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The recognition and management of protracted alcohol withdrawal may improve and modulate the pharmacological treatment of alcohol use disorder

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Abstract

About 50% of persons with an alcohol use disorder may have symptoms of alcohol withdrawal syndrome (AWS) when they reduce or discontinue their alcohol consumption. Protracted alcohol withdrawal (PAW), an underestimated and not yet clearly defined clinical condition that follows the acute stage of AWS, is characterized by the presence of substance-specific signs and symptoms (i.e. anxiety, irritability, mood instability, insomnia, craving) common to acute AWS, but persisting beyond the generally expected acute AWS time frames. Considering that PAW symptoms are mainly related to the neuro-adaptive changes of gamma-aminobutyric acid (GABA) and *N*-methyl-d-aspartate (NMDA) systems, naltrexone, nalmefene, and disulfiram may not be able to suppress the symptoms of PAW. After treatment of the acute phase of AWS, a more specifically pharmacological therapy able to suppress PAW symptoms could perhaps be used earlier and may be more helpful in preventing the risk of alcohol relapse, which remains higher during the first months of treatment. In light of this, medications acting on GABA and NMDA neurotransmitter systems to counterbalance the up-regulation of NMDA and the down-regulation of GABA could be employed in combination and started as soon as possible.

Keywords

Protracted alcohol withdrawal, pharmacological management of alcohol use disorder, GABA agonists, NMDA antagonists

Introduction

Chronic use of alcohol can lead to the onset of an alcohol use disorder (AUD), as defined in the latest version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) (American Psychiatric Association, 2013). The prevalence of AUD ranges from 13% to 30% (about 20% of men and 10% of women) in most Western societies (Grant et al., 2015; World Health Organization, 2014). Within the range of treatments for AUD, some conditions such as alcohol withdrawal syndrome (AWS) may occur. In fact, about 50% of persons with an AUD may have symptoms of AWS when they reduce or discontinue their alcohol consumption. According to the DSM-V criteria, AWS is defined as: (a) cessation or reduction in alcohol use that has been heavy and prolonged; (b) two (or more) of the following symptoms, developing within several hours to a few days after alcohol cessation: autonomic hyperactivity, increased hand tremor, insomnia, nausea or vomiting, transient visual/auditory/tactile hallucinations or illusions, psychomotor agitation, anxiety, and generalized tonic-clonic seizures (American Psychiatric Association, 2013). Clinically, AWS follows a characteristic temporal course (Heilig et al., 2010). Namely, in the absence of comorbid conditions, other drug use or treatment, three distinct phases have been proposed: acute withdrawal, early abstinence and protracted abstinence. However, the last of these is not yet fully understood.

From the pathophysiologic point of view, chronic exposure to alcohol leads to significant modifications in the receptor systems present in the central nervous system (CNS). In particular, there is a reduction in the number, the functions and the sensitivity of the GABA-A receptor to gamma-aminobutyric acid (GABA) (the main inhibitory neurotransmitter present in the CNS) known as down-regulation, and an increase in the number, the sensitivity and the affinity of glutamate (the main excitatory neurotransmitter present in the CNS) for the *N*-methyl-d-aspartate (NMDA) receptors known as up-regulation (Himmelsbach, 1941; Koob and Le Moal, 2006; Littleton, 1998; Tabakoff and Hoffman, 2013). The abrupt reduction or suspension of alcohol intake in a subject with a severe AUD is receptorially characterized mainly by reduced GABA activity and increased glutamatergic activity with a hyperexcitability state that characterizes the main symptoms of AWS (Amato et al., 2011; Mayo-Smith, 1997). On the other hand, during the chronic use of alcohol, other neuroreceptor systems may be involved. Consequently, during AWS these neuro-receptoral disruptions may emerge. Namely,

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norepinephrine (NE) levels are higher during AWS, and decrease during recovery (Hawley et al., 1981). In addition, increased NE release in the brain may underlie anxiety associated with protracted withdrawal (Aston-Jones and Harris, 2004). Moreover, it has been shown that plasma noradrenaline (NA) levels are elevated during the chronic use of alcohol (Patkar et al., 2004), remain elevated during the first days of AWS, and then progressively decrease and return to physiological levels (Patkar et al., 2003). Serotonin (5-HT) is also reduced during AWS, and reduction of 5-HT seems to persist longer than NA (Patkar et al., 2003). It has also been demonstrated that the level of beta-endorphin is low during AWS, and is inversely correlated with anxiety (Kiefer et al., 2002). Therefore, high levels of NA during the first days of AWS may partially explain the onset of the adrenergic signs of AWS, and the increase of NE and the reduction of 5-HT and beta-endorphin levels may contribute to the onset of anxiety, a common disturbance during the acute phase of AWS.

