CME Information Page

Overall Objective: The objective of this continuing medical education program is to present participants with an expanded clinical skill set and raised awareness of clinically relevant issues in their profession. They will review key diagnostic criteria, cutting-edge treatment strategies, and practice points they can implement in the challenges of daily practice while providing evidence-based care to patients and clients suffering psychiatric and comorbid medical disorders. The expected outcomes include an increase in knowledge, competence, professionalism, and performance.

Target Audience: The primary target audience for this program includes, but is not limited to: psychiatrists, primary care physicians, psychiatric nurses, pharmacists, clinical psychologists, and social workers. Clinicians who have caseloads composed significantly of individuals with psychiatric disorders, and comorbid medical illnesses will find this course particularly useful.

Duration of CME Status: *Directions in Psychiatry* **begins May 31, 2019,** and the *preliminary* **expiration date is December 31, 2023.** At that point, the Hatherleigh Medical Director and the editorial staff will review the CME material to determine whether the program continues to be consistent with current accreditation guidelines and standards of care. A determination will be made as to whether the program can be used to earn full CME credit after that date.

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This CME program was created from a learning needs assessment of participants in previous CME programs, who are virtually all physicians and other mental health clinicians. Their expressed needs were assessed by the Medical Director, the Program Advisory Board members, and editorial staff in the development of this curriculum.

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Comorbid Posttraumatic Stress Disorder and Alcohol Use Disorder: From Mechanisms to Assessments and Treatments, Part 1: Neurobiological Correlates

Renie George; Janet M. Guo; Leah T. Weingast; Seth D. Norrholm, PhD

No commercial support was used in the development of this CME lesson.

KEY WORDS: Posttraumatic Stress Disorder • Alcohol Use Disorder • Neurobiological Correlates • Psychotherapy • Pharmacological treatment

LEARNING OBJECTIVES: Clinicians will be able to describe and differentiate between common neurobiological correlates, assessment methods, and treatments of *posttraumatic stress disorder* (PTSD), *alcohol use disorder* (AUD), and comorbid PTSD and AUD.

LESSON ABSTRACT: In part one of this lesson, the authors delineate common neurobiological correlates of PTSD, AUD, and comorbid PTSD and AUD. The neuroendocrine, neurochemical, and neuroanatomical markers of PTSD are explored, followed by an analysis of the neurotransmitter changes associated with AUD. The authors highlight the need for further research in uncovering the neurobiological mechanism of comorbid PTSD and AUD. In part two of this lesson, the authors outline common clinical assessments for PTSD and AUD. The psychotherapeutic and pharmacological treatments available for PTSD and AUD are also presented, followed by a call for more research into possible treatments for comorbid PTSD and AUD.

COMPETENCY AREAS: This lesson distinguishes the similarities and differences in PTSD, AUD, and comorbid PTSD and AUD regarding neurobiological markers, clinical assessments, and treatments. Clinicians will gain knowledge about many aspects of PTSD and AUD and will be able to use a holistic approach when treating patients with PTSD, AUD, and comorbid PTSD and AUD.

Introduction

Two common comorbid psychiatric conditions that can present within civilian and combat populations with a history of trauma exposure are *posttraumatic stress disorder* (PTSD) and *alcohol use disorder* (AUD).[1,2] As the rates of comorbid PTSD and AUD continue to increase in the U.S. general population, according to data from the National Comorbidity Survey,[3] it is important to explore the current treatment options for both conditions concomitantly. In addition, individuals with PTSD have an alarmingly high risk of developing AUD. For example, one study found those with PTSD symptoms have a three-fold increase in the risk of developing AUD[3] and alcohol is the most commonly abused drug by patients with PTSD.[4] Data from over one million former service members, collected by the Department of Veterans Affairs, revealed that 41% of those with substance use disorders also have comorbid PTSD.[5] Together, the high prevalence and frequent comorbidity of PTSD and AUD serve as compelling reasons to explore current and future diagnostic and therapeutic options for this clinical presentation.

PTSD is defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[6] as a psychiatric illness that develops after experiencing a traumatic event and is characterized by re-experiences, avoidance, negative cognitions and mood, and increased arousal.[7]

According to the DSM-5, AUD has been defined as a chronic relapsing disorder characterized by a compulsion to seek and drink alcohol, loss of control over alcohol intake, and the emergence of a negative emotional state (e.g., dysphoria, anxiety, and irritability) that defines a motivational withdrawal syndrome when access to alcohol is prevented.[6] The emergence of clinical AUD is accompanied by neurobiological changes that underlie the execution of motivated behaviors[8] (e.g., the midbrain, limbic system, and prefrontal cortex).

PTSD and AUD, while vastly different in diagnostic criteria and symptoms, overlap in affected populations, most prevalently in U.S. military veterans.[1] The rate of comorbid PTSD and AUD diagnoses in the civilian population was approximately 42% in 2011[9] and is estimated to be even higher in the veteran population.[10] The first part of the following lesson describes the neurobiological mechanisms of PTSD, AUD, and comorbid PTSD and AUD. The second part reviews the current assessments and treatments for PTSD and AUD individually and then considers future directions for the effective treatment of comorbid PTSD and AUD.

Neurobiological Mechanisms

Neurobiology of PTSD:

The neurobiological correlates of PTSD have a basis in neuroendocrinology, neurochemistry, neuroanatomy, and neurogenomics. A primary goal behind the identification of these neurobiological correlates is to improve the accuracy of PTSD diagnosis and, as such, improve patient outcomes. While a review of the available literature on the neurobiology of PTSD is outside the scope of this chapter, we will review important key points and findings below (see Liberzon & Ressler, 2016, for a thorough review of this topic[11]).

From a neuroendocrinological perspective, there are at least two major pathways to consider that have been targeted in patients with clinical features of PTSD: the *hypothalamic–pituitary–adrenal* (HPA) and *hypothalamic–pituitary–thyroid* (HPT) axes. With regard to neurochemistry, there have been significant changes detected in the upregulation and downregulation of important neurochemicals (both small-molecule neurotransmitters and large-molecule neuropeptides) in populations with PTSD symptomatology. **Neuroanatomically, PTSD-related changes have been detected within the brain in three primary areas: the hippocampus, extended amygdala, and prefrontal cortices.** With regard to the human genome, numerous candidate genes have been identified with contributions to PTSD phenomenology (for a review, see Norrholm & Ressler[12]), and much of the focus in this area has shifted to whole genome–level analyses. The genomic bases of PTSD are beyond the scope of this lesson, but many review resources are available in the literature (e.g., Skelton et al.[13]).

The HPA axis is critical for mammalian stress adaptation, and both prolonged hyper-and hypoactivities of this pathway have been linked to the clinical presentations of anxiety-, trauma-, and stressor-related disorders.[14] A substantial body of literature has been dedicated to PTSD-related alterations in the negative feedback loop that exists

within the HPA axis for the regulation and release of hypothalamic *corticotropin-releasing factor* or *hormone* (CRF or CRH), pituitary adrenocorticotropic hormone, and adrenal cortisol in response to stress (see Szeszko et al.[15]). It has been suggested that altered glucocorticoid receptor sensitivity plays a significant role in HPA axis dysfunction in PTSD and its related neurobiological sequelae.[16] Many patients with PTSD experience hypocortisolism as a result of the altered regulation and release of CRF and *norepinephrine* (NE)[17] (Table 1). However, there remains significant controversy regarding the mechanism(s) underlying hypocortisolism and its contribution to PTSD symptom presentation. One possibility is the underregulation of cortisol disinhibits CRF- and NE-releasing projections—which, in turn, may enhance stress response. For example, elevated NE levels are associated with an increase in arousal, startle response, and encoding of fear memories.[18] It has also been suggested that altered immune function (i.e., overactivity) contributes to PTSD progression as a result of decreased levels of suppressive glucocorticoids[19] (see Table 1).

In addition to dysregulation along the HPA axis, disruption along the HPT axis has also been linked to stress and anxiety disorders. Along the HPT axis, an abnormal triiodothyronine/thyroxine ratio (T_3:T_4) can increase anxiety.[22] T_3 is a thyroid hormone that is critical to maintaining the body's metabolic rate and heart rate; it is the active form of thyroxine. Studies conducted by Wang et al.[30] as well as Karlović et al.[25] involving combat veterans with PTSD found that elevated T_3 was associated with the severity of PTSD symptoms (Table 1). This disruption along the HPT axis can be linked to altered levels of stress observed in studies of PTSD populations, likely due to complex feedback mechanisms.[55]

In addition to these changes along the HPA and HPT axes, studies investigating the neuroendocrine underpinnings of trauma- and stressor-related disorders have also noted differences in sex hormone levels, including estrogen in female study subjects and participants (Table 1). Translational studies of both rodents and humans have reported facilitated fear extinction learning when estrogen levels are higher relative to control levels either through menstrual cycling or exogenous hormone administration.[24] In addition, sexual assault victims who took emergency estrogen-based contraceptives immediately after a traumatic event experienced less severe PTSD symptoms than those who declined the contraceptives.[23] Milad's research group's research suggested low estrogen levels may present a vulnerability for PTSD development in traumatized women.[27,28,29,31] Taken together, these studies demonstrate the crucial role of sex and endocrine differences in males and females in the development of PTSD.

