Understanding and Treating Alcohol Dependence

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and Nassima Ait-Daoud

This article represents the proceedings of a symposium presented at the 158th Annual Meeting of the American Psychiatric Association held in Atlanta, Georgia, on May 24, 2005. The organizer/chairman was Bankole A. Johnson, DSc, MD, PhD. The presentations included the following: (1) Neuropharmacological Basis of Alcohol Dependence, by George F. Koob, PhD; (2) Recent Developments in the Genetics of Alcohol Dependence, by Marc A. Schuckit, MD; (3) New Pharmacological Strategies for Treating Alcohol Dependence, by Barbara J. Mason, PhD; (4) New Medications: The Use of Anticonvulsants, Both Alone and in Combination, with Various Forms of Psychotherapy, by Bankole A. Johnson, DSc, MD, PhD; and (5) Differential Effects of Pharmacological Agents on Craving, by Nassima Ait-Daoud, MD.

Key Words: Alcohol Dependence, Anticonvulsants, Craving, Genetics, Neuropharmacology, Pharmacotherapy.

INTENSE INTEREST HAS been focused on the development of medications to treat alcohol dependence. Sophisticated animal models and advances in neuropharmacology have provided a framework for studying medications that act at particular receptor sites in the corticomesolimbic system for possible use in humans. We will lay a foundation for understanding the neurochemical, molecular-genetic, and cellular aspects of medications development for alcohol dependence; highlight critical new clinical advances and concepts; and provide evidence-based rational strategies for using these pharmacotherapies in clinical practice. First, Dr. Koob will provide data on perturbations in neurotransmitter function [particularly those involving the dopamine, γ-aminobutyric acid (GABA)/glutamate, and neurohormonal systems] that affect the development of dependence and can trigger relapse even after prolonged abstinence. Next, Dr. Schuckit will use twin and familial studies to elucidate the role of various molecular-genetic components in alcohol dependence and the use of endophenotypes that might better describe targets for pharmacogenomic studies. Then, Dr. Mason will compare and contrast the efficacy and safety of the 2 currently approved medications for treating alcohol dependence in the US—naltrexone and acamprosate. Next, Dr. Johnson will present data on other promising targets for medications development, with a focus on medications that modulate GABA or glutamate function or both, as well as new preliminary data on the potential for added efficacy when the GABA/glutamate modulator, topiramate, is combined with a serotonin-3 ($5\text{-}HT_3$) receptor antagonist (e.g., ondansetron). Finally, Dr. Ait-Daoud will show how the concept of craving can help to establish a neuropharmacological framework for developing medications to treat alcohol dependence, measure treatment response, and predict the likelihood of relapse.

NEUROPHARMACOLOGICAL BASIS OF ALCOHOL DEPENDENCE

George F. Koob

Alcohol and substance dependence are chronic relapsing disorders characterized by (1) compulsion to seek and take a drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (defined here as dependence) (Koob and Le Moal, 1997). Both clinically and in experimental animals, the occasional but limited use of alcohol is distinct from loss of control over alcohol use and the emergence of chronic alcohol dependence. An important goal of current research is to understand the neuropharmacological and neuroadaptive mechanisms within specific neurocircuits that mediate the transition between occasional, controlled drug use and the loss of behavioral control over drug seeking and drug taking that defines chronic addiction (Koob and Le Moal, 1997). While much focus in animal studies has been on the

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neurobiological systems on which drugs of abuse act initially to produce their positive reinforcing effects, new animal models of components of the negative reinforcing effects of dependence have been developed to explore how the nervous system adapts to drug use. The present review explores the neurobiological mechanisms of addiction that change in the transition from drug taking to drug addiction, with a focus on the motivational effects of withdrawal and protracted abstinence (Koob and Le Moal, 1997).

Positive and Negative Reinforcement Characteristics of Alcohol and Drug Dependence

From a psychiatric perspective, alcohol dependence and drug addiction have aspects of both impulsivity and compulsivity at different stages of the addiction cycle. Impulse control disorders are characterized by an increasing sense of tension or arousal before committing an impulsive act, feelings of pleasure, gratification, or relief at the time of committing the act and possible regret, self-reproach, or guilt following the act (American Psychiatric Association, 1994). In contrast, compulsive disorders are characterized by anxiety and stress before committing a compulsive repetitive behavior and relief from the stress by performing the compulsive behavior. As an individual moves from an impulsive to a compulsive disorder, there is a shift from positive to negative reinforcement driving the motivated behavior. Drug addiction is a disorder that progresses from impulsivity to compulsivity in a collapsed cycle of addiction.

Animal Models and Neurobiological Evidence for the 3 Stages of the Addiction Cycle

The addiction cycle comprises 3 stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (''craving''). Much of the recent progress in understanding the neurobiological mechanisms of alcohol dependence is derived from the study of animal models. While animal models do not fully emulate human addiction processes, they do permit investigation of specific elements of the stages of the addiction cycle. Each stage of the addiction cycle will now be discussed presenting animal models currently used in research and the neurobiological evidence supporting the effects of alcohol in a given stage of the cycle in dependent animals.

Binge/Intoxication Stage of the Addiction Cycle. Animal models for the binge/intoxication stage have been well established from the perspective of the positive reinforcing effects of alcohol (alcohol drinking). Using an oral preference paradigm where animals are allowed to drink alcohol or water, alcohol consumption can be measured in dependent and postdependent rats (Roberts et al., 1999, 2000). Similarly, rats with a history of alcohol dependence show increased self-administration of alcohol, even weeks after acute withdrawal (Roberts et al., 2000). More recent results have shown that intermittent exposure to chronic alcohol using alcohol vapor chambers (14 hours on/10 hours off) produces a more rapid escalation to increased alcohol intake (O'Dell et al., 2004).

The neurobiological substrates for the acute reinforcing effects of alcohol involve elements of the mesolimbic dopamine system [ventral tegmental area (VTA) dopamine projection to the nucleus accumbens (NAc)] and dopamine-*independent* interactions in the extended amygdala (central nucleus of the amygdala, bed nucleus of the stria terminalis, and shell of the NAc) (Heimer and Alheid, 1991). This system links the prelimbic cortex to the classical reward systems of the lateral hypothalamus, possibly via a descending component of the medial forebrain bundle. One hypothesis is that many of the neuropharmacological effects of alcohol, including its rewarding and ''anxiolytic'' or ''tension-reducing'' effects, may be mediated by this circuitry, and neuroadaptive changes in this reward circuit provide the motivation for excessive drinking characterized by dependence and relapse.

