

Alcohol Use Disorder And Genetic Variability In The Opioidergic System

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Abstract

Alcohol use disorder impacts millions of people and is associated with significant morbidity and mortality. Various neuroanatomical pathways and neurotransmitters, including the opioidergic system and endogenous opioids, contribute to the development and persistence of alcohol use disorder. The opiate receptor antagonists nalmefene and naltrexone are effective in decreasing alcohol consumption and drinking relapse by modulating the opioidergic system. This may be advantageous for individuals who have certain alleles of the μ -opioid receptor, but further research is needed.

INTRODUCTION

Formerly classified as alcohol abuse or alcohol dependence, alcohol use disorder (AUD) is defined as a pattern of drinking ethanol that leads to impairment or distress. It is manifested by at least two of the following symptoms within one year: unintended increased quantity or duration of consumption; desire or unsuccessful efforts to decrease use; spending time to obtain, use, or recover from its effects; craving; failure to fulfill obligations; social or interpersonal problems; loss of social, occupational, or recreational activities; use in hazardous situations; physical or psychological problems caused or exacerbated by alcohol; tolerance; or withdrawal.¹ In the United States, AUD has a 12-month prevalence of 8.5% among adults ages 18 and older, and rates are greater in men as compared to women.¹ It is most prevalent in Native Americans and Alaskan Natives, followed by whites, Hispanics, African-Americans, and then Asian-Americans or Pacific Islanders.¹

AUD results from an interaction among hormonal, environmental, psychosocial, and neurobiological factors.^{2,3} Genetics are implicated, with family, twin, and adoption studies estimating heritability between 50%-60%.^{2,3} Also implicated in the pathogenesis of AUD, dopamine and endogenous opioids are modulated in "reward pathways" in the ventral tegmental area, ventral striatum, nucleus accumbens, olfactory tubercle, amygdala, and frontal cortex.^{2,4,5} Repeated alcohol ingestion sensitizes the

system so that behavioral stimuli alone result in dopamine release.⁶ Endogenous opioids also mediate the reinforcing properties of ethanol by stimulating dopamine release.⁷

THE OPIOIDERGIC SYSTEM

Endogenous opioids are synthesized in various parts of the central nervous system (Table 1), and each group of endogenous opioid peptides is derived from precursor hormones: endorphins from β -endorphins, adrenocorticotrophic hormone (ACTH) and pro-opiomelanocortin (POMC); enkephalins from pro-enkephalin; and dynorphins from pro-dynorphins.^{8,9} Each peptide binds to mu (μ), delta (δ), or kappa (κ) opioid receptors: β -endorphin binds with equal affinity to μ and δ -receptors, enkephalin binds with a 20-fold greater affinity to δ -receptors as compared to μ -receptors, and prodynorphins bind to κ -receptors.¹⁰ While β -endorphins and enkephalins increase dopamine release and are important in rewarding and reinforcing behaviors, prodynorphins decrease dopamine release and produce aversive feelings (Table 2).¹¹

Table 1
Endogenous Opioid Peptides

Precursors	Site of CNS Synthesis	Post-translational Product
Pro-opiomelanocortin	arcuate nucleus and tractus solitari	B-endorphins
Pro-enkephalins A,B	wide CNS distribution	enkephalins, met-enkephalins, leu-enkephalins
Pro-dynorphin	wide CNS distribution	dynorphins, leu-enkephalins, alpha-neoendorphins

Table 2
Receptor Binding Properties And Effects Of Opioid Peptides

Opioid receptor/subtypes	Endogenous ligands	Effects of receptor-ligand interactions
Mu (μ)	β-endorphins	euphoria, constipation, miosis
	enkephalins	analgesia, respiratory depression
Delta (δ)	enkephalins (met/leu-enkephalins), β-endorphins	euphoria, analgesia
Kappa (κ)	dynorphins	dysphoria
	enkephalins	analgesia

Research on the relationship between opiate receptors and alcohol use disorder has focused on genes encoding the μ-opioid receptor (OPRM1), the δ-opioid receptor (OPRD1), and the κ-opioid receptor (OPRK1).¹² Some individuals have a single nucleotide polymorphism in OPRM1 which substitutes aspartate for asparagine (abbreviated Asn40Asp); they can be heterozygous or homozygous for this G allele.¹³ Its frequency is lowest in African-Americans, intermediate in European-Americans, and highest in Asian-Americans.¹⁴ People with 1 or 2 G alleles (i.e. heterozygotes or homozygotes) have reported greater intoxication, sedation, stimulation, or happiness following alcohol infusion than those without this allele.¹⁴

