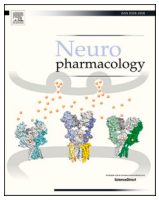
Neuropharmacology 283 (2026) 110745

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm



Phase-sensitive individualized pharmacotherapy for alcohol use disorder

Christian P. Müller [a,b,*], Bernd Lenz [c,d], Johannes Kornhuber [a], Ulrich W. Ebner-Priemer [d,e,f], Emanuel Schwarz [d,e,g], Karen D. Ersche [c,h,i], Falk Kiefer [c,d], Rainer Spanagel [b,d]

[a] Department of Psychiatry and Psychotherapy, University Clinic, Friedrich-Alexander-University of Erlangen-Nürnberg, Schwabachanlage 6, 91054, Erlangen, Germany
[b] Institute of Psychopharmacology, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[c] Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[d] DZPG (German Center for Mental Health), Partner Site Mannheim/Heidelberg/Ulm, Germany
[e] Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[f] Institute of Sports and Sports Science, Karlsruhe Institute of Technology, Karlsruhe, Germany
[g] Hector Institute for Artificial Intelligence in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[h] Department of Psychiatry, University of Cambridge, Cambridge, UK
[i] Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

ARTICLE INFO

Keywords:
Alcohol use disorder
Pharmacotherapy
Ecological momentary assessment
Phase-sensitive treatment

ABSTRACT

Alcohol use disorder (AUD) is a prevalent psychiatric disorder that continually causes significant suffering. Although pharmacotherapies are available, they have low efficacy and show little compliance. Thus, new approaches for AUD treatment are still needed. The core symptoms of AUD include drug seeking, consumption, and withdrawal, which occur in distinct shifted time phases. Recent neurobiological research has revealed that these phases have rather unique underlying neurobiological processes and neuropharmacology. We propose a new treatment strategy based on available pharmacotherapies with small effects on individual AUD phases and independent advancements in diagnosis tool technology. The strategy combines a pharmacological toolbox with an ecological momentary assessment (EMA) tool. An artificial intelligence-coupled EMA device is provided to patients and can act as a near real-time diagnostic monitor, a phase-sensitive individualized treatment guide, and a metric for therapeutic success. The EMA tool will allow highly individual AUD phases to be targeted with tailored neuropharmacology in near real time. This approach may revolutionize the pharmacotherapies used for mental disorders.

1. Alcohol use disorder in need for treatment

The consumption of psychoactive drugs such as alcohol and their use for the improvement of everyday tasks and well-being are a worldwide phenomenon in virtually all human cultures (Wadley, 2016; Müller, 2020; Müller et al., 2023). The consumption of alcohol is well controlled by the vast majority of consumers. Thereby, alcohol has effects on physical parameters (Wojtowicz, 2023; Carr et al., 2024, but see also: Zhao et al., 2023), subjective performance perception (Müller and Schumann, 2011; Müller et al., 2021), and other behaviors (Heyman, 1996, 2021) of the individual. Recent meta-analyses and Mendelian randomization studies, however, suggest that there is no safe level of alcohol consumption for overall health (Rehm et al., 2017; Carvalho et al., 2019; GBD 2020 Alcohol Collaborators, 2022; Shield et al., 2020).

A significant risk of such behavior is the development of alcohol use disorder (AUD). The disorder is highly prevalent, and approximately 609 million people suffer from AUD or alcohol dependence (WHO, 2024). Current monitoring is showing a rising trend in many cultures towards an increase in adverse effects and mortality (Tran et al., 2024). Affected individuals lose quality of life, experience severe health impairments, and have shorter lifespans (UNODC, 2024; WHO, 2024). Moreover, it has disastrous effects on the social environment and the general economy (Shield et al., 2020; Manthey et al., 2021). This has sparked a universally accepted drive to diagnostically identify maladaptive drug use, i.e., when negative effects clearly outweigh the positive effects (Müller and Schumann, 2011; Müller et al., 2023), as a mental disorder and to develop a treatment that can reverse the disorder (Koob, 2024).

* Corresponding author. Section of Addiction Medicine, Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University Erlangen-Nürnberg, Schwabachanlage 6, 91054, Erlangen, Germany.
E-mail address: christian.mueller@uk-erlangen.de (C.P. Müller).

https://doi.org/10.1016/j.neuropharm.2025.110745
Received 4 June 2025; Received in revised form 23 October 2025; Accepted 24 October 2025
Available online 26 October 2025

In addition to psychotherapies, pharmacological interventions for AUD have also been developed and are intended to function similarly to treatments that target systemic disorders, i.e., where the disease symptoms are permanently present in more or less the same way, e.g., tissue growth in cancer. The available AUD pharmacotherapies primarily stem from a history of neuropharmacological research (Koob and Mason, 2016). Once the main mechanisms of action of many psychoactive drugs in the brain were identified (McBride et al., 1999; Koob and Volkow, 2016), research endeavored to isolate the effects that contribute to the development of AUD-related behaviors from those that are epiphenomenal (without functional consequences) and those responsible for side effects that are not directly related to addiction. For AUD behaviors, relevant brain areas and neurobiological circuits have been predicted, and neuropharmacological targets for altering drug action have been identified. Moreover, the significant interaction with other organs has begun to be considered (Tyler and Leggio, 2024), and AUD is now viewed as a holistic system disorder (Spanagel, 2009; Carbia et al., 2021).

Preclinical research approaches have yielded a plethora of potentially effective compounds, which have typically shown success in preclinical models of drug use and addiction (Negus and Banks, 2020; Strickland et al., 2022). Most of them were successful in blocking one or more AUD-related behaviors in specific animal models without severe side effects (e.g., Kalinichenko et al., 2021; Müller and Homberg, 2015; König et al., 2020). However, none of these compounds block all AUD behaviors (Walker and Lawrence, 2018; Day and Daly, 2022; Meredith et al., 2023; Punia et al., 2024a; 2024b; Dionisi et al., 2024). To translate these results into clinical applications, a key symptom is typically selected for treatment, although a multitude of secondary and exploratory variables are also frequently tested. Often, the primary outcome is a consummatory behavior during a specific occasion (e.g., consumption over time or during relapse).

Several substances have entered clinical use and are now considered evidence-based interventions for AUD (Fairbanks et al., 2020; Kotake et al., 2024; Witkiewitz et al., 2019; Imperio et al., 2024). However, there is still no widely effective AUD pharmacotherapy (Walker and Lawrence, 2018) that can significantly reduce the high relapse rates and suffering (Durazzo and Meyerhoff, 2017). Although there is still high openness for interventions among patients (Wellensiek et al., 2024), upon critical evaluation, the efficacy of pharmacotherapy in the treatment of AUD has been found to be modest in general (Biso et al., 2024). Thus, there is still a strong need for an effective pharmacotherapy for AUD.

Recent developments in preclinical pharmacology and AUD diagnostics have established a novel convergence between two research lines, which has paved the way for a fresh pharmacotherapeutic strategy that is *technologically augmented and phase-sensitive*. This article discusses concurrent advancements in the implementation of a new generation of diagnostic tools that incorporate the usage of technology and near real-time patient care are discussed. The aim is to delineate the principles of a new innovative pharmacotherapy approach. While some basic pharmacological tools are currently available (Fig. 1), we outline the need for additional research and development for the requisite pharmacological toolkit.

2. Search strategy and selection criteria

We searched PubMed, Google Scholar, PsycINFO, und CINAHL for relevant high-quality studies published in English. These included empirical data reports, epidemiological studies, cohort studies, and population surveys. The focus was on publications from January 1, 1990, to January 1, 2025. The sources also included commonly cited and highly regarded older publications. The search terms used were “drug/alcohol”, “drug/alcohol use”, “drug/alcohol abuse”, “drug/alcohol addiction”, “drug/alcohol dependence”, and “drug/alcohol use disorder”. Furthermore, reference lists from the identified articles were searched and analyzed when relevant.

3. Unique characteristics of substance use disorders

To design a better AUD pharmaco-treatment, we reassessed the characteristics of the disease that have received little consideration during the development of current pharmacotherapies. These insights form the foundation of our new proposal. The diagnosis of an AUD encompasses a wide range of individual symptoms from various classes. While the initial diagnostic criteria were not related to the brain, current neurobiological insights support the notion that different mental functioning capacities are concurrently or sequentially impaired (Schumann et al., 2014). As such, there *is not just one pathological process underlying AUD, but many different ones* affecting both peripheral body functioning and behavior in parallel or sequentially. Notably, the sequential nature of key symptoms has only recently started being addressed with the introduction of just-in-time adaptive interventions (JITAIs) in pharmacotherapy (Wang et al., 2024). The sequential nature can be further complicated by polysubstance use, where different substances are used in different instances and states (Müller and Schumann, 2011; Müller et al., 2023).

A characteristic feature of an AUD is that key symptoms are dynamic and dependent on the environment (Ahmed et al., 2020; Meyer-Lindenberg, 2023). For a phase-sensitive pharmacotherapy of individual symptoms, it may be advantageous when they occur sequentially and not at the same time. For instance, cue exposure, mood change, drug seeking, and drug taking may change within a short timeframe of minutes to few hours (McKay et al., 2006; Treloar et al., 2015). Acute and late withdrawal and subsequent abstinence occur over much longer timescales of days to weeks or beyond (Patrick et al., 2023; Dunn et al., 2020). Changes in these distinct disease phases can be spontaneous when no trigger is recognizable (Hornoiu et al., 2023) or might be related to interoceptive or external events such as stress (Bach et al., 2024) or cues (Sangchooli et al., 2024).

These distinct phases of behavior can easily be recognized. Accumulating research increasingly shows that single-symptom behaviors have distinct neuronal patho-mechanisms and a unique neuropharmacology (Milivojevic and Sinha, 2018; Ersche et al., 2020; Nicolas et al., 2022; Lungwitz et al., 2023; Valentino et al., 2024; Morais-Silva and Lobo, 2024). A potential pharmacotherapy might not only need to rectify one malfunctioning brain circuit but could be aimed at a “moving target” where distinct systems are in action at different time scales.

AUD symptoms exhibit significant interindividual variability (Carbia et al., 2021; Skóra et al., 2020). While core symptoms, such as escalated and difficult-to-control drug use, are similar among patients, there is significant variation in the total number of symptoms, such as the type and extent of mental and physical comorbidities (Sanjuan et al., 2019). Moreover, the expression of individual AUD symptoms in terms of their frequency, sequence, and intensity is not uniform among all patients. This variation also encompasses notable differences related to sex or gender (Lenz et al., 2012; Müller et al., 2021; Hoffmann et al., 2023). Although this idea is increasingly acknowledged in personalized medicine, it must also be incorporated into AUD pharmacotherapies.

AUD is primarily a brain disorder (Lüscher et al., 2020), but its pathogenesis also involves other organs. This disease can negatively impact many if not all organ systems either independently or through close brain–organ interaction, which is often bi-directional (Kalinichenko et al., 2021). The physical aspects of AUD can interact with mental symptoms and potentially exacerbate them (Kalinichenko et al., 2021). This has been extensively detailed in recent years, including research on the gut–brain axis (Shevchouk et al., 2021; Carbia et al., 2021). Current pharmacotherapies largely neglect the significant systemic influences on AUD behaviors.

