No progression to DTs
Flyngering et al,[94] 1984; DBRCT	Male inpatients, N = 72	Barbital vs CBZ: 400–1200 mg d 1 200–600 mg d 2–6	—	• No overall difference between groups • AWS duration shorter (~9 h) in CBZ group • No difference in dropout rate
Malcolm et al,[97] 1989; DBRCT	VAMC, I/P unit, N = 66	Oxazepam (OXA) 120 mg/d vs CBZ 800 mg/d, tapering over 5 d	CIWA-Ar	• No differences between the 2 groups (both groups achieved maximum reduction of symptoms (CIWA-Ar) between days 4 and 5)

Hillbom et al,[98] 1989; DBRCT	I/P Adults; N = 138	CBZ (max 1200/d) vs VPA (max 1200/d), vs PBO	Episodes of seizure (SZ) or DTs	• SZ episodes: CBZ (n = 2), VPA (n = 1), PBO (n = 3) • DTs: CBZ (n = 0), VPA (n = 2), PBO (n = 1)
Stuppaeck et al,[159] 1992; DBRCT	University Med Center Substance Abuse I/P Unit, N = 60	OXA 120 mg (÷) vs CBZ 800 mg (÷) tapering over 7 d	CIWA-Ar	• No clinical differences between the 2 groups • Greater progression to DTs & SZ in OXA group (OXA 7% & 3%, CLO 0% & 0%, respectively)
Malcolm et al,[91] 2002; DBRCT	University Medical Center Substance Abuse O/P clinic, N = 136	LOR 6–8 mg (÷) on day 1, tapering to 2 mg vs CBZ 600–800 mg on day 1, tapering to 200 mg	CIWA-Ar	• Both drugs were equally efficacious at treating AWS • CBZ had greater efficacy than LOR in preventing post-treatment relapses to drinking over the 12 d of follow-up • There was a greater reduction in anxiety symptoms, as measured by the Zung Anxiety Scale, in CBZ group
Lucht et al,[100] 2003; OL	I/P Adults; N = 127	Sx-triggered: Tiapride (≤1800 mg/d) + CBZ (≤1200 mg/d) vs CLOM (≤1200 mg/d) vs DIA (≤80 mg/d)	AWS	• No significant differences in AWS scores between the Tx groups throughout the study • No significant differences in SZs or DTs
Schik et al,[119] 2005	Single-blinded and randomized pilot study, N = 29 subjects	Oxcarbazepine (OXC) vs CBZ	—	• OXC group showed a significant decrease of AWS and reported significantly less craving for alcohol compared with the CBZ group • Subjectively experienced side effects, normalization of vegetative parameters, and improvement in cognitive processing speed was no different between groups

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Table 3
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Study	Population	Intervention	AWS Definition	Outcome
Polycarpou et al,[101] 2005	Various, Cochrane Review, 48 studies, N = 3610 subjects	Anticonvulsant vs PBO comparison	CIWA-Ar	• For the ACA vs PBO comparison, therapeutic success tended to be more common among the ACA-treated subjects (relative risk [RR] 1.32, 95% CI 0.92–1.91) • ACA tended to show a protective benefit against SZs (RR 0.57; 95% CI 0.27–1.19) • For the subgroup analysis of CBZ vs BZDP; • A statistically significant protective effect was found for the anticonvulsant (P = .02) • Side-effects was less common in the ACA-group (RR 0.56; 95% CI 0.31–1.02)
Minozzi et al,[102] 2010	Various, Cochrane Review, 56 studies, N = 4076 subjects	Anticonvulsant vs PBO vs BZDPs	CIWA-Ar, AWSz, DTs	• CBZ was associated with a significant reduction in alcohol withdrawal symptoms (CIWA-Ar mean difference = −1.04, 95% CI −1.89 to −0.20) when compared with the BZDPs lorazepam and OXA
Barrons & Roberts,[103] 2010	Systematic review	Anticonvulsant vs PBO vs BZDPs	CIWA-Ar, AWSz, DTs	• CBZ was found safe and tolerable when administered at daily doses of 800 mg (fixed or tapered over 5–9 d) • CBZ was associated with a significant reduction in alcohol withdrawal symptoms as measured by CIWA-Ar

Abbreviations: (÷), in divided daily doses; ACA, anticonvulsant agents; CBZ, carbamazepine; CLOM, clomethiazole; DB-BD, double-blind; DBPCRCT, double blind, placebo controlled, randomized clinical trial; DBRCT, double blind randomized clinical trial; DIA, diazepam; I/P, in-patient; O/P ETOH, out-patient alcohol detoxification; Sx, symptom; Tx, treatment.

Gabapentin

GAB acts by inhibition of the neuronal Ca^{2+} channel and amplification of GABA synthesis.[138] Mechanisms of action include increased GABA-ergic tone and reduced glutamatergic tone through inhibition of GLU synthesis, modulation of Ca current, inhibition of Na channels, and reduction of NE and DA release, leading to a reversal of the low GABA–high GLU state found during AWS.[139–145]

An advantage to GAB use is its extrahepatic metabolism or elimination, particularly in alcoholic subjects with hepatic dysfunction.[146] Early animal data suggested the usefulness of GAB in the treatment of AWS.[145,147] GAB has performed as well as barbiturates[148] and BZDP, with subjects experiencing less craving, anxiety, and sedation.[149] Clinical data supporting the use of GAB in the management of AWS are summarized in **Table 5**.[139,150–152]

Other antiepileptic agents

Both lamotrigine and topiramate significantly reduced observer-rated and self-rated withdrawal severity, dysphoric mood, and supplementary diazepam administration when compared with placebo, and were as effective as diazepam.[153] Other drugs for which there is positive evidence for the treatment of AWS include pregabalin,[154–156] topiramate,[153,157] tiagabine,[158] and vigabatrin.[159] In addition, topiramate has shown promise in the treatment of alcohol dependence.[160–165]

In summary, "anticonvulsants appear to be more effective against a larger range of withdrawal symptoms than benzodiazepines, especially among alcoholics with moderate to severe withdrawal symptoms".[166] These agents "might have a further advantage to benzodiazepines in that they appear useful both for treating the acute withdrawal symptoms and, once abstinence has been achieved, for preventing relapse by modulating post-cessation craving and affective disturbance."[166]

Alpha-2 Adrenergic Receptor Agonist

AWS are characterized by a reduction in the inhibitory effects of GABA (disinhibition) and activation of the sympathetic nervous system (stimulation). The severity of AWS correlates positively with the amount of released NE.[167,168] Clinical data have shown significant elevations of cerebral spinal fluid 3-methoxy-4-hydroxyphenylglycol (a major NE metabolite) concentrations in subjects with active AWS, suggesting that enhanced NE turnover is causally associated with the severity of AWS.[167] Excess NE activity may indeed drive the excess GLU activity even further, contributing to agitation, psychosis, and even seizure activity.

