Emerging pharmacological targets for alcohol use disorder

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ABSTRACT

Alcohol Use Disorder (AUD) remains a challenging condition with limited effective treatment options; however new technology in drug delivery and advancements in pharmacology have paved the way for discovery of novel therapeutic targets. This review explores emerging pharmacological targets that offer new options for the management of AUD, focusing on the potential of somatostatin (SST), glucagon-like peptide-1 (GLP-1), nociceptin, neuropeptide S (NPS), and vasoactive intestinal peptide (VIP). These targets have been selected based on recent advancements in preclinical and clinical research, which suggest their significant roles in modulating alcohol consumption and related behaviors. SST dampens cortical circuits, and targeting both the SST neurons and the SST peptide itself presents promise for treating AUD and various related comorbidities. GLP-1 interacts with the dopaminergic reward system and reduces alcohol intake. Nociceptin modulates mesolimbic circuitry and agonism and antagonism of nociceptin receptor offers a complex but promising approach to reducing alcohol consumption. NPS stands out for its anxiolytic-like effects, particularly relevant for the anxiety associated with AUD. VIP neurons are modulated by alcohol and targeting the VIP system presents an unexplored avenue for addressing alcohol exposure at various stages of development. This review aims to synthesize the current understanding of these targets, highlighting their potential in developing more effective and personalized AUD therapies, and underscores the importance of continued research in identifying and validating novel targets for treatment of AUD and comorbid conditions.

INTRODUCTION

Despite extensive efforts in prevention and intervention, Alcohol Use Disorder (AUD) remains a pervasive and challenging condition to treat[1–3]. AUD is a major public health issue, affecting over one-tenth of Americans aged 12 and older in 2020, with a notable increase following the Covid-19 pandemic[4–7]. AUD, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is characterized by a pattern of alcohol use leading to significant impairment or distress[8]. In the United States, 78% of individuals over the age of 12 have consumed alcohol, with similar consumption rates among both men and women[8]. Alarmingly, about 21% engage in problematic forms of alcohol consumption, such as binge drinking, and nearly 6% report heavy drinking. The economic impact of alcohol misuse is staggering, estimated at $249 billion in 2010, a figure that has likely grown in the wake of increased alcohol consumption during the pandemic[7,8]. Furthermore, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has identified an increasing trend of high intensity drinking [8,9]. The lack of reliable biomarkers for AUD impedes the development and testing of new treatments[10], and despite significant research investments by the National Institutes of Health

(NIH) and others in understanding the brain mechanisms of AUD, the last decade has seen a scarcity of new FDA-approved treatments for this disorder[11].

Advancements in understanding the neurocircuitry and neuromodulators involved in alcohol misuse and the transition to dependence have provided valuable insights[12–19], yet there remains a critical need for further exploration of novel pharmacological targets. This exploration is essential to address the complex nature of AUD and to develop new treatment options that can effectively mitigate the multifaceted impact of alcohol consumption[20,21]. The current pharmacotherapies for AUD, while moderately effective, are primarily focused on specific stages of the disorder, such as reducing consumption or aiding in maintaining abstinence[22]. However, these treatments often fall short in addressing the broader spectrum of AUD-related behaviors and symptoms – for example, cognitive decline[23], inflammation[24,25], mitochondrial damage[26–29], and liver dysfunction[30]. Targets such as corticotrophin releasing factor[31–36], neuropeptide y[37–39], and dynorphin[40] have been reviewed at length[41] – therefore here we speculate on interesting emerging novel targets that we believe warrant further investigation. While many other emerging targets exist, we have focused on somatostatin (SST), glucagon-like peptide 1 (GLP-1), nociceptin, neuropeptide S (NPS), and vasoactive intestinal peptide (VIP).

In addition, the field of neuropharmacology is rapidly evolving, leveraging innovative animal models and cutting-edge research techniques. Rapid and high-throughput animal models have become crucial in swiftly identifying and validating new potential targets for AUD. These models expedite the translation of preclinical findings into clinical applications, bridging the gap between laboratory research and real-world treatment scenarios. Technological advancements in neuropharmacology are significantly enhancing the potential of emerging targets in the treatment of AUD. Innovations in drug delivery systems, ultrasound, small molecule analogues, nanoparticles, nanodroplets, and nanoemulsions, are enabling more effective therapeutics and localized penetration of the blood-brain barrier[42–50]. This is crucial for the greater efficacy of new pharmacological targets, ensuring that therapeutic agents effectively reach specific brain areas involved in AUD. Additionally, advancements in gene therapy[51] and novel neuromodulation techniques[52,53] are providing novel ways to directly influence neural systems associated with AUD. These technologies are making previously challenging targets more accessible and open new avenues for exploring and validating emerging targets in AUD treatment.