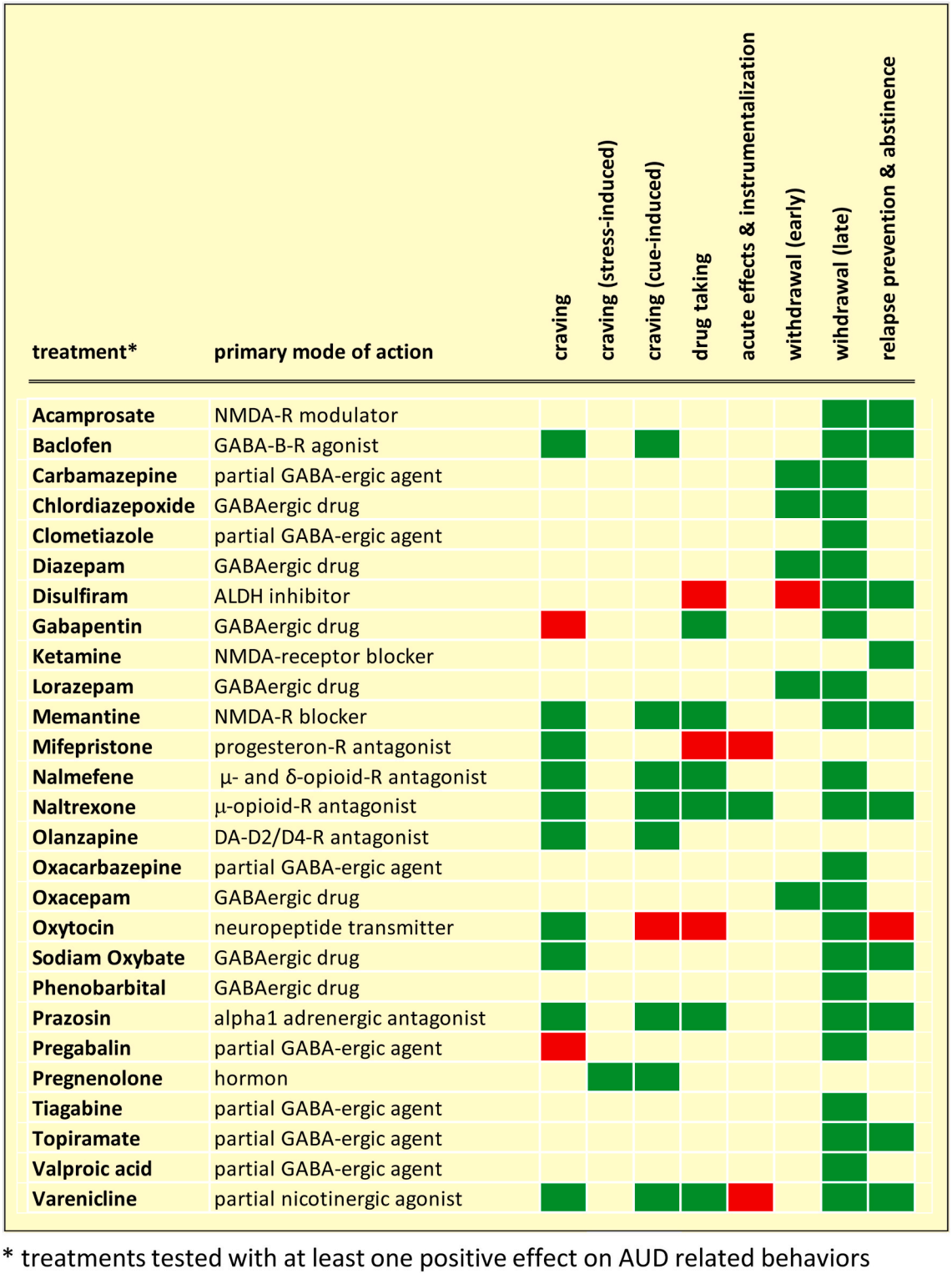


Fig. 1. Pharmacotherapies currently used for the treatment of alcohol use disorder (AUD) show efficacy only for individual or a few AUD-related behaviors with a high interindividual variance. This may suggest treatment combinations with different options to address individual AUD-related behaviors sequentially. The summary is based on metanalyses and reviews of preclinical studies and laboratory trials that confirmed specific drug effects in more than one study (see main text for references). Green – beneficial treatment effect, red – no beneficial treatment effect, empty – effect not tested or insufficiently tested for this behavior; ALDH – aldehyde-dehydrogenase; GABA – γ-amino-butyric acid; NMDA – N-methyl-D-aspartate; R – receptor. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4. New developments in preclinical pharmacology

Many available medications that combat drug cravings do not help in the context of withdrawal and abstinence, and vice versa (Fig. 1). For instance, olanzapine was found to reduce cue-elicited craving (Hutchison et al., 2006), no beneficial effects, or even adverse effects on withdrawal are known (Uzbay, 2012). In turn, drugs such as benzodiazepines effectively diminish acute withdrawal symptoms, but are not effective for prolonged withdrawal (Venniro et al., 2020). Likewise, a drug like mifepristone may be used to attenuate stress-induced craving, but not to reduce actual drinking (Haass-Koffler et al., 2023). This phenomenon can be best explained by the distinct neuronal and molecular substrates that underpin the diverse behavioral symptoms (McBride et al., 1999; Koob and Volkow, 2016; Müller et al., 2017; Fredriksson et al., 2021; Nall et al., 2021; Kalinichenko et al., 2023; Pagano et al., 2023; Wank et al., 2024). Current animal models and translational research strategies make it possible to explore not only the brain circuitry for each AUD's associated behaviors (Skóra et al., 2020; Venniro et al., 2020), but also how these behaviors interact with physical symptoms (Kalinichenko et al., 2022). These functional dissociations in the brain circuits of drug use can be dissected, which has been done for alcohol and AUD (Carvalho et al., 2019; MacKillop et al., 2022):

Craving is the overpowering desire to consume alcohol and is a cardinal symptom of AUD (Skóra et al., 2020; Venniro et al., 2020; MacKillop et al., 2022). It is a subjectively perceived state of mental occupation with the drug involving memories of drug seeking, taking, instrumentalization, and acute positive hedonic drug effects (Müller and Schumann, 2011). It is usually expressed in a drug-free state and can be spontaneous or triggered by environmental stimuli, including the drug itself, but also cues related stress and alcohol (Hoffmann et al., 2023).

Individuals who report greater stress and cue-induced cravings are more likely to have relapses of heavy drinking. Craving is associated with a decline in activity in the prefrontal cortical areas, such as the ventromedial and lateral prefrontal, supplementary motor, and anterior cingulate regions, as well as the bed nucleus of the stria terminalis (Radoman et al., 2024). Stress-induced and alcohol-cue-induced cravings are associated with striatal responses (Skóra et al., 2020; Venniro et al., 2020; MacKillop et al., 2022).

Drug seeking is an approximation behavior that brings an individual to the vicinity of the drug, which can then be consumed (Müller and Homberg, 2015; Skóra et al., 2020; Venniro et al., 2020; MacKillop et al., 2022). It includes not only physical approximation, but also operant behaviors that make the drug available (e.g., working for money to buy alcohol). It is a critical behavior for AUD as it usually precedes a relapse. It may be triggered by the subjective state of craving. Although craving may accompany it, it is not a necessary condition for this behavior. Drug seeking can arise from conditioned drug effects and may also include conditioned place preference (e.g., seeking out one's favorite pub) (Huston et al., 2013; Childs and de Wit, 2016) or operant behavior for conditioned drug cues (Spanagel, 2009). There is strong involvement of the dopamine (DA) and serotonin (5-HT) systems in the ventral tegmental area (VTA), ventral striatum, and prefrontal cortex (PFC), which serve as a functional basis to display such behaviors (Müller and Homberg, 2015; Skóra et al., 2020; Venniro et al., 2020).

Drug taking is a consummatory behavior that is initiated in a sober state and results in the ingestion of the drug. It has been suggested that acute drug-taking behavior involves the hypothalamus and ventral striatum (Müller and Homberg, 2015; Skóra et al., 2020; Venniro et al., 2020; MacKillop et al., 2022). Once the drug has reached the brain, drug-taking behavior may be maintained by immediately rewarding consummatory responses that are controlled by the hypothalamus. Stimulatory effects of alcohol are believed to be mediated by its interaction with glutamate receptors and an indirect stimulation of DA release from VTA neurons (McBride et al., 1999; Koob and Volkow, 2016). In conditions of AUD, this behavior becomes increasingly controlled by the nigrostriatal DA system and the dorsal striatum, along with an influence of the globus pallidus–thalamocortical pathway (Everitt and Robbins, 2005). In particular, the orbitofrontal cortex connection to the dorsal striatum and its control by DA receptors plays an important role in this behavior (Uhl et al., 2019).

Drug-taking behavior may be driven by peripheral organ signals reaching the brain (Kalinichenko et al., 2021; Tyler and Leggio, 2024). For example, it was found that osteocalcin, a hormonal signal released from osteoblasts in the skeletal system, may reduce alcohol-drinking behavior in mice when alcohol is freely available (Kalinichenko et al., 2021, 2022, 2023). Other such signals include leptin, ghrelin (Richardson et al., 2023, 2025), and glucagon-like peptide1 (GLP-1; Farokhnia et al., 2025), which can modulate alcohol seeking and drinking behavior in mice and humans (for a review, see: Koopmann et al., 2018; Bach et al., 2019).

Acute drug effects: The acute effects of alcohol include locomotor and subjective rewarding effects. The locomotor activation is mediated by ascending monoaminergic systems of the brain stem (Müller and Homberg, 2015; Skóra et al., 2020; Venniro et al., 2020; MacKillop et al., 2022). Sedation and attenuation of locomotor activity at higher doses may result from an interaction with $GABA_A$ receptors and a decrease of N-methyl-D-aspartate (NMDA) receptor activity (Koob and Volkow, 2016). Via receptors, the activation of monoaminergic signaling, including DA and 5-HT, drives activity in mesolimbic target areas such as the ventral striatum.

Reward is considered as any event that increases the probability of a distinct behavior with a positive hedonic component. Thus, dopaminergic and serotonergic activation may trigger reward learning and behavioral changes, while DA and D1 receptors together with local endogenous opiates activating μ-opioid receptors drive the subjective perception of hedonic effects. Besides these transmitters, numerous other transmitters and modulators of these pathways are also involved, including glutamate, acetylcholine, and endocannabinoids, which act at the level of either the VTA, the ventral striatum, or its output structures (McBride et al., 1999; Wise, 2002; Berridge and Robinson, 2003).

When a drug is instrumentalized, it may affect a 'challenged' brain, i.e., a nervous system that gives rise to a disease state, such as alcohol used for self-medication of a depressed mood (Müller and Schumann, 2011; Müller et al., 2023; Fairbanks et al., 2020). It has been observed that alcohol may at least partially reverse the patho-mechanisms of an aversive state, such as by rectifying enhanced acid sphingomyelinase and ceramide activity and attenuated DA and 5-HT signaling (Müller et al., 2017; Müller and Kornhuber, 2017). This may also include subcortical circuits for stress reactivity, which encompass the amygdala, hypothalamus, and habenula, as well as circuits for interoception involving the insula and anterior cingulate cortex (Seif et al., 2013; Müller et al., 2017, 2019).

Withdrawal is the state that occurs when the drug effects have subsided. It is usually aversive and accompanied by chronic irritability, malaise, dysphoria, alexithymia, and states of stress. There is a loss of motivation for natural rewards, resulting in a suppression of normal behaviors (Müller and Homberg, 2015; Koob and Volkow, 2016; Skóra et al., 2020; Venniro et al., 2020). During early withdrawal, many processes are active in the brain and counteract the acute drug effects to re-establish homeostatic function. However, this may involve other receptors in the affected transmitters systems. Increased activity of corticotropin releasing factor (CRF), enhanced receptor activation, and enhanced noradrenergic activity are characteristic mechanisms (Zorrilla et al., 2014; Varodayan et al., 2025).

There appears to be a strong involvement of other neuropeptide transmitters in the withdrawal from alcohol, such as dynorphin, neuropeptide Y, oxytocin, and neurotensin (Koob and Volkow, 2016; Uhl et al., 2019). The amygdala, lateral habenula, and ventral striatum are important areas of the brain associated with aversive states. During such states, an individual is in particular danger of relapse as a new drug-taking episode would usually end the aversive symptoms. Once acute withdrawal symptoms have subsided, a period of late withdrawal

begins while abstinence is maintained. In non-addicted individuals, this may result in normal life activities. In AUD, no drug taking behavior is shown, but phases of craving and (unsuccessful) drug seeking may emerge.

Thus, a highly extinction-resistant drug memory is frequently activated, and information about the drug is retrieved (Robbins et al., 2008; Müller and Schumann, 2011). This involves brain structures of normal non-drug-related memories and key transmitter systems such as the glutamatergic, GABAergic, serotonergic, and dopaminergic systems. During this phase, memories established during previous episodes of acute drug effects consolidate and shape the drug memories (Müller, 2013). Reduced hippocampal neurogenesis may account for the depression-like state in this phase and the reduced capability of extinguishing the drug memory (Stevenson et al., 2009; Le Maitre et al., 2018). Withdrawal from alcohol in particular involves synaptic changes and NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in glutamatergic projections from the PFC, hippocampus, and amygdala to the VTA and nucleus accumbens (Müller and Homberg, 2015; Skóra et al., 2020; Venniro et al., 2020).

Relapse of alcohol consumption describes the resumption of consumption after one or usually many periods of abstinence. Naturally, it follows "successful" drug-seeking behavior that has made the drug available for an individual (Müller and Homberg, 2015; Skóra et al., 2020; Venniro et al., 2020). Relapse behavior can also be either spontaneous or triggered by internal or external cues (Hoffmann et al., 2023). The latter may involve drug-associated cues (Pagano et al., 2023), stress, or a small amount of the drug (König et al., 2020). In humans and animals, it is often expressed as a period of overshooting consumption (Spanagel and Hölter, 2000; Froehlich et al., 2015). As such, relapse is initiated in a drug-free state but results in a temporally restricted episode of escalating drug intake (Müller and Homberg, 2015; Skóra et al., 2020; Venniro et al., 2020).

One mechanism of relapse involves FK506-binding protein 51 (FKBP51), which is a negative regulator of the glucocorticoid receptor signaling pathway that modulates the stress-induced glucocorticoid feedback circuit. In a preclinical study, the FKBP51 inhibitor SAFit2 was able to reduce alcohol consumption when given during a period of abstinence immediately before relapse. However, this pathway is not involved in the maintenance of alcohol consumption during the relapse phase (König et al., 2020).

It should be mentioned that while there are unique neuroanatomical and neuropharmacological features underlying each of the AUD associated phases, there is also some overlap among them. In previous pharmaco-treatment strategies, overlapping mechanisms have often been targeted with the idea of addressing as many symptoms as possible. In the approach suggested here, however, the focus is on the non-overlapping mechanisms for phase-sensitive targeting. Nevertheless, if a certain neuropharmacological mechanism works best for more than one phase, a consideration as a treatment target for more than one phase should not be ruled out.

These real-life phases are part of the use disorder for virtually all addictive drugs, but their details significantly depend on the individual drug that is consumed, such as opiates (Srivastava et al., 2020), psychostimulants (Yates, 2024; Mancusi et al., 2024), cannabis (Connor et al., 2021; Le Foll et al., 2024), and others (Groff et al., 2022). Even within classes of drugs, differences may emerge (Ozburn et al., 2015; Ashok et al., 2017), which may further require individually tailored pharmacotherapy. These findings may suggest that while they partially overlap, the neuronal circuits for each substance-use disorder behavior are largely separate and have unique neuropharmacological profiles with distinct underlying molecular processes (Koob and Volkow, 2016; Nall et al., 2021; Jones et al., 2024). This may support the idea of having a pharmacotherapy that combines the efficacy of different approaches through an explicit sequential and *phase-sensitive* application of several different pharmaco-treatments (Imperio et al., 2024). However, implementing such an approach would require a new level of dynamic and personalized decision making and application for treatment.