Table 1:
Common Neurobiological Correlates of PTSD Categorized By Neuroendocrine, Neurochemical, and Neuroanatomical Changes

Neurobiological Correlate	Upregulation ↑	Downregulation ↓	References
Neuroendocrine	NE, T_3, estrogen	cortisol, GCs	Almli et al., 2013; Dias & Ressler, 2013; Dayan & Panicker, 2018; Feree et al., 2012; Glover et al., 2015; Karlović et al., 2004; Lang et al., 2013; Lebron-Milad et al., 2012; Milad et al., 2010; Milad et al., 2009; Rohleder et al., 2004; Sherin & Nemeroff, 2011; Somvanshi et al. 2019; Szeszko et al., 2018; Wang et al.,1995; Zeidan et al., 2011
Neurochemical	DA, Glu	GABA, NPY, serotonin	Enman et al., 2014; Feder et al., 2009; Fogaca & Duman, 2019; Kelmendi et al., 2016; Kovacic et al., 2008; Kozlovsky, 2006; Lisieki et al., 2018; Pezze & Feldon, 2004; Popoli et al., 2011; Reul & Nutt, 2008; Takei et al., 2011; Thorsell & Mathe, 2017; Sah & Gericioti, 2012; Sherin & Nemeroff, 2011
Neuroanatomical	Amygdalar activity	HC activity and volume; PFC volume	Akiki et al., 2017; Bremner (2006, 2007); Hayes et al., 2011; Logue et al., 2017; Morey et al., 2012; Norrholm & Jovanovic, 2010; Norrholm et al., 2013; Shin et al., 2006; Zhu et al., 2017
Key: norepinephrine (NE), glucocorticoids (GCs), T_3 (triiodothyronine), dopamine (DA), glutamate (GA), neuropeptide Y (NPY), prefrontal cortex (PFC), hippocampus (HC)			

Sources in Table 1:[15-17,19-54]

Not surprisingly, the development and maintenance of PTSD symptoms following trauma includes the recruitment of several neurotransmitter systems, including small-molecule neurotransmitters and large-molecule neuropeptides such as *dopamine* (DA), *serotonin* (5-HT), *γ-aminobutyric acid* (GABA), *glutamate* (Glu), and *plasma neuropeptide Y*(NPY;[17, 32, 34, 43, 44] see Table 1). For example, elevated levels of DA and Glu within the hippocampus and **reduced levels of GABA, NPY, and 5-HT within the limbic system (the amygdala, hypothalamus, hippocampus, basal ganglia, thalamus, and cingulate gyrus) have been detected in populations experiencing PTSD symptoms when faced with traumatic reminders, compared to baseline levels.**[17, 35–38]

While the neurochemical underpinnings of PTSD are still being investigated, there are some pivotal findings of the putative role of key neurotransmitters. DA, for example, is a catecholamine neurotransmitter that mediates stress responses and aids the regulation of fear conditioning in the limbic brain regions, including the extended amygdala and medial prefrontal cortex.[56, 57, 58] PTSD symptoms such as restlessness, nightmares, fear memory, and impulsivity, have been empirically associated with increased DA levels within the amygdala, medial prefrontal cortex, and nucleus accumbens.[39] These areas are target structures of the mesolimbic DA system originating from the ventral tegmental area. The exact mechanisms underlying the upregulation of the excitatory neurotransmitter Glu in principal brain regions associated with PTSD is still the subject of considerable debate. One possibility is a change in the relationship between Glu and the brain-derived neurotrophic factor within the hippocampus.[59] Glutamatergic projections from the ventromedial prefrontal cortex and hippocampus are critical for the modulation of fear extinction and contextual fear conditioning. These connections could be affected by the change in brain-derived neurotrophic factor expression found in single prolonged stress and predator exposure, two different PTSD rodent animal models.[37–42] Another possibility is the dysfunction in the glial cells that regulate extra-synaptic Glu within the hippocampal CA1 region.[40–41] This region of the brain is critical for encoding memories and has implications in PTSD symptomology.[60] Glial cells, including astrocytes, are implicated in clearing neurotransmitters from the synaptic cleft, hence dysfunction in these cells could also lead to an increased amount of Glu available to bind to receptors within the hippocampal region.[61] Furthermore, increased Glu levels can cause excitotoxic effects, which have been shown to lead to dendritic remodeling and reductions in spine density within the hippocampus and prefrontal cortex.[59, 62] Many stressors—whether chronic, mild, or acute—have been associated with the retraction of dendrites on the pyramidal neurons involved in the limbic region of the prefrontal cortex in rodents.[63–64] It is likely several of these mechanisms contribute to high levels of Glu in human PTSD symptomology.

In addition to the aforementioned changes in DA and Glu, the downregulation of GABA, NPY, and 5-HTalongthe limbic circuitry has the potential to affect one's response to stressors and anxiety.[17, 33, 36, 44, 65] Reduced plasma GABA concentrations may be a preliminary biomarker for PTSD,[66] as they may reliably reflect brain GABA levels.[67] The reduction in this major inhibitory neurotransmitter has been associated with changes in $GABA_A$ receptor sensitivity in patients with anxiety-related disorders.[68] In addition, NPY is abundantly expressed in forebrain limbic and brainstem areas that regulate stress and emotional behaviors and may be involved in PTSD symptom maintenance.[44] Lastly, 5-HT, a monoamine neurotransmitter, has a critical role in fear response regulation. In short, 5-HT serves to regulate stress response and emotional behaviors through changes to $5\text{-HT}_{1\text{-}7}$ receptors in regions such as the amygdala, hypothalamus, prefrontal cortex, and nucleus accumbens. Changes to the $5\text{-HT}_{1\text{-}7}$ receptors in these regions allow for the upregulation of 5-HT when faced with acute stressors.[17] The mechanism responsible for fear response regulation due to NPY and 5-HT activity is currently being debated. There is evidence that platelet 5-HT concentrations are significantly lower in suicidal PTSD and suicidal non-PTSD patients compared with nonsuicidal patients or healthy controls.[36] These neurochemicals (GABA, NPY, and 5-HT) have possible roles in regulating stress, anxiety, and fear response. Alongside these neurochemical changes, there are several structural changes within the neuroanatomy of the brain that have been associated with a change in PTSD symptom expression and severity.

The hippocampus, amygdala, and cortex (i.e., prefrontal, anterior cingulate) have been highlighted as key

structures involved in the presentation of PTSD symptoms (Table 1). The hippocampus is a critical region in the limbic system of the forebrain that is involved in memory consolidation and spatial memory,[60] while the amygdala is strongly related to emotional processing and adaptive behaviors, including fear responses.[69] In populations with PTSD, there has been evidence of reduced volume and activity of the hippocampus and increased activity of the amygdala.[46] This increased amygdala activity has been linked to decreased inhibition from the prefrontal cortex—which, under nonpathologic circumstances, serves as a "brake" on amygdala activity and behavioral output[52–51] (e.g., fear responses). Alongside these functional changes in the hippocampus and amygdala, there is structural evidence of reduced prefrontal cortex volume.[47] These structural changes in neurocircuitry could play a role in altering fear memories, fear responses, and the extinction of fear once the aversive consequences of a fear trigger are consistently removed.[70]

Identifying biomarkers and neurobiological risk factors for PTSD is pivotal for developing preventative and individualized interventions for this disorder.

Neurobiology of AUD:

Alcohol-seeking behavior can be explained by different types of reinforcements that vary based on the stage of dependence. The early stages of alcohol dependence are based on positive reinforcement, while the motivation underlying the later stages is rooted in the principles of negative reinforcement.[71] Reinforcement refers to learning associated with the repetition of an action resulting in an appetitive result or the removal of an aversive consequence.[72] In this case, the reinforced action is repeated alcohol use. Positive reinforcement pairs the action with the addition of an appetitive stimulus or reward. This pairing leads a person to repeat the action in order to experience the reward. On the other hand, negative reinforcement pairs the action with the removal of an aversive stimulus that leads the person to repeat the action in order to avoid punishment.

In the early stages of alcohol use, drinking activates the brain's dopaminergic mesolimbic reward system, which can induce feelings of euphoria and relaxation. Alcohol use is therefore initially positively reinforced through repeated drinking in order to reproduce these euphoric, rewarding feelings.[71]As alcohol use becomes more prolonged over time (chronic), however, people tend to experience aversive withdrawal symptoms after abruptly discontinuing the consumption of alcohol. Alcohol use is then negatively reinforced, as drinking continues in order to avoid these aversive symptoms.[71] However, negative reinforcement may also be the underlying motivation behind the early stages of alcohol use in those struggling with various psychiatric symptoms and disorders.[71] These patients will usually begin drinking to alleviate the symptoms of depression, anxiety, trauma and stressor-related disorders, and other psychiatric conditions.

In most cases, the transition to alcohol dependence is marked by the reinforcement of alcohol use shifting from positive to negative. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, the transition from alcohol "abuse" to alcohol "dependence" involves three primary processes: sensitization, tolerance, and withdrawal. These processes are believed to arise from maladaptive neural changes associated with chronic alcohol use.[71] Sensitization refers to addictive drugs activating neural systems that give incentive salience to the stimuli that activate those systems, thus increasing the neural response to those stimuli.[73] As alcohol activates reward systems in the brain, it assumes an incentive salience, meaning a "like" of alcohol becomes a "want."[71] In other words, one develops a strong desire for alcohol and will become more motivated to perform alcohol-seeking behaviors. As one begins drinking chronically, tolerance emerges, meaning higher amounts of alcohol are necessary to experience the same effects as when one started drinking[71, 74, 75, 76] (in lower quantities). As will be discussed in the sections that follow, tolerance stems from changes in the receptor sensitivities of several neurotransmitter systems with which alcohol interacts. Changes in receptor sensitivity have also been linked to the development of withdrawal symptoms. Withdrawal symptoms arise when one who is chronically exposed to alcohol abruptly abstains from alcohol use and can include convulsions, motor abnormalities, autonomic disturbances (sweating, increased heart rate, and restlessness), and a negative affective state (anxiety, irritability, and dysphoria).[77] These three processes (sensitization, tolerance, and withdrawal) reinforce the psychological and physiological "need" for alcohol and lead to the development of alcohol dependence.