AAG induces activation of inward rectifying G-protein-coupled K^+ channels and block voltage-gated Ca channels.[169] Activated alpha 2-adrenergic receptors will hyperpolarize neurons and inhibit the presynaptic release of GLU, aspartate, and NE.[170] This potentially contributes to its neuroprotective qualities against various sources of cerebral ischemic injury and explain the role of AAG in the management of AWS.[171] In addition, AAG decreased cerebellar cyclic guanosine 3′,5'-monophosphate (cGMP), which correlates with their anesthetic and anticonvulsant effects.[172] Given the current understanding of the effects of chronic alcohol use in the CNS and the effects of AWS in the catecholamine system, it makes sense to consider the potential use of alpha-2 agonists in the management of AWS.[29,173] Data on the clinical effectiveness of AAG are summarized in **Table 6**.

The variability in clinical and side-effect profiles observed between the various alpha-2 agonists is related to differences in affinities for the 3 identified alpha-2 noradrenergic receptor subtypes: A, B, and C.[174–176] Alpha-2A receptor agonism promotes sedation, hypnosis, analgesia, sympatholysis, neuroprotection, and inhibition of

Table 4
Glutamate and calcium channel modulators: valproic acid

Study, N = 7	Population	Intervention	AWS Definition	Outcome
Lambie et al,[128] 1980; randomized, single-blind trial	I/P (Detoxification) Detox Unit, N = 49	VPA 400 mg tid × 7 d vs PBO	Severity of Sxs scale; occurrence of AWS	• There were 5 cases of SZ activity, all in the control group (none in VPA) • Physical symptoms disappeared slightly more quickly in the VPA-treated group than in the control group despite that 22 subjects in the control group were on CMT compared with only 5 subjects in the VPA group
Hillbom et al,[98] 1989; DBRCT	I/P Adults; N = 138	CBZ (maximum [max] 1200/d) vs VPA (max 1200/d) vs PBO	Episodes of SZ or DTs	• SZ episodes: CBZ (n = 2), VPA (n = 1), PBO (n = 3) • DTs: CBZ (n = 0), VPA (n = 2), PBO (n = 1)
Rosenthal et al,[129] 1998; open, randomized trial	I/P Detox Unit N = 42	VPA vs PHB Day 1–500 mg po stat loading dose, followed by 500 mg po 6 h later Day 2–500 mg po bid Day 3–500 mg po bid Day 4–250 mg po bid Day 5–250 mg po × 1	ASQ	• This study offers confirmation that VPA is as effective as PHB in the management of AWS ◦ Subjective and objective ratings of abstinence symptoms and subjective mood disturbance decreased significantly in intensity in both groups over 5 d ◦ There were no withdrawal-related SZs or other acute sequelae
Myrick et al,[130] 2000; prospective, randomized, single-blind trial	I/P Detox Unit N = 11	LOR 2 mg for CIWA-Ar scores >6 vs VPA 500 mg tid for 4 d plus LOR 2 mg for CIWA-Ar >6	CIWA-Ar	• The group-by-CIWA-Ar score interaction was determined to favor VPA significantly ($P \leq .01$) • Subjects in the VPA group seemed to use less LOR than those in the control group over the study period

Reoux et al,[131] 2001; DBPCRCT	I/P Detox Unit, N = 36	VPA 500 mg tid × 7 d vs PBO in a double-blind manner OXA PRN in both as rescue	CIWA-Ar	• Use of VPA resulted in less use of OXA (*P*<.033) • The progression in severity of withdrawal symptoms (based on CIWA-Ar) was also significantly greater in the PBO group (*P*<.05)
Longo et al,[132] 2002; randomized, open-label study	I/P Detox Unit, N = 16	BZDP vs VPA (5 d detox) vs VPA (+6 wk maintenance) Loading dose of 20 mg/kg/d in 2 divided doses 6–8 h apart on day 1, then bid thereafter	CIWA-Ar	• AWS reduction occurred more rapidly and consistently in the VPA-treatment group than the BZDP-control group at 12 and 24 h intervals (based on CIWA-Ar scores), not statistically significant • Although the protocol allowed for the availability of a BZDP rescue in the event of VPA nonresponse, none of the VPA-treated subjects required prn BZDP
Eyer et al,[133] 2011; retrospective chart review	I/P Detox Unit, N = 827	CBZ (200 mg tid) vs VPA 300 mg tid)	CIWA-Ar	• VPA may offer some benefits compared with CBZ in the adjunct treatment of moderate-to-severe AWS ○ Shorter need for pharmacologic treatment ○ Fewer ICU transfers ○ A more favorable side-effect profile • Trend that VPA may be more effective than CBZ in reducing complications during AWS, especially WSz