5. New developments in AUD diagnostics

The current AUD diagnosis is primarily based on single or a few question-based patient encounters and a checklist based on the established diagnostic manuals ICD-10 or DSM-5. These measures currently suffice for AUD diagnosis and initiation of therapy, including pharmacotherapy. Nevertheless, more comprehensive methods are now available and provide a detailed and highly individualized picture of the expression and severity of AUD symptoms beyond the standard assessment.

Ecological Momentary Assessment (EMA) employs an electronic tool that can capture dynamic context-dependent AUD-related behaviors (Stone and Shiffman, 1994; Shiffman, 2009; Trull and Ebner-Priemer, 2013; Deeken et al., 2022), as well as mental and physical parameters and drug-use side effects in daily life (Hoffmann et al., 2023). This tool can be used with a smartphone so that it is constantly with the patient. It periodically asks about AUD-related activities while continuously using audio recordings to monitor for relevant environmental factors, such as nearby bars (Gustafson et al., 2014) or social contexts (Wadle and Ebner-Priemer, 2023). After transferring the data to a central server, automated real-time analysis may reveal individual phases of AUD behaviors and mental states of the patient in a real-world context (Ebner-Priemer and Santangelo, 2023). This can be achieved with high time resolution and quantification in contexts such as the acute drinking phase (Atkinson et al., 2025).

EMA assessment of cognitive impairments has been successfully implemented using smartphone-based behavioral tasks with an entertaining theme (Zech et al., 2022). The feasibility of EMA and its acceptance by drug users show promise (Bos et al., 2015; Mackesy-Amiti and Boodram, 2018). The inherent temporal resolution (Poulton et al., 2018) reveals dynamic symptom patterns that provide an individualized guide for therapeutic interventions. By evaluating this real-time patient-oriented data, interventions can now be applied in a *phase-sensitive* and *symptom-specific* approach (Fig. 2). Here, a "phase" refers to the time when a key AUD symptom, such as craving, drug seeking, or a consumption episode, dominates ongoing behavior or mental activity.

With the remote tool connection to the patient and its implementation for a spontaneous lifestyle (e.g., smartphone use with apps), EMA can be easily applied by substance users (Piasecki, 2019). A large-scale prospective digital phenotyping trial was performed over one year with nearly 800 individuals with AUD and over 200 control subjects. The trial demonstrated that the application of EMA is feasible for individualized high-resolution diagnostic assessment (Zech et al., 2023; Spanagel et al., 2024), which is a prerequisite for any EMA-based pharmacotherapy. However, information is still needed in regard to how long and to what extent patients are willing to use EMA without experiencing burden or fatigue (Spanagel et al., 2024). Although such investigations are usually not published, they generate individual EMA-based time records of information such as AUD-related behaviors, which can be used for relapse prediction and planning future therapy (Hoffmann et al., 2023). With the introduction of more selective pharmacological interventions, it is suggested that EMA could also be used as a guide for *phase-sensitive* treatment.

6. Real-time predictive systems to augment pharmacotherapy

We propose an implementation of augmentation devices to guide selective and highly individualized pharmacotherapy. Examples of successful diagnostic applications can already be found in the German ReCoDe project (Heinz et al., 2020; Zech et al., 2023). However, the development of a generally augmented pharmacotherapy for mental disorders may only be successful when pharmacology and real-life augmentation tools are developed in close interaction. This will encompass enhanced data processing for individual patients for

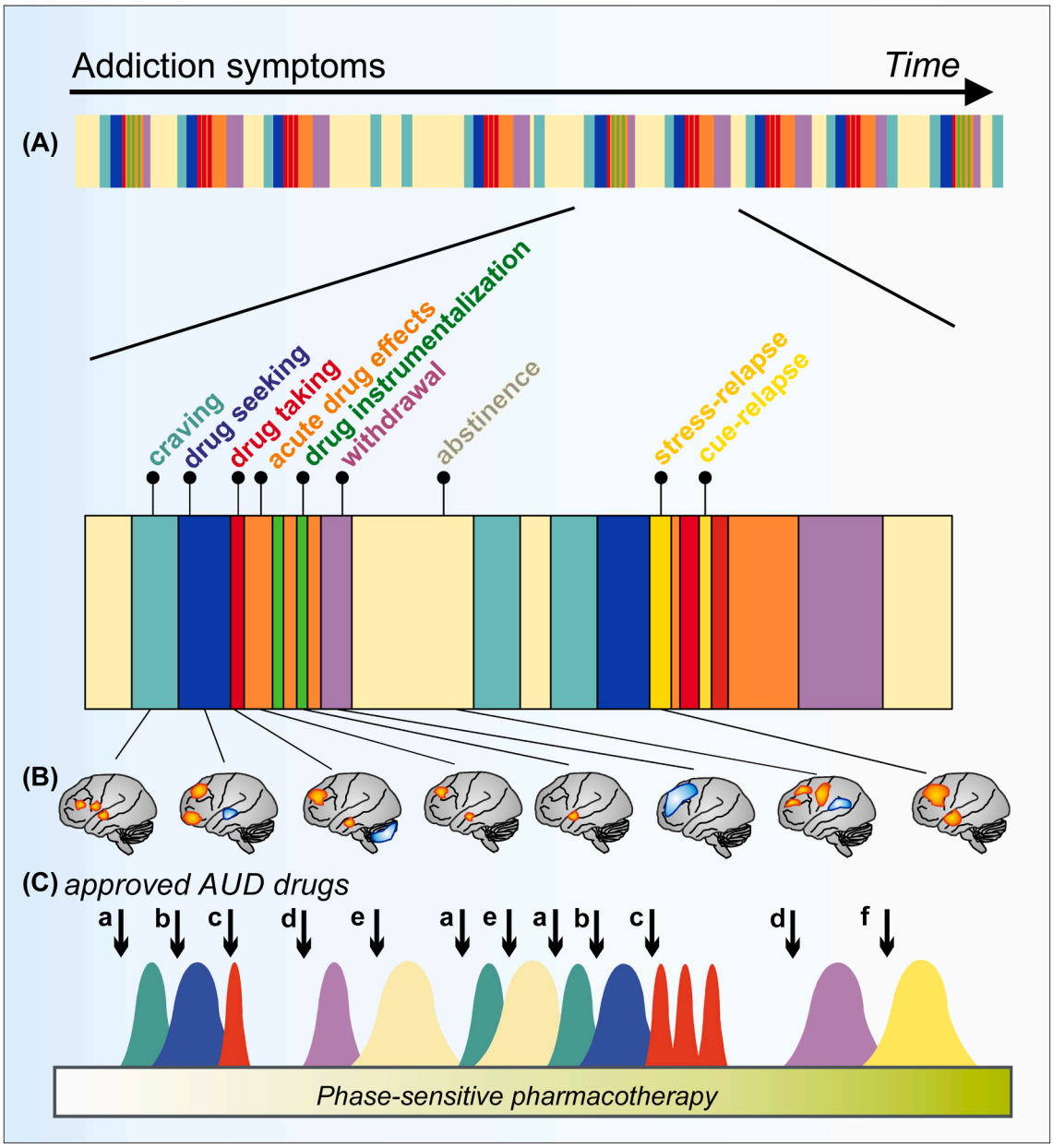


Fig. 2. Conceptual representation of that Specific treatment needs for alcohol use disorder (AUD). (A) In contrast to many somatic disorders, AUD does not appear as constant symptoms but as a loosely repeating sequence of pathological behaviors and mental states, which is illustrated here as a color-coded bar sequence for AUD. Individual color bars represent distinct behaviors or mental states that occur repeatedly but with variable sequence. (B) Individual behaviors and mental states related to AUD show distinct and dissociating neuronal and neurobiological mechanisms. The figures show typical cortical activation patterns determined by positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) in AUD patients or heavy drinkers to illustrate the unique nature of the brain processes (yellow-red – activation; blue-white – inhibition of cortical activity). Besides its general vasodilatory effects in the brain (Newlin et al., 1982), *acute alcohol* particularly increased cerebral blood flow in the temporal and prefrontal cortex but reduces it in the cerebellum (Volkow et al., 1988; Tiihonen et al., 1994; Tolentino et al., 2011). During *withdrawal,* greater severity is associated with greater disruption of medial prefrontal/striatal functioning (Sinha et al., 2022). During *abstinence*, cortical network activity is changed in the default mode, executive control, attention, salience, somatosensory, and reward networks (Müller-Oehring et al., 2015). An *alcohol-cue*-induced activation in the anterior cingulate cortex and dorsolateral prefrontal cortex correlates with craving for alcohol (Bach et al., 2015). *Stress* elicits higher alcohol-cue-induced activation in the left anterior insula (Bach et al., 2024). Please note that these findings are not always homogenous throughout all studies and that the different phases are characterized by many more distinct functional circuits in subcortical brain areas. For detailed references, please see main text. Other phases show symbolic cortical activation. (C) Current pharmacotherapies of AUD target only one mechanism (or very few). For improved treatment outcomes, it is suggested to target specific AUD behaviors/mental states selectively and use their unique identified brain mechanisms for neuropharmacological mechanism selection that results in pharmacological (or behavioral) just-in-time interventions with selective phase-sensitive treatment duration. A plethora of preclinical studies have identified pharmacological interventions that effectively block individual AUD-related behaviors, but not all of them as a whole. On the pharmacological side, the toolbox needs to be revisited and sorted. There are already compounds available for treatment that can be used for a single-phase approach. Many more have emerged in the pipeline of preclinical research but were abandoned for further development as they do not cure all/key AUD symptoms. These may be reconsidered not as a sole pharmacotherapy but as part of the *phase-sensitive* toolbox. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

phase-sensitive diagnostics, as well as for treatment selection and success monitoring. Similar to how psychological interventions can be provided in real time in the form of "ecological momentary interventions" (EMIs) (Heron and Smyth, 2010), real-time algorithms may be helpful for personalized pharmacological recommendations. Randomized controlled trials have already tested personalized and adaptive alarm systems to help treating psychiatrists guide pharmacotherapy (Mühlbauer et al., 2018). But now, the most promising are statistical process-control methods (Helmich et al., 2024; Ludwig et al., 2025), which continuously match exponentially weighted moving averages to baseline characteristics.

Machine learning tools are also at the forefront, which includes recurrent neural networks that can capture time-series data acquired from EMA devices and construct models to forecast individual-level trajectories (Koppe et al., 2019). Furthermore, deep learning models integrate various measures acquired by mobile devices, such as sleep quality, motor movements, and typing dynamics (Durstewitz et al., 2019). However, before utilizing artificial intelligence (AI) in broader settings, certain problems must be solved (Torous and Blease, 2024), including data privacy and security (Duffourc and Gerke, 2024), algorithm bias and interpretability (Kraus et al., 2024), ethical implications (Putica et al., 2025), and regulatory challenges (Kahane et al., 2025; Warraich et al., 2025). The potential benefits of AI in mental health care are widespread and include the leveraging of real-world studies, multimodal predictors identification, and adverse event monitoring (Hartnagel et al., 2024; Torous and Blease, 2024; Upadhyay et al., 2024).

7. Technologically augmented pharmacotherapy

When a disorder manifests as a relatively permanent dysfunction of an organ system, as in hypertension, pharmacotherapy is typically adjusted to maintain constant drug levels while taking into account the pharmacokinetic properties of the treatment (Spanagel et al., 2024). However, when the symptoms of a disorder present in a time-shifted manner, like a fluctuating sequence of symptoms (disease phases), we propose that the pharmacotherapy should be applied dynamically rather than consistently, which might otherwise exacerbate some AUD symptoms (König et al., 2020). The treatment might necessitate a highly individualized real-time approach to pharmacotherapy that exceeds the capabilities of a physician or pharmacist, who only sees the patient at certain times and prescribes relatively static medication patterns.

To achieve this, we suggest the introduction of a *technological augmentation* to ensure (near) real-time diagnostic assessments (Smith et al., 2024) and pharmacotherapeutic decisions. As both steps cannot be separated in our opinion, we propose the implementation of a *phase-sensitive* augmented pharmacotherapy specifically intended for AUD. The distinctive features of this new therapeutic approach include phase-sensitive diagnosis of individual AUD symptoms, treatment allocation for individual symptoms, EMA augmentation of self-administered treatment, and EMA monitoring of phase-specific treatment success.

7.1. Phase-sensitive diagnosis of individual AUD symptoms with EMA

Following an initial AUD diagnosis, an EMA tool is implemented for high-resolution *phase-sensitive* detection of individual AUD symptoms and their progression over time. EMA data are collected remotely, processed, and stored by the caregiver (Serre et al., 2024). The caregiver must confirm the general diagnosis and expand upon it with insights into individual phases, drug-instrumentalization periods, and personal suffering from AUD symptoms. Any concurrent mental deficits in dimensions unrelated to the primary disease should be diagnosed, with attention given to their timelines. This could include cognitive impairments and emotional disorders (Serre et al., 2024).

These impairments may not always be persistent or apparent and may only manifest when a specific mental capacity is in demand (for example, solving an abstract problem). Consequently, these issues can express themselves individually and potentially lead to personal suffering. Additionally, accompanying physical symptoms will be recognized and measured, and their potential progressions over time need to be tracked (Fig. 3).

7.2. Phase-sensitive treatment allocation of individual symptoms with EMA

EMA-enhanced diagnosis is followed by a series of JITAIs that have been suggested as EMIs (Bayrakdarian et al., 2024; Blevins et al., 2021). These may encompass behavioral interventions and pharmacotherapies, in addition to other intervention strategies such as increased physical activity or involvement in various aspects of social life (Wang et al., 2024; Perski et al., 2024; Coughlin et al., 2024). Importantly, all of these JITAIs must be individualized and applied in a *phase-sensitive* manner to address a specific AUD behavior within a time-limited scale. During each personalized treatment allocation, phases that lead to the greatest suffering and inflict the most harm are identified. It is important to pinpoint phases where patients would be tempted to self-medicate.