SOMATOSTATIN

Somatostatin (SST) neurons play a critical role in the central nervous system, functioning as key modulators of neurotransmission and neuroendocrine signaling[54–58]. These neurons, which produce the inhibitory neuropeptide somatostatin, are widely distributed across various brain regions, including the cortex, hippocampus, and amygdala[59–61]. SST exists in two primary isoforms, SST-14 and SST-28, and exerts its effects through activation of 5 G-protein-coupled somatostatin receptors (SSTRs)[57,62–64]. Known for their inhibitory action on the release of hormones and neurotransmitters, SST neurons are integral to regulating neuronal excitability and synaptic plasticity and have gained attention for their role in substance use disorders[54–57,65,66]. SST is released from SST neurons[67] and acts to dampen cortical signaling in a long-lasting manner through activation of SST receptors[68]. The involvement of SST neurons and SST in a range of physiological processes including neurological conditions highlights its importance[58] and potential in modulating other states involving the cortex.

Both SST neurons and their namesake neuropeptide are promising therapeutic pursuits for AUD. SST neurons within the prefrontal cortex (PFC)[66,69,70] and regions of the amygdala[70–72] display robust alterations from multiple animal models of alcohol exposure and consumption. Glutamatergic drive onto PFC SST neurons is reduced in early abstinence from alcohol[70,73]. Consistent with this effect, the intrinsic excitability of SST neurons is reduced in abstinence from alcohol[69]. The specific effects of alcohol on SST neurons in the PFC may be dose[74] and receptor dependent[75], and adolescent-exposure specific changes may emerge due to the unique circuitry of the developmental brain[66,76,77]. Further investigation into alcohol modulation of SST neurons throughout development in the cortex and elsewhere is necessary. Alcohol consumption reduces SST immunoreactivity[75,78] further supporting the role for these neurons, and potentially the peptide itself, in sensitivity to alcohol. G-protein coupled receptors (GPCRs) uniquely expressed on SST neurons such as mGluRs[79] may provide a promising route for pharmacological restoration of SST neuron function following alcohol[80].

In addition, emerging evidence suggests SST may be a therapeutic target itself. Modulating SST receptor activation in the PFC can alter exploratory and anxiety-like behaviors related to alcohol consumption[69]. Modulation of SST through cannula administration (of both SST and SSTR4 agonists) to the amygdala can reduce binge drinking[75]. Further work on the peptidergic promise of SST should focus on sex differences[69] as well as SST's potential additional actions as a vasoconstrictor in the central nervous system[81]. Studies have shown that the response of SST neurons to alcohol and the impact of SST on behavior can vary significantly between males and females[68,69]. This variation highlights the importance of considering sex as a critical factor in developing SST- and SSTR-targeted therapies for AUD[58]. Additionally, the broader physiological role of SST, including its potential to modulate non neuronal cell types[82] within the central nervous system warrants further exploration.

New translational clinical work has further enthused SST's relevance in AUD. Cortical SST gene expression strongly correlates with alcohol-induced changes in resting-state activity in a protective-fashion in healthy men[83]. SST gene expression is also reduced in the hippocampus of individuals with broader substance use disorders[84]. While SST has a strong correlation with multiple psychiatric disorders[58], this emerging clinical literature suggests its potential unique role in substance misuse and alcohol misuse – further enthusing it as a potential target. Multiple FDA-approved analogues of SST exist (e.g., Octreotide, Sandosin) and have modest risk profiles[85–87]. The SST analogue Octreotide has long been used to mitigate alcohol-induced hypotension[88] in patients, and in animal models, may reduce alcohol-mediated neuropathic pain[89], and alcohol induced gastric damage[90] suggesting further therapeutic relevance for treating AUD simultaneously with comorbid conditions.

GLUCAGON-LIKE PEPTIDE 1

Glucagon-like peptide-1 (GLP-1)- and its g-protein coupled receptor (GLP-1R)- targeting drugs, widely recognized for their benefits in diabetes and weight management, have also sparked significant scientific interest due to their potential impact on the neurocircuitry of food intake and drug reward[91,92]. Secreted by the gut, GLP-1 is a 30 amino acid peptide[93] predominantly known for its role in stimulating insulin secretion and inhibiting glucose secretion[94]. GLP-1 produced in the central nervous system itself has been implicated in inducing satiety[95], stress responses[96], and playing a role in the regulation of glucose levels[97]. GLP-1Rs are found throughout the brain with high levels in the hypothalamus and brainstem[98]. However, its overall pharmacological profile both in the periphery and the brain are not fully known.