Table 5
Glutamate and calcium channel modulators: Other anticonvulsant agents

Study, N = 11	Population	Intervention	AWS Definition	Outcome
Stuppaeck et al,[159] 1996; ROLCT	I/P Detox unit, N = 10	Vigabatrin 1 mg bid × 3 d Individuals were studied for a total of 7 d, OXA PRN	CIWA-Ar	• Overall, AWS suppression, as measured by CIWA-Ar seemed efficacious • 1 subject had a SZ on d 3 (even after having received OXA 250 mg over 2 previous days)
Myrick et al,[158] 2005; retrospective chart review	O/P Detox unit; N = 13	Tiagabine 2–4 mg bid vs OXA initiated at 30 mg bid to qid	CIWA-Ar	• Both TGB and BZDP-treated subjects were detoxified without serious side-effects • No subjects experienced DTs, SZs, or other complications
Mariani et al,[148] 2006; ROLCT	University Med Center Substance Abuse I/P Unit, N = 27	PHE vs GAB Day 1 GAB 1200 mg po loading dose, followed in 6 h with 600 mg po, followed in 6 h with 600 mg po (total of 2400 mg in the first 24 h) Day 2 600 mg po tid Day 3 600 mg po bid Day 4 600 mg po qd	CIWA-Ar	• There were no significant differences in the proportion of subjects in each group requiring rescue medication for breakthrough signs and symptoms of AWS • No group differences on alcohol withdrawal, craving, mood, irritability, anxiety, or sleep were observed • There were no serious adverse events on GAB group
Ponce et al,[122] 2005	I/P Detox unit; N = 84	BZDP vs OXC	CIWA-Ar side effects	• Both OXC and BZDP were equally efficient in preventing the appearance of epileptic complications and in reducing withdrawal symptoms • Overall, OXC produced fewer adverse events (P<.001) and offered fewer problems when it came to ending administration (P<.001)

Krupitsky et al,[153] 2007; PBO-controlled randomized single-blinded trial	I/P Detox Unit, N = 127	Assigned × 7 d to • PBO • Diazepam (DZP) 10 mg tid • Lamotrigine 25 mg qid • Memantine 10 mg tid • Topiramate 25 mg qid • Additional DZP rescue	CIWA-Ar	• All active medications significantly reduced withdrawal severity, dysphoric mood, and supplementary DZP administration vs PBO • The active medications did not differ from DZP • First systematic clinical evidence supporting the efficacy of several antiglutamatergic approaches for treating alcohol withdrawal symptoms
Myrick et al,[149] 2009; DBRCT	I/P Detox Unit, n = 100	Randomized to low-dose GAB (300 mg tid × 3 d, then 400 mg bid on d 4); high-dose GAB (400 mg tid × 3 d, then 400 mg bid on d 4); vs LOR (2 mg tid × 3 d, then 2 mg bid on d 4); follow-up up to 12 d	CIWA-Ar	• High-dose GAB was statistically superior but clinically similar to LOR ($P = .009$) • During treatment, LOR-treated participants had higher probabilities of drinking compared with GAB-treated ($P = .0002$) • Post-treatment, GAB-treated participants had less probability of drinking during the follow-up post-treatment period ($P = .2$ for 900 mg) compared with LOR-treated ($P = .55$) • The GAB groups also had less craving, anxiety, and sedation compared with LOR
Di Nicola et al,[155] 2010; OLP	N = 40	Pregabalin flexible dosing 200–450 mg/d for O/P treatment of mild-to-moderate AWS	CIWA-Ar	• Pregabalin was safe and tolerable and associated with a significant reduction in CIWA-Ar scores and alcohol craving
Muller et al,[229] 2010; OLOS	O/P Detox Program, N = 131	Levetiracetam, mean initial dose was 850 mg/d	AWSS score	• 93.1% completed the program successfully • The AWSS score decreased clearly over 5 d • The medication was well-tolerated • There was no treatment discontinuations due to side effects of levetiracetam • No serious medical complications, especially SZs or deliria, were observed during the detox • At the 6-mo follow-up, 57 subjects (43.5%) were still abstinent

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Table 5
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Study, N = 11	Population	Intervention	AWS Definition	Outcome
Martinotti et al,[156] 2010; MCRSBCT	O/P Detox program, N = 111	Pregabalin vs tiapride vs lorazepam; multicenter, single-blind trial	CIWA-Ar	• All medications significantly reduced AWS, with pregabalin demonstrating significantly better treatment for headache and orientation withdrawal symptoms
Forg et al,[225] 2012; RPCT	I/P Detoxification, N = 42	For 6 d, participants either received pregabalin vs PBO according to a fixed dose schedule starting with 300 mg/d; with rescue DZP based on AWSS score	AWSS, CIWA-Ar and neuropsychological scales	• Pregabalin and PBO were equally safe and well-tolerated • No statistically significant difference was found comparing the total amount of additional DZP medication required in the 2 study groups • Pregabalin and PBO also showed similar efficacy according to alterations of scores of the AWSS, CIWA-Ar, and neuropsychological scales • The frequency of adverse events and dropouts did not differ between the both treatment groups
Stock et al,[231] 2013; DBRPCT	O/P VA Clinic, N = 26	GAB (1200 mg/d starting dose) vs chlordiazepoxide (100 mg/d starting dose) were administered according to a fixed-dose taper schedule over 6 d	Sleepiness, alcohol craving, and ataxia in addition to CIWA-Ar scores	• There were no significant differences in AWS symptoms by medication • GAB group reported decreased daytime sleepiness compared with those who received chlordiazepoxide

Abbreviations: DBRPCT, double; DZP, diazepam; PHE, phenobarbital; PRN, pro re nata, or as needed; qd, daily; ROLCT, randomized, open label, clinical trial; VA, Veterans Administration.

