Summary
Griffith Edwards
History of prevention of relapse

Extensive drinking tends to be a relapsing condition. That evident fact is central to the problem that alcohol sets society. Over historical time punishment and moral persuasion comprised the two main responses to the problem with treatment making its entry at the end of the 18th century. Developments within the treatment movement are traced. Inferences for present endeavours are identified.

Key words: excessive drinking, relapse, history, punishment, religion, treatment

Summary
Rainer Spanagel
How to measure relapse in animals

Characteristics of addictive behavior are compulsive drug use, craving and chronic relapses that can occur even after years of abstinence. So far, in the alcohol research field, two animal models have been developed, which measure some behavioral dimensions of craving and relapse: the reinstatement model and the alcohol deprivation model. The reinstatement model should be considered as a model, which predominantly measures one dimension of drug craving, namely ethanol-seeking behavior, which can be elicited by conditioned cues and stress. The alcohol deprivation effect typically occurs following cessation of alcohol drinking behavior and can be viewed as a short episode of compulsive alcohol drinking behavior. Both models have been successfully validated with acamprosate and naltrexone. Thus, cue-induced reinstatement can be blocked by acamprosate and naltrexone and the alcohol deprivation effect can be completely abolished by acamprosate and shows some sensitivity to naltrexone treatment. Furthermore, both models have now been transferred to mice, which will allow us in the future to study conditional transgenic mouse models with respect to addictive behaviour. In conclusion, there appears to be a good correspondence between the events that induce craving and relapse in laboratory animals and those that provoke these phenomena in humans. Even more important, the pharmacology, which underlies craving and relapse, seems to include the same pathways in rodents and humans, giving us an ideal basis for the development of new pharmacotherapies.

Key words: reinstatement, alcohol deprivation effect, craving, relapse, conditioned cues, stress, pharmacological validation, transgenic mice

Summary
Henry R. Kranzler and Howard Tennen
How to measure relapse in humans

In this chapter, we review methods and measures used to evaluate the success of alcohol treatment trials, with a focus on those used in pharmacotherapy trials. We describe self-report outcome indicators, biological measures of recent alcohol use, and collateral informant reports of drinking. Because self-report is the most widely used approach, we focus primarily on these methods, including quantity-frequency measures and a variety of daily drinking estimation

methods such as the Timeline Follow-Back method. We compare these methods to prospective daily monitoring of alcohol use, and we summarize the advantages and potential limitations of daily monitoring approaches. Finally, we describe the efforts of a recent NIAAA panel to develop an optimal measure of alcohol use in clinical trials. We then summarize methodological aspects of studies conducted with a number of medications used to treat alcohol dependence, including lithium, alcohol sensitizing medications, acamprosate, and opioid antagonists. We encourage investigators to consider the use of prospective daily monitoring of drinking behavior to evaluate the effects of medications in treatment trials. When combined with new technologies such as interactive voice response (IVR) technology, daily monitoring holds considerable promise for enhancing outcome measurement in alcohol treatment trials, particularly multi-center trials.

Key words: outcome measurement, self-report, biological markers, collateral informants, Timeline Follow-Back, prospective daily assessment, interactive voice response (IVR)

Summary
Dieter Ladewig and Ulrich von Bardeleben
Disulfiram (Antabuse®): the first medication to stop drinking

Disulfiram (Antabuse®) is historically one of the first medications found to stop drinking. The principle of its action resembles more a crutch than a classical medication. Its efficiency depends on the quality of integrated psychosocial interventions. Results of our own randomized open efficacy study comparing disulfiram with acamprosate, naltrexone and "no medication" in combination with a standardized cognitive behavioral group therapy are reported. With regard to the time period of the first relapse, there were no significant differences between the treatment groups but there was a significant difference in comparison with the "no-medication group", with subjects from this group displaying a significantly shorter period of abstinence. In conclusion, the efficacy of disulfiram depends on the treatment setting and regarding future pharmacotherapies, different disulfiram / anti-craving drug combinations might be more promising.