Alcohol has been hypothesized to interact with a number of ligand-gated ion channels, and the action on the GABA receptor system has long been linked to alcohol reinforcement (Deitrich et al., 1989; Tabakoff and Hoffman, 1992). At the pharmacological level, GABA receptor antagonists can antagonize the effects of alcohol. For example, the potent GABA antagonist, SR 95531, when microinjected into distinct sections of the basal forebrain, significantly decreased alcohol consumption (Hyytia and Koob, 1995), with the most sensitive site being the central nucleus of the amygdala.

Significant evidence also supports a role for other reward neurotransmitters at basal forebrain sites, such as the NAc and central nucleus of the amygdala, in alcohol reinforcement. Very low doses of fluphenazine, a dopamine antagonist, injected into the NAc blocked alcohol self-administration at doses that do not affect water intake (Rassnick et al., 1992b). Also, acute alcohol self-administration in nondependent rats increased extracellular levels of dopamine in the NAc (Weiss et al., 1993). Such increases occur not only during but also preceding the self-administration session, possibly reflecting the incentive motivational properties of alcohol (Weiss et al., 1993). Opioid antagonists have been shown to block the oral self-administration of alcohol in a number of animal models (Altshuler et al., 1980; Froehlich et al., 1990; Reid and Hunter, 1984; Samson and Doyle, 1985; Weiss et al., 1990). Brain sites for these effects involve the VTA, NAc, and central nucleus of the amygdala, with injections of an opiate antagonist into the central nucleus of the amygdala significantly reducing alcohol consumption at lower doses compared with other sites such as the NAc or lateral ventricle (Heyser et al., 1999). Both glutamate and serotonin have also been implicated in the acute reinforcing effects of alcohol. Glutamate/*N*-methyl-D-aspartate (NMDA) receptor antagonists have been shown to substitute for alcohol in drug discrimination tests (Grant et al., 1991). In

addition, 5-HT_3 receptor antagonists block alcohol self-administration (Beardsley et al., 1994; Fadda et al., 1991; McKinzie et al., 1998).

Withdrawal/Negative Affect Stage of the Addiction Cycle. Animal models for the withdrawal/negative affect stage include not only classical physical withdrawal syndromes (Majchrowicz and Hunt, 1976) but also models of the motivational aspects of withdrawal, such as elevations in brain reward thresholds and anxiety-like responses (Rassnick et al., 1992a; Schulteis et al., 1995). In the withdrawal/negative affect stage of the addiction cycle, the neurobiological basis for the negative reinforcement leading to the development of alcohol dependence and the vulnerability to relapse has been argued to include counteradaptive neurochemical events normally used to maintain emotional homeostasis (Koob and Le Moal, 2001). Key to this hypothesis is the observation that during acute withdrawal from alcohol, there is a compromised brain reward system, as reflected by an increase in brain reward thresholds. Significant evidence from animal models showed elevations in reward thresholds following acute withdrawal from all major drugs of abuse: nicotine (Epping-Jordan et al., 1998), alcohol (Schulteis et al., 1995), amphetamine (Paterson et al., 2000), cocaine (Markou and Koob, 1991), and opiates (Schulteis et al., 1994). Alcohol-dependent rats showed elevations in reward thresholds during withdrawal from alcohol that persisted up to 72 hours postexposure (Schulteis et al., 1995). These changes in reward function are accompanied by changes in neurochemical systems within the extended amygdala that include decreased GABAergic, opioid peptidergic, dopaminergic, serotonergic, and glutamatergic function, as well as recruitment of brain stress systems such as corticotropin-releasing factor (CRF).

Neuropharmacological studies have shown that the enhanced alcohol self-administration during acute withdrawal can be reduced in a dose-dependent manner by intracerebral pretreatment of a GABA agonist into the central nucleus of the amygdala (Roberts et al., 1996). This suggests that the GABAergic system is hypofunctional during acute withdrawal. The glutamate system also undergoes changes during withdrawal as evidenced by acamprosate, a hypothesized partial modulator of brain glutamate receptors, decreasing excessive drinking associated with dependence and abstinence in rats (Heyser et al., 1998; Holter et al., 1997; Spanagel et al., 1996). Intracerebral administration of acamprosate suggests that the bed nucleus of the stria terminalis is a particularly sensitive site (Morse and Koob, 2002). Identical doses and administration of these neuropharmacological agents to nondependent rats had no effect on the self-administration of alcohol. Dopaminergic function is also compromised during acute alcohol withdrawal. During acute withdrawal, animals show a decrease in extracellular levels of dopamine in the NAc and a decrease in firing in the VTA (Weiss et al., 1996). Thus, there is evidence that GABA, glutamate, and dopamine systems show a neuroplasticity during the development of dependence that has motivational consequences. GABAergic and dopaminergic function in the extended amygdala is compromised during acute withdrawal and may contribute to the motivation to consume excessive alcohol via negative reinforcement mechanisms (i.e., to restore normal tone). In contrast, glutamatergic function may be increased in the extended amygdala and may also contribute to the motivation to increase alcohol consumption during the development of dependence.

However, another major contribution to the aversive state associated with increases in brain reward thresholds during acute withdrawal has been hypothesized to be dysregulation of the brain CRF stress system. CRF is a 41-amino-acid polypeptide with a wide distribution throughout the brain, but with particularly high concentrations of cell bodies in the paraventricular nucleus of the hypothalamus, the basal forebrain (notably the extended amygdala), and the brain stem (Swanson et al., 1983). CRF not only controls the hypothalamic–pituitary–adrenal (HPA) response to stress but it also has an important role in the extended amygdala to mediate behavioral responses to stress. CRF itself has anxiogenic-like effects, and CRF receptor antagonists injected into the central nervous system can reverse many behavioral responses to stress. Increased activity of the CRF system in the extended amygdala has been observed during acute withdrawal from virtually all major drugs of abuse (Merlo Pich et al., 1995; Rodriguez de Fonseca et al., 1997; Zorrilla et al., 2001).

