
Alcohol use is a major cause of disability and death globally. These negative consequences disproportionately affect those who develop alcohol addiction, a chronic relapsing condition characterized by increased motivation to use alcohol, choice of alcohol over healthy, natural rewards, and continued use despite negative consequences. Available pharmacotherapies for alcohol addiction are few, have effect sizes in need of improvement, and remain infrequently prescribed. Research aimed at developing novel therapeutics has in large part focused on attenuating pleasurable or “rewarding” properties of alcohol, but this targets processes that primarily play a role as initiation factors. As clinical alcohol addiction develops, long-term changes in brain function result in a shift of affective homeostasis, and rewarding alcohol effects become progressively reduced. Instead, increased stress sensitivity and negative affective states emerge in the absence of alcohol and create powerful incentives for relapse and continued use through negative reinforcement, or “relief.” Based on research in animal models, several neuropeptide systems have been proposed to play an important role in this shift, suggesting that these systems could be targeted by novel medications. Two mechanisms in this category, antagonism at corticotropin-releasing factor type 1, and neurokinin 1/substance P receptors, have been subject to initial evaluation in humans. A third, kappa-opioid receptor antagonism, has been evaluated in nicotine addiction and could soon be tested for alcohol. This paper discusses findings with these mechanisms to date, and their prospects as future targets for novel medications.

Keywords: addiction, alcohol, corticotropin-releasing hormone, dynorphin, neuropeptides, neurokinin 1, stress

Abbreviations: BNST, bed nucleus of stria terminalis; CeA, central nucleus of amygdala; CNS, central nervous system; CRF, corticotropin-releasing factor; DA, dopamine; fMRI, functional magnetic resonance imaging; GPCR, G-protein coupled receptor; KOR, kappa-opioid receptor; NK1, neurokinin 1; MOR, mu-opioid receptor; PET, positron emission tomography; RO, receptor occupancy; SP, substance P; SSRI, selective serotonin reuptake inhibitor

Alcohol addiction: an area of great unmet medical needs

Alcohol is one of the most commonly used psychoactive substances worldwide. It has been documented as a source of enjoyment for a majority of users since the beginning of written history, and the Greek word “symposion” literally means “to drink together.” But alcohol is also the cause of disease and death for a significant minority of those who drink [1, 2]. Presently, excessive alcohol use accounts for about 5% of global disease burden and close to 6% of all deaths [3]. People with alcohol addiction (hereafter equated with alcohol dependence, moderate—severe alcohol use disorder or simply alcoholism; for a discussion of these terms, see [1]) and very heavy drinking (>100 or 60 g/day for males or females, respectively) are disproportionately affected. In a group of European countries, those that fall in this category were found to make up about 0.8% of people aged 15–65, account for about half of all liver cirrhosis cases, and have a life expectancy that is shortened by 25–31 years [4].
Only a minority of people with alcohol addiction, estimated to 10%–25%, ever receive treatment, and then only after a lag from diagnosis to treatment that averages about a decade [5, 6]. Stigma, lack of prescriber expertise and other extrinsic factors contribute to this state of affairs, but limitations of current treatment options are also critically important in order to understand and address this treatment gap. A balanced view is needed: Existing pharmacotherapies for alcohol addiction are useful enough that systematic efforts should be made to ensure their provision to patients [2, 6]. However, they are also few and have an efficacy and tolerability that calls for improvement, contributing to their low uptake in clinical practice [6].

Medications that are approved for the treatment of alcohol addiction by European and US regulators target three distinct mechanisms. Disulfiram, the oldest among them, continues to be most commonly prescribed. It is an aldehyde dehydrogenase inhibitor that upon alcohol intake results in accumulation of acetaldehyde, an alcohol metabolite that is aversive at low levels, and becomes toxic as plasma concentrations increase. This mechanism is intended to deter drinking but does not specifically influence central nervous system (CNS) processes that underlie key clinical phenomena of alcohol addiction, such as increased motivation to use alcohol or inability to control its use despite negative consequences [1]. Unless its administration is supervised, patient compliance with disulfiram is low, and meta-analysis of randomized controlled trials does not support its efficacy under those conditions. In contrast, efficacy is supported with supervised administration [7]. Disulfiram continues to have a place in clinical practice, but mostly so in special settings, for example, when sobriety must be ensured for a surgical procedure, contributing to their low uptake in clinical practice [6].