Key words: Disulfiram, alcoholism treatment, acamprosate, naltrexone

Summary
Michael S. Cowen
Naltrexone: preclinical data

Naltrexone has been shown to decrease ethanol consumption in a range of animal models. Naltrexone appears to be most effective when the access period is limited and is also particularly effective in decreasing reinstatement subsequent to deprivation or when induced by cues associated with ethanol availability. The effects of naltrexone appear to be centrally mediated and may involve decreasing the rewarding value of ethanol (subsequent to consumption), increasing the perceived aversiveness of ethanol's flavor, and disrupting the neural signalling involved in mediating the connection between cues and ethanol-seeking behavior. However, the pre-clinical data indicating the development of tolerance and lack of specificity for ethanol consumption (i.e.

effects on food and water intake) may indicate that naltrexone is best used in a lower dose range in combination with other drugs.

Key words: naloxone, naltrexone, opioid receptors, tolerance, reinstatement of ethanol-seeking behavior

Summary
Charles P. O'Brien, Helen M. Pettinati and David W. Oslin
Naltrexone: clinical data

Naltrexone is an opiate receptor antagonist that was found to reduce preference for alcohol in several animal models of alcoholism. Based on these laboratory findings it was tested in the clinic beginning in 1983. It was found to be effective in the majority of double blind trials as measured by a reduction in relapse to heavy drinking. The presumed mechanism involves reduction of the reward produced by alcohol and, based on some of the studies, by reducing alcohol craving. A key factor in the efficacy of naltrexone is its specificity for opiate receptors. Unless there is an activation of the endogenous opioid system following ingestion of alcohol, the known pharmacology of naltrexone indicates that the drug will have no effect. Adherence to the medication is another key factor and nausea when the medication is initiated can be a limiting factor. Early results from trials of new depot formulations suggest that adherence problems and side effects will be less troublesome. Family history of alcoholism has been found in several trials to predict success with naltrexone and a recent study has found that a specific polymorphism of the μ opiate receptor is associated with successful naltrexone treatment.

Key words: naltrexone, opiate receptors, alcoholism, medication

Summary
Philippe De Witte, Daniel Bachteler and Rainer Spanagel
Acamprosate: preclinical data

Numerous preclinical studies on alcohol drinking and relapse behavior have been performed with acamprosate. Besides the demonstration of its anti-relapse and anti-craving properties, it has been shown that acamprosate neither produces discriminative stimulus properties nor does it produce place conditioning. This implies that acamprosate is lacking any rewarding properties and cannot be regarded as a substitution drug. The primary site of action is the glutamatergic system and it has been shown that a hyper-glutamatergic state of the brain is effectively blunted by acamprosate treatment. This effect of acamprosate on the glutamatergic system might involve its modulatory action on NMDA receptor subunits. However, the detailed mode of action is still not clear. An interaction with mGlu5 receptors has recently been described and other studies suggest that acamprosate reduces the preference for alcohol in dependent animals through the release of taurine. A better understanding of the precise mode of action of acamprosate would help in identifying treatment responders and could lead to compound optimization. The following chapter should provide insights into the latest research on acamprosate, especially its relation to brain taurine and its action on the glutamate system.

Key words: acamprosate, glutamate, taurine, NMDA receptors, mGlu5 receptors

Summary
Karl F. Mann
Acamprosate: clinical data

Acamprosate was developed and first tested in the early 1980s in France. It has been approved in many countries for relapse prevention in alcohol-dependent patients, most recently in the USA (2004). Its major mechanism of action is the reduction of cerebral hyperexcitability by interacting with glutamate receptors. A large series of studies has been conducted with this compound including more than 20 randomized placebo-controlled trials. With very few exceptions these studies showed a significant benefit of acamprosate over placebo. Several meta analyses confirm the findings of these individual studies showing an overall relative risk (relative benefit) of 1.47 for continuous abstinence after 6 month of treatment. This represents a number needed to treat (NNT) of 7.5. Side effects of acamprosate such as diarrhoea are benign and transient.
Future research will turn to combining acamprosate and other medications influencing alcohol drinking. Studies where acamprosate was given with disulfiram or naltrexone showed very promising results but need to be extended including larger numbers of patients. A different approach is currently being tested by identifying potential acamprosate responders on the basis of neurobiological variables. If successful this would allow an individually targeted prescription of acamprosate which would then certainly further improve its efficacy and cost effectiveness.