Reward System Neurotransmitters

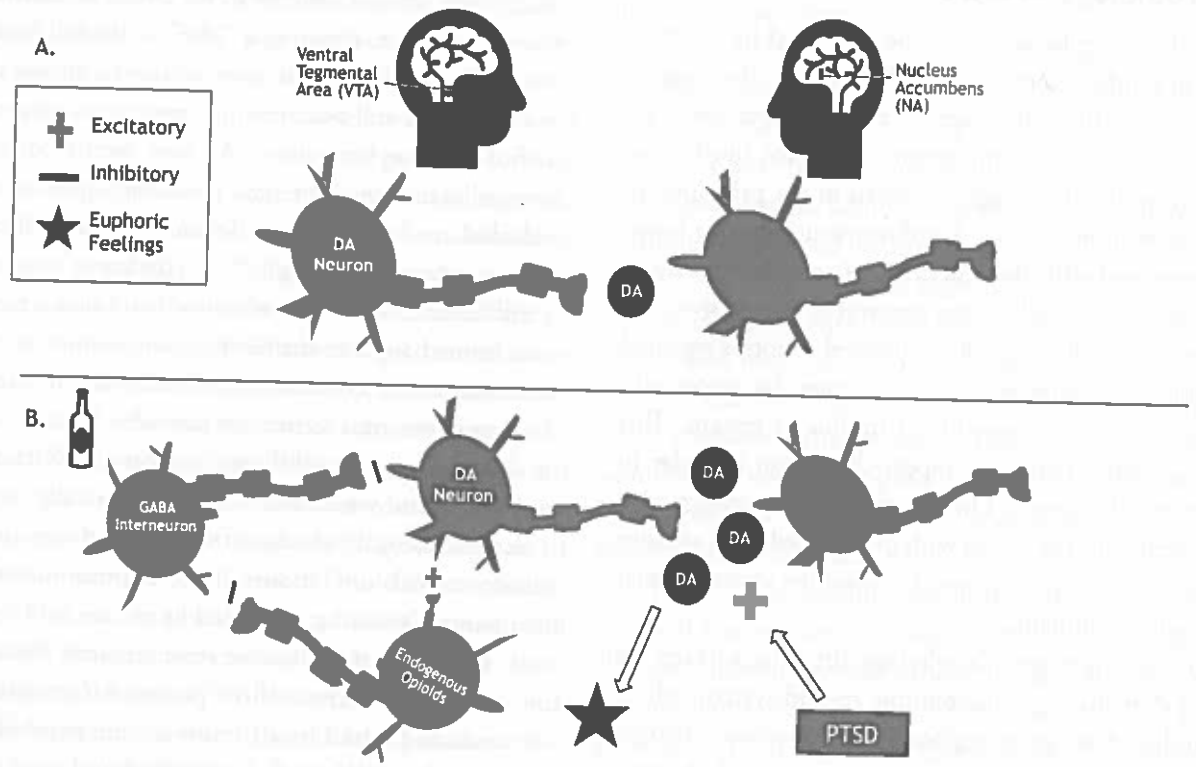
As introduced above, the neural changes that lead to the development of alcohol sensitization, tolerance, and withdrawal stem from the substance's interaction with several neurotransmitters in the brain's reward and stress systems.[71]

The main reward system in the brain is known as the mesolimbic pathway (Figure 1A), which includes DA-releasing neurons that project from the midbrain ventral tegmental area to the subcortical *nucleus accumbens* (NA) or ventral striatum. It is considered a reward system, as the release of DA in these brain regions leads to feelings of euphoria.[71, 78] Both rodent and human studies have shown alcohol consumption leads to an increase in DA released in the NA (Figure 1B). For example, Weiss et al.[79] showed alcohol consumption, or signaling alcohol was available, led to an increase in extracellular DA concentration in the NA of alcohol-preferring rats, and Aalto al.[80] showed an increase of DA release in the NA of humans in response to intravenous or oral doses of ethanol. Furthermore, it was shown that injecting low doses of a DA receptor antagonist into the NA of rodents

Figure 1:
The Effect of Acute Alcohol Consumption on Dopamine (DA) Levels in the Mesolimbic Pathway

A. The mesolimbic pathway ("reward system") without the effects of alcohol or PTSD. Dopaminergic neurons originate in the ventral tegmental area and release DA in the nucleus accumbens (NA).

B. Both rodent[79] and human[83] studies have found alcohol directly increases the release of DA in the NA by stimulating the dopaminergic neurons in the ventral tegmental area. Furthermore, rodent studies[84] show alcohol also stimulates the release of endogenous opioids that work to increase DA concentrations in the NA in two different ways. Endogenous opioids (B-endorphins and enkephalins) bind to mu- and kappa-opioid receptors on the DA neurons, activating the neurons, and stimulating increased DA release.[85] There are also mu-opioid receptors on the GABA interneuron—where B-endorphins can bind and inhibit the interneuron, disinhibiting the DA neurons and increasing DA release in the NA.[85] Overall, alcohol consumption leads to increased concentrations of DA in the NA, which accounts for the feelings of euphoria (positive reinforcement of alcohol). Posttraumatic stress disorder is also associated with increased DA levels.[39]



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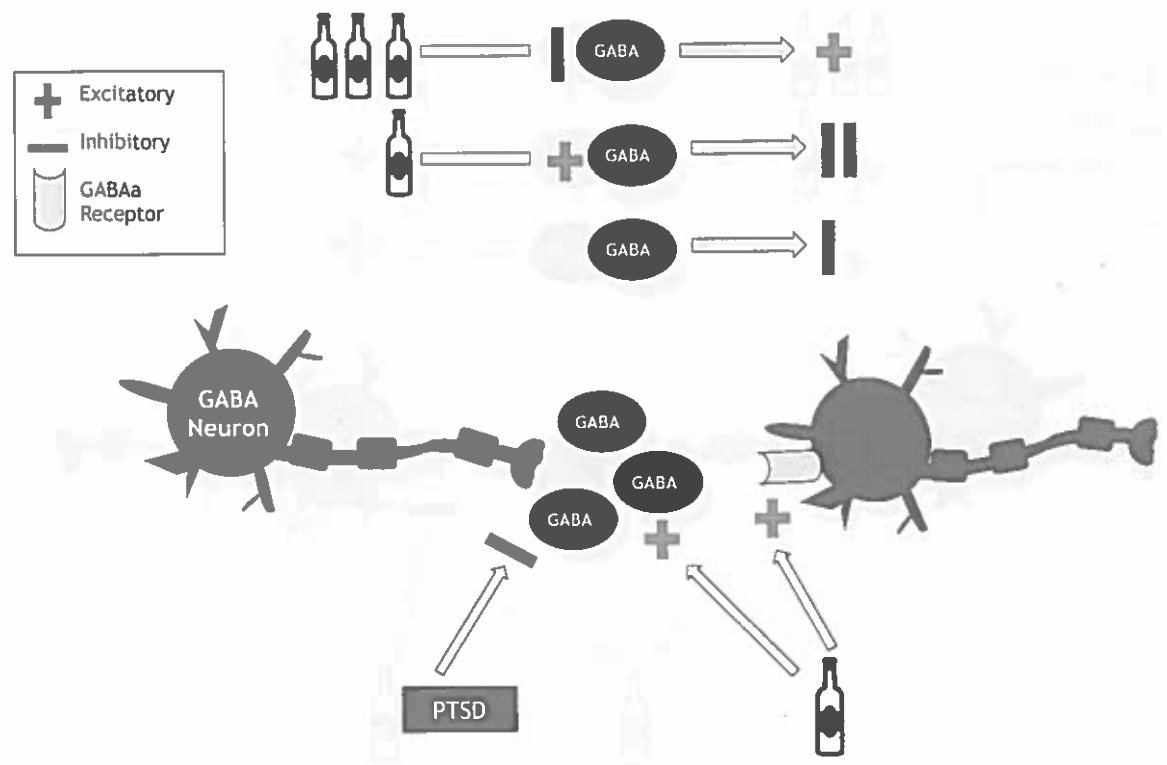
can block alcohol consumption.[81-82] An increase in DA release from terminals along this pathway leads to greater feelings of euphoria, which acts as a positive reinforcer.

It is important to note that DA levels in the mesolimbic pathway are also modulated by endogenous opioids (see Figure 1B). To review, there are three classes of endogenous opioids: endorphins, enkephalins, and dynorphins, which act on three different receptor types (mu, delta, and kappa receptors).[71, 86] One of the primary functions of endogenous endorphins, in addition to the regulation of pain responses and homeostatic functions, is the modulation of brain reward systems.[85] Mu and delta receptors can be found on DA-releasing neurons in the NA, where B-endorphins and enkephalins can bind and directly increase DA release[85] (Figure 1B). There are also mu receptors on the GABA interneurons of the mesolimbic pathway that act to inhibit DA-releasing neurons in the NA. B-endorphins bind to mu receptors on the GABA interneurons—which, in turn, inhibits them, disinhibits DA neurons, and increases DA release in the NA[85] (Figure 1B).

Figure 2:
The Effect of Acute Alcohol Consumption Versus Chronic Alcohol Consumption on γ-Aminobutyric Acid (GABA) Levels

Rat studies show that initial alcohol use leads to increased levels of GABA, leading to an overall calming effect.[88] Alcohol increases GABA levels both by activating GABA-releasing presynaptic neurons and by activating postsynaptic $GABA_A$ receptors.[71] Posttraumatic stress disorder has the opposite effect on GABA,[66] which is why someone with posttraumatic stress disorder may seek alcohol. As one transitions into alcohol dependence, $GABA_A$ receptor sensitivity is decreased as the body tries to maintain a balance of neurotransmitter levels.[71] This is why, when someone who is dependent withdraws from alcohol, there is a less than normal amount of GABA. With decreased GABA levels, the calming effect that initial alcohol use once resulted in is no longer present; in other words, patients become tolerant, a marker of alcohol dependence.



Note: Most synaptic connections occur on dendrites and not on the cell body, which is depicted above for simplicity.

Alcohol consumption increases the release of the endogenous opioids that act on the mesolimbic pathway, leading to increased DA levels and increased feelings of euphoria that contribute to the positive reinforcement of alcohol (Figure 1B). The hypothesis that positive alcohol reinforcement is mediated in part by the release of endogenous opioids in the brain is supported by rodent studies, suggesting opioid receptor antagonists suppress alcohol drinking.[8] For example, Roberts et al.[84] found that a knockout of the mu-opioid receptor blocks alcohol self-administration in mice.

Along with increasing the effects of the DA reward pathway, acute alcohol consumption leads to an overall inhibitory effect on the brain by increasing GABA release and decreasing Glu release in several brain regions. Rodent studies show alcohol increases the release of GABA, the main inhibitory neurotransmitter in the brain, by acting on GABA-releasing presynaptic neurons or by activating postsynaptic $GABA_A$ receptors[71] (Figure 2). The presence of alcohol keeps the $GABA_A$ receptor open for a longer duration, allowing for the flow of more Cl^- ions into the neuron, thus enhancing the inhibitory effect of GABA.[88] Alcohol exposure to rat brain microsacs and synaptoneurosome preparations was shown to increase GABA-gated chloride uptake by 260%.[89] Conversely, rodent studies show alcohol inhibits the effects of Glu, the principal excitatory neurotransmitter. Gluacts by binding to various receptor subtypes—including *N-methyl-D-aspartate* (NMDA) receptors, which causes an influx of positive calcium ions (Ca^{2+}) into the cell. Alcohol inhibits the functioning of the NMDA receptors, which decreases the influx of Ca^{2+} into neurons and lessens the excitatory effect of Glu.[90] Lovinger et al.[91] showed alcohol concentrations as low as 0.03% inhibited ion flow through the NMDA receptors of rat hippocampal neurons. Furthermore, acute alcohol exposure in rats reduced extracellular Glu concentrations in the striatum, which includes the NA, and suppressed Glu-mediated signal transmission in the amygdala.[92] As a result of increased GABA and decreased Glu concentrations, acute alcohol consumption can lead to an overall feeling of relaxation or fatigue.