The three phases of AWS

The first phase of AWS, the acute withdrawal stage, reflects generalized CNS hyperexcitability and is dominated by tremors, hyperactivity, and a risk of delirium tremens and seizures. Seizures typically occur within the first 48 h following discontinued consumption, with a peak around 24 h; the tremor follows a similar time course, while delirium tremens typically peaks around 72 h. After the first week, symptoms in the acute category are rarely encountered. During acute withdrawal, the treatment focus is to control and suppress generalized hyperexcitability, and to prevent the onset of seizures and delirium tremens (Mayo-Smith, 1997; Victor and Adams, 1953).

The second phase is the early abstinence stage, an intermediate period that follows the acute phase during which anxiety, low mood and disturbed sleep may continue, but are expressed in the absence of acute physical symptoms. The increased anxiety resolves over 3–6 weeks after discontinued alcohol use (Schuckit and Hesselbrock, 1994), somewhat more slowly in women than in men (Bokström et al., 1991).

The third phase is the protracted abstinence stage. There has been no clear evidence of protracted alcohol withdrawal (PAW) syndrome due to a lack of studies (Darshani et al., 2019; Bonnet et al., 2009; Le Bon et al., 2003), therefore the concept of PAW has not been included in the DSM-V (American Psychiatric Association, 2013). However, the UCLA Dual Diagnosis Program showed that during the period following acute AWS almost 75% of alcohol addicted individuals experience symptoms of PAW (Semel and Semel, 2020). During PAW, increased anxiety and dysphoria are not necessarily detected by standard assessment methods, but patients continue to report them, and in this period even small, normally insignificant challenges may provoke negative effects, craving and relapse (Sinha and Li, 2007; Sinha et al., 2011a, 2011b). Even though not yet clearly defined and fully investigated, PAW seems to be characterized by the presence of substance-specific signs and symptoms common to acute AWS, but persisting beyond the generally expected acute AWS time frames. Common PAW symptoms include anxiety, hostility, irritability, depression, mood instability, fatigue, insomnia, difficulties concentrating and thinking, reduced interest in sex, and unexplained physical complaints especially of pain. Despite clinical observation and patients' reports of symptoms experienced past the acute withdrawal stage, the research on PAW is limited, and no consensus on the term or definition exists.

Symptoms of PAW

Anecdotal literature (Darshani et al., 2019; Le Bon et al., 2003) and case studies going back several decades suggest that signs and symptoms of PAW may last 2 years or longer after alcohol discontinuation. In particular, a review of seven sleep studies using polysomnograph recordings of the brain while people slept found evidence that sleep abnormalities can persist for 1 to 3 years after stopping alcohol consumption (Angarita et al., 2016; Brower, 2001, 2015; Brower and Perron, 2010, Brower et al. 2011; Colrain et al., 2009). These abnormalities include difficulty falling asleep, decreased total sleep time, and sleep apnoea. Moreover, adaptive changes in the CNS may lead to affective and behavioural alterations that persist for many weeks or longer beyond acute withdrawal (Aston-Jones and Harris, 2004; Goldstein and Volkow, 2002; Koob, 2008; Koob and Le Moal, 2001; Weiss et al., 2001). Specifically, repeated use of a substance (i.e. ethanol) causes the brain to respond more readily to its effects but less readily to naturally rewarding activities such as listening to music, eating, sleeping, and so forth. This state, in which a person's ability to experience pleasure is decreased, is called anhedonia, which is typically a symptom of PAW. In this regard, Pozzi and colleagues examined anhedonia in individuals who had been abstinent from alcohol, opioids, and/or other drugs for some time, and who had no other identified psychiatric disorders, concluding that anhedonia appeared to be a symptom of PAW unrelated to other clinical and psychosocial features (Pozzi et al., 2008). Martinotti and colleagues found that signs and symptoms, including anhedonia, lasted the duration of a year-long study of people recovering from AUD (Martinotti et al., 2008). From the pathophysiological point of view, the neurological basis of anhedonia may be explained by the disruption of the dopaminergic system. The dopamine (DA) D2 receptor is implicated in reward mechanisms. It is well known that, under normal conditions, the DA reward site works to maintain a physiological condition; indeed, DA is known as the 'pleasure molecule'. When a dysfunction in the brain reward cascade occurs, it causes a hypodopaminergic trait; this trait leads to multiple drug-seeking behaviours of substances that may cause activation and neuronal release of DA in the brain. Therefore, a lack of D2 receptors causes individuals to be at high risk of multiple addictive, impulsive and compulsive behaviours (i.e. alcoholism, gambling, cocaine and heroin addiction). In order to explain this breakdown of the reward cascade, Blum and co-workers named this hypodopaminergic trait: the 'reward deficiency syndrome' (Blum et al., 2000). In addition, it has also been shown that the generalized hedonic deficit for natural rewards may reflect changed plasticity within the ventral tegmental area, amygdala and hypothalamus, and this hedonic deficit is thought to generate symptoms of PAW including anhedonia and depression (Aston-Jones and Harris, 2004). These symptoms gradually emerge during the period of the complete abstinence from substances (i.e. alcohol), and may persist for a long time.