Emerging research has revealed that peripheral injections of GLP-1 or an analogue reduced alcohol intake in male rats, an effect replicated by direct administration of these drugs to the ventral tegmental area (VTA)[99] – broadly suggesting an interaction with dopaminergic reward circuitry. These findings have been extended to mice in thematically complementary studies[100], though notably, more work is needed to establish the role of GLP-1 in females. Importantly, the co-reduction in food intake along with alcohol intake[101] may limit or enhance its treatment efficacy in various clinical populations and should be specifically and thoroughly characterized.

Similar to SST, the human clinical literature has provided corresponding support for GLP-1 as a target for AUD. Variability in GLP-1 receptor gene variants is correlated with functional connectivity measurements in individuals with high or low risk for AUD[102]. Further comprehensive work by the same group has shown not only an interaction between GLP-1R expression levels and individuals with AUD (with greater receptor mRNA expression in the hippocampus of postmortem brains of individuals

with AUD), but that intravenous alcohol administration reduced GLP-1 levels[103]. Importantly, as GLP-1R targeting drugs are now rapidly available in the global market[104–106], correlational studies of alcohol use in these populations will likely emerge with time and provide further important insight. GLP-1's multifaceted role in metabolic regulation and its emergent impact on reward pathways underscore its potential as a therapeutic target for disorders extending beyond diabetes, including AUD, warranting further research to fully harness its clinical applications.

NOCICEPTIN

Nociceptin (also known as orphanin FQ) is a unique member of the opioid peptide family, binding to the nociceptin opioid peptide (NOP) receptor (originally named opioid receptor-like 1)[107–109]. It is far less investigated as compared to mu- delta- and kappa- opioid systems. Nociceptin is 17 amino acids long[110], and is involved in various neural processes, ranging from pain modulation[111] to behavioral responses to stress[112] and reward mechanisms[113]. Although it shares structural features with classical opioids, nociceptin's effects are often distinct, indicating a complex role in both normal physiology and the pathophysiology of addiction[114]. Nociceptin mediates consumption of other natural liquid rewards[115], and likely alters the rewarding properties for multiple drugs[116–121].

Increasing evidence suggests nociception agonism and antagonism can reduce alcohol consumption. While intracerebroventricular administration of nociceptin increases alcohol intake, indicating a facilitative effect on alcohol's rewarding properties, repeated exposure to nociceptin leads to a decrease in alcohol consumption[122]. This dichotomy suggests a sophisticated interaction between nociceptin and the reinforcing attributes of alcohol, pointing to potential receptor specific effects. Later work by the same group showed nociception analogues reduce alcohol intake in males[120]. Another study found that nociceptin agonists reduce alcohol consumption and prevented reinstatement and withdrawal symptoms in alcohol preferring rats[123]. A separate study corroborated these results indicating nociceptin reduces withdrawal symptoms and anxiety-like behaviors in rats with acute and chronic alcohol intoxication[124]. Similar results were obtained in the rostromedial tegmental nucleus where nociception signaling reduced alcohol consumption and attenuated anxiety- and depressive- like behaviors in alcohol withdrawn rats[125]. Dysregulation of nociception receptor signaling in the central amygdala (CeA) contributes to excessive alcohol intake and is rescued by local micro-infusion of nociceptin[126].

Interestingly, peripheral injections of NOP receptor antagonists can also reduce alcohol consumption, stress-induced alcohol seeking, and alcohol-induced stimulation of brain reward pathways in alcohol preferring rats[127]. The effects of NOP receptor antagonism in the brain may depend on the precise brain

region compounds are targeted to, with reductions in consumption seen following micro-injections to the CeA and VTA, but not nucleus accumbens (NAc), of male and female alcohol preferring rats [128]. A similar separate study from this same group found that antagonism of NOP receptors in the VTA and the CeA, but not in the NAc reduced alcohol seeking[129]. These studies highlight the complex bidirectional role of nociceptin in alcohol use and point to its role in particular key addiction related regions such as the CeA and VTA. Future work should address the role of NOP receptor agonism and antagonism in the same study. Overall this literature suggests that alcohol intake might downregulate the endogenous nociceptin system, disrupting stress regulation and enhancing alcohol consumption[114]. The role of both NOP receptor agonists and antagonists in decreasing alcohol consumption could be due to receptor desensitization or differential modulation of brain regions associated with reward and addiction, indicating a need for further region-specific and mechanistic research to precisely deliver treatments for AUD.