In addition to these phase-sensitive approaches, it is also important to independently target relevant comorbidities that frequently appear among patients with AUD (Kalinichenko et al., 2021; de Jonge et al., 2024). For instance, a patient with AUD who also suffers from major depression may require supplementary treatment with an antidepressant drug (Schuckit et al., 1997). A specific pharmacological intervention or an equivalent JITAI is chosen for each *of these* discrete phase-sensitive symptoms (Wang et al., 2024) (Fig. 3). Unsupported drug interactions may result from phase-sensitive treatments involving various pharmacological compounds. Therefore, their appropriateness and safety must be evaluated, potentially through an online AI safety tool (Coughlin et al., 2024), which may also incorporate individual diagnostic information into personalized phase-sensitive treatment recommendations (Shane and Denomme, 2021).

7.3. EMA augmentation of self-administered treatment

After an initial diagnostic period, the patient is provided with a pharmacological toolbox for self-treatment. This toolbox may initially contain a range of potential treatment substances, which are adjusted based on EMA feedback at the point of refill (Rimpler et al., 2024). It may be a device designed to dispense EMA-guided pharmaco-treatments at designated phases for self-medication. The subsequent individual compound prescription is dynamic and entirely dependent on EMA. In this way, EMA continues but is now linked to *phase-sensitive* JITAI recommendations.

EMA identifies previously developed critical phases, selects a predetermined treatment that is valid only for that phase, and oversees adherence to these recommendations (Fig. 3). The aim of each subtreatment is to interfere with one specific AUD-related behavior or aversive subjective state at a time, but not all that occur over lengthy periods. This treatment strategy may have a potential advantage over current treatment methods in that even if one treatment objective fails, there may still be numerous others that can be met, thereby potentially improving the general treatment trajectory. Given the individual nature of the planned treatment, we do not propose a new individual substance for treatment, but rather suggest a new treatment-design principle. This could first be applied to select and combine available drugs that have proven efficacy for at least one of the AUD-related behaviors detailed in Fig. 1. For an AUD, this might entail dynamic combinations of baclofen, pregnenolone, naltrexone, prazosin, lorazepam, acamprosate, and varenicline for spontaneous craving, cue/stress-induced craving, alcohol drinking, early withdrawal, late withdrawal, and relapse prevention, respectively (Fairbanks et al., 2020; McPheeters et al., 2023).

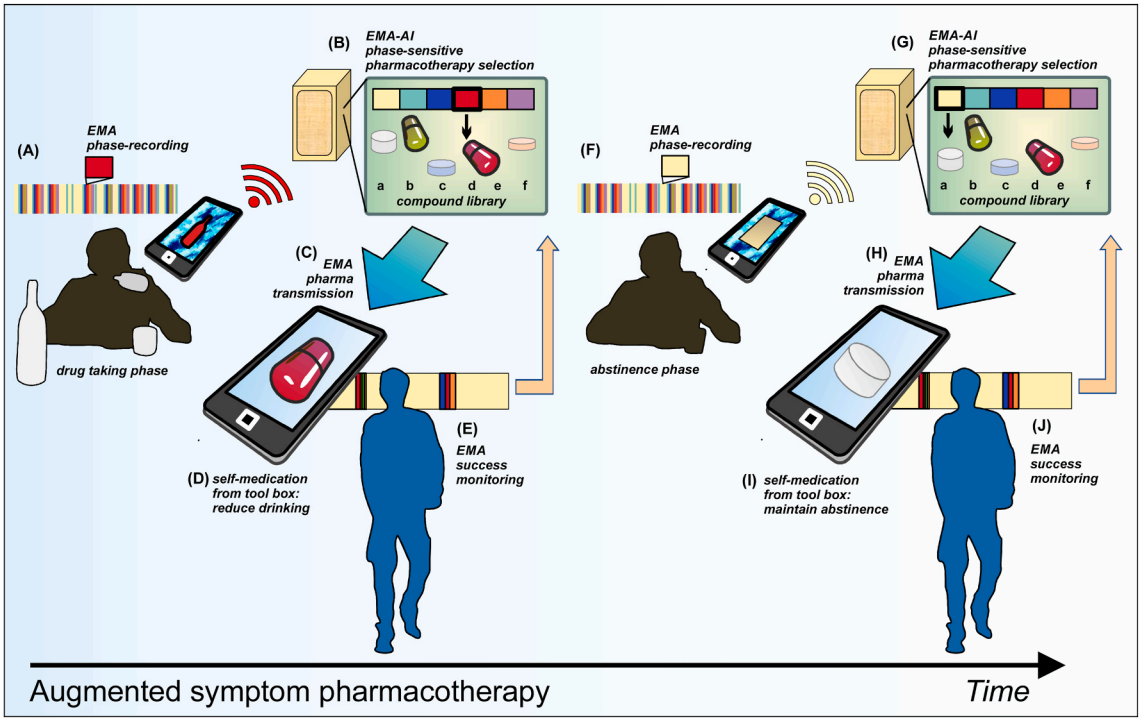


Fig. 3. Ecological momentary assessment (EMA)-augmented pharmacotherapy of alcohol use disorder (AUD) provides enhanced diagnostics and phase-sensitive just-in-time drug (or behavioral) intervention. (A) EMA augments high-resolution temporal diagnostics for AUD behaviors and mental states, identifies AUD phases in near real time, and transmits the information to a central server. (B) An artificial intelligence (AI)-based EMA library identifies a phase-selective pharmaco-therapy to address one specific AUD behavior or mental state for a limited time. (C) The treatment choice is transmitted to the patient, who has a repository of distinct pharmacotherapies for self-medication. (D) The suggested pharmacotherapy is self-administered. (E) The EMA tool records compliance and efficacy of the selective treatment. These parameters are fed back to the server, where an AI can optimize the next treatment recommendations (e.g., drug, dose, timing, and frequency). (F) In the sequence of AUD behaviors, other phases (behaviors and mental states) emerge over time. (G–J) Phases are recorded in near real time by the EMA device and set off a new treatment sequence with a different pharmacotherapy. The diagnosis and treatment sequence repeats until a defined success is recorded (i.e., AUD behaviors decline in frequency or intensity).

7.4. EMA monitoring of selective treatment success

Each treatment phase is monitored by EMA. Compliance is recorded, and the patient assesses the subjective treatment effect (Bos et al., 2015). The success of the JITAI is mainly evaluated through a comparison of database information with symptom timelines and subjective ratings from untreated periods. Based on this comparison, the intervention may be adjusted. For instance, in the case of drug treatment, the AI may adjust the dose and administration time or even substitute it with another drug. The monitoring should also track the success of treating comorbidities. Here, EMA can at least determine when such monitoring is required (Fig. 3).

Numerous studies have demonstrated that patients are willing and compliant in using EMA for diagnostics (Bos et al., 2015; Zech et al., 2022) and for monitoring therapeutic success (Serre et al., 2024; Bayrakdarian et al., 2024). This suggests that the proposed phase-sensitive augmented therapy could be established as a routine. This approach would provide detailed insights into the individual course of the disease, including core and side symptoms, as well as reveal individual phase characteristics, potential shifts, and dynamic adaptations.

8. Phase-sensitive individualized pharmacotherapy as an advanced polypharmacy JITAI

JITAI interventions have been suggested for the reduction of alcohol drinking and AUD treatment. Initial test trials were performed, but there has been mixed success (Gustafson et al., 2014; Witkiewitz et al., 2014; Wright et al., 2018; Perski et al., 2022). The present strategy can be seen as an attempt of further developing the JITAI concept. New and different aspects can be pointed out according to the criteria defined that have been accepted in previous concept papers, studies, and first reviews (Nahum-Shani et al., 2018; Hardeman et al., 2019; Perski et al., 2024). The present approach is a *neuropsychopharmacology theory-based polypharmacy and polytreatment* approach. The underlying theory is the neuropharmacology of individual AUD symptoms, which suggests that there is distinct pharmacology for individual symptoms with respect to interindividual differences at the brain level of causality.

Nahum-Shani et al. (2018) have described different JITAI components. *Decision points* are the times when intervention decisions are made. In this model, they involve the detection of individual symptoms such as cravings or withdrawal (Figs. 2 and 3). As outlined above, the intervention options are a broad range of polypharmaceutical substances (Fig. 1), in addition to behavioral interventions and classical counseling options as they are already implemented. These interventions are phase-sensitive for individual symptoms and are individualized as they underlie adjustment based on EMA feedback about efficacy.

Tailoring variables are information that is used to decide upon the time of an intervention. In this model, the process always involves two steps that shape *decision rules*. In the first step, the EMA status information is used to determine the AUD phase that a person is in, e.g., current alcohol drinking. In the second step, the expression and severity of that stage is determined, e.g., the number of drinks consumed so far in this phase. An intervention decision is formed according to a phase-sensitive threshold, which still has to be agreed upon. This may result in recommendation and release of a pharmacological intervention at an additional determined dose level or behavioral and counseling interventions.

As treatment allocation will be both individualized and highly dynamic, AI feedback-based decision making may optimize each

individual treatment decision in a phase-sensitive way. Thus, adaptations occur separately for each phase and involve changing pharmaco-treatment doses and whole compounds, as well as replacing them with behavioral interventions or counseling. Accordingly, a short-term outcome of this intervention will be the reduction of the frequency and severity of only a single symptom. The long-term outcome, however, concerns the sum of all symptoms that form the AUD diagnosis, ideally to such an extent that no criteria for AUD are met or that general suffering is markedly reduced.

9. Challenges and limitations for the augmented phase-sensitive treatment

The new treatment management still has some important issues to resolve (Rimpler et al., 2024; Wenzel et al., 2024). Of foremost importance is the creation of an individualized pharmacological toolbox that can eventually be used without direct supervision by a human clinician. Such a toolbox may be initially equipped with a number of available treatments for each known AUD phase. A clinician has to provide the first choices, and then software would check the limitations of the possible combinations and always include them in recommendations.

To avoid errors in pharmaco-treatment, it may be recommended to couple the toolbox with the EMA device so that it releases only approved treatments at designated times. This would require an additional repository that can be electronically coupled to the EMA tool, which would be straightforward to implement. This type of pharmacological toolbox may provide feedback about the proper release of respective treatments to the patient. Actual pharmaco-treatment compliance, however, will remain difficult to properly control.

The EMA feedback after successful pharmaco-treatment will be collected automatically and can be used by the software to increase or decrease the likelihood of future recommendations. If no success is detected by the EMA feedback, e.g., no reduction in drinking amount in one episode has occurred, the likelihood of a treatment choice will be decreased, or an alternative pre-loaded pharmaco-treatment will be recommended and dispensed. The same procedure may apply for unwanted side effects.

After collecting this information, the EMA software may automatically apply it. For example, it could reduce the dose of the treatment or change it completely. However, it is still recommended that regular supervision sessions with clinicians be integrated to evaluate the practicality and success of the whole procedure. As with any technical device, the EMA and augmented toolbox will need to be regularly maintained under supervision, and the mechanics and electronics will need to be checked for function and replaced when necessary.

A related problem is the time scale for these check-ups of the therapy and the devices. Real-life experiences with a remote pharmaco-treatment allocation and a treatment dispenser are not yet available, and the first test trials have yet to be performed. The treatment dispenser could be a remote-controlled box that is prefilled with different compounds. It should be connected to the EMA and have a screen for immediate user interaction. Drug delivery may then only take place when there is a remote EMA signal that determines the type and dose of the pharmacotreatment, as well as immediate confirmation by the user.

Initially, regular supervision every week may be reasonable. As the EMA is also a feedback tool for the feasibility and efficacy of the treatment, the EMA software may be programmed to identify attention-requiring states early, when direct contact is pivotal. When no such emergencies occur, time intervals may be extended until shortly before the pharmaco-toolbox runs out of treatment.

A challenge for the treatment allocation system may be that when targeting individual symptoms, the frequency of the pharmaco-treatment may become rather high. In fact, in AUD, phases like abstinence, craving, and relapse may change so fast that selective targeting of underlying neuropharmacology may become critical. The latency of the main effect of one treatment may overlap with that of another phase treatment. A general solution for this may be that all phases of the AUD should not always be targeted by the EMA with a pharmaco-treatment. Instead, only every second or third instance could be treated to prevent temporal overlap of the treatment effects.

In the process of EMA-guided phase-sensitive treatments, the EMA feedback may be used to determine the most effective intervention among all those possible for a particular phase. Accordingly, a temporary omission of pharmaco-treatments that are less effective for a specific phase may be an appropriate initial strategy, as well as a permanent option for adjustment. These omissions may alternatively be replaced by non-pharmacological but phase-sensitive treatment options, such as internet-based cognitive behavioral interventions (Gushken et al., 2025).

Regarding drug safety, current pharmacotherapies rely on the personal feedback from the patient to the caregiver. This is usually based on personal contact. Such feedback can be realized by the EMA in the proposed approach, which acquires information about phase-specific treatment success and can ask the patient about any unwanted side effects. The decision making would then be similar to that of a real physician in that treatment success would be balanced against all adverse effects.

The results may then be a change in the dose of the pharmaco-treatment, the treatment compound, or the treatment type for this phase, e.g., switching to a non-pharmacological recommendation. For safety reasons, the EMA will also require an emergency mode, which can be initiated by the patient when unexpected severe side effects occur. This would then result in timely personal contact with the caregiver.