Alcohol is also a powerful modulator of ''stress'' systems, an effect that may be crucial in understanding dependence and relapse. Both acute alcohol and chronic alcohol activate the HPA axis, and this appears to be the result of CRF release in the hypothalamus, which, in turn, activates the classic neuroendocrine stress response (Rasmussen et al., 2000; Rivier et al., 1984). This response shows tolerance due, at least in part, to a negative feedback response of glucocorticoids, but also an activation of the extrahypothalamic, extraneuroendocrine CRF system implicated in behavioral responses to stress (Koob et al., 1994; Kreek and Koob, 1998; Lee et al., 2001). The anxiogenic-like effect of alcohol withdrawal can be reversed by intracerebral administration of the CRF antagonist into the central nucleus of the amygdala (Rassnick et al., 1993). An increase in extracellular levels of CRF in the amygdala and the bed nucleus of the stria terminalis is observed during alcohol withdrawal (Merlo Pich et al., 1995). Even more compelling is the observation that a competitive CRF antagonist that has no effect on alcohol self-administration in nondependent rats effectively eliminates excessive drinking in dependent or postdependent rats (Valdez et al., 2002).

Neuropeptide Y (NPY) is a 36-amino-acid polypeptide distributed widely throughout the central nervous system, but with particularly high concentrations within the

extended amygdala (Adrian et al., 1983), and it may have a role in alcohol dependence in contrast to that of CRF (Valdez and Koob, 2004). Acute withdrawal from alcohol is associated with decreases in the levels of NPY in the central and medial nuclei of the amygdala and the piriform cortex (Roy and Pandey, 2002) and a blunted electrophysiological response to central injections of NPY in the amygdala (Slawecki et al., 1999). NPY injected intracerebroventricularly decreases alcohol consumption in alcohol-preferring P rats (Badia-Elder et al., 2001). One hypothesis is that decreased activity of NPY, parallel to increased activity of CRF, may provide a motivational basis for alcohol self-administration during alcohol withdrawal.

These results suggest, during the development of dependence, not only a change in the function of neurotransmitters associated with the acute reinforcing effects of alcohol such as GABA and glutamate but also recruitment of the CRF brain stress system and dysregulation of the NPY brain antistress system.

Preoccupation/Anticipation (Craving) Stage of the Addiction Cycle. Animal models for the preoccupation/anticipation (craving) stage are based on conditioned reinforcement and stress. Environmental cues repeatedly paired with primary reinforcers can acquire reinforcing properties via classical conditioning processes (McFarland and Ettenberg, 1997; See et al., 1999; Weiss et al., 2000). These conditioned reinforcing effects have been hypothesized to contribute to drug craving and relapse to addiction. Human studies have shown that the presentation of stimuli previously associated with drug delivery or drug withdrawal increases the likelihood of relapse as well as self-reports of craving and motivation to engage in drug taking (Childress et al., 1999; O'Brien et al., 1977, 1992). Several animal models are available based on reinstatement of alcohol seeking (i.e., when formerly neutral environmental stimuli that have been associated repeatedly with alcohol self-administration as well as aversive stimuli are presented to animals) (Weiss, 2005).

In the preoccupation/anticipation (craving) stage, 2 factors combine to produce a strong motivation for drug seeking that leads to relapse: a reactivation of the neurotransmitter systems implicated in the acute reinforcing effects of alcohol (craving type 1) and residual deficits in reward function associated with protracted abstinence (craving type 2). Driving these neurochemical changes is a restructuring of functional activity in the prefrontal cortex and basolateral amygdala that facilitates cue-induced craving via glutamatergic, dopaminergic, and opioid peptide activation (See et al., 2003). In contrast, stress-induced reinstatement in animal models appears to depend on CRF in the extended amygdala. Superimpose basal hypoactivity in the prefrontal cortex and a residual dysregulation in the extended amygdala reward system on the craving circuit (Goldstein and Volkow, 2002; Valdez and Koob, 2004), and one has a powerful driving force for relapse to excessive alcohol consumption.

Summary

Multiple neurotransmitter systems have been implicated in the acute reinforcing effects of alcohol, including GABA, opioid peptides, dopamine, serotonin, and glutamate. These neurochemical interactions have been localized to circuitry with focal points in the VTA, NAc, and central nucleus of the amygdala. After the development of dependence, during the withdrawal/negative affect stage of the addiction cycle, the function of reward neurotransmitters is dysregulated and there is a recruitment of the brain stress (antireward) systems. These changes persist in protracted abstinence. During the preoccupation/anticipation (craving) stage of the addiction cycle, there is temporary reactivation of the reward neurotransmitter systems superimposed on a basal hypofunctioning state that provides a compelling motivation for drug seeking, which leads to relapse.

RECENT DEVELOPMENTS IN THE GENETICS OF ALCOHOL DEPENDENCE

Marc A. Schuckit

Alcohol dependence is a typical complex, genetically influenced disorder. Similar to adult-onset diabetes, heart attacks, and most forms of cancer, multiple genes contribute to a range of characteristics (of phenotypes), which then interact with other characteristics (e.g., attitudes and the environment) to produce the condition. This presentation reviews data that support the importance of such genetic influences in alcoholism, discusses the complexities associated with these risk factors, presents an approach for evaluating the relationships between gene and environment in contributing to the alcoholism risk, and discusses how such research can lead to enhanced prevention and treatment efforts.

Data Supporting the Importance of Genes in Alcohol Dependence

Genetic factors are likely to play a role in the decision to drink (explaining a small proportion of the variance), the predisposition toward alcohol dependence among drinkers (the focus of this lecture), and the vulnerability for various consequences among alcoholic individuals (Schuckit, 2002). For dependence, family studies indicate a 4-fold increased risk for alcoholism among relatives of alcoholics, with higher vulnerabilities for those with a greater number of alcohol-dependent close relatives (Prescott and Kendler, 1999; Schuckit, 2002). Support for the conclusion that genes explain at least part of the familial nature of these disorders comes from both adoption and twin studies. The former shows that the enhanced alcoholism risk for offspring of alcoholic parents remains even if they are adopted away and raised by nonalcoholic parents, and the latter documents a higher level of similarity among pairs for identical twins who share 100% of their genes than for

fraternal twins who share only 50% (Goodwin et al., 1973; Heath et al., 1997; Prescott and Kendler, 1999).

Complexity of Genetic Influences

Few genetically influenced medical or psychiatric disorders operate through simple Mendelian dominant or recessive mechanisms, and alcoholism is no exception. For most conditions, genes influence a variety of characteristics (known as endophenotypes), which subsequently correlate with and interact with environmental events to increase the risk for the condition (Gottesman and Gould, 2003; McGue, 1997; Schuckit, 2002). For alcoholism, all the genes together explain 60% of the risk, and each genetically influenced endophenotype is likely to be impacted by multiple genes (i.e., they are polygenic) (Goldman, 1996; McGue, 1997).