Recently, clinical studies have emerged in the literature for nociception antagonists and AUD, with antagonists advancing to clinical trials with great promise[130]. NOP specific agonists and partial agonists have shown promise in primates[131]. Buprenorphine, a semi-synthetic derivative that functions as a partial agonist at μ-opioid and NOP receptors, reduces alcohol consumption in monkeys, is effective in treating opioid use disorder[132,133], and has been used off-label for depression[134], suggesting it may be beneficial in AUD with comorbid depression. Further research is warranted to investigate the potential of NOP receptors in AUD treatment, potential for mitigating alcohol abuse, and sex specific effects. These and related compounds may be particularly useful in individuals with comorbid depression and AUD[135].

NEUROPEPTIDE S

Neuropeptide S (NPS), a recently identified peptide, is notable for its distinctive behavioral effects, including anxiolytic-like actions and the promotion of wakefulness[136–138] (for review on NPS see[139,140]). NPS is a 20 amino acid neuropeptide[141] which binds to and activates the NPS receptor (NPSR), a previously orphan G-protein coupled receptor known as GPR154 or GPRA[142,143]. NPS is found in brain areas including the parabrachial region and the locus coeruleus [139], and the NPSR is unique in that it is an excitatory GPCR (Gαs and Gαq) leading to elevated intracellular levels of cAMP and calcium[142,143]. NPS is colocalized with excitatory neurotransmitters, further supporting the view that NPS is part of an excitatory signaling system.

In the context of AUD, NPS and its receptor, NPSR, are integral to the brain's response to alcohol and associated anxiety. Variations in the NPSR1 gene are linked to the risk and patterns of AUD, showing

notable differences based on sex and age [144,145]. Several preclinical studies have indicated that delivery of NPS (both intraperitoneal and intracerebroventricular) can decrease alcohol seeking in mice; however, some have shown conflicting results[139] likely having to do with comorbid variables such as stress and anxiety. The deletion of the NPSR gene in mice reduces sensitivity to the effects of alcohol, while intracerebroventricularly administered NPS can diminish alcohol effects in mice[146]. NPS may also be affected by alcohol with marked increases in expression during withdrawal [147]. Rats subjected to a week of alcohol intoxication exhibit increased NPSR gene expression in various brain areas, with more pronounced changes observed after 7 days of withdrawal[147]. Functionally, this upregulation correlates with enhanced anxiolytic effects of NPS[147]. An increase in NPSR during withdrawal from alcohol suggests a possible role in alleviating associated anxiety, a theory supported by genetic studies linking NPSR variations to anxiety traits in AUD[145]. Chronic alcohol exposure enhances the anxiolytic and anti-depressive effects of NPS[148] further supporting the potential of NPSR to reduce anxiety experienced in AUD patients. These studies indicate that NPS not only modulates anxiety but also is involved with and potentiated by alcohol, future studies are needed to offer insights into behavioral effect of NPS both during alcohol consumption and during withdrawal.

Intriguingly, NPS's impact on alcohol consumption varies across genetic lines[139] (known to have varying basal anxiety levels and alcohol preference) as best exemplified in the differential responses seen between alcohol-preferring (msP) rats and Wistar rats[149,150]. While NPS reduces alcohol intake in msP rats, known for their excessive alcohol consumption and anxiety-like behaviors, it promotes alcohol-seeking behavior in Wistar rats. NPS likely reduces alcohol consumption through anxiolytic-like effects, suggesting NPS may be most useful in treating AUD populations with comorbid anxiety. These studies underscore the complexity of NPS action and highlights the necessity of considering genetics, anxiety levels, and behavioral context in its potential therapeutic application for AUD.

Targeting the NPS/NPSR system holds significant promise for AUD treatment. The first NPSR specific agonist was only recently developed[151], which will hopefully spur greater clinical interests. Future developments in this area could help researchers elucidate a role for the NPSR in alcohol consumption and withdrawal symptoms. This approach could effectively tackle the challenges such as anxiety experienced during withdrawal and relapse, major obstacles in AUD therapy. NPS's capacity to regulate stress and anxiety responses, along with its enhanced efficacy in alcohol-withdrawn subjects[148] indicates that targeting this system could be highly beneficial in addressing AUD's mood-related complexities. Continued research is vital to enhance our understanding of NPS's impact on AUD and to create specialized treatments that leverage this neuropeptide system's therapeutic potential.