Another caveat for this approach and other pharmacotherapies for AUD may lie in the general treatment idea. As an AUD usually develops over long periods of high alcohol consumption, it coincides with multiple and long-lasting changes in brain structure and function (Spanagel, 2009). Many of these changes are ultimately considered to be the cause of the persistence and extinction resistance of AUD-related behaviors and mental states. Therefore, the idea of a causal therapy is not only to alleviate AUD behaviors and mental states, but also to do so by reverting changes in permanent brain function. One may readily assume that this does not occur after a single exposure to a treatment drug but may require multiple and often long-term drug treatments. Thus, the EMA adjustment will need to take this into account when evaluating patient feedback and potential phase-sensitive adjustment of treatment drugs by allowing for a specific drug to be recommended for some time before a change is considered.

While there is now an emerging understanding of how long-term alcohol consumption, that led to an AUD, changes brain structure and function at molecular, synaptic, circuit and gross morphological level (Spanagel, 2009; Koob, 2024). Even changes in peripheral organ function are increasingly considered. There is still no convincing biomarker, i.e. a physiological measure that can be obtained easily and repeatedly by a non-invasive procedure, for AUD in humans. However, to finally confirm therapeutic success it would be desirable to validate also at a biological level that disease related biological dysfunctions have normalized after this particular treatment scheme.

Another concern is the potential issues that may arise during clinical trials and in clinical practice when patients initiate and taper multiple medications under chiefly automated guidance and monitoring. As the augmented pharmacotherapy for AUD also incorporates non-pharmacological interventions (as recommendations) and the treatment of co-occurring disorders, other pharmaco-treatments may be included in the pharmacological toolbox and in the EMA-supervised treatment on an individual basis. Again, the EMA software will be programmed to avoid recommending and dispensing dangerous combinations. Monitoring for success, however, may be expanded in the EMA tool by asking about symptoms not related to AUD. For this very likely condition, close supervision with a clinician should be required initially. This supervision may later be deferred to automatized treatment management. Furthermore, security and alarm modes need to be

implemented to assure proper treatment of the individual pattern of diseases.

10. Initial clinical trials

Pharmacological tools and EMA devices have improved to a level where a new direction of development may be identified, and developers may be directed towards further needs. This will bring research to a stage where the new type of therapy has to be tested in clinical trials. This may best be done in AUD inpatient trials after detoxification. Patients could be trained to use an EMA device and a pharmacological toolbox that is still under development. The software receiving EMA information can be closely supervised for proper analysis of patient status and therapy effects and compared with a parallel real-life diagnosis. This would allow for the software to be adjusted and for treatment recommendations to be made, and patient feedback about the feasibility of the EMA measurements could also be collected.

The initial options for phase-sensitive treatment will need to be chosen. A physician will choose among available drugs for each phase separately. The criteria for this choice may include patient acceptance in a preliminary individual phase-selective test. Once it works for a patient in an inpatient setting with close supervision, the patient may be released with the EMA and toolbox for remote treatment with only intermittent clinical supervision. Finally, a patient would be completely released to outpatient remote treatment with only intermittent in-house checks and toolbox refills (perhaps monthly).

One issue is the question of how would clinical trials ensure adequate statistical power given the sporadic nature of the outcome events, such as lapses among individuals striving for abstinence or instances of problematic use among those with controlled-use goals. As this is a completely new type of treatment, novel evaluations are needed. Given the highly individual nature of diagnosis and treatment allocation, classical study design and treatment groups are no longer possible. Every person receives different treatment.

These challenges could be addressed by creating a new EMA-based dynamic addiction index (DAIX), which could incorporate the real length and duration of suffering from individual AUD phases. Although previous attempts at an addiction score have not been widely used in the past, the high resolution and dynamically updated EMA diagnostics (Deeken et al., 2022) may now offer a new chance for reconceptualization. This diagnostic may be supported by regular clinician assessments of the overall health status during scheduled visits. A primary outcome measure of a randomized controlled trial could then be the overall improvement of the DAIX over a defined time. Secondary outcome measures may still comprise classical AUD measures related to single phases in frequency and amplitude, such as the amount of alcohol consumed per time unit.

11. Conclusions

Classical pharmacotherapy for AUD is insufficient for patients. A reanalysis of this inadequacy identifies AUD as a mental disorder with distinct phases, individual symptom composition, and variable time courses. These core symptoms arise from distinct underlying neurobiological disease processes, and single-target pharmacotherapy cannot sufficiently treat such a multidimensional disorder. Accumulated preclinical and clinical psychopharmacology research demonstrates that while many available pharmacotherapies can address individual symptoms, they seldom address them all.

We have proposed an entirely new approach to pharmacotherapy. We recommend using different drugs to address the sequentially emerging symptoms. Given that the sequence and intensity of individual symptoms vary widely among patients, we also suggest combining this pharmacological toolbox with an EMA tool. An AI-assisted EMA device that all patients would receive will serve as a diagnostic aid, a *phase-sensitive* individualized treatment guide, and a therapeutic success monitor.

We hope that this new concept of technology-boosted pharmacotherapy will provide a fresh perspective for therapy developers and ultimately lead to significant advancement in AUD therapy. However, future research will determine how effective single treatment combinations can address symptoms in sequence and how the overall therapy will look. Moreover, for this evaluation, an EMA extension will be the best emerging tool available.

In this novel perspective on enhanced pharmacotherapy, drug development focuses on treating specific symptoms and emphasizes the use of augmentation devices that offer better resolution for diagnostics and treatment allocation. Recent developments in preclinical research have shaped our understanding of AUD as a major mental disorder. However, several core properties are common to mental disorders that do not manifest in the same way in somatic diseases. These properties include a dimensional symptom structure that is influenced by various factors, including multiple brain circuits and organ involvement, spontaneous fluctuation, and high individual variance (Schumann et al., 2014). The proposed EMA-augmented *phase-sensitive* pharmacotherapy may also serve as a pharmacotherapy template for psychiatric disorders like depression, anxiety (Bos et al., 2015; Reichert et al., 2021), or schizophrenia (Ben-Zeev et al., 2014; Amato et al., 2020).

CRediT authorship contribution statement

Christian P. Müller: Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Bernd Lenz:** Writing – review & editing, Formal analysis, Conceptualization. **Johannes Kornhuber:** Writing – review & editing, Formal analysis, Conceptualization. **Ulrich W. Ebner-Priemer:** Writing – review & editing, Formal analysis, Conceptualization. **Emanuel Schwarz:** Writing – review & editing, Formal analysis. **Karen D. Ersche:** Writing – review & editing, Formal analysis. **Falk Kiefer:** Writing – review & editing, Formal analysis. **Rainer Spanagel:** Writing – original draft, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no competing financial interests.

Acknowledgements

The research of the authors was funded by the Deutsche Forschungsgemeinschaft (DFG) grants, MU 2789/7-2, MU 2789/18-1, KO 947/20-1, KO 947/17-2, KO 947/13-3, the TRR265, and by funding from the Federal Ministry of Education and Research (BMBF) e:Med Program Target-OXY (031L0190B). The funding sources had no role in the design, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

References

Ahmed, S., Badiani, A., Miczek, K.A., Müller, C.P., 2020. Non-pharmacological factors that determine drug use and addiction. Neurosci. Biobehav. Rev. 110, 3–27.

Amato, D., Canneva, F., Cumming, P., Maschauer, S., Groos, D., Dahlmanns, J.K., Grömer, T.W., Chiofalo, L., Dahlmanns, M., Zheng, F., Kornhuber, J., Prante, O., Alzheimer, C., von Hörsten, S., Müller, C.P., 2020. A dopaminergic mechanism of antipsychotic drug efficacy, failure, and failure reversal: the role of the dopamine transporter. Mol. Psychiatr. 25, 2101-2018.

Ashok, A.H., Mizuno, Y., Volkow, N.D., Howes, O.D., 2017. Association of stimulant use with dopaminergic alterations in users of cocaine, amphetamine, or methamphetamine: a systematic review and meta-analysis. JAMA Psychiatry 74 (5), 511–519.

Atkinson, E.A., Fischer, A.M., Cursio, J.F., King, A.C., Fridberg, D.J., 2025. Pace of alcohol drinking during in natural-environment drinking is associated with heightened alcohol-related reward and negative consequences in risky drinkers. Psychopharmacology (Berl) 242 (8), 1769–1781.

Bach, P., Kirsch, M., Hoffmann, S., Jorde, A., Mann, K., Frank, J., Charlet, K., Beck, A., Heinz, A., Walter, H., Rietschel, M., Kiefer, F., Vollstädt-Klein, S., 2015. The effects