Table 6
Centrally acting alpha-2 adrenergic receptors agonists

Drug	Alpha-2 or alpha-1 Selectivity	dT ½	eT ½	Product Availability	Bioavailability	Protein Binding
Guanfacine	2640	2.5 h	17 h	po	~100%	70%
Dexmedetomidine	1600	6 min	2 h	IV	70%–80%	94%
Medetomidine	1200	—	—	—	—	—
Clonidine	220	11 min	13 h	po TDS IV	100% po 60% TDS	40%
Methyldopa	—	12 min	105 min	po/IV	50%	<20%
Guanabenz	—	60 min	6 h	Po	75%	90%

Abbreviations: dT ½, drug plasma half-life; eT ½, elimination half-life; TDS, transdermal system (or patch).

insulin secretion.[177,178] Alpha-2B receptor agonism suppresses shivering centrally, promotes analgesia at spinal cord sites, and induces vasoconstriction in peripheral arteries.[179] Alpha-2C receptor is associated with modulation of cognition, sensory processing, mood-induced and stimulant-induced locomotor activity, and regulation of epinephrine outflow from the adrenal medulla.[180,181] Although inhibition of NE release seems equally affected by all 3 alpha-2 receptor subtypes.[181] The hypotensive effects of alpha-2 agonists are attributable to their actions at alpha-2A and alpha-2C in the nucleus tractus solitaries.[182,183] Alpha-2A is densest in the PFC[184] and is primarily responsible for the cognitive enhancing effects of alpha-2 agonists. Meanwhile the alpha-2B subtype is found predominantly in the thalamus[183] and predominantly mediates alpha-2 agonists' sedative actions.[185]

There are data on 3 AAGs for the treatment of AWS: lofexidine, clonidine, and dexmedetomidine (DEX). Lofexidine has animal[186] and human[187,188] data supporting its effectiveness in the treatment of AWS but because it is not available in the United States, it is not discussed further.

Clonidine

Case reports confirmed the usefulness of adding clonidine (CLO) to help resolve AWS not responding to conventional sedative therapy.[189] Seven double-blind, placebo-controlled trials demonstrate CLO's utility in managing AWS (**Table 7**). When compared with BZDP, subjects on CLO experienced significantly lower mean withdrawal scores ($P<.02$), significantly lower mean systolic blood pressure ($P<.01$), and significantly lower mean heart rate ($P<.001$).[92,190–193] However, subjects in the CLO group experienced less anxiety and better cognitive recovery.[191] In addition, CLO provided better management of psychological symptoms (eg, anxiety, irritability, agitation) and CNS excitation (ie, seizures, DTs) associated with alcohol withdrawal.[92,189,191–196] No subject developed seizures or progressed to DTs.

Dexmedetomidine

DEX is a selective AAG with sedative, analgesic, anxiolytic, and sympatholytic properties, generally devoid of significant respiratory depression.[197] Its specificity for the alpha-2 receptor is 8 times that of CLO.[198,199] The FDA recently approved the use of DEX for sedation without intubation, which provides clinicians with an additional medication to treat patients with alcohol withdrawal who require ICU placement, while

Table 7
Centrally acting alpha-2 adrenergic receptors agonists in alcohol withdrawal syndrome

Study, N = 11	Population	Intervention	AWS Definition	Outcome
Bjorkqvist,[92] 1975; DBRPCT	I/P Detox Unit, N = 60	Fixed titration of po CLO (over 4 d) vs PBO	• Nurses evaluation • Self-report	• Self-rated and nurse observer–rated symptoms of alcohol withdrawal were significantly reduced with CLO as compared with PBO on day 2 of treatment ($P<.025$ and $P<.01$, respectively), with no hypotension • Subjects in the CLO group did better in every index measured: the movements and tremor improved faster; systolic blood pressure (BP), need for additional medication
Walinder et al,[195] 1981; ROL	I/P Detox Unit, N = 19	Fixed titration of po CLO vs fixed CBZ dose (200 mg tid) × 4 d	Comprehensive Psychopathological Rating Scale	• CLO treatment seems at least as effective as CBZ in suppression and management of the AWS
Wilkins et al,[196] 1983; randomized, crossover double-blind fashion	I/P Detox Unit, N = 11	Randomized, crossover double-blind fashion CLO vs PBO	Autonomic reactivity	• CLO significantly suppressed heart rate (HR; $P = .002$), arterial BP ($P = .006$), and an accumulated score of withdrawal symptoms and signs ($P = .004$)
Manhem et al,[193] 1985; DBRCT	I/P Detox Unit, N = 20	Fixed titration of po clonidine (0.15–0.3 mg qid) vs CMT (500–1000 mg qid) × 4 d	Alcohol withdrawal assessment scales (various) Autonomic reactivity	• During treatment, BP & HR were significantly lower following CLO compared with CMT ($P<.05$ for both) • CLO treatment reduced physical AWAS symptoms more effectively than CMT • Plasma NE and epinephrine levels were significantly lower in subjects treated with clonidine starting on day 1 of treatment ($P<.01$) • No specific adverse effects with clonidine, including SZs, were reported, although 1 subject in each group developed alcohol withdrawal delirium
Baumgartner & Rowen,[190] 1987; DBRPCT	I/P Detox Unit, N = 61	Fixed titration of chlordiazepoxide (50–150 mg/d, over 4 d) vs transdermal CLO (0.2–0.6 mg/d)	AWSS	• CLO mean AWAS score was significantly lower than CDP group ($P<.02$) • Mean systolic BP was significantly lower in CLO group ($P<.01$) • Mean HR was significantly lower in CLO group ($P<.001$) • No subject in either group developed SZs or progressed to DTs

Baumgartner & Rowen,[191] 1991; DBRPCT	I/P Detox Unit, N = 50	Fixed titration of chlordiazepoxide (over 4 d) vs transdermal CLO (0.2-mg oral loading dose + 0.2 mg/24 h transdermal patches × 2 on day 1)	AWAS	• There was no significant difference in subject-reported subjective symptoms of alcohol withdrawal • Mean systolic and diastolic BP and pulse were significantly lower for subjects in the CLO group (P<.001 for all) • CLO group had a better response to therapy as assessed by the AWAS, less anxiety as assessed by the Ham-A Rating Scale (P<.02), better control of HR and BP; better cognitive recovery • No SZ or DTs in either group
Adinoff,[221] 1994; DBRPCT	I/P Detox Unit, N = 25	DZP (10 mg) vs APZ (1 mg) vs CLO (0.1 mg) vs PBO, all given q 1 h until AWS ratings dropped to <5	CIWA-Ar Autonomic reactivity	• APZ was significantly more efficacious than both clonidine and PBO in decreasing withdrawal symptoms but did not significantly decrease BP compared with DZP or PBO • DZP was more effective than clonidine and PBO on some measures of withdrawal • CLO decreased systolic BP significantly more than the other 2 active drugs and PBO but was no more effective than PBO in decreasing other symptoms of withdrawal
Dobrydnjov et al,[192] 2004; DBRCT	Surgical subjects, n = 45	DZP vs clonidine given preoperative to subjects undergoing transurethral resection of the prostate under spinal anesthesia	CIWA-Ar Autonomic reactivity	• Median CIWA-Ar score: 12 vs 1 (P<.001) • Development of AWS: 80% vs 10% (P<.002) ○ Anxiety: 67% vs 0% (P<.001) ○ Agitation: 40% vs 0% (P<.05) ○ Progression to DTs: 27% vs 7% • VS: hyperdynamic circulatory reaction observed in D group; slightly decreased mean arterial BP in CLO