Key words: acamprosate, alcoholism, alcohol relapse, glutamate system, randomized controlled trials, meta analysis

Summary
Anh Dzung Lê and Douglas R. Funk
Serotonergic compounds: preclinical data

The role of 5-hydroxytryptamine (5-HT) in alcohol dependence has been a subject of study for many years. The results of preclinical studies on laboratory animals have revealed that subtypes of the 5-HT1, 5-HT2 and 5-HT3 receptor families exert important modulatory effects on alcohol consumption. The availability of selective ligands has recently allowed the role of each of these receptor types in their effects of alcohol intake to be more clearly articulated. Similarly, the development of transgenic animals with knock out or over expression of selected receptors has also helped to clarify the roles of the different 5-HT receptors in alcohol-associated behaviors. In this chapter, the evidence for the involvement of 5-HT1, 5-HT2 and 5-HT3 receptor types and their associated subtypes in the modulation of alcohol consumption will be reviewed. For each of the receptor classes, their neuroanatomical distribution, especially regarding their localization to structures implicated in the effects of alcohol and other abused drugs will be described. Preclinical studies on the effects of agonists and antagonists that act selectively at these 5-HT receptors on alcohol intake will be discussed in detail. The effects of targeted modifications of 5-HT receptor expression in transgenic animals on alcohol consumption will also be discussed. Finally, the evidence that the 5-HT systems play a role in the reinstatement of alcohol seeking will be evaluated.

Key words: 5-hydroxytryptamine receptors, alcohol, animal models, self-administration, reinstatement, relapse

Summary
Bankole A. Johnson
Serotonergic compounds: clinical data

Preclinical studies have led to the development of new knowledge about the neurochemical pathways associated with the acquisition and maintenance of the reinforcing effects of alcohol associated with its abuse liability.
Serotonergic pathways exert modulatory effects on cortico-mesolimbic dopamine function, the critical substrate by which alcohol mediates its reinforcing effects associated with its abuse liability. Naturally, this has resulted in the study of serotonergic agents as treatments for alcoholism.
Development of serotonergic agents for treating alcohol-dependent individuals remains an intense area of scientific interest. Various types of serotonergic medication do, however, appear to have differential effects on drinking behavior. Selective serotonin reuptake inhibitors (SSRIs) are not efficacious treatment for a heterogeneous group of alcohol-dependent individuals. SSRIs may, however, be efficacious in treating alcoholics who develop the disease later in life, or among alcoholics with co-morbid depression. The 5-HT_{1A} partial agonist, buspirone, is not efficacious for treating alcoholics without co-morbid disease. Buspirone may, however, be useful in treating alcoholics with co-morbid anxiety disorder. Ritanserin, a 5-HT_2 antagonist, at pharmacologically relevant clinical doses, does not appear to be an effective treatment for alcoholism. Ondansetron, a 5-HT_3 antagonist, is an efficacious and promising medication for the treatment of alcoholics who develop the disease early in life. The differential response to SSRIs and ondansetron among various subtypes of alcoholic is intriguing. New knowledge on the relationship between molecular genetic and environmental predisposition might aid in better characterizing alcoholics by subtype. Such knowledge would improve our chances of predicting what subtype of alcoholic would respond best to a particular serotonergic agent.

Key words: ondansetron, selective serotonin reuptake inhibitor, alcohol, ritanserin, buspirone, serotonin, dopamine, humans

Summary
Petri Hyytiä
Opiodergic compounds: preclinical data

The roles of the different opioid receptor types, especially the μ- and δ-opioid receptors, in the reinforcing and conditioned effects of ethanol have been studied using opioid receptor antagonists selective for these receptors. In various free-choice drinking and operant self-administration models, the selective μ-antagonists (β-funaltrexamine, CTOP, naloxonazine) have consistently been shown to suppress ethanol consumption. The δ-antagonists (naltrindole, naltriben, ICI 174864) have also been reported to attenuate ethanol reinforcement, however, there are discrepancies in the results, possibly due to procedural differences among the behavioral

models. Generally, the suppressive effects of selective opioid antagonists are not specific for ethanol as they produce reductions in intake of other solutions. At present, there is little data, dealing with the involvement of different opioid receptor types in the mediation of the conditioned appetitive effects on ethanol seeking. However, there is evidence that both μ- and δ-antagonists could attenuate ethanol-seeking behavior, maintained by ethanol-associated stimuli.