of single nucleotide polymorphisms in glutamatergic neurotransmission genes on neural response to alcohol cues and craving. Addict. Biol. 20 (6), 1022–1032.
Bach, P., Bumb, J.M., Schuster, R., Vollstädt-Klein, S., Reinhard, I., Rietschel, M., Witt, S. H., Wiedemann, K., Kiefer, F., Koopmann, A., 2019. Effects of leptin and ghrelin on neural cue-reactivity in alcohol addiction: two streams merge to one river? Psychoneuroendocrinology 100, 1–9.
Bach, P., Zaiser, J., Zimmermann, S., Gessner, T., Hoffmann, S., Gerhardt, S., Berhe, O., Bekier, N.K., Abel, M., Radler, P., Langejürgen, J., Tost, H., Lenz, B., Vollstädt-Klein, S., Stallkamp, J., Kirschbaum, C., Kiefer, F., 2024. Stress-induced sensitization of insula activation predicts alcohol craving and alcohol use in alcohol use disorder. Biol. Psychiatry 95 (3), 245–255.
Bayrakdarian, N.D., Bonar, E.E., Duguid, I., Hellman, L., Salino, S., Wilkins, C., Jannausch, M., McKay, J.R., Staton, M., Dollard, K., Nahum-Shani, I., Walton, M.A., Blow, F.C., Coughlin, L.N., 2024. Acceptability and feasibility of a mobile behavioral economic health intervention to reduce alcohol use in adults in rural areas. Drug Alcohol Depend. Rep 11, 100225.
Ben-Zeev, D., Brenner, C.J., Begale, M., Duffecy, J., Mohr, D.C., Mueser, K.T., 2014. Feasibility, acceptability, and preliminary efficacy of a smartphone intervention for schizophrenia. Schizophr. Bull. 40, 1244–1253.
Berridge, K.C., Robinson, T.E., 2003. Parsing reward. Trends Neurosci. 26, 507–513.
Biso, L., Spini, A., Petragnano, F., Maggio, R., Scarselli, M., Carli, M., 2024. Long-term efficacy and safety of sodium oxybate in treating alcohol use disorder: a systematic review and meta-analysis. Curr. Neuropharmacol. 23 (5), 579–593.
Blevins, C.E., Marsh, E.L., Stein, M.D., Schatten, H.T., Abrantes, A.M., 2021. Project CHOICE: choosing healthy options in coping with emotions, an EMA/EMI plus in-person intervention for alcohol use. Subst. Abuse 42 (4), 569–576.
Bos, F.M., Schoevers, R.A., aan het Rot, M., 2015. Experience sampling and ecological momentary assessment studies in psychopharmacology: a systematic review. Eur. Neuropsychopharmacol. 25, 1853–1864.
Carbia, C., Lannoy, S., Maurage, P., López-Caneda, E., O'Riordan, K.J., Dinan, T.G., Cryan, J.F., 2021. A biological framework for emotional dysregulation in alcohol misuse: from gut to brain. Mol. Psychiatr. 26 (4), 1098–1118.
Carr, S., Bryazka, D., McLaughlin, S.A., Zheng, P., Bahadursingh, S., Aravkin, A.Y., Hay, S.I., Lawlor, H.R., Mullany, E.C., Murray, C.J.L., Nicholson, S.I., Rehm, J., Roth, G.A., Sorensen, R.J.D., Lewington, S., Gakidou, E., 2024. A burden of proof study on alcohol consumption and ischemic heart disease. Nat. Commun. 15 (1), 4082.
Carvalho, A.F., Heilig, M., Perez, A., Probst, C., Rehm, J., 2019. Alcohol use disorders. Lancet 394, 781–792.
Childs, E., de Wit, H., 2016. Alcohol-induced place conditioning in moderate social drinkers. Addiction 111 (12), 2157–2165.
Connor, J.P., Stjepanović, D., Le Foll, B., Hoch, E., Budney, A.J., Hall, W.D., 2021. Cannabis use and cannabis use disorder. Nat. Rev. Dis. Primers 7 (1), 16.
Coughlin, L.N., Campbell, M., Wheeler, T., Rodriguez, C., Florimbio, A.R., Ghosh, S., Guo, Y., Hung, P.Y., Newman, M.W., Pan, H., Zhang, K.W., Zimmermann, L., Bonar, E.E., Walton, M., Murphy, S., Nahum-Shani, I., 2024. A mobile health intervention for emerging adults with regular cannabis use: a micro-randomized pilot trial design protocol. Contemp. Clin. Trials 145, 107667.
Day, E., Daly, C., 2022. Clinical management of the alcohol withdrawal syndrome. Addiction 117, 804–814.
Deeken, F., Reichert, M., Zech, H., Wenzel, J., Wedemeyer, F., Aguilera, A., Aslan, A., Bach, P., Bahr, N.S., Ebrahimi, C., Fischbach, P.C., Ganz, M., Garbusow, M., Großkopf, C.M., Heigert, M., Hentschel, A., Karl, D., Pelz, P., Pinger, M., Riemerschmid, C., Rosenthal, A., Steffen, J., Strehle, J., Weiss, F., Wieder, G., Wieland, A., Zaiser, J., Zimmermann, S., Walter, H., Lenz, B., Deserno, L., Smolka, M. N., Liu, S., Ebner-Priemer, U.W., Heinz, A., Rapp, M.A., ReCoDe Consortium, 2022. Patterns of alcohol consumption among individuals with alcohol use disorder during the COVID-19 pandemic and lockdowns in Germany. JAMA Netw. Open 5, e2224641.
de Jonge, D., van der Meer, P.B., Kramers, C., Schellekens, A., 2024. Psychedelic research for alcohol use disorder with comorbid major depressive disorder: an unmet need. Curr. Psychiatry Rep. 26 (12), 832–842.
Dionisi, T., Di Sario, G., De Mori, L., Spagnolo, G., Antonelli, M., Tarli, C., Sestito, L., Mancarella, F.A., Ferrarese, D., Mirijello, A., Vassallo, G.A., Gasbarrini, A., Addolorato, G., 2024. Current treatments of alcohol use disorder. Int. Rev. Neurobiol. 175, 127–152.
Duffourc, M.N., Gerke, S., 2024. Health care AI and patient privacy — dinerstein v google. JAMA 331 (11), 909–910.
Dunn, K., Bergeria, C., Huhn, A.S., Strain, E.C., 2020. Differences in patient-reported and observer-rated opioid withdrawal symptom etiology, time course, and relationship to clinical outcome. Drug Alcohol Depend. 215, 108212.
Durazzo, T.C., Meyerhoff, D.J., 2017. Psychiatric, demographic, and brain morphological predictors of relapse after treatment for an alcohol use disorder. Alcohol Clin. Exp. Res. 41 (1), 107–116.
Durstewitz, D., Koppe, G., Meyer-Lindenberg, A., 2019. Deep neural networks in psychiatry. Mol. Psychiatr. 24, 1583–1598.
Ebner-Priemer, U.W., Santangelo, P., 2023. Viva experience sampling: combining passive Mobile sensing with active momentary assessments. In: Mehl, M.R., Eid, M., Wrzus, C., Harari, G.M., Ebner-Priemer, U.W. (Eds.), Mobile Sensing in Psychology: Methods and Applications. The Guilford Press, pp. 311–328.
Ersche, K.D., Meng, C., Ziauddeen, H., Stochl, J., Williams, G.B., Bullmore, E.T., Robbins, T.W., 2020. Brain networks underlying vulnerability and resilience to drug addiction. Proc. Nat. Acad. Sci. USA 17 (26), 15253–15261.
Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat. Neurosci. 8 (11), 1481–1489.
Fairbanks, J., Umbreit, A., Kolla, B.P., Karpyak, V.M., Schneekloth, T.D., Loukianova, L. L., Sinha, S., 2020. Evidence-based pharmacotherapies for alcohol use disorder. Mayo Clin. Proc. 95 (9), 1964–1977.
Farokhnia, M., Tazare, J., Pince, C.L., Bruns, N., Gray, J.C., Lo Re 3rd, V., Fiellin, D.A., Kranzler, H.R., Koob, G.F., Justice, A.C., Vendruscolo, L.F., Rentsch, C.T., Leggio, L., 2025. Glucagon-like peptide-1 receptor agonists, but not dipeptidyl peptidase-4 inhibitors, reduce alcohol intake. J. Clin. Investig. 135 (9), e188314.
Fredriksson, I., Venniro, M., Reiner, D.J., Chow, J.J., Bossert, J.M., Shaham, Y., 2021. Animal models of drug relapse and craving after voluntary abstinence: a review. Pharmacol. Rev. 73 (3), 1050–1083.
Froehlich, J.C., Hausauer, B., Fischer, S., Wise, B., Rasmussen, D.D., 2015. Prazosin reduces alcohol intake in an animal model of alcohol relapse. Alcohol Clin. Exp. Res. 39, 1538–1546.
GBD 2020 Alcohol Collaborators, 2022. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the global burden of disease study 2020. Lancet 400 (10347), 185–235.
Groff, D., Stuckey, H., Philpott, C., Van Dyke, E., Silvis, M., Leong, S.L., Bone, C., 2022. Kratom use disorder: a primer for primary care physicians. J. Addict. Dis. 40 (1), 131–141.
Gushken, F., Costa, G.P.A., de Paula, S.A., Heringer, D., Anand, A., 2025. Internet-based cognitive behavioral therapy for alcohol use disorder: a systematic review of evidence and future potential. J. Subst. Use Addict. Treat. 171, 209627.
Gustafson, D.H., McTavish, F.M., Chih, M.Y., Atwood, A.K., Johnson, R.A., Boyle, M.G., Levy, M.S., Driscoll, H., Chisholm, S.M., Dillenburg, L., Isham, A., Shah, D., 2014. A smartphone application to support recovery from alcoholism: a randomized clinical trial. JAMA Psychiatry 71, 566–572.
Haass-Koffler, C.L., Magill, M., Cannella, N., Brown, J.C., Aoun, E.G., Cioe, P.A., Sinha, R., Swift, R.M., Ciccocioppo, R., Leggio, L., 2023. Mifepristone as a pharmacological intervention for stress-induced alcohol craving: a human laboratory study. Addict. Biol. 28 (7), e13288.
Hardeman, W., Houghton, J., Lane, K., Jones, A., Naughton, F., 2019. A systematic review of just-in-time adaptive interventions (JITAIs) to promote physical activity. Int. J. Behav. Nutr. Phys. Activ. 16, 31.
Hartnagel, L.M., Emden, D., Foo, J.C., Streit, F., Witt, S.H., Frank, J., Limberger, M.F., Schmitz, S., Gilles, M., Rietschel, M., Hahn, T., Ebner-Priemer, U.W., Sirignano, L., 2024. Momentary depression severity prediction in patients with acute depression who undergo sleep deprivation therapy: speech-based machine learning approach. JMIR Ment. Health 11, e64578.
Heinz, A., Kiefer, F., Smolka, M.N., Endrass, T., Beste, C., Beck, A., Liu, S., Genauck, A., Romund, L., Banaschewski, T., Bermpohl, F., Deserno, L., Dolan, R.J., Durstewitz, D., Ebner-Priemer, U., Flor, H., Hansson, A.C., Heim, C., Hermann, D., Kiebel, S., Kirsch, P., Kirschbaum, C., Koppe, G., Marxen, M., Meyer-Lindenberg, A., Nagel, W. E., Noori, H.R., Pilhatsch, M., Priller, J., Rietschel, M., Romanczuk-Seiferth, N., Schlagenhauf, F., Sommer, W.H., Stallkamp, J., Ströhle, A., Stock, A.K., Winterer, G., Winter, C., Walter, H., Witt, S., Vollstädt-Klein, S., Rapp, M.A., Tost, H., Spanagel, R., 2020. Addiction research consortium: losing and regaining control over drug intake (ReCoDe)-From trajectories to mechanisms and interventions. Addict. Biol. 25 (2), e12866.
Helmich, M.A., Schreuder, M.J., Bringmann, L.F., Riese, H., Snippe, E., Smit, A.C., 2024. Slow down and be critical before using early warning signals in psychopathology. Nature Rev. Psychol. 3 (11), 767–780.
Heron, K.E., Smyth, J.M., 2010. Ecological momentary interventions: incorporating mobile technology into psychosocial and health behaviour treatments. Br. J. Health Psychol. 15 (1), 1–39.
Heyman, G.M., 1996. Resolving the contradictions of addiction. Behav. Brain Sci. 19 (4), 561–610.
Heyman, G.M., 2021. How individuals make choices explains addiction's distinctive, non-eliminable features. Behav. Brain Res. 397, 112899.
Hoffmann, S., Gerhardt, S., Mühle, C., Reinhardt, I., Reichert, D., Bach, P., Jazi, R.B., Kühner, C., Aguilera, A., Aslan, A., Bahr, N.S., Deeken, R.F., Ebrahimi, C., Fischbach, P., Ganz, M., Garbusow, M., Großkopf, C.M., Heigert, M., Hentschel, A., Belanger, M., Karl, D., Pelz, P., Pinger, M., Riemerschmid, C., Rosenthal, A., Steffen, J., Strehle, J., Wedemeyer, F., Weiss, F., Wenzel, J., Wieder, G., Wieland, A., Zaiser, J., Zech, H., Zimmermann, S., Kornhuber, J., Müller, C.P., Deserno, L., Ebner-Priemer, U., Flor, H., Kirsch, P., Liu, S., Rietschel, M., Vollstädt-Klein, S., Walter, H., Rapp, M., Witt, S., Smolka, M.N., Heinz, A., Tost, H., Kiefer, F., Reichert, M., Lenz, B., ReCoDe-Consortium, 2023. Associations of menstrual cycle and Progesterone/estradiol ratio with real-life alcohol consumption in alcohol use disorder: a sex-separated multicenter intensive longitudinal study. Am. J. Psychiatr. 181 (5), 445–456.
Hornoiu, I.L., Lee, A.M., Tan, H., Nakovics, H., Bach, P., Mann, K., Kiefer, F., Sommer, W. H., Vollstädt-Klein, S., 2023. The role of unawareness, volition, and neural hyperconnectivity in alcohol use disorder: a functional magnetic resonance imaging study. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 8 (6), 660–671.
Huston, J.P., de Souza Silva, M.A., Topic, B., Müller, C.P., 2013. What's conditioned in conditioned place preference? Trends Pharmacol. Sci. 34 (3), 162–166.
Hutchison, K.E., Ray, L., Sandman, E., Rutter, M.C., Peters, A., Davidson, D., Swift, R., 2006. The effect of olanzapine on craving and alcohol consumption. Neuropsychopharmacology 31 (6), 1310–1317.
Imperio, C.G., Levin, F.R., Martinez, D., 2024. The neurocircuitry of substance use disorder, treatment, and change: a resource for clinical psychiatrists. Am. J. Psychiatr. 181 (11), 958–972.
Jones, J.D., Arout, C.A., Luba, R., Murugesan, D., Madera, G., Gorsuch, L., Schusterman, R., Martinez, S., 2024. The influence of drug class on reward in substance use disorders. Pharmacol. Biochem. Behav. 240, 173771.