In addition, both preclinical and clinical evidence has indicated that alcohol exerts acute anxiolytic effects, and its protracted exposure triggers a series of neuro-adaptive changes on

Table 1. Hypothesis of a pharmacological approach for the treatment of early AWS and protracted alcohol withdrawal with label and off-label drugs after the conclusion of the first stage of detoxification (acute AWS). §Approved in Italy and Austria (Caputo et al., Int Emerg Med, 2019). ^When high doses of benzodiazepines are not able to control specific symptoms or complicated and severe AWS, beta-blockers or alpha-adrenergics to control hypertension and tachycardia, haloperidol for hallucinations, and anticonvulsants for seizures are suggested (Carvalho et al., Lancet, 2019). *Safety, efficacy and duration of the combined treatment need to be investigated in controlled clinical trials.

Stages of alcohol withdrawal syndrome (AWS)	Acute alcohol withdrawal	Early abstinence, protracted alcohol withdrawal
Medications	Bezodiazepines (or sodium oxybate§) plus (if indicated) symptomatic drugs^	NMDA antagonist* plus GABA agonist*
Period of treatment	7–10 days	To be defined*

GABA and NMDA neurotransmitter systems, which persist for a long time during abstinence (Koob and Volkow, 2010). This long-lasting malfunctioning in association with the increase of NE and the reduction of 5-HT and beta-endorphin levels in the brain may predispose and promote anxiety (Aston-Jones and Harris, 2004; Hawley et al., 1981; Kiefer et al., 2002; Patkar et al., 2003), which is a symptom of PAW, and may also increase the risk of relapse (Aston-Jones and Harris, 2004; Heilig et al., 2010; Sinha et al., 2011a, 2011b). Finally, craving may also be considered a symptom of PAW. Indeed, for many years craving was considered part of the spectrum of symptoms of AWS. However, in the last few years craving has been classified as an independent behavioural condition (Verheul et al., 1999), and its correlation with PAW has thus been progressively abandoned. So, a question may arise: taking into account the symptoms of PAW, is our current pharmacological approach for the treatment of AUD correct or does the starting time to use medications need revising? So far, it is not possible to answer this question even though, in our opinion, it needs to be rethought and revisited.