Several different phenotypes have been shown to affect the risk of alcohol use disorders. In Asian individuals, genes that control the pattern of both alcohol and aldehyde dehydrogenases determine the drinking-related levels of the intermediate metabolite in the breakdown of alcohol, acetaldehyde. Some forms of these enzymes produce subsequent relative or absolute (depending on the enzyme) protection from alcoholism but demonstrate little, if any, impact on the risk for other substance use disorders (Li, 2000). A different set of genes affects the characteristics of impulsivity, enhanced sensation seeking, and disinhibition. These are reflected in a variety of ''externalizing'' or acting out behaviors, and they correlate with several neurophysiological measures and an enhanced vulnerability for dependence on all substances and additional externalizing conditions such as the antisocial personality disorder (Porjesz et al., 2002; Slutske et al., 1998). A third phenotype, unrelated to the 2 aforementioned characteristics, is the need for higher levels of alcohol to achieve the desired effects from early in one's drinking history, a phenomenon referred to as a low level of response (LR) to alcohol (Schuckit, 2002; Schuckit and Smith, 2000; Schuckit et al., 2000, 2005a). This enhances the risk for alcohol abuse and dependence but not for other substance use disorders (Schuckit, 2002). The search for genes contributing to LR and for a greater understanding of how these relate to the environment is described below.

Searching for Genes Contributing to Endophenotypes

This section will use the LR to alcohol as an example of the work going on with each of the endophenotypes mentioned above. Here, both human genetic linkage studies and genotyping in animals guide the selection of genetic candidates likely to affect the LR to alcohol (Schuckit et al., 2004; Wilhelmsen et al., 2003). Subsequently, subjects shown to be at a high or low LR can be genotyped, and specific variations (mutations of polymorphisms) in specific candidate genes can be evaluated for their correlation or level of association with LR. Data evaluated to date point toward the potential contribution of specific genetic variations (or polymorphisms) in several subunits of receptor genes for the neurotransmitter GABA, $GABA_{A\alpha6}$, and $GABA_{A\alpha2}$ (Hu et al., 2005; Pierucci-Lagha et al., 2005; Schuckit et al., 1999). Another genetic variation potentially related to LR may rest with the long form of the allele of the serotonin transporter, a polymorphism associated with the more rapid uptake of another neurotransmitter, serotonin, from the space between neurons in the brain (Hu et al., 2005; Schuckit et al., 1999). Additional preliminary information points to the possible role of an intracellular metabolizing enzyme active in the brain, CYP2E1 (Schuckit et al., 2005b). While none of these genes have been definitively proven to affect the LR to alcohol as a risk factor for alcoholism, these results serve as an example of the type of studies carried out to find genes contributing to phenotypes that have an impact on the alcoholism risk.

The Search for Environment That Contributes to the Risk

As genes together explain only part of the risk, there are multiple relevant phenotypes, and several genes contribute to each (Prescott and Kendler, 1999; Schuckit, 2002); any 1 gene is likely to explain less than 5% of the variance of risk. Therefore, it is important to study how the genes and phenotypes relate to major environmental events in enhancing or decreasing the risk. One approach to this challenging task is to use structural equation models in different populations to evaluate how the genetically related characteristics relate to multiple environmental events. The latter might include levels of stress, drinking among peers, attitudes toward alcohol, and ways of coping with stress. Two recent articles have evaluated such models in both adolescents and adults (Schuckit et al., 2004, 2005a), confirming the relationship between a low LR and a family history of alcoholism and showing that LR at least partially mediates how family history contributes to alcoholic outcome. In these models, a low LR is associated with both the selection of heavier-drinking peers and the development of more positive expectations of the effects likely to be produced by alcohol, with all of these characteristics both directly impacting alcoholic outcomes and operating through an increased probability of using alcohol to cope with stress.

Implications for Prevention and Treatment

As described previously, not everyone carries the same type of vulnerability toward alcoholism. Therefore, the more we know about specific genes that relate to a predisposition toward alcohol-related problems, and the greater our understanding of the environmental events that correlate with and interact with specific genes, the greater our ability to develop more specific and focused intrapersonal and environmentally based interventions to diminish the risk for alcoholism related to specific vulnerabilities.

A similar algorithm is appropriate for treatment. Not every alcoholic individual responds equally well to the same interventions. While such differences are likely to reflect a variety of influences, at least some of the variation may relate to different neurochemical vulnerabilities that affected the original alcoholism risk. Therefore, the greater our knowledge of specific genetic influences in this disorder, the greater our ability to evaluate why some individuals do and others do not respond to specific pharmacotherapies. Additionally, greater knowledge of specific biological vulnerabilities might also lead to the development of new pharmacological and psychological approaches for treating alcoholism.

Summary

Alcoholism is typical of types of complex genetic influences likely to be seen in most medical and psychiatric conditions. This lecture has reviewed an approach for identifying relevant intermediate characteristics, searching for related genes, and evaluating these factors in the context of real-life situations.

NEW PHARMACOLOGICAL STRATEGIES FOR TREATING ALCOHOL DEPENDENCE

Barbara J. Mason

In the past decade, 2 medications have been approved by the US Food and Drug Administration (FDA) for the treatment of alcohol dependence—naltrexone and acamprosate. This synopsis compares and contrasts clinical experiences with both of these medications.

Similarities and Differences Between Naltrexone and Acamprosate

Naltrexone and acamprosate are similar in that both have proved to be efficacious and well-tolerated pharmacotherapies for alcohol dependence in double-blind, placebo-controlled trials (Garbutt et al., 1999; Litten and Allen, 1998; Mason, 2001; Mason and Ownby, 2000; Swift, 1999). Their pharmacological profiles show neither any interaction with alcohol nor any abuse liability, tolerance, or rebound effects with discontinuation (Durbin et al., 1995; Mason, 2003; Saivin et al., 1998; Streeton and Whelan, 2001). Additionally, both are acceptable to alcoholic individuals; however, neither drug is a panacea, so there will be a proportion of individuals who will not respond to treatment.

The 2 treatments differ in their mechanisms of action; they act on distinct neural pathways and may act on different behavioral aspects of alcoholism (Littleton and Zieglgansberger, 2003; Mason, 2003). The distinct mechanisms of action for naltrexone and acamprosate may also explain why the safety profiles differ between the 2 drugs.