One of the other many neurotransmitters that alcohol consumption has an effect on is 5-HT. Serotonergic neurons originate in the raphe nucleus and extend to various brain regions, including the amygdala and the NA. As a result, 5-HT plays a role in the control of emotions and

Figure 3:
The Effect of Acute Versus Chronic Alcohol Consumption on Glutamate (Glu) Levels

Rat studies show initial alcohol use results in decreased levels of glutamate (Glu)—the main excitatory neuron—by inhibiting postsynaptic NMDA receptors (NMDARs).[91] In addition to increased GABA levels (Figure 2), decreased Glu levels result in an overall calming effect. As one transitions into alcohol dependence, the body tries to reverse the effects of decreased Glu levels by upregulating NMDARs and increasing NMDAR sensitivity. Therefore, when someone who is dependent on alcohol withdraws from alcohol, there is a higher than normal level of Glu. This increased Glu level leads to hyperexcitability and withdrawal symptoms—such as tremors and, in some cases, seizures. The occurrence of withdrawal symptoms is a marker of the transition into dependence, and patients usually relapse in order to alleviate their symptoms.

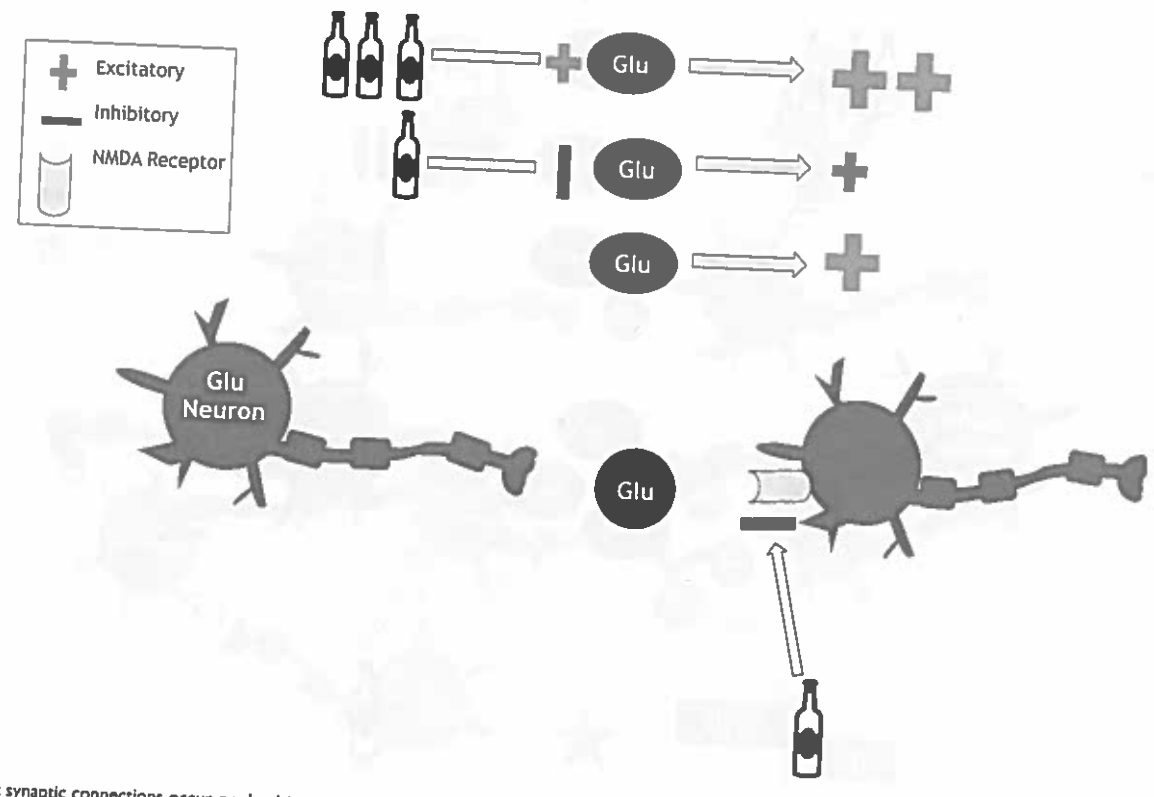


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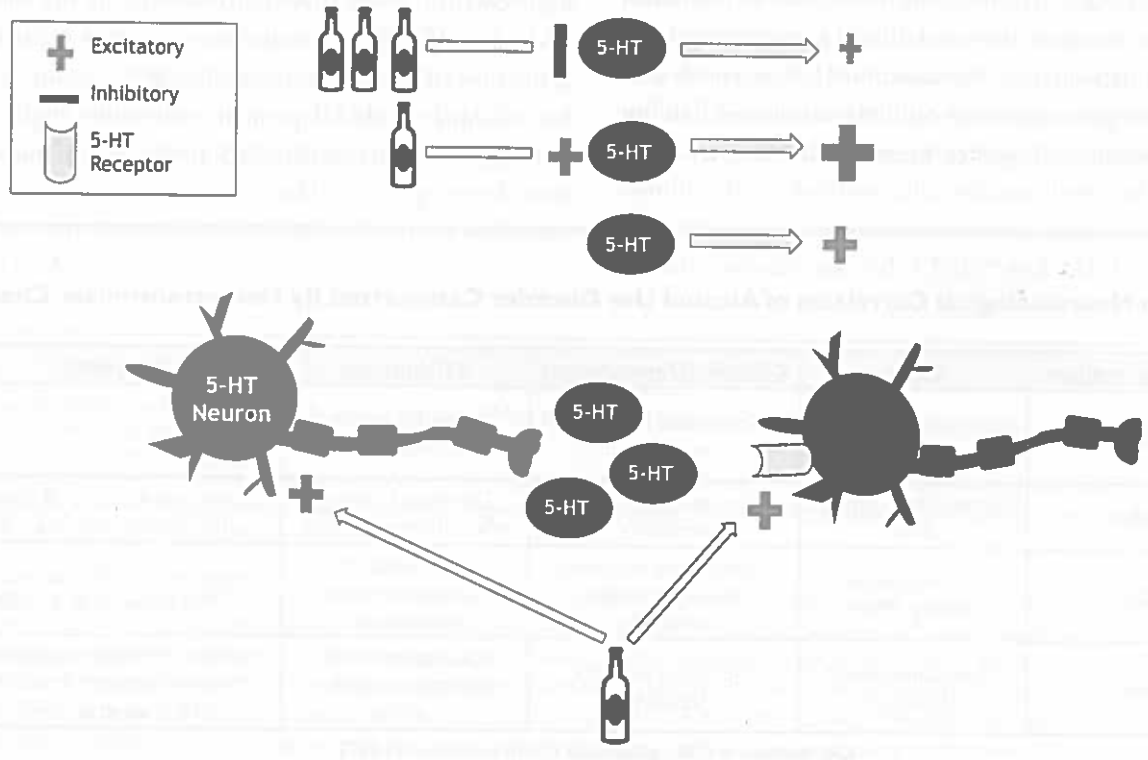
Figure 4:
The Effect of Acute Alcohol Consumption Versus Chronic Alcohol Consumption On Serotonin (5-HT) Levels

Rat[36] and human studies[94] show that initial alcohol use leads to increased 5-HT levels, resulting in a mood stabilization effect. Alcohol exerts this effect on 5-HT both by activating the 5-HT pre-synaptic neuron and the postsynaptic 5-HT receptor. As one transitions into alcohol dependence, the body tries to reverse the effects of increased 5-HT levels by decreasing 5-HT receptor sensitivity.[93] Therefore, when someone who is alcohol dependent withdraws from alcohol, there is a lower than normal 5-HT level. Decreased 5-HT levels lead to the withdrawal symptom of anxiety, a marker of the transition into alcohol dependence.



Note: Most synaptic connections occur on dendrites and not on the cell body, which is depicted above for simplicity.

the motivation for certain behaviors, such as continued alcohol use.[93] Alcohol impacts the levels of 5-HT both by increasing the concentration of the neurochemical and by modulating 5-HT receptors (Figure 4) in various ways that play roles in alcohol craving, the rewarding properties of alcohol, and withdrawal symptoms.[93] Early studies show acute alcohol use leads to increased 5-HT metabolites in human urine and blood, indicating high 5-HT levels in the nervous system.[94] In addition, higher levels of 5-HT were found in rat brains after acute alcohol consumption, indicating a higher rate of serotonergic release and/or a slower rate of reuptake.[95] While the therapeutic effects of selective serotonin reuptake inhibitors are the result of long-term neuroplastic changes, acute increases in 5-HT levels may account for some short-term mood changes associated with acute alcohol consumption and contribute to positive alcohol reinforcement.

With chronic alcohol use, neurons adapt to increased GABA levels by decreasing GABA receptor sensitivity (Figure 2). Neuronal adaptation also includes decreased Glu activity by increasing the number and sensitivity of NMDA receptors (Figure 3) and increased 5-HT levels by decreasing 5-HT receptor sensitivity[88] (Figure 4). Decreased GABA receptor sensitivity leads to tolerance, one of the processes that underlies a person's transition to alcohol dependence. Increased NMDA receptors and NMDA receptor sensitivity can lead to hyperexcitability and excitotoxicity. Together, increased Glu activity levels and decreased 5-HT receptor sensitivity may reverse the mood-stabilizing effects associated with acute alcohol use and lead to alcohol withdrawal symptoms—such as hyperactivity, seizures, and increased anxiety.[93] These symptoms make patients consume more alcohol to avoid symptoms, which marks the transition to alcohol dependence.

A summary of alcohol's effects on neurotransmission during both acute and chronic alcohol use can be found in Table 2.