OPIOID ANTAGONISTS FOR AUD

Acamprosate, baclofen, disulfiram, gabapentin, nalmefene, naltrexone, ondansetron, and topiramate have demonstrated efficacy in decreasing alcohol consumption and lengthening abstinence periods.¹⁵⁻¹⁷ However, only nalmefene and

naltrexone modulate the opioidergic system to target opiate receptors in reward pathways.

Not available in the United States, nalmefene is a non-selective opiate receptor antagonist. Whether taken on a schedule or “as needed,” it reduced the number of heavy drinking days more than placebo.¹⁸⁻²² Naltrexone is available in the United States and is a non-selective opioid receptor antagonist. By blocking endogenous opioid activity, it causes decreased dopamine release and may result in subsequent reductions in alcohol craving and usage.¹⁵ In one meta-analysis, naltrexone was superior to placebo at decreasing the frequency of alcohol drinking relapses.²³

Given the heritability of alcohol use disorder, naltrexone’s efficacy in reducing alcohol consumption in subjects with a family history of AUD, and the genetic variability of the opioid receptor, nalmefene and naltrexone may have specific utility for individuals with the G allele.²⁴ However, results from studies have been mixed.

OPIOID ANTAGONISTS AND GENETIC VARIABILITY

Only one study has evaluated efficacy of nalmefene in relation to individuals with or without the G allele. While nalmefene reduced the number of heavy drinking days in persons with alcohol use disorder, there was no difference in efficacy between groups of subjects with or without the G allele.²⁵ Although naltrexone has greater affinity for μ-receptors in individuals carrying the G allele, heavy drinkers with the G allele paradoxically experienced a greater urge to drink after receiving naltrexone during a cue-reactivity exercise.²⁶ Surprisingly, in a meta-analysis of naltrexone-treated patients with at least one copy of the G allele, a lower relapse rate was documented among those without the G allele.²⁷ In contrast, other research subjects with the G allele demonstrated greater blunting of alcohol-induced euphoria, reduced craving, and lower ratings of satisfaction or liking alcohol intoxication after receiving naltrexone.²⁸ Less alcohol-induced stimulation, vigor, or positive mood was also reported.

DOSING AND CONTRAINDICATIONS

Naltrexone is available as a tablet and a depot injection. Before prescribing, clinicians should check liver function and toxicology screening. To prevent withdrawal, patients should abstain from opioids for 7-10 days prior to starting naltrexone. The initial dose is 25 mg daily, titrated to 50 mg daily. Alternative dosing may improve compliance, such as 50 mg each weekday and 100 mg every Saturday, 100 mg

every other day, or 150 mg every three days.²⁹ The starting dose for the naltrexone injection is 380 mg intramuscularly every four weeks in alternate gluteus muscles.³⁰ Naltrexone should not be administered to anyone who is receiving opioid medications or who has hepatic or renal disease. It is classified as Category C drug and it is not known whether it crosses into breast milk.³⁰

CONCLUSION

Alcohol use disorder yields significant adverse medical, psychological, and socioeconomic impact. The opioidergic system and its genetic variability have been implicated in AUD. Nalmefene and naltrexone modulate this system and have demonstrated efficacy in decreasing alcohol consumption and prolonging abstinence. Given the efficacy of these drugs in AUD, their mechanism of action, and the genetic variability in opiate receptors, it is plausible that an opiate antagonist might be the preferable therapy for patients who have AUD and who are heterozygous or homozygous for the G allele.

However, the few studies exploring efficacy of opiate antagonists in subjects with AUD and the G allele do not clearly support the preferential use of opiate antagonists in this population based solely on patients' genetic variability.

Regardless, they are still indicated for the treatment of AUD, whether or not a patient possesses the G allele. Additional studies of longer duration and higher power are needed to determine whether patients with the G allele and alcohol use disorder would benefit preferentially from opiate receptor antagonist treatment compared to other therapies.

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