The first medication to target CNS mechanisms of alcohol addiction was the mu-opioid receptor (MOR) preferring opioid antagonist naltrexone [8–10]. Naltrexone and its analog nalmefene [11] are thought to acutely attenuate alcohol reward, by blocking a cascade in which endogenous opioid peptides released following alcohol intake activate MORs, and promote multiple reward-related processes mediated by the ventral striatum, both by influencing these directly, and also through interactions with mesolimbic DA [12–16]. The average effect size of naltrexone is modest [6], but this metric only tells a part of the story, as the response is highly heterogenous. Predictors of naltrexone response are male sex, a family history of alcohol problems, early onset of problem drinking, and pronounced subjective alcohol reward [17, 18]. In cases selected for these predictors, response can be robust, whereas other patients are unlikely to benefit. Similar to disulfiram, compliance is a key factor for the efficacy of naltrexone. This is likely related to the fact that MOR signaling plays a key role for the “liking” of a wide range of rewards [19], limiting patient incentives to comply with treatments that interfere with it. Based on elegant animal studies, GSK1521498, a highly selective and potent MOR antagonist, has been proposed as a potential improvement over naltrexone [20, 21]. Its potential to improve clinical outcomes may, however, be limited, as near-complete MOR blockade can already be achieved using naltrexone [22], and the lack of patient incentives to comply with treatment is likely related to the pharmacodynamic mechanism that is shared by both molecules.

The homotaurine analogue acamprosate, thought to exert complex effects on glutamatergic mechanisms [23, 24], is also effective with a modest effect size [6]. Based on animal studies, patients with the most pronounced disease severity are most likely to respond [25]. The exact mechanism through which acamprosate influences glutamatergic transmission is not known, and it has been suggested that it simply functions as a carrier of calcium-ions into the CNS [26]. This could explain its low potency, with daily doses required to be around 2 g. Limited efficacy, a need for administration three times daily, and a high frequency of gastrointestinal side effects also pose challenges to patient compliance, leading to low clinical uptake of acamprosate.

Finally, some medications that are approved for indications other than alcohol use disorders also have support for efficacy on this indication and can be prescribed off-label. The antiepileptic topiramate, a state-dependent blocker of neuronal sodium channels, has shown robust effect sizes in treatment of alcohol addiction [27–29], but is associated with cognitive and other side effects that limit its utility. Gabapentin, a ligand of the α2δ voltage-dependent calcium channel subunit, is approved for the treatment of focal seizures and neuropathic pain, and has also demonstrated efficacy in AUD trials [30]. Both topiramate and gabapentin are recommended for the treatment of
alcohol addiction in the guidelines of the American Psychiatric Association (APA). In addition, the nicotinic partial agonist varenicline has marketing approval for smoking cessation, and some support for efficacy in alcohol addiction, potentially making it useful in patients with comorbidity of smoking and alcohol problems [31, 32]. The GABA-B agonist baclofen, long used for spasticity, is particularly effective in patients with severe alcohol addiction [33–41], but its utility is limited by a frequent need for dose escalation, associated with a potential for adverse events.

Transforming alcohol addiction treatment: targeting stress- and aversion-systems

No mechanistically novel alcohol addiction therapeutics have been brought to market in close to 20 years. This is frequently attributed to a lack of commercial potential, but the market in alcohol treatment provision in fact exceeds $35 billion/year in the US alone. Unfortunately, in a pattern that is similar for both the US and Europe, commonly offered treatments, such as extended residential care, are expensive and ineffective, whereas medications with support for efficacy are rarely prescribed [42–45]. A premise of the present paper is that this landscape will only be transformed, if novel medications are brought forward that combine clinically meaningful efficacy with high patient acceptance. Only then will there be a demand for treatment from patients and their families, creating a pressure to implement treatments, and reducing stigma. The development of selective serotonin reuptake inhibitors (SSRIs) for treatment of major depression in the late 1980, spearheaded by fluoxetine (Prozac), may provide a template for this scenario. Despite the fact that effect sizes and tolerability profiles of SSRIs are not necessarily superior to those found for alcohol addiction medications, their arrival drove a patient demand for treatment that expanded access to treatment, and altered the perception of depression and its treatment among the general public, patients, and treatment providers alike. The alcohol field needs its “Prozac-moment.”

Transforming alcohol addiction treatment in this manner will first and foremost require an improved understanding of the unmet needs from a patient perspective. To date, a major focus of alcohol research has been on mechanisms of alcohol reward, and on associated phenomena of progressively increased motivational salience attributed to alcohol-associated stimuli. Mesolimbic dopamine (DA) system activity is widely thought to contribute to both these processes, and it is now four decades since the demonstration that alcohol can activate this system [46]. This observation continues to guide much of the search for novel treatment targets [47]. However, two sets of considerations suggest that this strategy is insufficient, at best.