AUD and Withdrawal: The Contribution of Stress Circuitry

The primary stress circuit within the autonomic nervous system is the HPA axis. CRF or CRH released from the hypothalamus stimulates the release of adrenocorticotropic hormone from the anterior pituitary gland, which triggers the release of cortisol (the primary glucocorticoid in humans) from the adrenal gland.[99] Rodent studies show acute alcohol consumption activates the HPA axis, resulting in increased levels of cortisol;[100] however, prolonged alcohol use dysregulates the HPA axis, resulting in abnormally low cortisol responsivity and abnormally high cortisol levels (hypercortisolism) in the blood.[99] Rodent studies show alcohol consumption leads to the activation of extra hypothalamic CRF systems as well. For example, alcohol-dependent rats exhibit higher concentrations of extracellular CRF in the central nucleus of the amygdala;[101] and CRF antagonists injected into this area of the amygdala suppress the anxiety-like behavior and alcohol consumption associated with alcohol dependence.[102] **Increased activation of this stress circuit and increased levels of these stress hormones could contribute to the anxiety-like withdrawal symptoms.**

In addition, the neuropeptide NPY has been implicated in the pathophysiology of AUD and appears to have downstream effects that oppose those produced by CRF. For example, in general, NPY is anxiolytic (anxiety reducing), while CRF is anxiogenic (anxiety inducing).[71] Alcohol consumption decreases NPY levels in the central nucleus of the amygdala in rats—a finding that is supported by Roy and Pandey.[103] Decreased NPY levels, along with increased CRF and cortisol levels, appear to increase the severity of the anxiety experienced during withdrawal. Such severe anxiety plays a critical role in the negative reinforcement of alcohol and is a component of the withdrawal process associated with alcohol dependence.

Table 2:
Common Neurobiological Correlates of Alcohol Use Disorder Categorized By Neurotransmitter Changes

Neurotransmitter	Acute	Chronic (Dependence)	Withdrawal	References
DA	Upregulated-euphoric effect	Decreased receptor sensitivity	Decreased euphoric effect, negative mood	Gilpin and Koob, 2008; Weiss et al., 1993; Hodge et al., 1997; Rassnick et al., 1992; Ma and Zhu, 2014
GABA	Upregulated-calming effect	Decreased receptor sensitivity	Decreased calming effect, hyperexcitability	Gilpin and Koob, 2008; Davies, 2003; Suzdak and Paul, 1987
Glu	Downregulated-calming effect	Upregulated receptors, increased receptor sensitivity	Hyperexcitability: restlessness, tremors, seizures, etc.	Lovinger et al., 1989; Carboni et al., 1993; Roberto et al., 2004
5-HT	Upregulated-mood stabilization	Decreased receptor sensitivity	Decreased mood stabilization, negative affect	Lovinger, 1997; LeMarquand et al., 1994a; LeMarquand et al., 1994b; McBride et al., 1993
Key: dopamine (DA), glutamate (Glu), serotonin (5-HT)				

Sources in Table 2:[71, 79, 81, 83, 88, 89, 91, 96–98]

Neurobiology of Comorbid PTSD and AUD

Currently, there is no consensus as to the neurobiological mechanisms of comorbid PTSD and AUD. However, it is known that a dual diagnosis of PTSD and AUD exacerbates the symptoms of each individual disorder.[105] One of the hallmarks of both PTSD and AUD is a heightened stress response and hyperarousal—such that this comorbidity may elicit an additive, heightened stress response with hyperarousal, compared to those with only PTSD or AUD.[46, 106]

The heightened stress response seen in comorbid PTSD and AUD populations is likely due to a change along the HPA axis, which is critical for stress adaptation and prolonged hyperactivity or hypoactivity.[14] CRF, cortisol, and NE all contribute to the regulation of the HPA axis. Interestingly, some past studies in PTSD populations found downregulated cortisol levels,[17] while other studies found upregulated cortisol levels in AUD populations.[99] These differences in cortisol levels may be due to a change in cortisol receptor sensitivity. For example, glucocorticoid receptor responsivity was found to be significantly decreased in AUD populations,[107] while there was an increase in glucocorticoid receptor responsivity in PTSD populations.[19]

Alongside dysregulations in HPA axis activity, changes in neurotransmitter signaling likely have implications for the atypical stress response seen in patients with comorbid PTSD and AUD. Three neurotransmitters independently implicated in the stress-related phenomena of PTSD and AUD are DA, GABA, and NPY. These neurotransmitters are instrumental for reward, impulsivity, arousal, and anxiety circuitry. Notably, upregulation of DA has been detected in populations with either PTSD[39] or AUD[87] alone. In contrast, *downregulated* GABA may be a preliminary biomarker of PTSD. Conversely, *upregulated* GABA may be a specific biomarker of AUD.[88] This difference in GABA levels may be due to receptor responsivity and sensitivity under various stressor- and alcohol-related conditions.[108] Additionally, reduced levels of NPY, an important molecule in stress circuitry, have been detected in both populations with PTSD[44] and AUD.[103]

Looking Ahead: A Biochemical Marker of Chronic Alcohol Use

When assessing and treating patients with AUD, it is imperative to use measures that reliably gauge alcohol use and abstinence. Individuals with AUD may be motivated to deny or minimize the magnitude of their drinking behavior, perhaps to please their clinician or due to guilt associated with the disorder.

There is a need to establish objective clinical measures of alcohol use for determining appropriate interventions. One alternative to subjective self-reported alcohol use may be biochemical tests. A meta-analysis conducted by Viel et al.[104] examined phosphatidylethanol (PEth) as a reliable biomarker of chronic and excessive drinking. Other markers include blood ethanol levels, of which PEth is a derivative. In terms of the mechanism of this phospholipid molecule, it is abnormally formed in red blood cell membranes when in the presence of ethanol and detectably degraded in human blood for up to 15–28 days after sobriety.[104] Furthermore, the PEth test has the potential for differentiating drinking patterns (i.e., binge drinking episodes vs. light-moderate drinking vs. abstinence). This is particularly applicable for monitoring addiction treatment success.

While neuroendocrine and neurochemical changes have been detected within clinical samples experiencing PTSD symptoms (independent of AUD) and those experiencing AUD symptoms (independent of PTSD), there is a lack of clinical studies that examine these changes when comorbidity occurs. Future studies examining comorbid PTSD and AUD patient populations will be vital for establishing new pharmacotherapeutic approaches targeting the clinical symptoms and neurobiological mechanisms underlying comorbid PTSD and AUD.

Conclusion and Future Directions

Overall, this first part of the review highlights the many different neurobiological correlates of PTSD and AUD, focusing on the brain structures and neurotransmitter pathways involved. It brings to attention the high prevalence of patients with comorbid PTSD and AUD and calls for more research into the associated neurobiological mechanisms. There are many other overlapping neurobiological correlates of PTSD and AUD researchers could use as targets of study. For example, changes in the HPA axis[17,99] and the neurotransmitter systems—including pathways releasing GABA, DA, and NPY—occur with both PTSD and AUD symptoms.[39, 44, 87, 103, 107] The second part of this lesson examines the current clinical assessments used to diagnose and treat PTSD, AUD, and comorbid PTSD and AUD. ■

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Key Point 3: The Hypothalamus-Pituitary-Adrenal Axis and Hypothalamic–Pituitary–Thyroid Axis Are Both Activated in PTSD and AUD Neurobiological Mechanisms

The hypothalamus–pituitary–adrenal axis is critical for stress adaptation and prolonged hyperactivity or hypoactivity through regulation by corticotropin-releasing factor. The hypothalamus–pituitary–adrenalaxis plays a central role in stress response.[14, 112] The hypothalamus–pituitary–thyroid axis determines the set point of thyroid hormone production, which is required for normal development and metabolism regulation.[113–114]

Key Point 4: The Mesolimbic Pathway Is Known as the Brain's Reward System and Plays a Role in the Neurobiological Mechanism of AUD

The mesolimbic pathway includes dopaminergic neurons projecting from the ventral tegmental area to the subcortical nucleus accumbens, where there are inhibitory GABA interneurons that act on the dopaminergic neurons and modulate the release of dopamine. Opioid receptors modulate neurotransmitter release of both the inhibitory GABA interneurons and the dopaminergic neurons.

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Comorbid Posttraumatic Stress Disorder and Alcohol Use Disorder: From Mechanisms to Assessments and Treatments, Part 2: Psychological and Pharmacological Treatment

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KEY WORDS: Posttraumatic Stress Disorder • Alcohol Use Disorder • Neurobiological correlates • Psychotherapy • Pharmacological treatment

LEARNING OBJECTIVES: Clinicians will be able to describe and differentiate between common neurobiological correlates, assessment methods, and treatments of *posttraumatic stress disorder* (PTSD), *alcohol use disorder* (AUD), and comorbid PTSD and AUD.

LESSON ABSTRACT: In part one of this lesson, the authors delineate common neurobiological correlates of PTSD, AUD, and comorbid PTSD and AUD. The neuroendocrine, neurochemical, and neuroanatomical markers of PTSD are explored, followed by an analysis of the neurotransmitter changes associated with AUD. The authors highlight the need for further research in uncovering the neurobiological mechanism of comorbid PTSD and AUD. In part two of this lesson, the authors outline common clinical assessments for PTSD and AUD. The psychotherapeutic and pharmacological treatments available for PTSD and AUD are also presented, followed by a call for more research into possible treatments for comorbid PTSD and AUD.

COMPETENCY AREAS: This lesson distinguishes the similarities and differences in PTSD, AUD, and comorbid PTSD and AUD regarding neurobiological markers, clinical assessments, and treatments. Clinicians will gain knowledge about many aspects of PTSD and AUD and will be able to use a holistic approach when treating patients with PTSD, AUD, and comorbid PTSD and AUD.

Introduction

The exposure to a potentially traumatic event referred to as "Criterion A," is required for a *posttraumatic stress disorder* (PTSD) diagnosis by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5).[1] Criterion A trauma refers to exposure to death, threatened death, actual or threatened serious injury, or threatened sexual violence.[1] PTSD was the third most prevalent psychiatric diagnosis among veterans seeking care at U.S. *Veterans Affairs* (VA) hospitals in 2015.[2] Specifically, PTSD prevalence estimates ranged from 8.1% to 15.2%, depending on gender and service, which was higher than the general population's estimates which were around 7.8% among study participants who were representative of the general U.S. population aged 15–54 years.[3] Up to 31% of male and female service members returning from Iraq and Afghanistan after deployment were diagnosed with PTSD.[4] These startlingly high prevalence rates of PTSD within the U.S. veteran population beg the need for a thorough evaluation and enhancement of current treatment approaches.

There are many possible assessment methods clinicians can use to diagnose *alcohol use disorder* (AUD). It is important to critically evaluate the differences between these methods, as data collected in the United States reveal the lifetime AUD prevalence among a representative sample of adults was 30.3% in 2007.[5] Similar to the frequency of PTSD diagnoses in combat veterans versus civilians, there is a much higher incidence of heavy drinking in current and former service member populations when compared to nonmilitary populations.[6] In 2015, a 10% prevalence of AUD among a sampled U.S. veteran population using VA services was reported.[7] However, unlike PTSD, which had higher prevalence in women than in men,[8] AUD prevalence among U.S. veterans was found to be higher in men (11%) than in women (5%).[9] Current treatments for this disabling disorder should be regularly examined and evaluated to provide insight for novel interventions.