Efficacy of Naltrexone in the Treatment of Alcohol Dependence

Approved by the FDA in 1994, naltrexone is hypothesized to reduce the rewarding effects of drinking through the blockade of the endogenous opioid system (Spanagel and Zieglgansberger, 1997). Naltrexone has a rapid onset of action and precipitates withdrawal symptoms in opioid-dependent patients (Gonzalez and Brogden, 1988; Judson et al., 1981). Additionally, it blocks the self-administration of alcohol in animal models, and in humans, it blunts the rewarding effects of alcohol (Altshuler et al., 1980; Volpicelli et al., 1992). Naltrexone shows no tolerance or abuse potential or interaction with alcohol (Mason, 2003).

In data across 6 double-blind, placebo-controlled trials, naltrexone 50 mg/d did not show a significant effect over placebo for the rate of total abstinence (Anton et al., 1999; Gastpar et al., 2002; Guardia et al., 2002; Kranzler, 2000; Volpicelli et al., 1992, 1997). Naltrexone 50 mg/d appears to have its most robust effect in reducing relapse to heavy drinking. In 4 of 8 clinical trials, significantly fewer individuals treated with naltrexone relapsed to heavy drinking compared with individuals receiving placebo (Anton et al., 1999; Guardia et al., 2002; Latt et al., 2002; Volpicelli et al., 1992). A review of published double-blind, placebo-controlled trials suggests that naltrexone has beneficial effects in the short-term treatment of alcohol dependence, especially in compliant patients.

Efficacy of Acamprosate for the Treatment of Alcohol Dependence

Acamprosate might act by ''normalizing'' post–alcohol cessation hyperexcitability at the NMDA receptor (Littleton, 1995; Naassila et al., 1998; Zeise et al., 1993). Acamprosate is not metabolized in the liver (Durbin et al., 1995; Saivin et al., 1998). It does not induce or inhibit liver enzyme activity, and it appears to have few interactions with other drugs (Johnson et al., 2003b; Mason et al., 2002; Saivin et al., 1998). Because of the fact that acamprosate is excreted mostly unchanged in the urine (Durbin et al., 1995; Wilde and Wagstaff, 1997), its administration can be considered among alcoholic individuals at risk of hepatic impairment. Further, there appear to be no differences in acamprosate's pharmacokinetic profile as a result of gender or the presence of alcohol in the system (Saivin et al., 1998).

Experience Gained from International Clinical Trials

In 18 double-blind, placebo-controlled clinical trials of 2-, 3-, 6-, or 12-month duration conducted in Europe, Brazil, and Korea, acamprosate 1,998 mg/d overall had a statistically significant advantage over placebo in the rate of total abstinence (Mason, 2005). However, in 1 study where patients were followed up a year after study endpoint off-drug, patients who had been treated with

acamprosate sustained a significant advantage over placebo in the rate of complete abstinence (Sass et al., 1996). In studies measuring days to first drink, of the patients who did return to drinking, those treated with acamprosate tended to have a significantly longer latency in return to drinking compared with patients receiving placebo across studies. The cumulative abstinence duration (CAD), defined as the total number of days of complete abstinence or the percentage of abstinent days during the total possible duration of exposure to double-blind treatment, was also measured across studies. For acamprosate-treated patients, CAD was significantly greater across studies compared with placebo, suggesting clinical benefits to acamprosate treatment following a lapse to drinking.

From these studies comprising more than 5,000 alcohol-dependent patients from 13 countries, acamprosate showed a significant benefit compared with placebo in 15 of 18 clinical trials on abstinence outcomes. The principal adverse event reported with acamprosate use was mild diarrhea; however, this symptom was not associated with drug discontinuation.

Experience Gained from US Clinical Trials

A US study designed to confirm the efficacy and safety of acamprosate in alcohol-dependent patients had several objectives that differed from the European clinical trials. The 6-month, double-blind, placebo-controlled study included a 3 g/d dose and a different dosing schedule with a 2 g/d dose (two 500 mg tablets b.i.d., whereas previous studies had used two 333 mg tablets t.i.d.). The US study was designed to establish the safety of acamprosate in alcohol-dependent individuals who were nondetoxified and had urine samples positive for drugs while on the study, as well as to allow for inclusion of older alcohol-dependent patients (no upper age limit). Because of the open admission criteria, the ratio of randomized to screened subjects was very high. In addition, the US study used a standardized counseling program (available at www.alcoholfree.info), unlike the European clinical trials, where subjects received the counseling typically offered for alcoholism at their site.

Using an intention-to-treat analysis, CAD and change from baseline in γ-glutamyltransferase showed a linear dose response with acamprosate, although it did not reach statistical significance. Secondary reanalysis of the data, adjusted for covariates (such as baseline goal of abstinence, drug addiction severity, alcoholism severity, stage of readiness for change, psychological antecedents, and treatment exposure), showed a significant linear dose response for CAD, with acamprosate 3 g/d being more significantly effective than 2 g/d and placebo, and with a particularly robust treatment effect for patients who indicated at baseline that their treatment goal was to achieve abstinence. Safety results indicated no deaths or serious drug-related adverse events associated with acamprosate. The study had positive acceptability (high medication compliance $>88\%$) and generalizability results (81% of screened patients were randomized).

The benefits of acamprosate treatment are the favorable long-term treatment of alcohol dependence across a range of behavioral therapies, an increased rate of abstinence relative to placebo, sustained efficacy posttreatment, and an excellent safety profile with no serious adverse events. Since 1989, when acamprosate was first approved for treating alcoholism in France, there has been no observed health risk in more than 1.5 million patients treated with acamprosate. Based on the results of the US study, therapeutic results are optimized when patients are highly motivated to have abstinence as their treatment goal.

Risk–Benefit Analysis: Efficacy and Safety

In a comparison of the published efficacy of acamprosate and naltrexone for risk–benefit analysis, the evidence shows that acamprosate is more likely to increase abstinence, whereas naltrexone's prominent effect is to decrease heavy drinking (Mason, 2003). Acamprosate has also shown long-term efficacy, sustained efficacy posttreatment, and an overall higher rate of compliance with medication relative to naltrexone (Mason, 2003). Nevertheless, compliance with naltrexone might be facilitated by sustained release (depot) formulations that eliminate the potential for oral doses to be missed and could reduce nausea because of the relatively lower blood levels (Kranzler et al., 2004).

The safety profiles for both drugs are generally favorable; however, naltrexone has, perhaps, the greater potential for significant adverse events. For example, high dosing with naltrexone might increase the risk of accentuating hepatic impairment; however, these doses (>300 mg/d) exceed greatly that typically used for the treatment of alcoholism. Caution should be excercised in prescribing naltrexone to individuals who might require opiate medication for analgesia, and naltrexone may precipitate withdrawal symptoms in opiate addicts. Also, there have been some reports of increased depressive symptoms in depressed patients, as well as the potential for an interaction with nonsteroidal antiinflammatory medications (Mason, 2003).