First, “reward system” activation by alcohol, whether mediated through interactions with DA, or independently of those, varies markedly as a function of biological sex and other individual factors, including genetics [15, 48, 49]. It also varies over the lifespan of an individual patient. Stimulating and rewarding effects of alcohol may be an important initiation factor that reinforces recreational alcohol use and mediates genetic risk for developing addiction [50]. However, these effects decrease progressively as a function of drinking severity. When alcohol-induced activation of the ventral striatum, the canonical hub of “brain reward systems,” is assessed using functional magnetic resonance imaging (fMRI), it closely correlates with subjective intoxication in social drinkers [48], but is no longer detectable in treatment-seeking patients, at least at the alcohol doses tested [51, 52]. Furthermore, even when attenuation of alcohol reward can be achieved, it is not a mechanism well suited to promote patient compliance with treatment. Highly motivated, well-functioning patients may accept that attenuating alcohol reward could help prevent adverse consequences of their disorder. But not even these patients are likely to view this effect as an inherently appealing treatment goal.

Second, many patients who seek treatment no longer experience much reward from alcohol at all. Instead, they seek treatment hoping to alleviate negative affective states that emerge over time and come to dominate their lives, in which sobriety is associated with “emotional pain”: low mood, increased anxiety, and disrupted sleep [53, 54]. Negative emotional responses to stress are also sensitized at this stage, commonly described by patients as an inability to ignore minor challenges that did previously not bother them (Fig. 1). Both animal [55–59] and human findings [60, 61] show that, following a prolonged history of brain alcohol exposure, a link is established between stress and escalation of alcohol use that is otherwise not present. Stress also promotes relapse-like behavior in experimental animals [62] and is clinically
Progression from early stages of experimental and recreational alcohol use to alcohol addiction. Over the course of this process, which typically lasts years and sometimes decades, the initial role of "rewarding" alcohol effects is progressively attenuated. Meanwhile, a pathological recruitment of stress- and aversion-systems occurs, resulting in a shift of affective homeostasis. At this point, a dominant motivation to seek and take alcohol is for the relief of a negative affective state that is experienced in its absence.

Multiple neurobiological systems could potentially be targeted to impact alcohol—stress interactions [54]. Among these, the biology and role of CRF in alcohol-related behaviors have been the subject of multiple reviews (e.g., [57, 66, 67]). In brief, CRF-expressing neurons are present in stress-responsive brain structures involved in both anxiety-related behaviors and alcohol seeking, including the central nucleus of amygdala (CeA) and bed nucleus of stria terminalis (BNST). CRF acts through two subtypes of Gs-coupled G-protein coupled receptors (GPCRs), with rodent studies indicating that behavioral stress responses such as anxiety-like behavior and stress-induced alcohol seeking are predominantly mediated by CRF1 receptors (but see below). In these rodent studies, effects of CRH2 activation are more variable, and, depending on receptor localization, can mediate both “pro-stress” and “anti-stress”-responses. Similar to many neuropeptide systems, CRF signaling that mediates behavioral stress responses is an "alarm system," that is, it is largely quiescent under basal conditions but becomes activated in the presence of uncontrollable stress. This is an attractive profile, as it predicts that CRF1 antagonists may be able to selectively target excessive, maladaptive stress responses, while leaving normal function largely unaffected, leading to minimal side effects.