Key words: ethanol consumption, ethanol self-administration, ethanol-seeking behavior, reinstatement, μ-opioid receptor, δ-opioid receptor, selective opioid antagonist, CTOP, β-funaltrexamine, naloxonazine, naltrindole, naltriben, ICI 174864

Summary
John David Sinclair
Opioidergic compounds: clinical data

Nalmefene is the only second generation opioid antagonist for which there is clinical data. Injectable nalmefene has been approved by the FDA for overcoming opiate overdoses, but the oral form used for alcoholism is still under investigation in both Europe and the USA. Nalmefene is similar in action to naltrexone, except for a somewhat greater ability to block delta and kappa opioid receptors. It has advantages over naltrexone in that it is longer lasting, has less first pass metabolism and higher bio-availability, has less individual variability in its metabolism, has no active metabolite, and is not toxic to the liver even in patients with existing liver disorders. Double-blind placebo-controlled clinical trials have repeatedly shown nalmefene to be safe and effective in treating alcoholism, when given with no structured psychosocial therapy or with therapy aimed at developing coping skills for dealing with drinking small amounts of alcohol. Like naltrexone, however, the effects did not reach significance, when given with Motivational Enhancement Therapy. The primary benefit is a decrease in the chances of relapsing to heavy drinking, when sampling alcohol. Nalmefene appears to be an appropriate medicine for preventing alcohol abuse but not for maintaining abstinence.

Key words: nalmefene, naltrexone, naloxone, metabolism, toxicity, clinic trials, coping, supportive controlled drinking, gambling, abstinence

Summary
Friedbert Weiss
Dopaminergic compounds: preclinical data

Mesocorticolimbic dopamine (DA) transmission participates in mediating the reinforcing as well as other important neurobehavioral effects of ethanol. Evidence has accumulated in recent years implicating this system also in behavioral and neurobiological functions relevant for alcohol craving and relapse. Activation of mesolimbic DA transmission by ethanol-related environmental stimuli has been implicated in conditioned cue reactivity, alcohol craving, and relapse associated with exposure to such stimuli. Chronic ethanol administration results in long-lasting DA hypofunction that has been implicated as a neural basis for dysphoria and negative affect that accompanies acute and protracted ethanol withdrawal, and may motivate resumption of drinking. Lastly, persistent ethanol-induced changes in DA receptor function may contribute to increased ethanol intake associated with the alcohol-deprivation effect, a model of loss of control and

relapse. Despite substantial evidence on a role for DA in relapse associated with both alcohol cue exposure and neuroadaptive changes in DA function, only a small number of preclinical studies have examined the effects of pharmacological manipulation of DA neurotransmission on ethanol-seeking in animal models of relapse. Available data suggest that D1 and D2-selective antagonists consistently attenuate the effects of ethanol-related environmental stimuli on conditioned reinstatement, appetitively-motivated responding, and conditioned reinforcement. Evidence also exists to suggest that the exacerbation of ethanol intake following deprivation (i.e., the alcohol deprivation effect) is sensitive to reversal by D2 antagonists. On the other hand, studies examining the potential of D2 agonists to reduce proclivity to relapse linked to chronic ethanol-induced DA hypofunction suggest that such treatments not only fail to reduce ethanol intake but may even increase ethanol consumption. Overall, although the neurobiological literature reveals a significant role for DA neurotransmission in ethanol-seeking and relapse, direct manipulation of this system is associated with complications that limit therapeutic promise. DA antagonists may have potential in preventing or ameliorating craving and relapse associated with alcohol cue exposure, but such treatments are likely to exacerbate the DA hypoactivity that accompanies acute and protracted withdrawal and has been linked to increased relapse risk. DA agonists treatments to reduce susceptibility to relapse by ameliorating DA hypofunction are problematic as well. Particularly with chronic treatment, DA agonists produce autoinhibitory reductions in dopaminergic tone that counteract the therapeutic effects of these agents, and may even increase the likelihood of relapse. It remains to be determined whether low-dose D1 antagonist treatments or agents that act as partial agonists at the D2 receptor may prove beneficial. Additionally, indirect modification of DA activity via agents that act on other neurochemical systems may perhaps provide an effective approach, eliminating problematic side effects associated with chronic DA agonist or antagonist treatments.