Summary

Acamprosate and naltrexone appear to act on different behavioral aspects of alcohol dependence; acamprosate is more likely to increase abstinence, whereas naltrexone's prominent effect is to decrease heavy drinking. Whereas alcohol-dependent individuals who are motivated highly toward abstinence benefit most from acamprosate, those who are highly compliant with taking their medication experience the greatest treatment gains from naltrexone. As both treatments for alcohol dependence are effective on different behavioral aspects of the alcoholism disorder, the

risk–benefit analysis and treatment goals should be considered when determining the appropriate treatment for a particular patient.

NEW MEDICATIONS: THE USE OF ANTICONVULSANTS, BOTH ALONE AND IN COMBINATION, WITH VARIOUS FORMS OF PSYCHOTHERAPY

Bankole A. Johnson

The use of medications with anticonvulsant properties to treat alcohol dependence is emerging as a most promising area of medications development. Principal among the properties of such agents is that they may have a dual role in treating alcohol dependence; i.e., they might ameliorate the symptoms of alcohol withdrawal and, by continuing the treatment, prevent relapse. These actions are related to the effects of the medications to antagonize glutamate or facilitate GABA, or both, within the corticomesolimbic system. This presentation will include new data showing the efficacy of a variety of compounds (e.g., topiramate, gabapentin, and valproate) as either antiwithdrawal or relapse prevention agents or both. Finally, new data will be presented showing that the unique pharmacological characteristic of GABA/glutamate modulation by one of these agents, topiramate, appears to have an added effect with the 5-HT_3 antagonist ondansetron, perhaps through conjoint activity to potentiate GABAergic feedback to the VTA.

Efficacy of Gabapentin as a Treatment for Alcohol Dependence

Gabapentin is related structurally to GABA (McLean, 1999). Its mechanism of action includes the blockade of L-type calcium channels as well as facilitation of GABA synthesis (McLean, 1999; Petroff et al., 2000). Further, gabapentin is excreted unmetabolized in the urine and, therefore, will not exacerbate alcohol's hepatotoxic effects. Taken together, these pharmacological properties make it a promising candidate medication for treating alcohol withdrawal symptoms.

Gabapentin decreases ethanol withdrawal hyperexcitability in isolated slices of hippocampus (Bailey et al., 1998) as well as convulsions and anxiety in alcohol-withdrawn mice (Watson et al., 1997).

Initial evidence supporting the utility of gabapentin to reduce alcohol withdrawal symptoms is derived from a case report (Chatterjee and Ringold, 1999) and a few studies investigating open-label use in a case series (Bonnet et al., 1999; Bozikas et al., 2002; Karam-Hage and Brower, 2000; Myrick et al., 1998; Voris et al., 2003). Further, there is evidence from a case series that gabapentin might be useful for a specific aspect of a severe alcohol withdrawal syndrome, the decrease of tonic-clonic seizures (Rustembegovic et al., 2004). Nevertheless, in a controlled study, Bonnet et al. (2003) showed that patients who received gabapentin (400 mg q.i.d.) compared with placebo for treating alcohol withdrawal symptoms showed no significant difference in the frequency and severity of their withdrawal symptoms, and their consumption of the "rescue medication," clomethiazole, in the first 24 hours was similar.

In essence, gabapentin's potential as an antiwithdrawal agent remains to be substantiated by controlled trials. More studies are needed to determine whether gabapentin might be efficacious in treating 1 particular component of severe alcohol withdrawal—tonic-clonic seizures.

Efficacy of Valproate as a Treatment for Alcohol Dependence

Although sodium valproate's mode of action remains unclear, it does appear to increase GABA levels in the brain (Johannessen, 2000).

Following cessation of alcohol consumption, 1 aspect of maintaining improved treatment outcomes is to prevent relapse. In a small pilot study ($N = 16$), Longo et al. (2002) compared the safety and efficacy of the anticonvulsant agent divalproex (valproate) with standard benzodiazepine detoxification for alcohol withdrawal and relapse prevention. In this study, participants received standard benzodiazepine detoxification with chlordiazepoxide or lorazepam, divalproex detoxification for 5 days (including a loading dose on Day 1), or divalproex detoxification plus 6-week maintenance. The findings were that at the 6-week follow-up, 4 of 5 participants in the divalproex maintenance group were completely abstinent compared with either detoxification-alone group (5 of 11), and none relapsed to daily or heavy drinking. Despite the small sample size, divalproex might have utility as a postdetoxification relapse-prevention agent.

In a 12-week, double-blind, placebo-controlled trial of divalproex in 31 alcohol-dependent subjects, Brady et al. (2002) tested the idea that the continued use of an agent, such as divalproex, which is effective in alcohol withdrawal, might be effective in treating protracted-abstinence syndrome. Protracted-abstinence syndrome is characterized by sleep disturbance, irritability, anxiety, and dysphoria and is associated with the highest risk for relapse. Results showed that the only significant difference in drinking outcome was a trend toward a greater decrease in heavy drinking days, and a smaller percentage of individuals who relapsed to heavy drinking were seen among the divalproex-treated group. Further, there was a trend toward more reductions in the indirect hostility subscales of the Buss–Durkee hostility index, and there were significant differences in decreases in the irritability component of the anger, irritability, aggression scale between the divalproex-treated group and the placebo group ($p = 0.009$).

In 2005, Salloum et al. (2005) reported the results of a 24-week randomized, double-blind, controlled study that determined the efficacy of divalproex in the treatment of alcohol-dependent bipolar patients stabilized on lithium

carbonate and psychosocial intervention. The valproate-treated group compared with the placebo group had a significantly lower proportion of heavy drinking days ($p = 0.02$) and γ-glutamyltransferase levels and a trend toward fewer drinks per heavy drinking day ($p = 0.055$). Higher divalproex serum concentration was correlated significantly with improved alcohol use outcomes.

In summary, divalproex might be a promising medication for treating alcohol-dependent patients with comorbid bipolar disorder.

Efficacy of Topiramate as a Treatment for Alcohol Dependence

Topiramate, a sulfamate-substituted fructopyranose derivative, exerts its pharmacological action by decreasing dopamine-mediated corticomesolimbic function via suppression of glutamate activity at kainate and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors and augmentation of GABA activity (Johnson et al., 2003a). These properties make topiramate a promising medication for the treatment of alcohol dependence and the alleviation of withdrawal symptoms.