Corticotropin-releasing factor type 1 receptor (CRF1) antagonists

Corticotropin-releasing factor (CRF) is the prototypical stress-related neuropeptide. In addition to its textbook role as the hypothalamic releasing factor for adrenocorticotropic hormone (ACTH), CRF produced by extrahypothalamic neuronal populations is involved in coordinated behavioral, neuroendocrine, and autonomic responses to threats and other stressors. The biology and role of CRF in alcohol-related behaviors have been the subject of multiple reviews (e.g., [57, 66, 67]). In brief, CRF-expressing neurons are present in stress-responsive brain structures involved in both anxiety-related behaviors and alcohol seeking, including the central nucleus of amygdala (CeA) and bed nucleus of stria terminalis (BNST). CRF acts through two subtypes of Gs-coupled G-protein coupled receptors (GPCRs), with rodent studies indicating that behavioral stress responses such as anxiety-like behavior and stress-induced alcohol seeking are predominantly mediated by CRF1 receptors (but see below). In these rodent studies, effects of CRH2 activation are more variable, and, depending on receptor localization, can mediate both “pro-stress” and “anti-stress”-responses. Similar to many neuropeptide systems, CRF signaling that mediates behavioral stress responses is an "alarm system," that is, it is largely quiescent under basal conditions but becomes activated in the presence of uncontrollable stress. This is an attractive profile, as it predicts that CRF1 antagonists may be able to selectively target excessive, maladaptive stress responses, while leaving normal function largely unaffected, leading to minimal side effects.
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Fig. 2 Stress triggers relapse-like behavior (reinstatement of alcohol seeking) through a corticotropin-releasing factor (CRF)-dependent mechanism. In this commonly used model of relapse-like behavior, rats are first trained to self-administer alcohol by lever-pressing for it in daily operant sessions. Once self-administration rates are stable, behavior is extinguished by eliminating the delivery of the alcohol reward. After approximately 14 days of extinction, lever-pressing rates become very low. However, if a stressor, for example, a 10 min footshock stress, is introduced prior to the session, response rates on the lever previously delivering alcohol return to levels that are similar to those observed while lever presses resulted in the delivery of alcohol. This model is thought to reflect the observation that stress is a major trigger of relapse in patients with alcohol addiction. In this model, a wide range of CRF1 antagonists block relapse-like behavior and do so with an increased potency in animals with a history of alcohol dependence. Source: Adapted from Ref. [74].

Research in rodents has provided unusually persuasive evidence in support of CRH1 antagonists as promising therapeutics for several stress-related psychiatric disorders, including major depression, generalized anxiety disorder, post-traumatic stress disorder and alcohol addiction. For the latter indication in particular, CRF1 antagonists have accumulated a preclinical target validation that is as consistent as it is compelling. In rodents, expression of both CRF and its CRF1 receptor is upregulated following a history of alcohol dependence [55]. Accordingly, blockade of CRF signaling does not have a major influence on alcohol self-administration under basal conditions, but robustly suppresses escalated self-administration seen following a history of dependence, and blocks the increased stress-reactivity and anxiety-like behavior observed under these conditions [68–71]. Similarly, CRF1 antagonists block stress-induced relapse-like behavior, with a potency that is increased following development of dependence. In contrast, they do not influence relapse triggered by alcohol-associated stimuli (Fig. 2; [72–74]). Effects of CRF1 antagonists on stress- and alcohol-related behaviors are centrally mediated, and unrelated to CRF function within the HPA-axis [72].

Collectively, these and other rodent data supported the notion that a recruitment of the CRF system occurs following a prolonged history of alcohol dependence, contributes to several behaviors that are at the core of alcohol addiction, and results in increased sensitivity to blockade of both excessive drinking and relapse by CRF1 antagonists [57]. This suggested that CRF1 antagonists would suppress stress-induced craving in people with alcohol addiction, a biomarker that predicts clinical relapse [63, 64].

For more than a decade, the main barrier to human translation of these preclinical findings was a lack of potent, selective, brain penetrant CRF1 antagonists that would also be safe and well tolerated [67]. Early compounds, such as R121919 [75] or antalarmin [76], were halogenated to an extent that made the liver a target organ for toxicity, for obvious reasons rendering them less than ideal as candidate treatments for alcohol addiction. A subsequent generation of molecules that included pexacerfont and verucerfont had an improved safety profile [77, 78], but these molecules were initially prioritized for development in psychiatric indications thought to have a greater commercial potential than alcohol addiction, such as major depression.
Fig. 3 Functional implication of corticotropin-releasing factor type 1 (CRF1) receptor residence time. Slow dissociation appears to promote efficacy of CRF1 antagonists. Activity in this assay predicted activity in the human dex-CRF test. ACTH: Adrenocorticotropic Hormone. Source: Adapted from Ref. [81].

Depression and anxiety disorders. Meanwhile, an additional layer of complexity was introduced with the realization that dynamics of CRF1 antagonist-receptor interactions may differ between molecules with similar nominal receptor affinities, as determined by conventional assays, potentially implying that antagonists with slow dissociation from the receptor were required for efficacy (Fig. 3; [67, 79]).