The second part of this review describes different clinical assessments used to diagnose PTSD and AUD—followed by an evaluation of the psychological and pharmacological treatments of PTSD, AUD, and comorbid PTSD and AUD.

Psychotherapy

Psychotherapy for Comorbid AUD and PTSD:

There is currently no consensus on a universal regimen for treating comorbid PTSD and AUD with psychotherapy, thus demonstrating the need for guidelines such as the ones provided in this current lesson. However, there are three main approaches clinicians can take to treat patients that present with this comorbidity: sequential treatment, parallel treatment, and integrated treatment.[6] (Please see Table 1 for a list of commonly used psychotherapeutic approaches to AUD and PTSD, as well as references for further information. Also, Table 2 provides common self-report and interview measures that can be used in concert with psychotherapy.)

Sequential Treatment: The traditional approach has been to treat AUD before undergoing any specific PTSD treatment.[6] This is largely based on the notion that addressing trauma directly may bring up anxiety-related emotions, thoughts, and behaviors that could increase the risk of excessive drinking or relapse.[6, 41] If a patient has undergone effective AUD treatment and established prolonged abstinence from alcohol use, there is less concern about ongoing drinking behaviors interfering with successful PTSD treatment. An alternative sequential approach is to treat the symptoms of PTSD first. Exposure-based PTSD therapies have been found to reduce the fear and anxiety surrounding trauma-related triggers.[11] According to the self-medication theory, a reduction in PTSD symptoms has the potential to reduce alcohol craving.[6]

Parallel Treatment: Parallel treatment involves a patient undergoing separate treatment regimens for PTSD and AUD simultaneously. This simultaneous treatment can combine modalities and include a comprehensive treatment plan. However, it can lead to an uneven and confusing approach, as both treatments are typically done in different clinics with different providers.[6]

Integrated Treatment: More recently, there has been a push toward integrative therapies due to the possibility of unevenness from parallel treatment. An example of an integrated approach is to intermingle coping skills training specific to AUD treatment with PTSD-focused *prolonged exposure* (PE) or cognitive processing therapy.[6]

Table 1:
Psychotherapies for Alcohol Use Disorder and Posttraumatic Stress Disorder

PTSD Psychotherapies		AUD Psychotherapies	
Cognitive Processing Therapy (CPT)	Resick et al., 2016	*Relapse Prevention (RP)*	Marlatt & Donovan, 2005
Prolonged Exposure (PE)	Foa & Rothbaum, 2007	*Contingency Contracting (CC)/ Behavioral Treatment (BT)*	Petry et al., 2000
Eye Movement Desensitization & Reprocessing (EMDR)	Shapiro, 2001	*Cue Exposure (CE)*	Loeber et al., 2006
		Network Therapy (NT)	Galanter, 2015
Narrative Exposure Therapy (NET)	Schauer et al., 2011	*Aversion Therapy (AT)*	Elkins et al., 2017
Skills Training in Affective and Interpersonal Regulation (STAIR) Narrative Therapy	Cloitre & Schmidt, 2015	*Supportive-Expressive (SE) Therapy*	Luborsky, 1984; Crits-Christoph et al., 2008
		Interpersonal Therapy (IPT)	Brache, 2012
Brief Eclectic Psychotherapy for PTSD (BEPP)	Gersons & Schnyder, 2013	*Motivational Interviewing (MI)*	Miller & Rollnick, 2012; Bein et al., 1993

Sources in Table 1:[10-25]

Table 2:
Commonly Used Assessments for Posttraumatic Stress Disorder and Alcohol Use Disorder

PTSD Measurements				AUD Measurements			
Interview-Based		Self-Report		Interview-Based		Self-Report	
CAPS-5	Weathers et al., 2018	*DTS*	Davidson et al., 1997b	*CIWA-Ar*	Sullivan et al., 1989	*AUDIT*	Babor et al., 2001
		IES-R	Creamer et al., 2003			*SADQ-C*	Stockwell et al., 1983
SCID PTSD Module	First et al., 1995	*MISS*	Hyer et al., 1991			*ADS*	Skinner & Horn, 1984
SIP or SI-PTSD	Davidson et al., 1997a	*PCL-5*	Blevins et al., 2015	*TLFB*	Sobell & Sobell, 1995	*OCDS*	Anton et al., 1995
						DAQ	Courtney et al., 2013
PSS-I-5	Foa & Capaldi, 2013	*SPRINT*	Connor & Davidson, 2001			*SIP*	Kiluk et al., 2013

Sources in Table 2:[26-40]

Acronyms in Table 2:

(CAPS-5): Clinician-Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
(SCID PTSD Module): Structured Clinical Interview PTSD Module
(SIP or SI-PTSD): The Structured Interview for PTSD
(PSS-I-5): PTSD Symptom Scale Interview
(DTS): Davidson Trauma Scale
(IES-R): Impact of Event Scale
(MISS): Mississippi Scale for Combat-Related PTSD
(PCL-5): PTSD Checklist for DSM-5
(SPRINT): Short PTSD Rating Interview
(CIWA-Ar): Clinical Institute Withdrawal Assessment for Alcohol Scale, Revised
(TLFB): Timeline Follow Back
(AUDIT): Alcohol Use Disorders Identification Test
(SADQ-C): Severity of Alcohol Dependence Questionnaire
(ADS): Alcohol Dependence Scale
(OCDS): Obsessive Compulsive Drinking Scale
(DAQ): Desire for Alcohol Questionnaire
(SIP): Short Inventory of Problems

This teaches the patient how the two disorders interact and how to utilize skills to control both their alcohol intake and PTSD symptoms. Currently, there are two primary integrated treatment types: Seeking Safety and concurrent treatment of PTSD and substance use disorders using prolonged exposure (COPE).[41]

- **Seeking Safety:** This is a 25-session cognitive-behavioral therapy focused on developing and establishing strategies to maintain safety,[42] and many studies have demonstrated that the intervention has reduced PTSD symptoms in a wide range of populations.[43–44] This therapy does not include exposure-based practices. (For a manual on Seeking Safety, see Najavits 2002).[42]
- **Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure:** Previously, providers were concerned about including exposure-based practices in therapies for those suffering from AUD due to the possibility of trauma memories and exposure to triggers leading to relapse.[41] However, many studies have shown that employing exposure-based therapies for those with co-occurring PTSD and AUD can be done safely,[45] which led to the development of interventions such as Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure. Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure is a 12-session therapy that combines cognitive behavioral therapy for AUD and PE for PTSD, and many trials have found it to be effective in reducing PTSD and AUD severity.[46, 47]

The mixed results on the effectiveness of each of these approaches call for future studies to further explore the most effective psychotherapy for those that present with comorbid PTSD and AUD. For now, however, as with many treatment plans, clinicians should investigate each approach and decide the one that would best meet each patient's needs.

Pharmacological Treatment

Pharmacological Treatments for PTSD:

Treatment for PTSD can vary from individual to individual—ranging from psychological-based options, such as trauma-focused psychotherapy, to pharmacological-based drugs, such as sertraline and paroxetine, or a combination of these approaches.[48] While the mechanisms underlying their therapeutic benefits are still not well understood, prescribing psychiatric medications that have shown efficacy in mood disorders for PTSD is aimed at reducing the symptoms and thereby improving a patient's quality of life. Sertraline and paroxetine are currently the only two drugs approved by the *Food and Drug Administration* (FDA) for the treatment of PTSD.[49]

Sertraline and Paroxetine: **Sertraline and paroxetine are both selective serotonin reuptake inhibitors that primarily increase the amount of 5-HT available in an individual (Figure 1).** 5-HT regulates mood, anxiety, appetite, and other bodily functions.[50] Selective-serotonin reuptake inhibitors act by preventing its reuptake, causing its levels within the synapse to increase and leading to a cascade of long-term neuroadaptive changes in neural processing.

Placebo-controlled studies have shown that both sertraline and paroxetine are effective in decreasing the severity of PTSD symptoms.[53] Specifically, one 12-week study found that sertraline treatment yielded a significantly greater improvement than was seen in the placebo group.[54] In another study investigating the efficacy of paroxetine, patients' mean PTSD symptom scores were significantly reduced by 48%.[55] In addition, this study found that 65% of patients rated their PTSD symptoms as much or very much improved. Other studies have found similar results in that paroxetine treatment relieved PTSD symptomology.[56]

Sertraline and paroxetine have similar effects within the brain; however, clinical differences have been seen in studies that compared these drugs when treating PTSD patients. For example, one study found that while sertraline had greater tolerability than paroxetine, sertraline was associated with a significantly higher rate of upper abdominal discomfort.[57] Another study found that paroxetine was associated with a higher rate of weight gain

than sertraline.[58] Alternatively, a few studies have found similar symptom changes in both groups of participants.[58]