VASOACTIVE INTESTINAL PEPTIDE

Vasoactive intestinal peptide (VIP) is a 28 amino acid[152] neuropeptide in the neocortex, it is predominantly expressed in GABAergic neurons and modulates cortical circuits through its G-protein coupled receptors VPAC1R and VPAC2R[153–156]. VPAC1R and VPAC2R are expressed on neurons and immune cells[157] and VIP acts directly on both[158]. VIP reduces inflammation[159,160], acts as a vasodilator[161], and modulates insulin and somatostatin release[162]. It is known in the central nervous system for its involvement in the circadian cycle governed by the suprachiasmatic nucleus[163]. High levels of VIP are expressed in emotion and addiction related regions such as the frontal cortex, amygdala, hypothalamus and hippocampus[164]. VIP is thought to depolarize neurons and activate a hyperpolarization-activated cation current through hyperpolarization-activated cyclic-nucleotide-gated channels[172]. While pituitary adenylate-cyclase-activating polypeptide (PACAP), also activates VPAC1R and VPAC2R, VIP and PCAP are pharmacologically distinct[173]. Targeting PACAP has shown promise in modulating alcohol drinking behaviors[174–178] further supporting a role for VIP and VPAC1R and VPAC2R as emerging targets for AUD.[164] In addition to their role in the suprachiasmatic nucleus, VIP neurons are a major subset of 5HT3 serotonin receptor expressing neurons and are located throughout the superficial layers of the neocortex[172–175]. They are known to release both GABA and VIP[176]. VIP neurons primarily target somatostatin (SST) neurons, playing a vital role in modulating cortical excitability and output through a disinhibitory mechanism[60,177,178]. [172173174–178]

The influence of VIP extends to a significant interaction with alcohol. Alcohol is known to increase plasma levels of VIP[179], suggesting alcohol may stimulate VIP release. VIP-stimulated release of β-endorphin is affected by alcohol[180]. Genetic studies have identified a link between VIP gene polymorphisms and increased alcohol consumption[181].[180] Further alcohol exposure has been shown to decrease expression of VIP. Long-term exposure to alcohol and withdrawal significantly reduces the synthesis and expression VIP in rats, with a notable decrease in VIP mRNA levels in the suprachiasmatic nucleus[182]. Neonatal exposure to alcohol can lead to a reduction in the density of VIP neurons in the rat suprachiasmatic nucleus[183], indicating potential circadian disruptions and a increased vulnerable to early alcohol exposure. This relationship between VIP and alcohol has been extended to animal models, where VIP has been shown to affect the development of alcohol tolerance[184] however, further behavioral testing on the effects of VIP on alcohol consumption in both males and females are warranted.

Alcohol has also been shown to modulate VIP neurons. A recent study found that bath application of alcohol in cortical slices activates cortical VIP neurons, while chronic alcohol consumption in mice can

lead to a decrease in the excitability of VIP neurons, a potential compensatory mechanism[185]. Further, VIP neurons in the cortex of male mice were found to remain hypoactive in withdrawal while females return to normal levels, suggesting sex differences in recovery of VIP signaling during withdrawal[185]. Increased VIP neuron activity following exposure to acute alcohol may correspond to increased VIP releaese. Modulation of VIP neuron activity by alcohol highlights the intricate relationship between VIP and alcohol exposure and underscores the importance of future investigations into the effect of alcohol and withdrawal on VIP neurons throughout development and across sexes.

The relationship between VIP and alcohol consumption suggests potential therapeutic applications. VIP may cross the blood brain barrier[186], and delivery to the brain can be enhanced using intranasal administration of VIP incorporated into nanoparticles[187]. Like SST, targeting VIP neurons also presents promise in reducing alcohol consumption. Since VIP-INs express 5-HT3 receptors, and their antagonism reduces alcohol consumption[188], targeting VIP neurons through other receptors for instance GPCRs expressed on VIP neurons offers a promising alternative to 5-HT3 antagonists. Moreover, targeting VIP presents promise as an unexplored target for AUD and comorbid conditions such as diabetes and inflammatory diseases, as well as protective against the effects of early alcohol exposure. Multifaceted approaches targeting VIP neurons, VIP release, and VPAC1 and 2 could lead to novel and effective treatments for alcohol-related disorders. The largely unexplored role of the VIP system in alcohol use, circuit modulation, and behavior, underscores the importance of future studies into VIP needed to further establish its role as a therapeutic target for Alcohol Use Disorder.