Ultimately, our program at the US National Institute on Alcohol Abuse and Alcoholism in Bethesda (MD) was able to begin evaluating pexacerfont and verucerfont in patients with alcohol addiction [80, 81]. Two studies were carried out that targeted patients with alcohol addiction and high anxiety, the population thought to be most likely to respond based on the animal research. The studies went to considerable length to minimize some common causes of failure in clinical development programs. Most importantly, they ensured target engagement through the use of objective biomarkers. Target engagement for CNS drugs is typically demonstrated using positron emission tomography (PET), but no PET ligands for the CRF1 receptor are available. To circumvent this, a separate pharmacokinetic study was carried out with pexacerfont in healthy volunteers, who were dosed with the same dose regimen as patients in the main trial. Participants provided samples of cerebrospinal fluid that were analyzed for pexacerfont levels using a novel, ultrasensitive liquid chromatography–mass spectrometry method. This allowed it to be established that a >90% central receptor occupancy (RO) was achieved with the pexacerfont dosing used. The verucerfont study instead relied on a neuroendocrine biomarker of target engagement, ACTH release in the dexamethasone-CRF test [82]. This was robustly blocked, providing an appealing translation of preclinical data, in which verucerfont, (a slow-dissociating CRF1 antagonist; but not the fast-dissociating antagonist pexacerfont), potently blocked ACTH release in adrenalectomized rats.

Initially reported effective in depression, but toxic

Despite demonstration of target engagement in both studies, and robust rodent-to-human translation of efficacy on the neuroendocrine biomarker with verucerfont, none of these two studies found a signal on stress-induced craving, the surrogate marker thought to predict efficacy in alcohol addiction. Both these studies had multiple limitations and are by no means conclusive per se. Due to safety concerns, both were inpatient Phase 2a/experimental medicine studies, and therefore evaluated effects on a surrogate biomarker thought to be predictive of efficacy, stress-induced alcohol craving, rather than on drinking endpoints that assess actual clinical efficacy. As is typical in this type of studies, sample sizes were limited, and one of the studies was limited to females, due to concerns about testicular toxicity with verucerfont. Thoughtful discussion of strengths and limitations in these studies, as well as their implications have been published [83, 84]. Multiple questions for clinical research remain. However, in parallel with these results, CRF1 antagonists failed on
other stress-related psychiatric indications [85–87]. With that, clinical development programs of CRF1 antagonists for psychiatric indications were terminated across the industry.

These failures remain equally surprising, disappointing, and difficult to interpret. Limitations to the design of clinical studies are always a possibility but are unlikely to uniformly explain failures across the range of indications where CRF1 antagonists have been examined. One explanation that may be more likely is that some important features of the CRF-system are not sufficiently well conserved between rodents and primates. Indeed, although overexpression of CRF within the amygdala of young rhesus macaques has been shown to produce an “anxious temperament” [88], it is unclear whether this reflects the function of endogenous CRF in this species, or whether the effect was mediated by CRF1 or CRF2 receptors. A more prominent role of CRF2 in producing stress-responses in primates compared to rodents could explain the translational failures with CRF1 antagonists [89]. An additional possibility is that in primates, redundancy has evolved, such that other systems are able to substitute for CRF-signaling when the latter is blocked. A prime candidate for such a system is dynorphin and its kappa-opioid receptors (KORs; see below), but the CRF system interacts with multiple other stress-related systems that could potentially be targeted, such as for example, oxytocin or orexin [54]. Some additional potential implications of the CRF1 findings are discussed in the “Conclusion” section.

**Substance P (SP) and its neurokinin 1 (NK1) receptor**

Together with neuropeptide A and neurokinin B, substance P (SP) belongs to the tachykinin neuropeptide family. These peptides exert their effects through three receptor subtypes, NK1–3. SP preferentially binds to the neurokinin 1 (NK1) receptor, a Gs/q-coupled GPCR expressed in brain regions that mediate aversive behaviors, modulate behavioral responses to stress, and regulate several alcohol-related behaviors [90, 91]. Rodent and human NK1 receptors differ in their ligand affinity profiles [91, 92]. However, mice with a genetic deletion of the receptor, and availability of an NK1 antagonist specifically developed to possess high affinity at rat NK1 receptors have allowed this receptor to be evaluated as a potential target for alcohol addiction treatments.

Overall, although much less extensive, preclinical findings suggest an activity profile for NK1 antagonists that is similar to that of CRF1 antagonists. In NK1 null mutant mice, alcohol intake and escalation are markedly attenuated [93]. In rats, systemic administration of an NK1 antagonist blocks stress-induced relapse, while leaving relapse triggered by alcohol-associated stimuli unaffected [94]. NK1 expression is also elevated in CeA of a ratline bred for high alcohol preference, and relapse triggered by a pharmacological stressor in this ratline is blocked by infusion of an NK1 antagonist into CeA [95]. Conversely, overexpression of NK1 receptors in the CeA of in regular Wistar rats increases their sensitivity to relapse [96].