Key words: D1, D2, D3 dopamine receptors, dopamine release, cue-induced reinstatement, conditioned place preference

Summary
Gerhard A. Wiesbeck
Dopaminergic compounds: clinical data

There is convincing evidence that dysfunction of the brain dopaminergic systems is implicated in the pathogenesis of alcoholism and earlier reports from human studies, suggested that dopamine agonists and antagonists are both beneficial for maintaining abstinence or reducing alcohol intake. Unfortunately, those early reports suffered from a variety of methodological shortcomings, which decisively limited their level of evidence. So far, there are only a limited number of studies, which qualify as randomized, double-blind, placebo-controlled trials. In those studies, neither dopamine agonists nor antagonist proved to be superior to placebo treatment. So far, there is no dopaminergic compound, which could be recommended for alcohol relapse prevention in humans.

Key words: alcoholism, dopaminergic compounds, lisuride, tiapride, bromocriptine, flupenthixol

Summary
Mauro A.M. Carai, Roberta Agabio, Giovanni Addolorato, Gian L. Gessa1, Giancarlo Colombo
Baclofen: preclinical data

The present paper provides a brief overview on the preclinical lines of evidence, which suggest the involvement of the GABAB receptor in the neural substrate controlling different aspects of alcohol drinking and alcohol relapse behaviors. With regards to the latter, this paper describes the results of a recent study testing the effects of the GABAB receptor agonists, baclofen and CGP 44532, on the alcohol deprivation effect (ADE) in selectively bred Sardinian alcohol-preferring (sP) rats. ADE has been defined as the transient increase in alcohol intake occurring in laboratory animals following a period of alcohol deprivation and is used as a standard model to measure alcohol relapse behavior The acute administration of non-sedative doses of baclofen and CGP 44532 resulted in the complete suppression of ADE in sP rats. These findings, together with those of recent, preliminary clinical surveys, feature baclofen as a promising agent in the pharmacotherapy of alcohol relapse.

Key words: GABAB receptor, baclofen, CGP 44532, animal models of alcohol relapse alcohol deprivation effect (ADE), sardinian alcohol-preferring (sP) rats

Summary
Giovanni Addolorato, Ludovico Abenavoli, Lorenzo Leggio, Giosuè DeLorenzi, Anna Ferrulli, Fabio Caputo, Roberta Agabio, Gian Luigi Gessa, Giancarlo Colombo and Giovanni Gasbarrini
Baclofen: clinical data

In recent years, several drugs useful in the treatment of alcohol addiction have been tested both in pre-clinical and clinical studies. Among them baclofen, a stereoselective GABAB receptor agonist, has displayed promising results. Clinical data has shown baclofen to be effective in the treatment of alcohol addiction. In particular, baclofen displayed a significant effect in reducing alcohol intake and craving in addicted patients. Moreover, recent preliminary studies indicated that baclofen could be useful in the treatment of alcohol-dependent patients affected by severe alcohol withdrawal syndrome (AWS) and further complicated by delirium tremens (DT). The ability of the drug in reducing the main components of craving, as well as suppressing alcohol intake and AWS symptoms emphasizes its efficacy as a drug having relapse prevention properties.
Finally, a growing number of both pre-clinical and clinical studies support the idea that baclofen may attenuate the craving and reinforcing effects of cocaine, heroin and nicotine. The findings reviewed in the present chapter suggest that the GABAB agonist baclofen may offer a powerful method of controlling drug abuse in humans.