Predicated on this hypothesis, Johnson et al. (2003a) showed that topiramate (up to 300 mg/d) was superior to placebo at improving drinking outcomes. Additionally, topiramate treatment was associated with a reduction in the harmful psychosocial consequences of alcohol and an improvement in quality of life (Johnson et al., 2004). More recently, topiramate appeared to ameliorate alcohol withdrawal symptoms (Choi et al., 2005).

Overall, these studies show that topiramate is a promising medication for the treatment of alcohol dependence and the alleviation of alcohol withdrawal symptoms.

Preliminary Data on the Efficacy of Combined Topiramate and Ondansetron for Treating Alcohol Dependence

Recently, there has been scientific and clinical interest in combining therapeutic agents for the treatment of alcoholism. This is predicated on the hypothesis that multiple neurochemical pathways may be deranged as either state or trait effects of the drinking behavior, and combining effective medications working at different neurotransmitters may produce a synergistic or at least added response.

There are both direct and indirect neurochemical mechanisms for specifically combining the effects of ondansetron and topiramate. In support of a direct mechanism, basic research has shown that the expression of alcohol's rewarding effects through enhancement of dopamine release in the NAc is mediated through activation of 5-HT_3 receptors (Campbell and McBride, 1995). The 5-HT_3 receptor antagonist ondansetron modulates suprabasal but not basal dopaminergic neuronal activity in the corticomesolimbic system (Fadda et al., 1991; Imperato and Angelucci, 1989). Dopaminergic input into the NAc is inhibitory on GABA neurons, which project from the NAc to cortical structures (Hemby et al., 1997; Koob, 1992). Therefore, the net functional effect of 5-HT_3 antagonism also would be to facilitate GABAergic output to the hippocampus and the cortex (Skradski and White, 2000; White et al., 1997).

It would be reasonable, therefore, to expect that topiramate's ability to facilitate GABAergic transmission in the hippocampus and cortex would be at least additive to that of ondansetron. In support of an indirect mechanism, 5-HT_3 antagonism would be expected to potentiate GABA input back to the VTA. Thus, dopamine firing in the VTA would be suppressed. The facilitation of GABA output back to the VTA by topiramate would be expected to enhance ondansetron-induced suppression of dopamine firing in the VTA. Also, topiramate would be expected through α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid/kainate glutamate receptors to decrease dopaminergic excitatory input from the VTA and the NAc, thereby further enhancing GABAergic function and suppressing midbrain dopamine nerve cell firing. Taken as a whole, this mechanistic proposal provides a sound and compelling rationale for the combination of ondansetron and topiramate for the treatment of alcoholism. Of course, the therapeutic effects of the combination can be expected to be most profound among early-onset compared with late-onset alcoholic individuals (who have higher familial and biological disease predisposition and antisocial behaviors) because ondansetron also might be ameliorating serotonergic abnormality. Nevertheless, it is also possible that the nonsignificant trend of ondansetron to improve drinking outcomes (Johnson et al., 2000b) might be improved by the addition of topiramate.

We have conducted an open-label pilot study to determine the safety of combining ondansetron (4 μg/kg b.i.d.) and topiramate (up to 300 mg/d) in 10 DSM-IV-diagnosed (American Psychiatric Association, 1994), alcohol-dependent subjects. As the neurochemical profiles of both medications are quite different (ondansetron—serotonergic; topiramate—GABAergic), and there are no known interactions between the medications, this pilot trial was conducted primarily to gain experience with the combination. For example, the adverse events that occurred with significantly greater frequency with topiramate than with placebo were in the central nervous system, whereas no gastrointestinal symptoms were reported (Johnson et al., 2003a). In contrast, ondansetron (1–16 μg/kg b.i.d.) does not have significantly more adverse events than placebo (Johnson et al., 2000b). Indeed, the few adverse events reported commonly were gastrointestinal (i.e., constipation), with a rate of 5.0 versus 1.4% for ondansetron and placebo, respectively. Hence, there is no significant symptom overlap in the adverse-event profile of both medications.

In the present pilot study, topiramate's dose escalation was similar to that described previously (Johnson et al., 2003a), and ondansetron (4 μg/kg b.i.d.) was administered

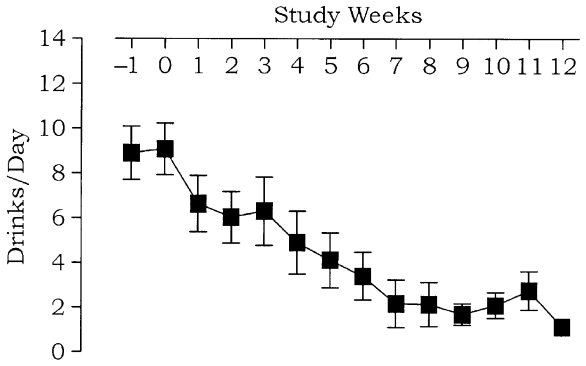

Fig 1. Effects of combined ondansetron (4 μg/kg b.i.d.) and topiramate (up to 300 mg/d) on daily drinking by study week.

from the beginning of the study. Despite the lack of a placebo comparison group, it is promising that the drinking data showed a marked and deepening decrease from baseline across study weeks (Fig. 1). The mean baseline drinking was 8.90 ± 1.20 drinks/d (Fig. 1). Also, percentage of days abstinent increased from 4.22 ± 1.96 to 78.57 ± 7.14 (data not shown). Notably, adverse-event rates for this ondansetron and topiramate combination versus those obtained for topiramate alone were as follows: dizziness—17% versus 28%; paresthesia—17% versus 57%; psychomotor slowing—17% versus 27%; memory or concentration impairment—17% versus 19%; and weight loss—33% versus 55%. All of these adverse events for the ondansetron and topiramate combination were reported as being mild, and no concomitant medication or medical intervention was needed. The combination of ondansetron and topiramate was not associated with any serious adverse events or subject withdrawal from the study. Only 2 participants were lost to follow-up. Hence, fewer adverse events appear to be associated with the combination of ondansetron and topiramate than with topiramate alone. We, therefore, conclude that the combination of ondansetron and topiramate is safe and feasible to administer.