Collectively, these and other findings showed that, in rodents, the activation of NK1 receptors in the CeA promotes escalation of alcohol intake, stress-induced relapse, and other alcohol-related behaviors. Activation of NK1 receptors in CeA by SP has also been reported to increase GABA-release in this structure, an effect that is upregulated following a history of prolonged brain alcohol exposure [97]. Upregulated GABA-release in CeA has, perhaps somewhat counterintuitively, emerged as an important mechanism that promotes alcohol use [98, 99]. Thus, NK1 antagonists may produce their effects on alcohol-related behaviors by targeting GABAergic pathology within CeA.

Based on these and other preclinical findings, we evaluated the NK1 antagonist LY686017 (subsequently named tradipitant) in a Phase 2a experimental medicine study. Similar to the CRF1 antagonist studies, this was an inpatient study that used as surrogate outcome stress-induced cravings. For exploratory analyses, brain responses to aversive stimuli were also measured using fMRI. Because preclinical findings suggested that NK1 antagonists primarily influenced stress-related mechanisms, the study targeted for inclusion patients with alcohol addiction and high anxiety [93]. In this population, NK1 antagonism suppressed both self-reported cravings triggered by an established social stressor, the Trier Social Stress Task [100], and brain responses to standardized aversive images from the International Affective Picture System (IAPS; [101]).

These promising results drove the initiation of a clinical development program by Eli Lilly, in which an outpatient Phase 2b trial for clinical efficacy outcomes was carried out. This study has not
been published, but its main design features and outcomes are available at www.clinicaltrials.gov (NCT00805441). It recruited 190 subjects, who were randomized 1:1 to tradipitant (50 mg daily; a dose that had previously been established to result in >90% central RO using PET [102]), or placebo. Patients received treatment for 12 weeks. The primary outcome was % change from baseline in heavy drinking days, referring to consumption within a single day of 5 or 4 standard drinks containing 10–12 g alcohol, for males or females, respectively. Multiple secondary outcomes were also collected. Drinking measures were derived from self-reports, obtained using time-line follow-back methodology (TLFB; [103]). This method has been validated and is accepted by regulators. However, in a recent example with the nicotinic partial agonist varenicline, it has become clear that TLFB is less sensitive than objective biomarkers, presumably due to greater variance, and perhaps also due to reporting bias [32].

The Phase 2b study did not find a significant effect of tradipitant on the primary outcome. However, numerical trends favored the NK1 antagonist both on the primary and on several secondary outcomes. For instance, the primary outcome, % change from baseline in heavy drinking days, was 10%–units greater in the active treatment arm (−69.5 ± 35.8 vs. −59.12 ± 40.4, mean ± SD). Similar trends were found for % days abstinent and the number of drinks per drinking day. In analogy with what has been found in the study with varenicline cited above [32], the strongest signal, and a near-significant trend, was obtained on an objective biomarker of alcohol use, gamma glutamyl transferase (GGT; −11.5 ± 42.6 vs. −2.1 ± 20.1; p = 0.07; units/L, mean ± SD). Another biomarker, carbohydrate deficient transferrin was unaffected, but this measure is much less sensitive and did not change from baseline in any of the study arms, despite marked overall reductions in alcohol use typically seen simply as a result of participating in an alcohol study.

Most importantly, due to commercial considerations, Eli Lilly was reluctant to limit market potential by targeting only a subpopulation of patients with alcohol addiction. As a result of this strategy, the tradipitant study targeted a population that critically differed from that in which the original surrogate marker signal suggestive of efficacy had been obtained. Based on preclinical findings, the original study had targeted treatment-seeking inpatients with high anxiety. In contrast, the outpatient trial was carried out in unselected patients recruited from newspaper ads, who were less severe and overall had a very low baseline level of anxiety. Nevertheless, when this study population was stratified by baseline anxiety, the effect of tradipitant on the objective biomarker of alcohol use, GGT, was significant, and it was evident that this effect was entirely driven by participants with baseline anxiety above the median (Fig. 4). It thus remains an important possibility that, in correctly selected populations, the beneficial effects of NK1 antagonism on stress-induced alcohol-related behaviors translate from rodents both to experimental and clinical outcomes in humans.

It was originally thought that NK1 antagonists would become effective, nonaddictive analgesics, but this hope was not supported, and subsequent development was primarily driven by the discovery of their potential as antidepressants [104]. Results in the depression studies that followed were, however, inconsistent. This ultimately resulted in termination of NK1 antagonist programs for stress-related psychiatric disorders throughout the pharmaceutical industry. It was only once these programs had been shut down that a likely
key factor behind the inconsistent depression results was identified. For most GPCR antagonists, central RO > 90% is typically considered sufficient to achieve efficacy. However, a reanalysis of multiple depression trials suggested that this is not the case for NK1 antagonists. Availability of a displacable PET-ligand allowed a detailed, quantitative analysis of central RO for different NK1 antagonists as a function of dose. This analysis identified a consistent pattern: Depression trials in which near-complete RO had been achieved were positive, whereas those with lower RO were not [105, 106].