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Table 7
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Study, N = 11	Population	Intervention	AWS Definition	Outcome
Khan et al,[227] 2008; case control study	N = 35	CLO	—	• Predictors associated with increased mortality by univariate analysis: hyperthermia in the first 24 h of DTs diagnosis, persistent tachycardia, and use of restraints • Predictors associated with decreased mortality: an emergency department diagnosis of DTs, and use of clonidine
Lizotte et al,[228] 2014; retrospective chart review	ICU-AWS, N = 41	AWS who received adjunctive DEX or propofol	BZDP & haloperidol use; 2ry measures included AWSS and sedation scoring, analgesic use, IUC-LOS, rates of intubation, and adverse events	• Among the DEX and propofol groups, significant reductions in BZDP ($P \leq .0001$ and $P = .043$, respectively) and haloperidol ($P \leq .0001$ and $P = .026$, respectively) requirements were observed • Shorter LOS in the DEX group (123.6 h vs 156.5 h; $P = .125$) • Rates of intubation (14.7% vs 100%) and time of intubation (19.9 h vs 97.6 h; $P = .002$) were less in the DEX group • Incidence of hypotension was 17.6% in the DEX group vs 28.5% in the propofol group
Wong et al,[233] 2015; review	13 studies, ICU treatment of AWS using DEX	DEX as an adjunctive agent for the treatment of alcohol withdrawal in adult subjects	CIWA-Ar	• DEX seems well-tolerated, with an expected decrease in BP and HR SZs have occurred in subjects with alcohol withdrawal despite the use of DEX, with and without BZDPs

Abbreviations: AWAS, alcohol withdrawal assessment scales (various); D group, diazepam group; ICU-LOS, intensive care unit-length of stay; ROL, randomized, open label (trial).

avoiding the potential problems associated with the use of BZDPs, barbiturates, and propofol (ie, respiratory depression, need for endotracheal intubation, sepsis, and increased morbidity and mortality).[26]

Animal data demonstrated its efficacy in managing all phases of AWS.[200–203] Several clinical reports suggest DEX has been efficacious in cases in which BZDP has failed to effectively manage AWS.[197,204–211]

Guanfacine

Guanfacine (GUA), an even more selective alpha-2 or alpha-1 agent, causes less hypotension and is a better anxiolytic with less sedative side effects than CLO[212]; yet it is 25 times more potent than CLO at enhancing spatial working memory performance.[213] Its effectiveness in the management of AWS has been demonstrated in animal models[214,215] but no human data are available. Yet the author has effectively and safely used GUA in the management of complicated AWS and hyperactive delirium. This agent is particularly useful when transitioning patients off prolonged use of DEX. Given its relatively long half-life, this agent may have a lower incidence of noradrenergic rebound on discontinuation.[216]

DEVELOPMENT OF A NOVEL ALGORITHM FOR THE PROPHYLAXIS AND TREATMENT OF ALCOHOL WITHDRAWAL

The author's institution created a multidisciplinary taskforce, including members from all clinical departments, tasked with reviewing the available literature regarding AWS assessment methods and treatment algorithms. Concerns regarding potential problems with oversedation, negative neurologic sequelae, development of medication-induced delirium, and codependence issues between alcohol and BZDP sparked interest in developing a BZDP-sparing protocol. Based on the taskforce findings, we developed an alternative BZDP-sparing protocol for the prophylaxis and treatment of AWS; with BZDP allowed as rescue to breakthrough AWS (**Box 2**, **Fig. 3**). The ultimate goal was to decrease excessive BZDPs use and its related side effects.

Using the Prediction of Alcohol Withdrawal Severity Scale (PAWSS)[217] (**Fig. 4**), a tool validated in medically ill patients as reliable at identifying patients at high risk for complicated AWS, we could better tailor interventions and minimize excessive medication use and side effects.[58,217,218] Thus, patients at low risk for complicated AWS (ie, PAWSS <4) are only monitored, and antihistaminic agents offered for the management of insomnia and sleep but not given active treatment.

Patients scoring at high risk for complicated AWS (ie, PAWSS 4), undergo examination with a severity scale, such as the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar)[219] or the Alcohol-Withdrawal Syndrome Scale AWSS).[220] If patient are currently not experiencing active AWS (ie, CIWA-Ar <15; AWSS <6)[220] they are placed on the prophylaxis protocol. The prophylaxis protocol is recommended for patients who (1) are at risk for complicated AWS but (2) who are not yet experiencing active AWS. By definition, a patient on active AWS should demonstrate signs of an adrenergic storm. The protocol calls for initiation of an alpha-2 agonist (either CLO or GUA; see **Box 2**). A patient experiencing severe hypotension, due to blood loss or sepsis, may not be able to tolerate the alpha-2 effect, in which case an antiglutamatergic-calcium-channel (Ca^{2+}Ch) modulator is indicated (either GAB or VPA). All patients are under ongoing surveillance for symptoms of clinical response or signs of AWS progression using a severity scale every 4 hours. Any patient whose withdrawal severity score rises despite adequate prophylactic management should be considered in active withdrawal and converted to the treatment protocol.