Kahane, K., Shumate, J.N., Torous, J., 2025. Policy in flux: addressing the regulatory challenges of AI integration in US mental health services. Curr. Treat. Opt. Psychiatry 12 (1), 24.
Kalinichenko, L.S., Mühle, C., Jia, T., Anderheiden, F., Datz, M., Eberle, A.L., Eulenburg, V., Granzow, J., Hofer, M., Hohenschild, J., Huber, S.E., Kämpf, S., Kogias, G., Lacatusu, L., Lugmair, C., Mbu Taku, S., Meixner, D., Sembritzki, N.K., Praetner, M., Rhein, C., Sauer, C., Scholz, J., Ulrich, F., Valenta, F., Weigand, E., Werner, M., Tay, N., Mc Veigh, C.J., Haase, J., Wang, A.L., Abdel-Hafiz, L., Huston, J.P., Smaga, I., Frankowska, M., Filip, M., Lourdusamy, A., Kirchner, P., Ekici, A.B., Marx, L.M., Suresh, N.P., Frischknecht, R., Fejtova, A., Saied, E.M., Arenz, C., Bozec, A., Wank, I., Kreitz, S., Hess, A., Bäuerle, T., Ledesma, M.D., Mitroi, D.N., Miranda, A.M., Oliveira, T.G., Lenz, B., Schumann, G., Kornhuber, K., Müller, C.P., 2021. Neutral sphingomyelinase mediates the comorbidity trias of alcohol abuse, major depression and bone defects. Mol. Psychiatr. 26 (12), 7403–7416.
Kalinichenko, L.S., Kornhuber, J., Müller, C.P., 2022. The system's genetics of depression and its somatic and mental comorbidities. Transl. Neurosci. 13 (1), 198–200.
Kalinichenko, L.S., Mühle, C., Jia, T., Anderheiden, F., Datz, M., Eberle, A.L., Eulenburg, V., Granzow, J., Hofer, M., Hohenschild, J., Huber, S.E., Kämpf, S., Kogias, G., Lacatusu, L., Lugmair, C., Mbu Taku, S., Meixner, D., Sembritzki, N.K., Praetner, M., Rhein, C., Sauer, C., Scholz, J., Ulrich, F., Valenta, F., Weigand, E., Werner, M., Tay, N., Mc Veigh, C.J., Haase, J., Wang, A.L., Abdel-Hafiz, L., Huston, J.P., Smaga, I., Frankowska, M., Filip, M., Lourdusamy, A., Kirchner, P., Ekici, A.B., Marx, L.M., Suresh, N.P., Frischknecht, R., Fejtova, A., Saied, E.M., Arenz, C., Bozec, A., Wank, I., Kreitz, S., Hess, A., Bäuerle, T., Ledesma, M.D., Mitroi, D.N., Miranda, A.M., Oliveira, T.G., Lenz, B., Schumann, G., Kornhuber, K., Müller, C.P., 2023. Adult alcohol drinking and emotional tone are mediated by neutral sphingomyelinase during development in males. Cerebr. Cortex 33, 844–864.
König, L., Kalinichenko, L.S., Huber, S.E., Voll, A.M., Bauder, M., Kornhuber, J., Hausch, F., Müller, C.P., 2020. The selective FKBP51 inhibitor SAFit2 reduces alcohol consumption and reinstatement of conditioned alcohol effects in mice. Addict. Biol. 25, e12758.
Koob, G.F., Mason, B.J., 2016. Existing and future drugs for the treatment of the dark side of addiction. Annu. Rev. Pharmacol. Toxicol. 56, 299–322.
Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 3, 760–773.
Koob, G.F., 2024. Alcohol use disorder treatment: problems and solutions. Annu. Rev. Pharmacol. Toxicol. 64, 255–275.
Koopmann, A., Schuster, R., Kiefer, F., 2018. The impact of the appetite-regulating, orexigenic peptide ghrelin on alcohol use disorders: a systematic review of preclinical and clinical data. Biol. Psychol. 131, 14–30.
Koppe, G., Guloksuz, S., Reininghaus, U., Durstewitz, D., 2019. Recurrent neural networks in Mobile sampling and intervention. Schizophr. Bull. 45, 272–276.
Kotake, K., Hosokawa, T., Tanaka, M., So, R., Banno, M., Kataoka, Y., Shiroshita, A., Hashimoto, Y., 2024. Efficacy and safety of alcohol reduction pharmacotherapy according to treatment duration in patients with alcohol dependence or alcohol use disorder: a systematic review and network meta-analysis. Addiction 119 (5), 815–832.
Kraus, B., Sampathgiri, K., Mittal, V.A., 2024. Accurate machine learning prediction in psychiatry needs the right kind of information. JAMA Psychiatry 81 (1), 11–12.
Le Foll, B., Tang, V.M., Rueda, S., Trick, L.V., Boileau, I., 2024. Cannabis use disorder: from neurobiology to treatment. J. Clin. Investig. 134 (20), e172887.
Le Maitre, T.W., Dhanabalan, G., Bogdanovic, N., Alkass, K., Druid, H., 2018. Effects of alcohol abuse on proliferating cells, stem/progenitor cells, and immature neurons in the adult human hippocampus. Neuropsychopharmacology 43, 690–699.
Lenz, B., Müller, C.P., Stoessel, C., Sperling, W., Biermann, T., Hillemacher, T., Bleich, S., Kornhuber, J., 2012. Sex hormone activity in alcohol addiction: integrating organizational and activational effects. Prog. Neurobiol. 96 (1), 136–163.
Ludwig, V.M., Bittendorf, C.A., Reinhard, I., Guth, M., Mühlbauer, E., Hartnagel, L.M., Severus, W.E., Bauer, M., Ritter, P., Ebner-Priemer, U.W., 2025. Predicting depressive and manic episodes in patients with bipolar disorder using statistical process control methods on passive sensing data. J. Psychopathol. Clin. Sci. 134 (8), 971–981.
Lungwitz, E.A., Dzemidzic, M., Shen, Y.I., Plawecki, M.H., Oberlin, B.G., 2023. Brain response in heavy drinkers during cross-commodity alcohol and money discounting with potentially real rewards: a preliminary study. Drug Alcohol Depend. Rep. 8, 100175.
Lüscher, C., Robbins, T.W., Everitt, B.J., 2020. The transition to compulsion in addiction. Nat. Rev. Neurosci. 21 (5), 247–263.
Mackesy-Amiti, M.E., Boodram, B., 2018. Feasibility of ecological momentary assessment to study mood and risk behavior among young people who inject drugs. Drug Alcohol Depend. 187, 227–235.
MacKillop, J., Agabio, R., Feldstein, E.S., Heilig, M., Kelly, J.F., Leggio, L., Lingford-Hughes, A., Palmer, A.A., Parry, C.D., Ray, L., Rehm, J., 2022. Hazardous drinking and alcohol use disorders. Nat. Rev. Dis. Primers 8 (1), 80.
Mancusi, G., Miuli, A., Santorelli, M., Cavallotto, C., Susini, O., Pernaci, G., Výborová, E., Rosa, I., d'Onofrio, A.M., Camardese, G., Pettorruso, M., Sensi, S.L., Martinotti, G., 2024. Exploring peripheral biomarkers in psychostimulant use: a systematic review on neurotrophins, stress-related hormones, oxidative stress molecules and genetic factors. Behav. Brain Res. 469, 115046.
Manthey, J., Hassan, S.A., Carr, S., Kilian, C., Kuitunen-Paul, S., Rehm, J., 2021. What are the economic costs to society attributable to alcohol use? A systematic review and modelling study. Pharmacoeconomics 39 (7), 809–822.
McBride, W.J., Murphy, J.M., Ikemoto, S., 1999. Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. Behav. Brain Res. 101, 129–152.
McKay, J.R., Franklin, T.R., Patapis, N., Lynch, K.G., 2006. Conceptual, methodological, and analytical issues in the study of relapse. Clin. Psychol. Rev. 26 (2), 109–127.
McPheeters, M., O'Connor, E.A., Riley, S., Kennedy, S.M., Voisin, C., Kuznacic, K., Coffey, C.P., Edlund, M., Bobashev, G., Jonas, D.E., 2023. Pharmacotherapy for alcohol use disorder: a systematic review and meta-analysis. JAMA 330 (17), 1653–1665.
Meredith, L.R., Burnette, E.M., Nieto, S.J., Du, H., Donato, S., Grodin, E.N., Green, R., Magill, M., Baskerville, W.A., Ray, L.A., 2023. Testing pharmacotherapies for alcohol use disorder with cue exposure paradigms: a systematic review and quantitative synthesis of human laboratory trial methodology. Alcohol Clin. Exp. Res. 47, 1629–1645.
Meyer-Lindenberg, A., 2023. The non-ergodic nature of mental health and psychiatric disorders: implications for biomarker and diagnostic research. World Psychiatry 22 (2), 272–274.
Milivojevic, V., Sinha, R., 2018. Central and peripheral biomarkers of stress response for addiction risk and relapse vulnerability. Trends Mol. Med. 24 (2), 173–186.
Morais-Silva, G., Lobo, M.K., 2024. Refining the circuits of drug addiction: the ventral pallidum. Curr. Opin. Neurobiol. 86, 102883.
Mühlbauer, E., Bauer, M., Ebner-Priemer, U.W., Ritter, P., Hill, H., Beier, F., Kleindienst, N., Severus, E., 2018. Effectiveness of smartphone-based ambulatory assessment (SBAA-BD) including a predicting system for upcoming episodes in the long-term treatment of patients with bipolar disorders: study protocol for a randomized controlled single-blind trial. BMC Psychiatry 18, 349.
Müller, C.P., Schumann, G., 2011. Drugs as instruments: a new framework for non-addictive psychoactive drug use. Behav. Brain Sci. 34 (6), 293–347.
Müller, C.P., 2013. Episodic memories and their relevance for psychoactive drug use and addiction. Front. Behav. Neurosci. 7, 34.
Müller, C.P., Homberg, J., 2015. The role of serotonin in drug use and addiction. Behav. Brain Res. 277C, 146–192.
Müller, C.P., Kornhuber, J., 2017. Biological evidence for paradoxical improvement of psychiatric disorder symptoms by addictive drugs. Trends Pharmacol. Sci. 38 (6), 501–502.
Müller, C.P., Kalinichenko, L.S., Tiesel, J., Witt, M., Stöckl, T., Sprenger, E., Fuchser, J., Beckmann, J., Praetner, M., Huber, S.E., Amato, D., Mühle, C., Büttner, C., Ekici, A. B., Smaga, I., Pomierny-Chamiolo, L., Pomierny, B., Filip, M., Eulenburg, V., Gulbins, E., Lourdusamy, A., Reichel, M., Kornhuber, J., 2017. Paradoxical antidepressant effects of alcohol are related to acid sphingomyelinase and its control of sphingolipid homeostasis. Acta Neuropathol. 133 (3), 463–483.
Müller, C.P., Chung, C., Qin, L., Liu, C., Xu, B., Gao, H., Ruggeri, B., Hieber, S., Schneider, J., Jia, T., Tay, N., Akira, S., Satoh, T., Banaschewski, T., Bokde, A.L.W., Bromberg, U., Büchel, C., Quinlan, E.B., Fllor, H., Frouin, V., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Martinot, J.L., Paillère Martinot, M.L., Artiges, E., Lemaitre, H., Nees, F., Orfanos, D.P., Paus, T., Poustka, L., Millenet, S., Fröhner, J.H., Smolka, M.N., Walter, H., Whelan, R., Bakalkin, G., Liu, Y., Desrivières, S., Elliott, P., Eulenburg, V., Levy, D., Crews, F., Schumann, G., 2019. The cortical neuroimmune regulator TANK affects emotional processing and enhances alcohol drinking: a translational study. Cerebr. Cortex 29, 1736–1751.
Müller, C.P., 2020. Drug instrumentalization. Behav. Brain Res. 390, 112672.
Müller, C.P., Mühle, C., Kornhuber, J., Lenz, B., 2021. Sex-dependent alcohol instrumentalization goals in non-addicted alcohol consumers versus patients with alcohol use disorder: longitudinal change and outcome prediction. Alcohol Clin. Exp. Res. 45 (3), 577–586.
Müller, C.P., Schumann, G., Rehm, J., Kornhuber, J., Lenz, B., 2023. Self-management with alcohol over lifespan: psychological mechanisms, neurobiological underpinnings, and risk assessment. Mol. Psychiatr. 28, 2683–2696.
Müller-Oehring, E.M., Jung, Y.C., Pfefferbaum, A., Sullivan, E.V., Schulte, T., 2015. The resting brain of alcoholics. Cerebr. Cortex 25 (11), 4155–4568.
Nahum-Shani, I., Smith, S.N., Spring, B.J., Collins, L.M., Witkiewitz, K., Tewari, A., Murphy, S.A., 2018. Just-in-Time adaptive interventions (JITAIs) in Mobile health: key components and design principles for ongoing health behavior support. Ann. Behav. Med. 52, 446–462.
Nall, R.W., Heinsbroek, J.A., Nentwig, T.B., Kalivas, P.W., Bobadilla, A.C., 2021. Circuit selectivity in drug versus natural reward seeking behaviors. J. Neurochem. 157 (5), 1450–1472.
Negus, S.S., Banks, M.L., 2020. Learning from lorcaserin: lessons from the negative clinical trial of lorcaserin to treat cocaine use disorder. Neuropsychopharmacology 45 (12), 1967–1973.
Newlin, D.B., Golden, C.J., Quaife, M., Graber, B., 1982. Effect of alcohol ingestion on regional cerebral blood flow. Int. J. Neurosci. 17, 145–150.
Nicolas, C., Zlebnik, N.E., Farokhnia, M., Leggio, L., Ikemoto, S., Shaham, Y., 2022. Sex differences in opioid and psychostimulant craving and relapse: a critical review. Pharmacol. Rev. 74 (1), 119–140.
Ozburn, A.R., Janowsky, A.J., Crabbe, J.C., 2015. Commonalities and distinctions among mechanisms of addiction to alcohol and other drugs. Alcohol Clin. Exp. Res. 39 (10), 1863–1877.
Pagano, R., Salamian, A., Zielinski, J., Beroun, A., Nalberczak-Skóra, M., Skonieczna, E., Cały, A., Tay, N., Banaschewski, T., Desrivières, S., Grigis, A., Garavan, H., Heinz, A., Brühl, R., Martinot, J.L., Paillère Martinot, M.L., Artiges, E., Nees, F., Orfanos, D.P., Poustka, L., Hohmann, S., Fröhner, J.H., Smolka, M.N., Vaidya, N., Walter, H., Whelan, R., Imagen, consortium, Kalita, K., Bito, H., Müller, C.P., Schumann, G., Okuno, H., Radwanska, K., 2023. Arc controls alcohol cue relapse by a central amygdala mechanism. Mol. Psychiatr. 28 (2), 733–745.