DISCUSSION AND FUTURE DIRECTIONS

The complexity of AUD, frequently presenting alongside other psychiatric disorders, highlights the urgent need for novel ligand and receptor targets to mitigate the diverse impacts of this disorder. Ideally, emerging treatments will focus not only on addiction management but also address the underlying physiological damage and co-occurring symptoms of AUD. It is crucial to also assess the addiction potential of new therapies themselves, and to consider sex-specific responses and genetic diversity. Additional priorities should include evaluating long-term health effects, managing side effects, and specialized treatments for vulnerable populations.

We have scrutinized a spectrum of emerging targets for AUD, each at various stages of development, from recent preclinical discoveries to those moving towards clinical trials. This is by no means an exhaustive list of emerging targets – others such as neuropeptide pituitary adenylate cyclase-activating polypeptide[167–171], neurotensin[189–196], neurokinins[197], cholecystokinin[198], and parvalbumin[73,199,200] similarly deserve further attention. For example, ghrelin, a hormone predominantly secreted by the

stomach, plays a critical role in regulating appetite, energy metabolism, and stimulating neurogenesis[201]. Antagonism of its receptor (growth hormone secretagogue receptor) is emerging therapeutic target for AUD and alcoholic liver disease, warranting clinical trials[202–205]. Likewise, orexins (also known as hypocretin), a neuronal and peptidergic population most well characterized for their role in energy homeostasis and wakefulness[206], may also play a pivotal role in alcohol and substance misuse (recently reviewed; see[207]). Further, there are several well-studied receptor targets such as the metabotropic glutamate receptor 2 ($mGlu_2$), which have shown promise in treating AUD[205,208,209]. While this review focuses largely on peptide targets, emerging targets ranging from natural products and psychedelic compounds to lipid transmitters have proven promising in reducing alcohol consumption[210–214].

With the advent of transgenic mouse lines, genetically encoded optical biosensors, and optogenetics, alongside advancements in electrophysiology and in-vivo microscopy, we are on the cusp of being able to monitor the interactions of drugs and their targets in real time within behaving organisms[67,215–218]. This not only enables precise mapping of receptor activity but also offers a window into the complex signaling pathways and temporal patterns that govern alcohol use and dependence. Beyond receptor interactions, the focus is expanding to encompass the role of these targets as biomarkers, and alternative means for modulation, such as enzymes that synthesize or degrade these targets[219], providing an innovative angle for therapeutic intervention. Furthermore, the integration of single-cell RNA sequencing into AUD research[220,221] promises to dissect the heterogeneity of neuronal responses to alcohol, enhancing the specificity of treatments across the spectrum of comorbidities that accompany AUD. New targets will continue to emerge along with technological advancements that allow for greater specificity in treatment during various stages of the transition of casual substance misuse to dependence[222,223] as well as for various individual comorbidities.

It's prudent to consider these innovative targets in conjunction with advancements in drug delivery and neuromodulation, like new methods of delivering treatments to the brain[50] and non-invasive techniques like focused ultrasound for neuronal modulation[52,53]. While targeted micro-infusion into specific brain regions is invaluable for isolating central effects and reducing peripheral side effects in studies, and a comprehensive examination of the systemic effects of these compounds is essential, as many of the targets discussed also significantly influence the gastrointestinal system and other peripheral organs[224–228]. Furthermore, the interplay between alcohol and various conditions such as eating disorders[229], diabetes[230], and cognitive decline[231] demands more research. This need is especially urgent given the increasing number of elderly in the U.S.[232]. Genetic models of neurodegenerative diseases are helping to shed light on the interaction between alcohol and aging[233–235]. Notably, certain targets, like SST have a multifaceted role in both alcohol effects and aging[233,236] while also exhibiting

protection against alcohol induced pathophysiology in the periphery[88–90] presenting a chance to address a variety of comorbid conditions. Additionally, *in-vitro* approaches like cerebral organoids[237] could facilitate high-throughput screening for AUD treatment targets, and the emergence of wearable biosensors promises more information on AUD and its diverse effects[238].

The literature suggests multiple favorable emerging targets for the treatment of AUD, some of which have FDA approved therapies already available, and all of which should be pursued with enthusiasm. The burgeoning array of potential targets and innovative technologies in our review heralds a new era of precision in treating AUD, promising to tailor therapies to individual needs and stages of addiction amidst an aging population with diverse comorbidities.

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