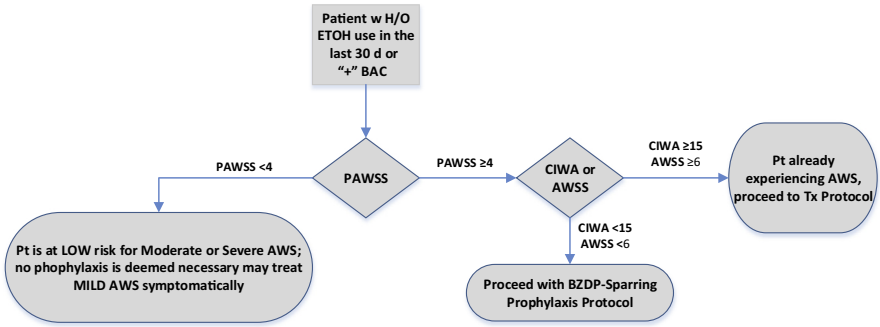
Box 2
Benzodiazepine-sparing: general management protocol

Assessment

Determine the patient's risk for AWS based on PAWSS score
PAWSS less than 4: low risk, suggest continued monitoring and only symptomatic management
PAWSS 4 or higher: high risk; prophylaxis management or active treatment is indicated, based on CIWA or AWSS[220] score (next)

Determine whether the patient is actively withdrawing; conduct CIWA or AWSS
CIWA less than 15 (AWSS <6): not actively withdrawing; proceed with prophylaxis, if indicated
CIWA 15 or higher (AWSS ≥6): patient already experiencing active AWS, proceed to treatment (not prophylaxis)

Decision algorithm



Monitoring

Monitor patient's progress with an AWS severity scale

AWS Severity	CIWA-Ar (Sullivan et al,[219] 1989; Shaw et al,[230] 1981; Holbrook,[226] 1999)	AWSS[220] (Wetterling et al, 1997[220]; 2006[234])
Mild	≤15	≤5
Moderate	16–20	6–9
Severe	≥20	≥10

Nonpharmacological management

1. Implement early mobilization techniques
   a. Aggressive physical therapy and occupational therapy as soon as it is medically safe to do so
      i. In bedridden patients, daily passive range of motion
      ii. The patient should out of bed as much as possible
         1. Get the patient up and moving as early as possible
   b. Patients out of bed as much as possible
   c. Provide patients with any required sensory aids (ie, eyeglasses, hearing aids)
   d. Promote as normal a circadian light rhythm as possible
      i. Environmental manipulations
         1. Light control (ie, lights on and curtains drawn during the day, off at night)
         2. Noise control (ie, provide ear plugs, turn off televisions, minimize night staff chatter)
      ii. Provide as much natural light as possible during the daytime

e. If possible, provide the patient with at least a 6-hour period of protected nighttime sleep (ie, no blood draws, tests, and medication administrations unless absolutely necessary)

2. Provide adequate intellectual and environmental stimulation
   a. Encourage visitation by family and friends
   b. Minimize television use
3. Monitor for seizures
4. Fall precautions
5. Basic laboratory tests: creatinine clearance (CrCl), LFTs, electrocardiogram, volatile screen order, toxicology screening test (if not already done)

Fluid and nutritional replacement

1. Correct and monitor fluid balances and electrolytes
   a. Magnesium (Mg) [1.7–2.2 mg/dL]
   b. Na [135–145 mEq/L]
   c. K [3.7–5.2 mEq/L]
2. Vitamin supplementation
   a. Thiamine 500 mg IV, intramuscular (IM), or by mouth 3 times a day × 5 days
      • Followed by thiamine 100 mg IV, IM, or by mouth for rest of hospital stay (or up to 14 d)
   b. Folate 1 mg by mouth daily
   c. Multivitamin, 1 tab by mouth daily
   d. B complex vitamin 2 tabs by mouth daily
   e. Vitamin K 5 to 10 mg subcutaneously × 1 (if international normalized ratio is >1.3)

BZDP-sparing AWS pharmacological prophylaxis

- Prophylaxis is suggested in patients who (1) are at risk for complicated AWS but (2) who are not experiencing active AWS yet
- If CIWA15 or higher, the patient is actively experiencing AWS, switch to treatment order set
  a. Alpha-2 agents
     i. Clonidine transdermal 0.1 mg (2 patches)
     ii. Plus, administer clonidine 0.1 mg by mouth or IV every 8 hours (×3 doses)
     iii. Alternatively, may use GUA 0.5, 1 mg by mouth twice a day; GUA has better anxiolytic effect and is less hypotensive than clonidine
  b. If patient's VS unable to tolerate alpha-2 effect may instead use GAB
     i. Day 0: 1200 mg loading dose + 800 mg 3 times a day
     ii. Day 1 to 3: 800 mg by mouth 3 times a day
     iii. Day 4 to 5: 600 mg by mouth 3 times a day
     iv. Day 5 to 7: 300 mg by mouth 3 times a day
     v. Day 8: D/C
     vi. Do not use GAB in patients with severe renal dysfunction who are unable to clear GAB (ie, CrCl is <60)
  c. In patient at extremely high risk for severe AWS (ie, PAWSS ≥7 or BAC ≥300 on admission) use both clonidine and GAB, as above; GAB may also be used as an alternative to BZDPs in patients experiencing extreme levels of anxiety, even in the absence of objective signs of AWS
  d. For adjunct management of insomnia, may use (choose from the following)
     i. Melatonin 6 mg by mouth every HS, plus one PRN
     ii. Doxylamine 25 to 50 mg every HS, PRN
     iii. Hydroxyzine 50 mg by mouth every HS, PRN
     iv. Doxepin 10 mg by mouth every HS, PRN
     v. Zolpidem 10 mg by mouth every HS, PRN
  e. For adjunct management of anxiety, may use (choose of the following)
     i. Doxylamine 25 to 50 mg every HS, PRN
     ii. Hydroxyzine 50 mg by mouth every HS, PRN
  f. BZDPs should be used only in the case of a patient who experiences breakthrough symptoms of AWS, despite of implementation of the BZDP-sparing protocol, as signaled by a CIWA score 15 or higher (AWSS ≥6)[220] over 8 hours; in that case, switch to a BZDP-sparing treatment protocol; for breakthrough AWS:

i. If CIWA-Ar greater than 15 (AWSS ≥6), lorazepam 1 mg q 4 hours
ii. If CIWA-Ar greater than 20 (AWSS ≥10),[220] lorazepam 2 mg q 4 hours