A new pharmacological view in the treatment of alcohol use disorder

Benzodiazepines (BDZs) remain the 'gold standard' for the pharmacological treatment of AWS since they are the only class of drugs with confirmed efficacy in preventing the development of AWS complications, with a reduction in the incidence of convulsions (84%), delirium tremens and the associated risk of mortality (Caputo et al., 2019; Carvalho et al., 2019; Mayo-Smith, 1997; Mayo-Smith et al., 2004). The efficacy of BDZs in the treatment of AWS appears to be mediated by stimulation of the GABA-A receptors, thus with alcohol-mimicking properties. Once AWS is resolved, the main objective of pharmacological treatment is the maintenance of alcohol abstinence. Due to their potential induction of tolerance and dependence (Tan et al., 2010), BDZs are no longer used for medium- or long-term therapy; thus, other medications aimed at treating the symptoms of PAW have necessarily to be employed. Considering that PAW symptoms are mainly related to the neuro-adaptive changes of GABA and NMDA systems induced by the chronic use of alcohol, naltrexone and nalmefene, with their antagonist effect, and disulfiram, which blocks the aldehyde dehydrogenase enzyme during the process of ethanol metabolism, are not able to suppress the symptoms of PAW. These drugs are, however, generally prescribed immediately after the first 10–15 days of the detoxification period (Carvalho et al., 2019; Kranzler and Soyka, 2018). A more specifically pharmacological therapy able to suppress PAW symptoms could perhaps be used earlier and may be more helpful in preventing the risk of alcohol relapse, which remains higher during the first months of treatment. In light of this, medications acting on GABA and NMDA neurotransmitter systems, severely dysregulated during chronic alcohol consumption and AWS to counterbalance the up-regulation of the NMDA and the down-regulation of the GABA, could be employed in combination and started as soon as possible. Namely, if no contraindications exist, the pharmacological approach with antagonists of the NMDA system (i.e. acamprosate) in association with GABA agonists (i.e. gabapentin, sodium oxybate) could be started during the early abstinence or PAW phases, and continued in the following weeks and months (see Table 1). For example, Mason and co-workers showed that gabapentin not only reduced alcohol intake but also improved symptoms of insomnia, dysphoria and craving, identified as the most frequent symptoms of PAW (Mason et al., 2009, 2014). Even though not aimed at suppressing symptoms of PAW, some reports of combined treatments with a GABA agonist and an opioid antagonist (Anton et al., 2011; Caputo et al., 2007, 2016), or an opioid antagonist (i.e. naltrexone) and an NMDA antagonist (i.e. acamprosate) have been published (Anton et al., 2006; Mann et al., 2013). However, studies using GABA in combination with an NMDA antagonist aimed at controlling symptoms of PAW have not yet been performed. Our personal data (not published) have shown a good safety profile using acamprosate and sodium oxybate in combination, starting together in the initial phase of AWS. We recruited eight in-patients with moderate AWS, and administered oral sodium oxybate (50 mg/kg t.i.d.) for 1 month (Caputo et al., 2019; Skala et al., 2013) to treat the acute and early phases of AWS in association with acamprosate (666 mg t.i.d.) administered with the aim of achieving 12 months of treatment for the prevention of relapses (Carvalho et al., 2019; Kranzler and Soyka, 2018). No patient presented symptoms of craving for sodium oxybate, and no side effects due to the combination of the two drugs were shown; six patients maintained complete abstinence from alcohol during the first 2 months of treatment. Sodium oxybate is a GABA agonist compound, approved in Italy and Austria since the early 1990s (Caputo and Bernardi, 2013) for the treatment of alcohol addiction, with positive results (Keating, 2014; Leone et al., 2010; Skala et al., 2013). In particular, it has been shown to suppress symptoms of moderate AWS similar to diazepam (Addolorato et al., 1999), clomethiazole (Nimmerrichter et al., 2002) and oxazepam

(Caputo et al., 2014). In addition, sodium oxybate used as an anti-craving drug has demonstrated its efficacy in the maintenance of alcohol abstinence in several studies (Keating, 2014; Leone et al., 2010; Skala et al., 2013). However, concerns about the chronic use of sodium oxybate remain due to the risk of developing a craving for and subsequent abuse of the drug (Keating, 2014; Leone et al., 2010; Skala et al., 2013). On the other hand, data from clinical trials and from pharmaco-vigilance (Addolorato et al., 2019) have shown that cravings for and abuse of the drug are very limited phenomena (10–15% of patients), episodes of death attributable to this drug have not been documented, and only patients with specific characteristics (polydrug addicts, and patients with borderline personality or bipolar disorders) may be more predisposed to developing such a craving and abusing the drug (Addolorato et al., 2019; Caputo et al., 2009, 2011). In addition, even though performed in healthy controls, no additional sedative effects have been shown using sodium oxybate when used in combination with ethanol (Pross et al., 2015). Furthermore, this drug is also currently approved by the Food and Drug Administration for the treatment of narcoleptic patients (Thorpy and Bogan, 2020).