Pharmacological Treatments for Alcohol Use Disorder

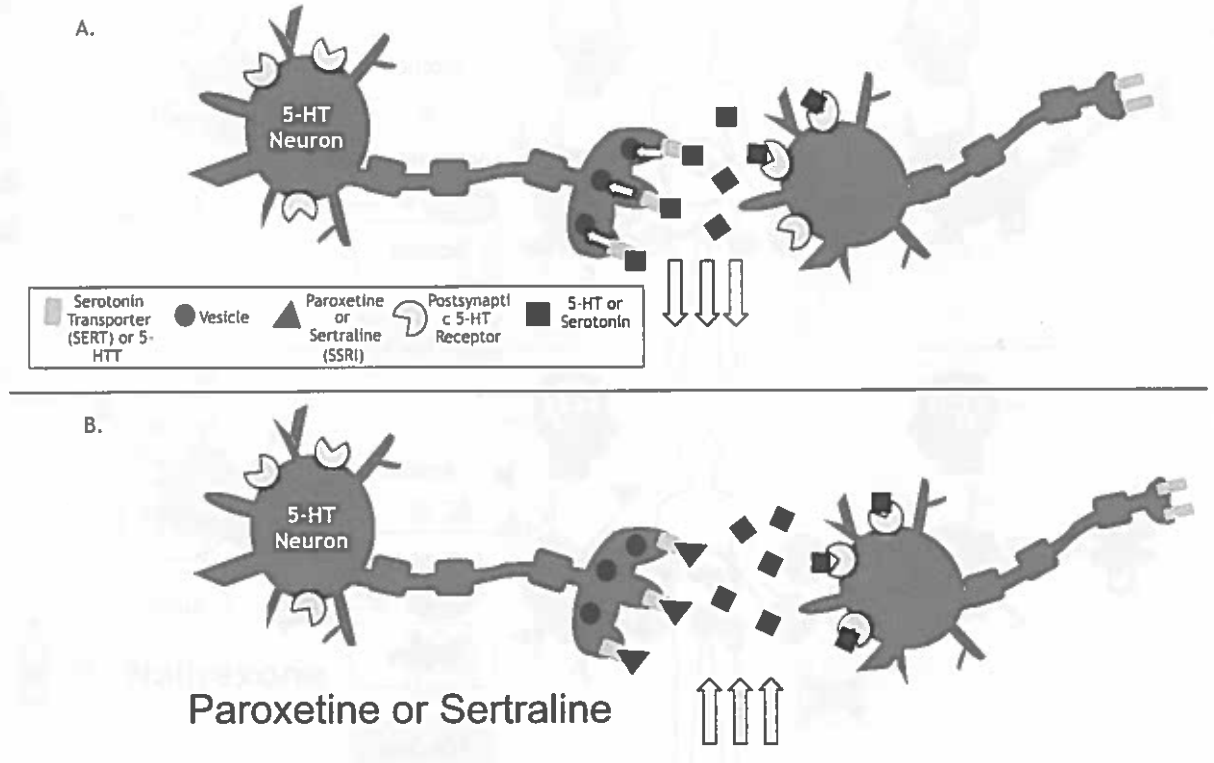
There are currently only four FDA-approved pharmacological treatments for AUD: disulfiram, oral naltrexone, long-acting injectable naltrexone, and acamprosate. The following is a brief overview of each drug's mechanism of action.

Disulfiram: The therapeutic effect of disulfiram stems from its incompatibility with alcohol. Disulfiram (trade name: Antabuse) inhibits aldehyde dehydrogenase, the enzyme that converts acetaldehyde to acetate during alcohol metabolism in the liver (Figure 2B).[59] Without this conversion, the consumption of alcohol leads to the buildup of acetaldehyde, which results in the alcohol–disulfiram reaction. Milder symptoms of this reaction include facial flushing, sweating, increased heart rate, nausea, hyperventilation, and hypotension.[59] However, some symptoms, such as toxic hepatitis, severe metabolic disorders, serious skin reactions, and a reduction in *norepinephrine* (NE), which can lead to psychiatric symptoms, can be life-threatening depending on the dosage and the individual.[59] The possibility of such life-threatening

Figure 1:
Mechanism of Action of Paroxetine and Sertraline, Two Drugs Used to Treat Posttraumatic Stress Disorder

A. After the release of serotonin or 5-HT, serotonin transporter (SERT) or 5-HTT allows the reuptake of serotonin into the presynaptic neuron for storage in vesicles.[51] Some of the serotonin released will bind to the postsynaptic 5-HT receptors located on the postsynaptic neuron.

B. Paroxetine or sertraline (selective serotonin reuptake inhibitors) bind to SERT or 5-HTT and inhibit the reuptake of serotonin into the presynaptic terminal.[52] This increases the amount of serotonin within the synaptic space compared to the amount of serotonin in the original serotonin reuptake mechanism with no drug.



Note: Most synaptic connections occur on dendrites and not on the cell body, which is depicted above for simplicity.

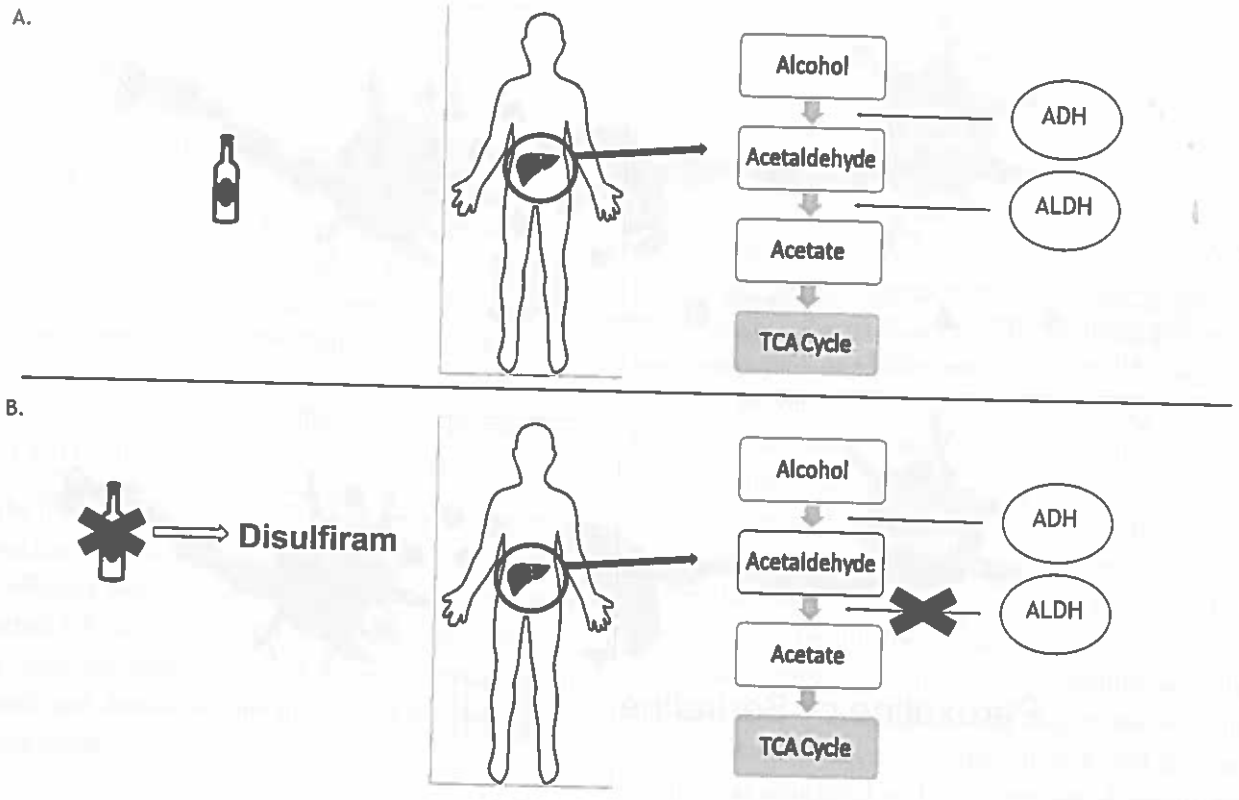
side effects limits its use in patients who have already established relatively consistent abstinence from alcohol (Figure 2). Multiple studies have been conducted to assess the effectiveness of disulfiram. Jorgensen et al.[60] conducted a meta-analysis of 11 double-blind studies and found significantly higher abstinence rates for disulfiram compared to placebo, no treatment, and control groups. Overall, disulfiram protects against a relapse in abstinent patients, largely due to the fear of an adverse reaction if alcohol is consumed rather than the adverse reaction itself.[59] However, patient compliance is required for this intervention to be effective.

Naltrexone: Many previous studies have shown that naltrexone reduces the occurrence of heavy drinking days, yields lower relapse rates, reduces the number of drinks per episode, and extends the latency between the first and second drink.[61] Naltrexone achieves these effects by acting as an opioid receptor antagonist (Figure 3B). As mentioned in the previous section entitled "Neurobiology of AUD," alcohol consumption increases the release of endogenous opioids, which leads to the release of *dopamine* (DA) in the *nucleus accumbens* (NA). An increased DA concentration results in the rewarding euphoric effect of alcohol, which acts as a positive reinforcer and leads

Figure 2:
Mechanism of Action of Disulfiram

A. Alcohol is metabolized in the liver as shown in the schematic below. Alcohol dehydrogenase converts ethanol to acetaldehyde, and aldehyde dehydrogenase converts acetaldehyde to acetate. Acetate can then be used in the tricarboxylic acid or Krebs cycle for energy production.

B. Disulfiram (Antabuse) blocks the conversion of acetaldehyde into acetate by inhibiting aldehyde dehydrogenase.[59] The buildup of acetaldehyde leads to an alcohol-disulfiram reaction that leads to aversive symptoms—facial flushing, sweating, increased heart rate, nausea, hyperventilation, and hypotension.[59] In some people, the symptoms can be life-threatening (such as toxic hepatitis), which is why disulfiram should only be taken by those who have already withdrawn from alcohol.



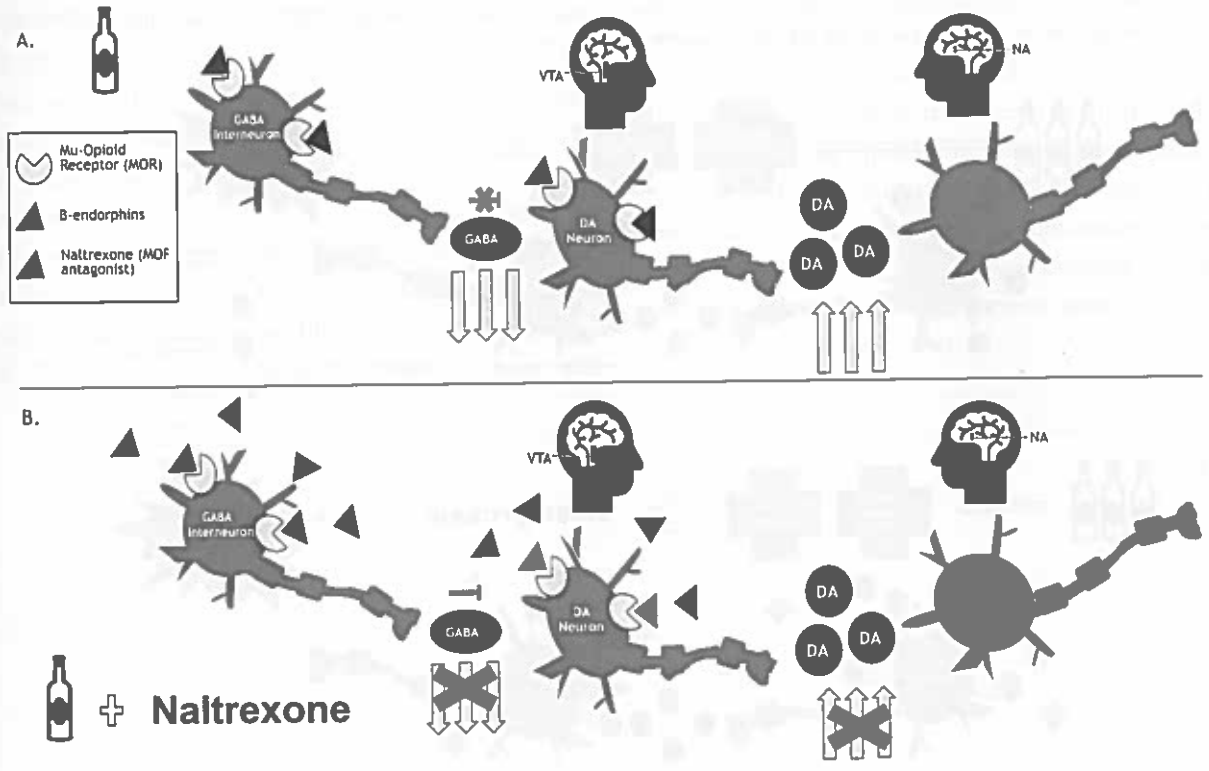
to continued alcohol use. Naltrexone reduces this effect by blocking the binding of endogenous opioids to its receptors[61] (Figure 3B). The most commonly used forms of naltrexone consist of an orally administered product (ReVia) and an intramuscularly injectable extended-release form (Vivitrol). Roozenet al.[62] found Vivitrol had an equal or greater effect in promoting total abstinence, reducing the time of first drink, and reducing the number of heavy drinking days compared to or naltrexone. While Roozen et al.[62] found oral naltrexone had fewer overall side effects, a study by Cramer et al.[63] showed higher compliance rates for injectable naltrexone. Overall, the studies have suggested that naltrexone decreases the rewarding effects of, and therefore the craving of alcohol.