In summary, is remains a distinct possibility that NK1 antagonism, delivered at sufficient doses to an adequately selected patient population, is a viable therapeutic mechanism in alcohol addiction. Whether this possibility will ever be evaluated is, unfortunately, unclear.

**Kappa-opioid receptor (KOR) antagonists**

Opioid systems play multiple roles in addictive disorders, including alcohol addiction [107, 108]. However, while MOR-signaling mediates the “liking” of multiple rewards, including alcohol (see above), KORS, and their endogenous ligand dynorphin do just the opposite: They mediate aversion, stress-reactivity and negative emotionality [109]. Preclinical research to establish the functional role of KOR signaling has been facilitated by the availability of excellent pharmacological tools. Although the prototypical KOR antagonist nor-binaltorphimine (nor-BNI) does not have properties that render it suitable for clinical development, its high potency and selectivity have been critical for preclinical research to validate KORS as a therapeutic target. Availability of a highly selective KOR agonist, U50,488, has further facilitated preclinical target validation efforts.

In a pattern similar to that described above for the CRF-system, rodent studies show that prolonged brain alcohol exposure results in an upregulation of the KOR/dynorphin system, leading to emergence of a negative affective state that in turn promotes alcohol intake through negative reinforcement [110]. Increased KOR sensitivity is a key mechanism both behind aversive properties of alcohol withdrawal, and attenuated mesolimbic DA signaling during this stage [111]. Together, this sets the scene for a particularly disruptive combination of negative affect and reward deficit.

In preclinical models, KOR-signaling also contributes to stress-induced relapse, as demonstrated by findings that this behavior is effectively suppressed by nor-BNI [112, 113]. Conversely, KOR activation by U50,488 is sufficient to trigger relapse, and this effect is blocked by nor-BNI. Interestingly, relapse triggered by U50,488 is also blocked by a CRF1 receptor antagonist, suggesting that these two systems interact, and pointing to the possibility that, in rodents, dynorphin acts upstream of CRH to trigger relapse upon exposure to stress [113]. Both CeA and the BNST appear to be involved in KOR-mediated mechanisms of excessive alcohol intake and stress-induced relapse to alcohol seeking [114–118]. Finally, in a difference from the profile of CRF1 antagonists, both nor-BNI and another KOR antagonist, JDTic, block relapse triggered by exposure to alcohol-associated stimuli [113, 119, 120]. However, for reasons discussed below, it is unclear whether these effects are mediated by acute KOR blockade.

Based on the preclinical findings, KOR antagonism was identified as an attractive mechanism for treatment of alcohol addiction, but for a long time, available KOR antagonists lacked properties that would make them suitable for clinical development. nor-BNI has effects that last long after it has dissociated from the receptor, attributed to phosphorylation of c-Jun N-terminal kinase [121]. This is also found with JDTic [121], which in addition turned out to be cardiotoxic [122]. A new generation of well-behaved, short-acting KOR antagonists was required for the therapeutic potential of KOR antagonists to be examined. A key advance was the discovery by Eli Lilly of aticaprant (originally designated LY-2456302, then licensed to Cerecor as CERC-501, and finally obtained by Janssen as JNJ-67953964 [123]). Phase 1 studies showed that aticaprant is safe and well-tolerated in both healthy and cocaine dependent subjects [124–126]. Despite the overwhelming body of preclinical evidence supporting a role for KOR-signaling primarily in negatively reinforced, stress-related substance use and relapse, Cerecor decided to evaluate aticaprant in a laboratory smoking model that evaluated latency to smoke in exchange for money, and the number of cigarettes self-administered during a 60-min ad lib smoking period, in the absence of any stressors [127]. This study was thoroughly negative.

The next human trial was much better informed by insights from preclinical research. It was
carried out under the Fast-Fail initiative of the US National Institute on Mental Health (NIMH; 128)). Because preclinical research had shown that KOR signaling produces a “reward-deficit,” presumably by suppressing mesolimbic DA release (see above), the study tested the hypothesis that aticaprant would reverse anhedonia, that is, the inability to experience pleasure, in patients with depression or anxiety disorders. Based on this rationale, the primary outcome was an established fMRI biomarker of brain reward system activation, the Monetary Incentive Delay task [129]. This was evaluated in patients with depression or anxiety who also reported suffering from anhedonia. The predicted effect of aticaprant was robustly found on the fMRI biomarker, and this was accompanied by a reduction in self-reported anhedonia [130]. Based on these findings, Janssen Pharmaceuticals initiated a development program of aticaprant for mood and anxiety disorders. An initial depression trial was recently completed, with promising results (NCT03559192).