Patrick, M.E., Parks, M.J., Peterson, S.J., 2023. High-intensity drinking and hours spent drinking. Alcohol Clin. Exp. Res. 47 (11), 2081–2089.
Perski, O., Hebert, E.T., Naughton, F., Hekler, E.B., Brown, J., Businelle, M.S., 2022. Technology-mediated just-in-time adaptive interventions (JITAIs) to reduce harmful substance use: a systematic review. Addiction 117, 1220–1241.
Perski, O., Kale, D., Leppin, C., Okpako, T., Simons, D., Goldstein, S.P., Hekler, E., Brown, J., 2024. Supervised machine learning to predict smoking lapses from ecological momentary assessments and sensor data: implications for just-in-time adaptive intervention development. PLOS Digit. Health 3 (8), e0000594.
Piasecki, T.M., 2019. Assessment of alcohol use in the natural environment. Alcohol Clin. Exp. Res. 43 (4), 564–577.
Poulton, A., Pan, J., Bruns Jr., L.Richard, Sinnott, R.O., Hester, R., 2018. Assessment of alcohol intake: retrospective measures versus a smartphone application. Addict. Behav. 83, 35–41.
Punia, K., Scott, W., Manuja, K., Sabbineni, M., Campbell, K., Balodis, I.M., MacKillop, J., 2024a. Saem grace: anti-craving medications for alcohol use disorder treatment in the emergency department: a systematic review of direct evidence. Acad. Emerg. Med. 31, 504–514.
Punia, K., Scott, W., Manuja, K., Campbell, K., Balodis, I.M., MacKillop, J., 2024b. Saem grace: phenobarbital for alcohol withdrawal management in the emergency department: a systematic review of direct evidence. Acad. Emerg. Med 31, 481–492.
Putica, A., Khanna, R., Bosl, W., Saraf, S., Edgcomb, J., 2025. Ethical decision-making for AI in mental health: the Integrated ethical Approach for Computational Psychiatry (IEACP) framework. Psychol. Med. 55, e213.
Radoman, M., Fogelman, N., Lacadie, C., Seo, D., Sinha, R., 2024. Neural correlates of stress and alcohol cue-induced alcohol craving and of future heavy drinking: evidence of sex differences. Am. J. Psychiatr. 181 (5), 412–422.
Rehm, J., Gmel, G.E.Sr., Gmel, G., Hasan, O.S.M., Imtiaz, S., Popova, S., Probst, C., Roerecke, M., Room, R., Samokhvalov, A.V., Shield, K.D., Shuper, P.A., 2017. The relationship between different dimensions of alcohol use and the burden of disease-an update. Addiction 112, 968–1001.
Reichert, M., Gan, G., Renz, M., Braun, U., Brüßler, S., Timm, I., Ma, R., Berhe, O., Benedyk, A., Moldavski, A., Schweiger, J.I., Hennig, O., Zidda, F., Heim, C., Banaschewski, T., Tost, H., Ebner-Priemer, U.W., Meyer-Lindenberg, A., 2021. Ambulatory assessment for precision psychiatry: foundations, current developments and future avenues. Exp. Neurol. 345, 113807.
Richardson, R.S., Sulima, A., Rice, K.C., Kucharczk, J.A., Janda, K.D., Nisbett, K.E., Koob, G.F., Vendruscolo, L.F., Leggio, L., 2023. Pharmacological GHSR (ghrelin receptor) blockade reduces alcohol binge-like drinking in male and female mice. Neuropharmacology 238, 109643.
Richardson, R.S., Kryszak, L.A., Vendruscolo, J.C.M., Koob, G.F., Vendruscolo, L.F., Leggio, L., 2025. GHSR blockade, but not reduction of peripherally circulating ghrelin via beta(1)-adrenergic receptor antagonism, decreases binge-like alcohol drinking in mice. Mol. Psychiatr. 30, 1047–1056.
Rimpler, A., Siepe, B.S., Rieble, C.L., Proppert, E.R.K.K., Fried, E.I., 2024. Introducing FRED: software for generating feedback reports for ecological momentary assessment data. Adm. Policy Ment. Health 51 (4), 490–500.
Robbins, T.W., Ersche, K.D., Everitt, B.J., 2008. Drug addiction and the memory systems of the brain. Ann. N.Y. Acad. Sci. 1141, 1–21.
Sangchooli, A., et al., 2024. Parameter space and potential for biomarker development in 25 years of fMRI drug cue reactivity: a systematic review. JAMA Psychiatry 81 (4), 414–425.
Sanjuan, P.M., Pearson, M.R., Poremba, C., de Los Angeles Amaro, H., Leeman, L., 2019. An ecological momentary assessment study examining posttraumatic stress disorder symptoms, prenatal bonding, and substance use among pregnant women. Drug Alcohol Depend. 195, 33–39.
Schuckit, M.A., Tipp, J.E., Bergman, M., Reich, W., Hesselbrock, V.M., Smith, T.L., 1997. Comparison of induced and independent major depressive disorders in 2,945 alcoholics. Am. J. Psychiatr. 154, 948–957.
Schumann, G., et al., 2014. Stratified medicine for mental disorders. Eur. Neuropsychopharmacol. 24 (1), 5–50.
Seif, T., Chang, S.J., Simms, J.A., Gibb, S.L., Dadgar, J., Chen, B.T., Harvey, B.K., Ron, D., Messing, R.O., Bonci, A., Hopf, F.W., 2013. Cortical activation of accumbens hyperpolarization-active NMDARs mediates aversion-resistant alcohol intake. Nat. Neurosci. 16, 1094–1100.
Serre, F., Gauld, C., Lambert, L., Baillet, E., Beltran, V., Daulouede, J.P., Micoulaud-Franchi, J.A., Auriacombe, M., 2024. Predictors of substance use during treatment for addiction: a network analysis of ecological momentary assessment data. Addiction 120 (1), 48–58.
Shane, M.S., Denomme, W.J., 2021. Machine learning approaches for parsing comorbidity/heterogeneity in antisociality and substance use disorders: a primer. Personal Neurosci 4, e6.
Shevchouk, O.T., Tufvesson-Alm, M., Jerlhag, E., 2021. An overview of appetite-regulatory peptides in addiction processes; from bench to bed side. Front. Neurosci. 15, 774050.
Shield, K., Manthey, J., Rylett, M., Probst, C., Wettlaufer, A., Parry, C.D.H., Rehm, J., 2020. National, regional, and global burdens of disease from 2000 to 2016 attributable to alcohol use: a comparative risk assessment study. Lancet Public Health 5, e51–e61.
Shiffman, S., 2009. Ecological momentary assessment (EMA) in studies of substance use. Psychol. Assess. 21, 486–497.
Sinha, R., Fogelman, N., Wemm, S., Angarita, G., Seo, D., Hermes, G., 2022. Alcohol withdrawal symptoms predict corticostriatal dysfunction that is reversed by prazosin treatment in alcohol use disorder. Addict. Biol. 27, e13116.
Skóra, M.N., Pattij, T., Beroun, A., Kogias, G., Mielenz, D., de Vries, T., Radwanska, K., Müller, C.P., 2020. Personality driven alcohol and drug abuse: new mechanisms revealed. Neurosci. Biobehav. Rev. 116, 64–73.
Smith, K.E., Panlilio, L.V., Feldman, J.D., Grundmann, O., Dunn, K.E., McCurdy, C.R., Garcia-Romeu, A., Epstein, D.H., 2024. Ecological momentary assessment of self-reported kratom use, effects, and motivations among US adults. JAMA Netw. Open 7 (1), e2353401.
Spanagel, R., Hölter, S.M., 2000. Pharmacological validation of a new animal model of alcoholism. J. Neural Transm. 107, 669–680.
Spanagel, R., 2009. Alcoholism: a systems approach from molecular physiology to addictive behavior. Physiol. Rev. 89, 649–705.
Spanagel, R., et al., 2024. The ReCoDe Addiction Research consortium: losing and regaining control over drug intake – findings and future perspectives. Addict. Biol. 29 (7), e13419.
Srivastava, A.B., Mariani, J.J., Levin, F.R., 2020. New directions in the treatment of opioid withdrawal. Lancet 395 (10241), 1938–1948.
Stevenson, J.R., Schroeder, J.P., Nixon, K., Besheer, J., Crews, F.T., Hodge, C.W., 2009. Abstinence following alcohol drinking produces depression-like behavior and reduced hippocampal neurogenesis in mice. Neuropsychopharmacology 34, 1209–1222.
Stone, A.A., Shiffman, S., 1994. Ecological momentary assessment in behavioral medicine. Ann. Behav. Med. 16, 199–202.
Strickland, J.C., Stoops, W.W., Banks, M.L., Gipson, C.D., 2022. Logical fallacies and misinterpretations that hinder progress in translational addiction neuroscience. J. Exp. Anal. Behav. 117 (3), 384–403.
Tiihonen, J., Kuikka, J., Hakola, P., Paanila, J., Airaksinen, J., Eronen, M., Hallikainen, T., 1994. Acute ethanol-induced changes in cerebral blood flow. Am. J. Psychiatr. 151, 1505–1508.
Tolentino, N.J., Wierenga, C.E., Hall, S., Tapert, S.F., Paulus, M.P., Liu, T.T., Smith, T.L., Schuckit, M.A., 2011. Alcohol effects on cerebral blood flow in subjects with low and high responses to alcohol. Alcohol Clin. Exp. Res. 35, 1034–1040.
Torous, J., Blease, C., 2024. Generative artificial intelligence in mental health care: potential benefits and current challenges. World Psychiatry 23 (1), 1–2.
Tran, A., Jiang, H., Lange, S., Rehm, J., 2024. Trend of alcohol use disorder as a percentage of all-cause mortality in North America. BMC Res. Notes 17 (1), 237.
Treloar, H., Piasecki, T.M., McCarthy, D.M., Sher, K.J., Heath, A.C., 2015. Ecological evidence that affect and perceptions of drink effects depend on alcohol expectancies. Addiction 110 (9), 1432–1442.
Trull, T.J., Ebner-Priemer, U., 2013. Ambulatory assessment. Annu. Rev. Clin. Psychol. 9, 151–176.
Tyler, R.E., Leggio, L., 2024. Biological basis of addiction and alcohol use disorder. Clin. Liver Dis. 23 (1), e0177.
Uhl, G.R., Koob, G.F., Cable, J., 2019. The neurobiology of addiction. Ann. N.Y. Acad. Sci. 1451, 5–28.
UNODC, 2024. World Drug Report 2024. United Nations publication.
Upadhyay, J., Nandave, M., Kumar, A., 2024. Role of artificial intelligence in pharmacovigilance. In: Pharmacovigilance Essentials: Advances, Challenges and Global Perspectives. Springer Nature Singapore, Singapore, pp. 347–363.
Uzbay, T.I., 2012. Atypical antipsychotic drugs and ethanol withdrawal syndrome: a review. Alcohol Alcohol 47 (1), 33–41.
Valentino, R.J., Nair, S.G., Volkow, N.D., 2024. Neuroscience in addiction research. J. Neural Transm. 131 (5), 453–459.
Varodayan, F.P., Erikson, C.M., Scroger, M.V., Roberto, M., 2025. Noradrenergic mechanisms and circuitry of hyperkatifeia in alcohol use disorder. Biol. Psychiatry 97 (6), 580–589.
Venniro, M., Banks, M.L., Heilig, M., Epstein, D.H., Shaham, Y., 2020. Improving translation of animal models of addiction and relapse by reverse translation. Nat. Rev. Neurosci. 21 (11), 625–643.
Volkow, N.D., Mullani, N., Gould, L., Adler, S.S., Guynn, R.W., Overall, J.E., Dewey, S., 1988. Effects of acute alcohol intoxication on cerebral blood flow measured with PET. Psychiatry Res. 24, 201–209.
Wadle, L.M., Ebner-Priemer, U.W., 2023. Smart digital phenotyping. Eur. Neuropsychopharmacol. 76, 1–2.
Wadley, G., 2016. How psychoactive drugs shape human culture: a multi-disciplinary perspective. Brain Res. Bull. 126, 138–151.
Walker, L.C., Lawrence, A.J., 2018. Investigational drug therapies in phase I and phase II clinical trials for alcohol use disorders. Expet Opin. Invest. Drugs 27, 1–14.
Wang, Y., Porges, E.C., DeFelice, J., Fridberg, D.J., 2024. Integrating alcohol biosensors with ecological Momentary Intervention (EMI) for alcohol use: a synthesis of the latest literature and directions for future research. Curr. Addict. Rep. 11 (2), 191–198.
Wank, I., Mittmann, C., Kreitz, S., Chestnykh, D., Mühle, C., Kornhuber, J., Ludwig, A., Kalinichenko, L.S., Müller, C.P., Hess, A., 2024. Neutral sphingomyelinase controls acute and chronic alcohol effects on brain activity. Neuropharmacology 253, 109948.
Warraich, H.J., Tazbaz, T., Califf, R.M., 2025. FDA perspective on the regulation of artificial intelligence in health care and biomedicine. JAMA 333 (3), 241–247.
Wellensiek, J., Specka, M., Just, J., Banger, M., Bonnet, U., Scherbaum, N., 2024. Patient perspectives on pharmacotherapy of alcohol dependence. Pharmacopsychiatry 57 (1), 21–29.
Wenzel, J.G., Reichert, M., Zech, H., Wedemeyer, F., Deeken, F., Spitta, G., Bach, P., Lenz, B., Ebner-Priemer, U.W., Kiefer, F., Rapp, M.A., Walter, H., Heinz, A., Banaschewski, T., 2024. One-year ecological momentary assessment of alcohol use, mood, and stress among individuals with alcohol use disorder during SARS-CoV-2 pandemics: a gender-specific reflection. Eur. Arch. Psychiatr. Clin. Neurosci. 275 (2), 451–461.

WHO, 2024. Global Status Report on Alcohol and Health and Treatment of Substance Use Disorders. World Health Organization, Geneva.
Witkiewitz, K., Desai, S.A., Bowen, S., Leigh, B.C., Kirouac, M., Larimer, M.E., 2014. Development and evaluation of a mobile intervention for heavy drinking and smoking among college students. Psychol. Addict. Behav. 28, 639–650.
Witkiewitz, K., Litten, R.Z., Leggio, L., 2019. Advances in the science and treatment of alcohol use disorder. Sci. Adv. 5 (9), eaax4043.
Wise, R.A., 2002. Brain reward circuitry: insights from unsensed incentives. Neuron 36, 229–240.
Wojtowicz, J.S., 2023. Long-Term health outcomes of regular, moderate red wine consumption. Cureus 15 (10), e46786.
Wright, C., Dietze, P.M., Agius, P.A., Kuntsche, E., Livingston, M., Black, O.C., Room, R., Hellard, M., Lim, M.S., 2018. Mobile phone-based ecological momentary intervention to reduce young adults' alcohol use in the event: a three-armed randomized controlled trial. JMIR Mhealth Uhealth 6, e149.
Yates, Y.R., 2024. Pharmacological treatments for methamphetamine use disorder: current status and future targets. Subst. Abuse Rehabil. 15, 125–161.
Zech, H.G., Reichert, M., Ebner-Priemer, U.W., Tost, H., Rapp, M.A., Heinz, A., Dolan, R. J., Smolka, M.N., Deserno, L., 2022. Mobile data collection of cognitive-behavioral tasks in substance use disorders: where are we now? Neuropsychobiology 81, 438–450.
Zech, H., et al., 2023. Measuring self-regulation in everyday life: reliability and validity of smartphone-based experiments in alcohol use disorder. Behav. Res. Methods 55 (8), 4329–4342.
Zhao, J., Stockwell, T., Naimi, T., Churchill, S., Clay, J., Sherk, A., 2023. Association between daily alcohol intake and risk of all-cause mortality: a systematic review and meta-analyses. JAMA Netw. Open 6 (3), e236185.
Zorrilla, E.P., Logrip, M.L., Koob, G.F., 2014. Corticotropin releasing factor: a key role in the neurobiology of addiction. Front. Neuroendocrinol. 35 (2), 234–244.