Conclusion

After the treatment of the acute phase of AWS, it could be hypothesised that using medications in order to control PAW (NMDA antagonists and GABA agonists) rather than to immediately reduce alcohol intake or to maintain complete abstinence may reduce the risk of relapses during the first months of treatment. In some cases, this may avoid wasting the opioid antagonists (i.e. naltrexone and nalmefene) and aversive drug (i.e. disulfiram) 'weapons' in the early phase, giving physicians the possibility of using them (if needed, later) as replacements or supplements for the PAW medications when the symptoms of PAW have at least improved or been suppressed. In addition, since some PAW symptoms may overlap symptoms of a psychiatric disorder, which tend to emerge (if they existed prior to the start of alcohol addiction existed) in the period of abstinence from alcohol, a diagnosis of comorbid psychiatric disorder needs to be planned to attribute these kinds of symptoms to a psychiatric disorder or specifically to PAW, and consequently adapting a specific psychiatric pharmacological therapy.

Thus, meta-analyses and clinical trials aiming to investigate and characterize the frequency of PAW and the efficacy of the combined treatment with GABA agonists and NMDA antagonists are warranted. This may lead to the recognition of a more appropriate and timed pharmacological treatment of AUD.

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References

Addolorato G, Balducci G, Capristo E, et al. (1999) Gamma-hydroxybutyric acid (GHB) in the treatment of alcohol withdrawal syndrome: A randomized comparative study versus benzodiazepine. *Alcohol Clin Exp Res* 23: 1596–1604.

Addolorato G, Lesch OM, Maremmani I, et al. (2019) Post-marketing and clinical safety experience with sodium oxybate for the treatment of alcohol withdrawal syndrome and maintenance of abstinence in alcohol-dependent subjects. *Expert Opin Drug Saf* 19: 159–166.

American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. Washington, DC: The American Psychiatric Association.

Amato L, Minozzi S and Davoli M (2011) Efficacy and safety of pharmacological interventions for the treatment of the Alcohol Withdrawal Syndrome. *Cochrane Database Syst Rev* 6: CD008537.

Angarita GA, Emadi N, Hodges S, et al. (2016) Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: A comprehensive review. *Addict Sci Clin Pract* 11: 9.

Anton RF, Myrick H, Wright TM, et al. (2011) Gabapentin combined with naltrexone for the treatment of alcohol dependence. *Am J Psych* 168: 709–717.

Anton RF, O'Malley SS, Ciraulo DA, et al. (2006) Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. *JAMA* 295: 2003–2017.

Aston-Jones G and Harris GC (2004) Brain substrates for increased drug seeking during protracted withdrawal. *Neuropharmacology* 47: 167–179.

Blum K, Braverman ER, Holder JM, et al. (2000) Reward deficiency syndrome: A biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. *J Psychoactive Drugs* 32: 1–112.

Bokström K, Balldin J and Långström G (1991) Individual mood profiles in alcohol withdrawal. *Alcohol Clin Exp Res* 15: 508–513.

Bonnet U, Specka M, Hamzavi Abedi R, et al. (2009) Severe protracted alcohol withdrawal syndrome: Prevalence and pharmacological treatment at an inpatient detoxification unit–a naturalistic study. *Pharmacopsychiatry* 42: 76–78.

Brower KJ (2001) Alcohol's effects on sleep in alcoholics. *Alcohol Res Health* 25: 110–125.

Brower KJ (2015) Assessment and treatment of insomnia in adult patients with alcohol use disorders. *Alcohol* 49: 417–427.

Brower KJ and Perron BE (2010) Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances. *Med Hypotheses* 74: 928–933.

Brower KJ, Krentzman A and Robinson EAR (2011) Persistent insomnia, abstinence, and moderate drinking in alcohol-dependent individuals. *Am J Addict* 20: 435–440.

Caputo F and Bernardi M (2013) Sodium oxybate to treat alcohol dependence: 20 years of clinical experience. *Add Biol* 18: 901–903.

Caputo F, Addolorato G, Stoppo M, et al. (2007) Comparing and combining gamma-hydroxybutyric acid (GHB) and naltrexone in maintaining abstinence from alcohol: An open randomised comparative study. *Eur Neuropsychopharmacol* 17: 781–789.