Key words: baclofen, GABAB receptor, alcohol-, heroin-, cocaine-addiction, relapse prevention, alcohol withdrawal syndrome

Summary
Mauro A.M. Carai, Carla Lobina, Gian Luigi Gessa and Giancarlo Colombo
Cannabinoid receptor antagonists: a perspective

The present paper describes current experimental evidence on the suppressing effect of the cannabinoid CB1 receptor antagonist SR 141716 on the so-called alcohol deprivation effect (ADE) in selectively bred Sardinian alcohol-preferring (sP) rats. ADE has been defined as the transient increase in alcohol intake, occurring in laboratory animals after a period of alcohol deprivation. Moreover, ADE has been validated as an experimental model of the loss of control over alcohol and alcohol relapse episodes in human alcoholics. The acute administration of SR 141716 resulted in a complete suppression of ADE in sP rats. Interestingly, a combination of SR 141716 with the opioid receptor antagonist naloxone synergistically suppressed ADE in sP rats. These results suggest an involvement of the cannabinoid CB1 receptor in the neural circuitry mediating ADE in sP rats, and showing as well that SR 141716, alone or in combination with opioid receptor antagonists may constitute a novel, promising strategy in the pharmacotherapy of alcohol relapse.

Key words: cannabinoid CB1 receptor; SR 141716 (rimonabant); animal models of alcohol relapse; alcohol deprivation effect (ADE); sardinian alcohol-preferring (sP) rats

Summary
Markus Heilig and Todd E. Thiele
Neuropeptide Y antagonists: a perspective

Neuropeptide Y (NPY), a 36-amino acid neurotransmitter that is widely distributed throughout the nervous system, antagonizes behavioral consequences of stress/depression and attenuates EtOH-seeking behavior through actions within the brain. NPY reduces anxiety, at least in part, by acting on NPY Y1 receptors in the lateral/basolateral nuclei of the amygdala. The anxiolytic actions of NPY are unusual both due their magnitude, and to their presence across a wide range of animals models normally thought to reflect different aspects of emotionality. Thus, NPY seems to act on a common core mechanism of emotionality and behavioral stress. Recent research – genetic and pharmacological – suggests that NPY is also involved in regulation of voluntary ingestion of EtOH. Low levels (or the absence) of NPY promote high EtOH drinking, and enhanced NPY signaling prevents excessive EtOH consumption. Furthermore, abnormally low levels of NPY have been found in brain tissue from alcoholics. Voluntary EtOH intake is potently regulated by compounds which act on the NPY Y1 and Y2 receptors, making these attractive targets for developing novel pharmacotherapies for alcoholism.

Key words: NPY Y1, NPY Y2 receptors, QTL-analyses, association studies

Summary
Daniel Bachteler, Rainer Spanagel
Glutamatergic compounds: preclinical data

In the development of novel pharmacotherapeutic concepts for treating alcohol dependence, the glutamatergic system has long been recognized as a major player in addictive processes. Being

directly involved in acute and chronic actions of ethanol, the complex composition of the glutamate system offers numerous potential targets for pharmacological interventions. As one of the primary targets, the ionotropic N-methyl-D-aspartate receptor (NMDAR) complex, offers several sites for drug action, whereas the role of the α-amino-3-hydroxy-5-methylisoxazole-4-proprionate (AMPA) and Kainate receptors is less clear and selective blockade of these receptors is more difficult to achieve. For example, substances like memantine, an NMDAR channel blocker and anti-Alzheimer drug, proved to be effective in the treatment of alcohol relapse in animal models. Only recently, have studies on metabotropic glutamate receptor (mGluR) been conducted. In particular, the mGluR5 antagonist MPEP revealed a crucial involvement of metabotropic receptors in alcohol-induced behavioral effects, suggesting a functional interplay between NMDA and mGluRs. However, although numerous compounds have been employed in different *in vitro* and *in vivo* systems, comparatively few of them have really been tested in animal models of alcoholism that closely mimic the human situation. Much research still needs to be conducted in exploring the complex involvement and interaction of different receptor types and systems in the search for successful pharmacotherapies. Future directions could point in the direction of combined therapies and in this way antagonizing several, rather than just a single type of receptor.

Key words: NMDA receptor, mGluR, relapse, craving, animal model, reinstatement, alcohol deprivation effect, iGluR, MPEP, ifenprodil, memantine, neramexane, rat, AMPA, kainate, glutamate

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