Acamprosate: Studies have shown that acamprosate has a complex effect on glutamatergic *N-methyl-D-aspartate* (NMDA) receptors, which are vital for learning and memory. Early studies support the inhibitory effect of acamprosate on NMDA receptors (Figure 4B).[65] Acamprosate also stimulates the release of taurine, a major inhibitory neurotransmitter (Figure 4B).[66] This inhibitory effect is important because chronic alcohol use leads to the upregulation of NMDA receptors, as discussed in the "Neurobiology of AUD" section. Upregulated NMDA

Figure 3:
Mechanism of Action of Naltrexone

A. Alcohol normally stimulates the release of B-endorphins that act on mu opioid receptors to inhibit the GABA interneurons and activate the dopaminergic neurons[64] (Figure 1 in lesson 1). This leads to an overall activation of the dopaminergic neurons, which increases dopamine release in the nucleus accumbens and leads to the euphoric effect that accompanies alcohol consumption.

B. Naltrexone (ReVia–oral, Vivitrol–injectable extended-release form) acts as a mu opioid receptor and agonist that reverses the effects of the B-endorphins that alcohol stimulates.[61] This means that the GABA interneuron inhibits the dopaminergic neuron, thus no increase in dopamine release in the nucleus accumbens. Lower dopamine levels do not cause much euphoric effect, and the positive reinforcement of alcohol is decreased.



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receptors, a characteristic of alcohol dependence, lead to hyperexcitation, which manifests as delirium tremens and seizures.[67] In summary, acamprosate inhibits NMDA receptor activation and hyperexcitation, which alleviates withdrawal symptoms, reduces cravings during abstinence, and protects against relapse.

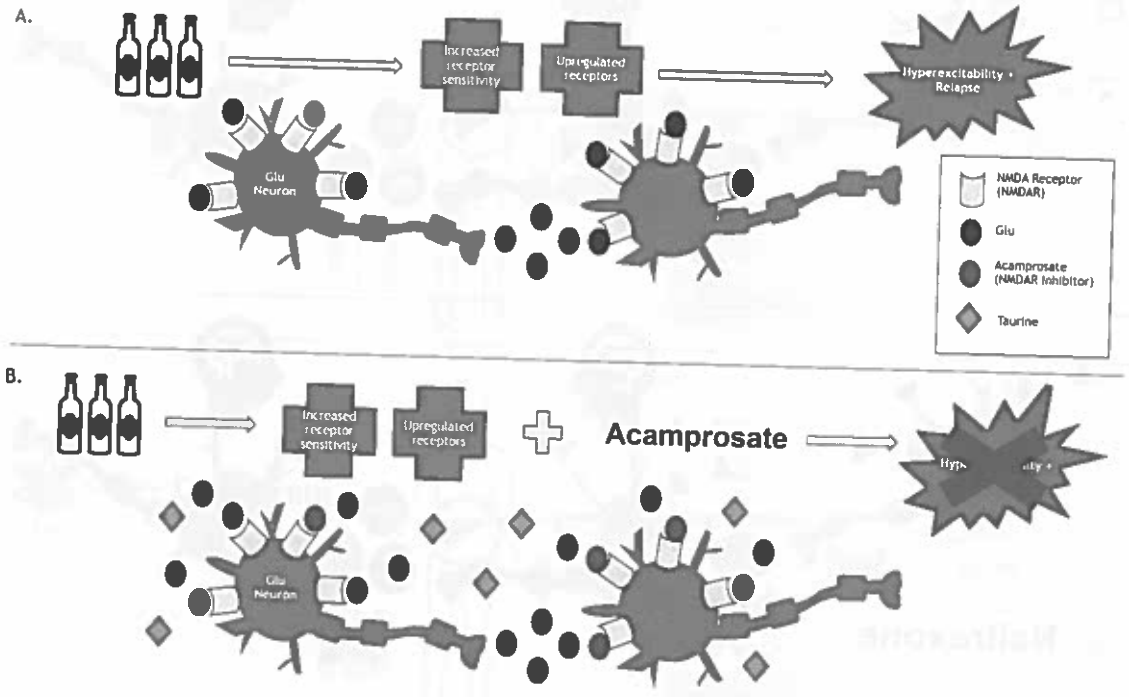
Pharmacotherapy for Co-occurring PTSD and AUD

At present, there is a considerable gap in available pharmacotherapies for substance use/alcohol use disorders and comorbid PTSD. Previous studies in this area have focused on medications that have shown success for either of these disorder classes individually, such as sertraline, naltrexone, and topiramate.[29, 54, 69, 70] A common therapeutic target for the concurrent treatment of AUD and PTSD maybe the noradrenergic brain system,[71] a neurochemical system that has been implicated in PTSD symptom expression, substance withdrawal, and addiction cue reactivity.[72–73] **Prazosin, an alpha-1 noradrenergic antagonist, has been studied as a pharmacotherapy for AUD, PTSD, and comorbid AUD/PTSD with some success, most notably in the treatment of PTSD-related hyperarousal, disturbed sleep, and nightmares** (for a representative study, see Raskind et al.[74]). There is currently an ongoing clinical trial of the alpha-1 noradrenergic blocker, doxazosin, as a pharmacological intervention for comorbid AUD/PTSD.[71] Initiatives such as the latter study are underway

Figure 4:
Mechanism of Action of Acamprosate

A. Those who are alcohol dependent have upregulated N-methyl-D-aspartate (NMDA) receptors and increased NMDA receptor activity, which increases the effect of glutamate when in withdrawal.[68] Increased glutamate levels lead to hyperexcitability and withdrawal symptoms, such as tremors and seizures. Many of those in withdrawal fall into relapse to alleviate withdrawal symptoms.

B. Acamprosate works by inhibiting the NMDA receptors, thereby reversing the effects of increased glutamate levels.[65] Acamprosate also stimulates the release of taurine, an inhibitory neurotransmitter, which also reverses glutamate's excitatory effects.[66] Patients on acamprosate do not experience intense withdrawal symptoms and are less likely to relapse.



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as part of a nationwide U.S. consortium to develop and evaluate treatments for PTSD and the disorder with which it is highly comorbid (Consortium to Alleviate PTSD, www.ConsortiumToAlleviatePTSD.org). It will take comprehensive collaborations such as Consortium to Alleviate PTSD to better understand and identify co-occurring substance use disorders and PTSD.

Conclusion and Future Directions

Although this review has explored the various treatment options for AUD and PTSD separately, there are currently no FDA-approved medications for the treatment of comorbid PTSD and AUD, nor is there a consensus on a psychological treatment approach. The prevalence of comorbid PTSD and AUD, especially among the veteran population, calls for further study of neuropsychopharmacological treatments with the potential to alleviate the symptoms of both disorders at once.

Research shows that the *kappa opioid receptor* (KOR) may be an effective target for intervention in individuals with both PTSD and AUD. The KOR is a part of the endogenous opioid system, which was briefly mentioned in the "Neurobiology of AUD" section, on which stress-related dynorphins selectively bind.[75] KORs transduce stress and are found in the mesocorticolimbic "reward" pathway, where they play a role in regulating motivation and promoting addictive behavior.[76–77] More specifically, stress stimulates the release of corticotrophin-releasing factor which induces dynorphin release, and dynorphins bind to and activate KORs.[78–79] KOR activation leads to dysphoria and depressive-like symptoms.[80]Dysphoria may lead to alcohol-seeking behaviors in those with PTSD, as alcohol use leads to DA release and euphoria. Furthermore, continued alcohol use activates KORs, precipitating tolerance, and withdrawal, which are markers of the transition into alcohol dependence.[81] Therefore, KORs are unique because they play a role in both PTSD and AUD symptoms. Future studies exploring the biomarkers of psychiatric disorders may provide relief for individuals with comorbid disorders such as addictions, PTSD, and major depression.[70, 82–83]

Overall, this review highlights the high prevalence of patients with comorbid PTSD and AUD and calls for future studies to explore possible pharmaco- and psychotherapies that can target PTSD and AUD symptoms simultaneously. Along with the KOR system, there are many other overlapping neurobiological correlates of PTSD and AUD that researchers could use as targets in their study. For example, changes in the hypothalamic–pituitary–adrenal axis[84–85] and the neurotransmitter systems, including pathways releasing GABA, DA, and neuropeptide Y[86–87] occur with both PTSD and AUD symptoms. Future studies should also explore the best combination of psychotherapies for patients with comorbid PTSD and AUD. These disorders both exacerbate the symptoms of each other, which provides a compelling rationale for finding both pharmacological and psychological treatments for this comorbidity to improve the quality of life of these patients. As always, clinicians must get the full (transaxial) picture of a patient's signs, symptoms, and socio-occupational impairments before deciding on a course of treatment. In most cases, clinicians cannot treat one condition without treating the other.