Based on a similar rationale, and the role of negative affect in alcohol addiction, we evaluated aticaprant in a battery of rat tests to assess its potential as a clinical candidate on this indication [131]. Systemic administration of aticaprant fully reversed anxiety-like behavior seen during acute alcohol withdrawal. Aticaprant also effectively blocked escalated, but not baseline, alcohol self-administration, and suppressed stress-induced relapse to alcohol seeking, while leaving relapse triggered by alcohol-associated stimuli unaffected. These findings are highly consistent with the activity profile predicted based on research to examine the role of KOR signaling in alcohol-related behaviors, pioneered by others [109, 110, 115, 117, 118, 132].

Thus, an analysis in animal models indicates that aticaprant acts on negative affective states that promote alcohol seeking and taking. This profile complements that of naltrexone, which selectively inhibits alcohol reward and relapse induced by alcohol-associated stimuli [73]. A particularly attractive therapeutic strategy thus may be to combine naltrexone (or nalmefene) and aticaprant. Because these two mechanisms target different elements of alcohol addiction, combining them has the potential of being additive, resulting in improved efficacy. Because KOR-antagonism is able to reverse anhedonia and negative affective states, it can be expected to meet with high patient acceptance and could provide incentives to promote patient compliance with a combined treatment.

Conclusions

To address the public health burden of alcohol use, treatment options for alcohol addiction need to be expanded. Discovering novel treatments that are effective, safe, and well tolerated is challenging, but the challenges do not stop there. To promote patient compliance with treatment, novel treatments will also need to address patient needs the way patients themselves perceive those. Treatments that attenuate alcohol reward do not align well with that perspective. In contrast, treatments that reverse anhedonia, stress sensitivity, and negative affective states, symptoms that over time dominate clinical presentation of alcohol addiction hold a much better potential of appealing to patients.

For decades, stress-related neuropeptide systems have seemed to offer targets for this type of therapeutics. The greatest promise seemed held by CRF1 antagonism. For reasons that remain enigmatic, this promise has to date not resulted in clinical therapeutics. Prospects of resurrecting this mechanism seem bleak, as clinical development programs across the pharmaceutical industry have been closed down. A signal for successful human translation of animal findings has been obtained for NK1 antagonists. Some of these are approved for clinical use, or in development for other indications. A review of findings obtained with NK1 antagonists. Some of these are approved for clinical use, or in development for other indications. A review of findings obtained with NK1 antagonists over the years points to two key factors likely to be critical for success: selection of the right patient population and dosing that results in near-maximal central RO. Because psychiatric NK1 programs have also closed, it is, however, unclear whether putting these insights to test will ever become possible.

Finally, KOR-antagonists have an activity profile very similar to that of CRF1 antagonists, and recent human findings in anhedonia and depression support a translational validity of preclinical findings with this mechanism. Among the mechanisms reviewed here, KOR antagonism currently may hold the greatest promise for becoming a novel alcohol addiction treatment. This promise should be put to test, possibly in combination with one of the already approved MOR antagonists, naltrexone, or nalmefene. However, in the
short—medium term, success of aticaprant in depression may paradoxically prevent its progress in alcohol addiction. In a parallel to the early days of CRF1 antagonist development, depression is the commercially more attractive indication. Development of KOR antagonists for alcohol addiction may therefore require public and academic efforts.

Finally, an important, underappreciated but ultimately potentially critical lesson may be embedded in the painful experience the field has had with CRF1 antagonists. Much discussion has been devoted to the predictive validity and translational value of animal models in developing psychiatric medications in general, and also in alcohol addiction [133–136]. But, as discussed above, species differences may account for some translational failures, and the extent to which target systems are evolutionarily conserved may vary. When significant species differences exist, they may reduce the translational value of preclinical findings. Other systems may be highly conserved, making the same animal models highly predictive. If this is the case, then discussing the utility of animal models in general terms may be of limited value. Instead, the implication is that predictive, translational validity of these animal models will vary on a target-by-target basis. This makes the task of translationally examining possible cross-species differences in target systems. While daunting, this is by no means an impossible task. Huge unmet patient needs demand that we take it on.

Conflict of interest statement

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