BZDP-Sparing AWS: pharmacological treatment

- If CIWA less than 15, the patient is not actively experiencing AWS; switch to the prophylaxis order set
  a. Alpha-2 agents
     i. Transdermal clonidine 0.2 mg × 2 (total 0.4 mg)
     ii. Plus, administer clonidine 0.1 mg by mouth or IV every 8 hours (×3 doses)
     iii. Alternatively, may use guanfacine 1 mg, by mouth, twice a day 1 mg, by mouth, 3 times a day; GUA has better anxiolytic effect and is less hypotensive than clonidine
     iv. Closely monitor CIWA or AWSS every 4 hours; if AWS continues (eg, CIWA ≥15, AWSS ≥6), add VPA
  b. Plus, Ca^{2+}Ch modulator (GLU), either:
     i. GAB schedule (GAB can be used only if CrCl is greater than 60, must be renally dosed if CrCl <60)
        1. Day 0: 1200 mg loading dose plus 800 mg 3 times a day
        2. Day 1 to 3: 800 mg by mouth 3 times a day
        3. Day 4 to 5: 600 mg by mouth 3 times a day
        4. Day 5 to 7: 300 mg by mouth 3 times a day
        5. Day 8: D/C
     ii. VPA by mouth or IV
        1. Start VPA 250 mg by mouth or IV bid plus 500 mg every HS
        2. Cases of late severe AWS may require up to 1.5 gm in first 24 hours
        3. If Sx's escalate after 12 hours, increase total dose to 2 gm in divided doses
        4. If Sx's of AWS continue or worsen, add GAB

     Note: In the treatment protocol, clinicians are to use both an alpha-2 agonist plus an antiglutamatergic-Ca^{2+}Ch agent; GAB can be used if CrCl is less than 60; alternatively may use VPA
  c. For adjunct management of insomnia
     i. Melatonin 6 mg by mouth every 1800
     ii. Doxylamine 25 to 50 mg every HS, PRN
     iii. Hydroxyzine 50 mg by mouth every HS, PRN
     iv. Doxepin 10 mg by mouth every HS, PRN
     v. Zolpidem 10 mg by mouth every HS, PRN
  d. For breakthrough AWS (consider progression to rescue protocol, if the patient experiences a sustained elevation of the severity scale scores)
     i. If CIWA-Ar greater than 15 (AWSS >6), lorazepam 1 mg every 4 hours
     ii. If CIWA-Ar greater than 20 (AWSS ≥10),[220] lorazepam 2 mg every 4 hours
  e. Nonresponsive AWS, consider transfer to ICU; then add DEX drip, 0.4 μg/kg/h; titrate every 20 minutes to effect

BZDP-Sparing AWS: rescue treatment protocol

1. Alpha-2 agents
   a. Initiate DEX at 0.4 μg/kg/h (no loading)
   b. Titrate dose by 0.1 μg/kg/h every 20 minutes to effect or in response to an elevated assessment score (AWAS >10)
   c. There is no maximum dose, yet clinical experience suggests the maximum required DEX dose for alcohol withdrawal management is approximately 2.4 μg/kg/h
2. Valproic acid by mouth, or valproate sodium by IV
   a. Add VPA 250 mg by mouth or IV twice a day plus 500 mg every HS (if the patient is not already on it)
   b. It may be necessary to increase the dose to 500 mg twice a day plus 1000 mg every HS if the patient continues to be symptomatic after 12 to 24 hours
   c. If Sx's of AWS continue or worsen, add GAB
3. GAB schedule
   a. Day 0: 1200 mg loading dose plus 800 mg 3 times a day
   b. Day 1 to 3: 800 mg by mouth 3 times a day
   c. Day 4 to 5: 600 mg by mouth 3 times a day

d. Day 5 to 7: 300 mg by mouth 3 times a day
e. Day 8: D/C

4. The idea is to avoid BZDP, if possible, to minimize risk for delirium and prolonging BZDP or alcohol dependence
   a. Yet in some cases, lorazepam 2 mg by mouth or IV, every 1 hour PRN, may be used based on assessment scales or clinical picture, after the patient has been initiated on DEX and VPA (as above)
   b. If symptoms are severe (ie, AWSS $\geq$10), may use lorazepam 2 to 4 mg by mouth every 2 hours until the scores have dropped to the moderate range

Abbreviations: BAC, blood alcohol concentration; D/C, discontinue; HS, hora somni (or at bedtime); LFTs, Liver function tests; PRN, pro re nata, or as needed; Sx's, symptoms.

Patients scoring at high risk for complicated AWSS[220] (ie, PAWSS $\geq$4) and scoring on the active withdrawal range on a severity scale (ie, CIWA-Ar $\geq$15, AWSS $\geq$6) should be immediately transferred to the treatment protocol. An AAG (ie, CLO or GUA) at twice the dose of the prophylactic protocol, plus an antiglutamatergic-Ca^{2+}Ch modulator (choice of agent is made based on clinical circumstances and patient's characteristics) are initiated, as per protocol (see **Box 2**, **Fig. 3**).

