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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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

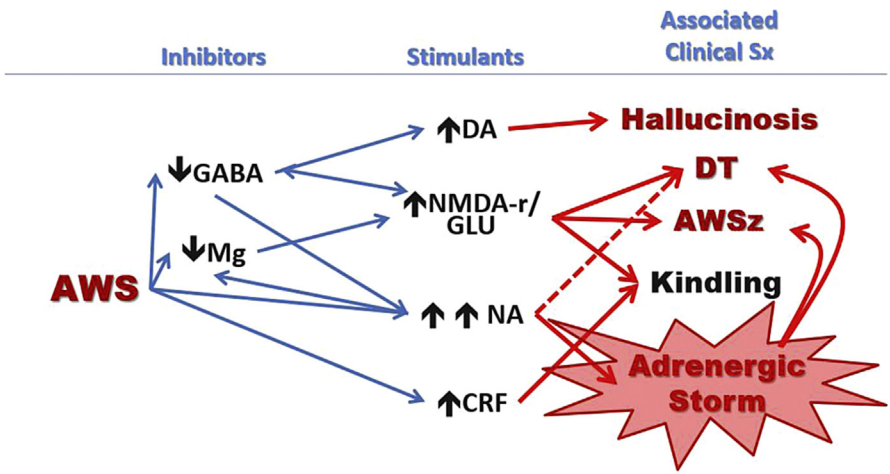

Fig. 1. Summary of neurotransmitter changes associated with AWSs. AWS, alcohol withdrawal syndrome; AWSz, alcohol withdrawal seizures; CRF, corticotropin-releasing factor; DA, dopamine; DT, delirium tremens; GABA, gamma-aminobutyric acid; GLU, glutamate; Mg, magnesium; NA, noradrenaline or norepinephrine;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