Caputo F, Agabio R, Vignoli T, et al. (2019) Diagnosis and treatment of acute alcohol intoxication and alcohol withdrawal syndrome: Position paper of the Italian Society on Alcohol. *Intern Emerg Med* 14: 143–160.

Caputo F, Francini S, Stoppo M, et al. (2009) Incidence of craving for and abuse of gamma-hydroxybutyric acid (GHB) in different populations of treated alcoholics: An open comparative study. *J Psychopharmacol* 23: 883–90.

Caputo F, Francini S, Brambilla R, et al. (2011) Sodium oxybate in maintaining alcohol abstinence in alcoholic patients with and without psychiatric comorbidity. *Eur Neuropsychopharmacol* 21: 450–456.

Caputo F, Maremmani AG, Addolorato G, et al. (2016) Sodium oxybate plus nalmefene for the treatment of alcohol use disorder: A case series. *J Psychopharmacol* 30: 402–409.

Caputo F, Skala K, Mirijello A, et al. (2014) Sodium oxybate in the treatment of alcohol withdrawal syndrome: A randomized double-blind comparative study versus oxazepam. The GATE 1 Trial. *CNS Drugs* 28: 743–752.

Carvalho AF, Heilig M, Perez A, et al. (2019) Alcohol use disorders. *Lancet* 394: 781–792.

Colrain IM, Turlington S and Baker FC (2009) Impact of alcoholism on sleep architecture and EEG Power Spectra in men and women. *Sleep* 32: 1341–1352.

Darshani AGS, Ranasinghe K and Gurukula BA (2019) A case of protracted alcohol withdrawal syndrome: Resistant lilliputian hallucinations with tremor. *As J Case Rep Med Health* 24: 1–7.

Goldstein RZ and Volkow ND (2002) Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *Am J Psych* 159: 1642–1652.

Grant BF, Goldstein RB, Saha TD, et al. (2015) Epidemiology of DSM-5 alcohol use disorder: Results from the national epidemiologic survey on alcohol and related conditions III. *JAMA Psychiatry* 72: 757–766.

Hawley RJ, Major LF, Schulman EA, et al. (1981) CSF levels of norepinephrine during alcohol withdrawal. *Arch Neurol* 38: 289–292.

Heilig M, Egli M, Crabbe JC, et al. (2010) Acute withdrawal, protracted abstinence and negative affect in alcoholism: Are they linked? *Addict Biol* 15: 169–184.

Himmelsbach CK (1941) The morphine abstinence syndrome, its nature and treatment. *Ann Intern Med* 15: 829–843.

Keating GM (2014) Sodium oxybate: A review of its use in alcohol withdrawal syndrome and in the maintenance of abstinence in alcohol dependence. *Clin Drug Investig* 34: 63–80.

Kiefer F, Horntrich M, Jahn H, et al. (2002) Is withdrawal-induced anxiety in alcoholism based on beta-endorphin deficiency? *Psychopharmacology* 162: 433–437.

Koob GF (2008) Neurobiological substrates for the dark side of compulsivity in addiction. *Neuropharmacology* 56: 18–31.

Koob GF and Le Moal M (2001) Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacol* 24: 97–129.

Koob GF and Le Moal M (2006) Alcohol. In: GF Koob and M Le Moal (eds) *Neurobiology of Addiction*. Oxford: Oxford Academic Press, pp. 173–241.

Koob GF and Volkow ND (2010) Neurocircuitry of addiction. *Neuropsychopharmacology* 35: 217–238.

Kranzler HR and Soyka M (2018) Diagnosis and pharmacotherapy of alcohol use disorder: A review. *JAMA* 320: 815–824.

Le Bon O, Murphy JR, Staner L, et al (2003) Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: Polysomnographic and clinical evaluations. *J Clin Psychopharmacol* 23: 377–383.

Leone MA, Vigna-Taglianti F, Avanzi G, et al. (2010) Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. *Cochrane Database Syst Rev* 17: CD006266.

Littleton J (1998) Neurochemical mechanisms underlying alcohol withdrawal. *Alcohol Health Res World* 22: 13–24.

Mann K, Lemenager T, Hoffmann S, et al. (2013) Results of a double-blind, placebo-controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. *Addict Biol* 18: 937–946.