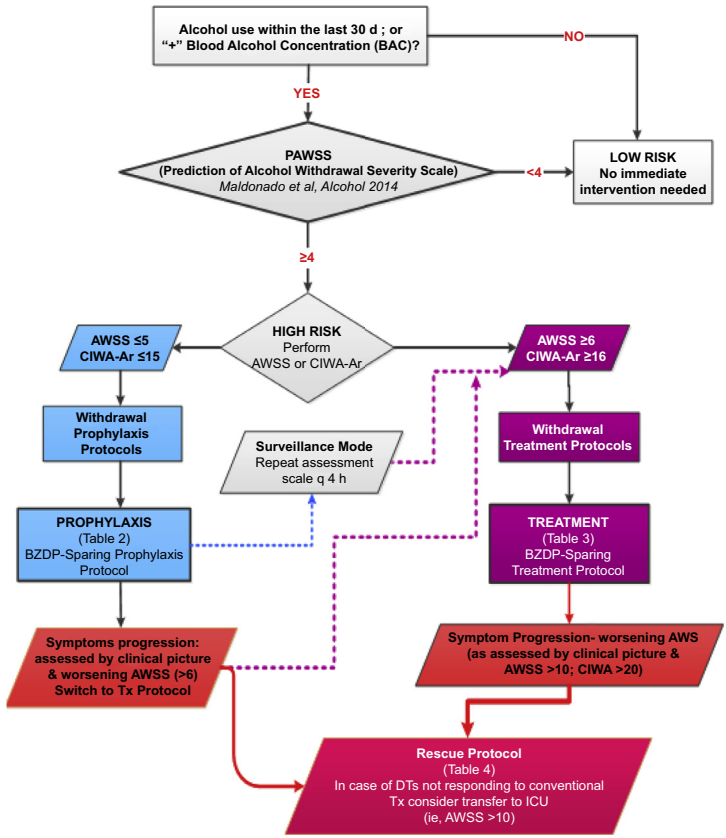


Fig. 3. Benzodiazepine-sparing alcohol withdrawal prophylaxis and treatment protocol. AWSS, Alcohol Withdrawal Syndrome Scale; BAC, blood alcohol concentration; BZDP, benzodiazepine; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol; PAWSS, Prediction of Alcohol Withdrawal Severity Scale.

Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Maldonado et al., 2014

Part A: Threshold Criteria: ("+" or "-", no point)

Have you consumed any amount of alcohol (i.e., been drinking) within the last 30 d? OR did the patient have a "+" BAL upon admission? _____

IF the answer to either is YES, proceed with test:

Part B: Based on patient interview: (1 point each)

1. Have you ever experienced previous episodes of alcohol withdrawal? _____
2. Have you ever experienced alcohol withdrawal seizures? _____
3. Have you ever experienced delirium tremens or DT's? _____
4. Have you ever undergone alcohol rehabilitation treatment? _____
   (i.e., in-patient or out-patient treatment programs or AA attendance)
5. Have you ever experienced blackouts? _____
6. Have you combined alcohol with other "downers" like benzodiazepines or barbiturates during the last 90 d? _____
7. Have you combined alcohol with any other substance of abuse during the last 90 d? _____
8. Have you been recently intoxicated/drunk within the last 30 d ? _____

Part C: Based on clinical evidence: (1 point each)

9. Was the patient's blood alcohol level (BAL) on presentation >200? _____
10. Is there evidence of increased autonomic activity?
    (e.g., HR >120 bpm, tremor, sweating, agitation, nausea) _____

Total Score: _____

Notes: Maximum score = 10. This instrument is intended as a SCREENING TOOL. The greater the number of positive findings, the higher the risk for the development of alcohol withdrawal syndromes. A score of ≥4 suggests HIGH RISK for moderate to severe AWS; prophylaxis and/or treatment may be indicated.

Fig. 4. PAWSS. (*From* Maldonado JR, Sher Y, Ashouri JF. The "Prediction of Alcohol Withdrawal Severity Scale" (PAWSS): systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. Alcohol 2014;48(4):375–90; with permission.)

VPA may be used as an alternative to GAB in cases of patients with severe renal dysfunction unable to clear GAB (creatinine clearance [CrCl] is <60). Once a patient has been stable for 2 days (48 hours), the clinician may begin a slow VPA titration by 250 mg per day until off. Do not use or discontinue its use if alanine aminotransferase (ALT) is greater than 150, aspartate aminotransferase (AST) is greater than 80, or if platelets decrease by 30% (from baseline) or are below 150, at baseline.

GAB and/or VPA may also be used as an alternative for patients unable to tolerate the hypotensive effect of an AAG agent.

Any patient whose withdrawal severity score rises despite of prophylactic management should be considered as deteriorating and thus requires more aggressive treatment. That usually includes first optimization of BZDP-sparing protocol by switching to the treatment protocol, minimal use of BZDP agents for breakthrough until stabilization, or implementation of the rescue protocol with the use of DEX.

SUMMARY

Current guidelines for the prophylaxis and management of AWS are based on the use of BZDPs. The rationale has always been that BZDPs effectively cover all phases of alcohol withdrawal. Yet clinical experience with the use of BZDPs suggests difficulties in implementing prophylaxis and treatment protocols adequately. The problem seems related to the way BZDPs are administered, whether objective physiologic or psychological methods are used to time dosing, and the type of BZDP agent used.

The author's clinical experience demonstrates that current BZDP-based, severity scale-triggered protocols can be fraught with complexities, breakthrough AWS, and significant side effects, particularly the development of BZDP-induced delirium. Available data suggest that non-BZDP agents may offer a safe and effective alternative for the prophylaxis and treatment of AWS.

The data for the use of non-BZDP agents are growing but larger, randomized, head-to-head studies comparing them with BZDP are necessary to assess efficacy and safety. In the author's experience, the use of a predictive tool to help identify patients at risk for complicated-AWS, in combination with monitoring by the use of severity scales, and coupled with the BZDP-sparing prophylaxis and treatment algorithms has been the best way to manage AWS while minimizing the side effects associated with BZDP use. In 4 years of experience, the use of the BZDP-sparing protocol has proven effective and safe. To date, there have been no significant adverse side effects requiring discontinuation of the protocol, no fatalities, no progression to alcohol withdrawal seizures, and no breakthrough DTs. Despite this positive experience, the author acknowledges that large, randomized studies are needed to confirm these findings.

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