Martinotti G, Di Nicola M, Reina D, et al. (2008) Alcohol protracted withdrawal syndrome: The role of anhedonia. *Subst Use Mis* 43: 271–284.

Mason BJ, Light JM, Williams LD, et al. (2009) Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: Effects of gabapentin. *Addict Biol* 14: 73–83.

Mason BJ, Quello S, Goodell V, et al. (2014) Gabapentin treatment for alcohol dependence: A randomized clinical trial. *JAMA Intern Med* 174:70–77.

Mayo-Smith MF (1997) Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. *JAMA* 278: 144–151.

Mayo-Smith MF, Beecher LH, Fischer TL, et al. (2004) Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Arch Intern Med* 164: 1405–1412.

Nimmerrichter AA, Walter H, Gutierrez-Lobos KE, et al. (2002) Double-blind controlled trial of gamma-hydroxybutyrate and clomethiazole in the treatment of alcohol withdrawal. *Alcohol Alcohol* 37: 67–73.

Patkar AA, Gopalakrishnan R, Naik PC, et al. (2003) Changes in plasma noradrenaline and serotonin levels and craving during alcohol withdrawal. *Alcohol Alcohol* 38: 224–231.

Patkar AA, Marsden CA, Naik PC, et al. (2004) Differences in Pheriphperal noradrenergic function among actively drinking and abstinent alcohol dependent individuals. *Am J Addict* 13: 225–235.

Pozzi G, Martinotti G, Reina D, et al. (2008) The assessment of post-detoxification anhedonia: Influence of clinical and psychosocial variables. *Subst Use Mis* 43: 722–732.

Pross N, Patat A, Vivet P, et al. (2015) Pharmacodynamic interactions of a solid formulation of sodium oxybate and ethanol in healthy volunteers. *Br J Clin Pharmacol* 80: 480–492.

Schuckit MA and Hesselbrock V (1994) Alcohol dependence and anxiety disorders: What is the relationship? *Am J Psych* 151: 1723–1734.

Semel J and Semel T (2020) Persistent Withdrawal Symptoms After Detox Dual Diagnosis Program. Semel Institute. UCLA Dual Diagnosis Program Information and Admissions, University of California, Los Angeles.

Sinha R and Li CS (2007) Imaging stress- and cue-induced drug and alcohol craving: Association with relapse and clinical implications. *Drug Alcohol Rev* 26: 25–31.

Sinha R, Shaham Y and Heilig M (2011a) Translational and reverse translational research on the role of stress in drig craving and relapse. *Psychpharmacol* 218: 69–82.

Sinha R, Fox HC, Hong KI, et al. (2011b) Effects of adrenal sensitivity, stress- and cue-induced craving, and anxiety on subsequent alcohol relapse and treatment outcomes. *Arch Gen Psych* 68: 942–952.

Skala K, Caputo F, Mirijello A, et al. (2013) Sodium oxybate in the treatment of alcohol dependence: From the alcohol withdrawal syndrome to the alcohol relapse prevention. *Exp Opin Pharmacother* 15: 245–257.

Tabakoff B and Hoffman PL (2013) The neurobiology of alcohol consumption and alcoholism: An integrative history. *Pharmacol Biochem Behav* 113: 20–37.

Tan KR, Brown M, Labouèbe G, et al. (2010) Neural bases for addictive properties of benzodiazepines. *Nature* 463: 769–774.

Thorpy MJ and Bogan RK (2020) Update on the pharmacologic management of narcolepsy: Mechanisms of action and clinical implications. *Sleep Med* 68: 97–109.

Verheul R, van den Brink W and Geerlings P (1999) A three-pathway psychobiological model of craving for alcohol. *Alcohol Alcohol* 34: 197–222.

Victor M and Adams RD (1953) Effects of alcohol on the nervous system. In: HH Merritt and CC Hare (eds) *Metabolic and Toxic Diseases of the Nervous System*. Baltimore, MD: Williams and Wilkins, pp. 526–573.

Weiss F, Ciccocioppo R, Parsons LH, et al. (2001) Compulsive drug-seeking behavior and relapse: Neuroadaptation, stress, and conditioning factors. *Ann NY Acad Sci* 937: 1–26.

World Health Organization (WHO) (2014) *Global Status Report on Alcohol and Health*. Geneva: World Health Organization.