Although this was an open-label study with no placebo control group, the rate of decline in drinking was striking. For instance, in our demonstration of the efficacy of ondansetron (4 μg/kg b.i.d.) among early-onset alcoholic individuals (Johnson et al., 2000b), the mean difference in drinks per day between enrollment and study end was –3.28. In contrast, the mean difference in drinks per day between enrollment and study end in this pilot study was –7.95, more than twice as large. Although these studies are not entirely directly comparable, and therefore this contrast must be interpreted very cautiously, these data are encouraging and would be consistent with our prediction that the therapeutic effects of ondansetron and topiramate will be additive.

In summary, these new preliminary data demonstrate that the combination of topiramate and ondansetron is safe and might yield greater therapeutic benefit than either alone in treating alcoholism.

DIFFERENTIAL EFFECTS OF PHARMACOLOGICAL AGENTS ON CRAVING

Nassima Ait-Daoud

Craving is a broad term that is used differently by investigators and clinicians. It has been difficult to reach agreement on a standard definition for this phenomenon because of its subjective nature (Anton, 1999). Most would agree that, generically, it could be defined as a specific strong subjective drive to use a substance or eat a specific food that is followed by "going out of one's way to get the object of the craving." Craving has been reported by patients during drug use as well as after months and years of abstinence. Importantly, craving has increasingly become an important target for the treatment of patients with alcohol problems, mainly by clinicians and by patients looking for help to ease the grip that the addictive disease has on them. An important point of discord is that in some alcohol treatment clinical trials, drinking reduction or abstinence was reported without any change in craving and sometimes without any report of craving by patients at baseline. This creates doubt about the role of craving, if any, in drinking behavior and raises 3 important points. First, patients need to be educated on the neural and behavioral adaptations that have occurred with chronic alcohol use, which make drinking feel more like a natural behavior and mask the real craving for alcohol. For these patients, helping them recognize craving when it occurs usually provides them with an additional tool to fight alcohol dependence. Second, improved methods are needed to measure craving neurobiologically without the creation of more time consuming, lengthy questionnaires that are not capturing this phenomenon. Finally, clinicians need to categorize craving into a more meaningful, standardized, and clearly defined typology as some medications or interventions may be more helpful with 1 type of craving than with another.

The Classification and Assessment of Craving

There are many ways to characterize craving. Verheul et al. (1999) used a biopsychosocial approach for their classification of craving to help select pharmacological agents targeted at specific biological underpinnings associated with each type of craving. Reward-craving symptoms include a spontaneous search for alcohol and its rewarding effects, the inability to abstain from binge drinking, and a hypersensitivity to the rewarding effects of alcohol. These characteristics are usually associated with a positive family history and the early development ("early onset") of alcoholism. As dopamine is at the center of the reward system, the dopaminergic/opioid pathway may be involved with the deficit of opioids/β-endorphins. Relief-craving symptoms include drinking for relief of stress and tension with a hypersensitivity to the sedative effects of alcohol. These characteristics are observed mainly among

late-onset alcoholic individuals and patients experiencing withdrawal symptoms and may be due to a dysregulation of neuronal excitability controlled by the GABAergic/glutamatergic pathway. Obsessive craving symptoms include a loss of control over intrusive thoughts associated with compulsive drinking. These obsessional-type behaviors lead patients to report a major bearing of drinking on their lives, with intrusive thoughts about alcohol monopolizing their days. Like other obsessional disorders, the serotonergic pathway may be involved with this type of craving. Although this typology is appealing from a clinical point of view and corroborates well with the Lesch typology (Lesch and Walter, 1996), which is widely used in Europe, the major drawback is that the brain is not divided into independent compartments dealing with separate subjective states such as craving, and most pharmacological agents do not target a single area or pathway in the brain. Additionally, there is no validated tool that can segregate between the different types of craving while recognizing that most patients may experience more than 1 type of craving.

The most widely used tools to measure craving are the visual analog scales (VAS), which assess craving "during the past 24 hours," or another specified time period such as "right now," using a 100-mm horizontal line. Single-item scales do, however, lack the parametric ability to assess fully the multidimensional nature of craving. For example, the obsessive–compulsive drinking scale (OCDS) is a well-validated, reliable, sensitive, and multidimensional measure of the obsessive type of alcohol craving (Anton et al., 1996). It is a 14-item self-assessment based on 4 empirically derived factors as follows: drinking obsessions, alcohol consumption, automaticity of drinking, and interference due to drinking. The OCDS is highlighted here because of its wide use in current pharmacotherapy trials in alcohol dependence.

Differential Effects of Pharmacological Agents on Craving

Naltrexone. Naltrexone, a μ-opioid antagonist, is hypothesized to reduce relapse to drinking by blocking the rewarding effects, and reducing the reward-associated craving, of alcohol. However, data regarding the effects of naltrexone on craving have been inconsistent. For example, 1 study ($N = 70$) demonstrated a positive effect of naltrexone 50 mg/d on craving (Volpicelli et al., 1992), but another study ($N = 97$) by the same group did not show the same effect (Volpicelli et al., 1997). In clinical trials, naltrexone-treated patients, compared with those who received placebo, showed a significantly lower percentage of full relapse, fewer drinks per drinking occasion, and a lower percentage of drinking days. The efficacy of naltrexone was increased when the treatment was combined with psychological support. Reduction in craving as measured by the VAS was substantial in patients who received naltrexone and coping skills therapy and who completed the trial (Anton et al., 1999; O'Malley et al., 1995). In another clinical trial ($N = 131$) that measured craving using the OCDS, naltrexone was found to reduce some of the obsessive components of craving and improve resistance/control impairment (Anton et al., 1999). This suggests that naltrexone-treated patients may experience greater control over drinking, especially after the first slip. In summary, naltrexone showed a tendency to decrease the desire to drink after a slip and may prevent relapse; however, there have not been consistently positive efficacy results on craving and its relationship with drinking.

Acamprosate. Acamprosate, an N-acetylated homotaurine analog, is thought to mediate the inhibition of NMDA/glutamate receptors as well as decrease the sensitivity of voltage-gated calcium ion channels, resulting in a decrease in the activity of the excitatory component of the central nervous system. This would theoretically make it an ideal treatment for patients with relief-craving or withdrawal symptoms. Double-blind clinical trials in detoxified alcohol-dependent patients have consistently shown the efficacy of acamprosate (1,332 or 1,998 mg/d) in lengthening time to relapse, reducing drinking days, and maintaining abstinence (Bouza et al., 2004; Mason, 2003; Paille et al., 1995; Sass et al., 1996; Weinstein et al., 2003). However, there have been conflicting results for craving. While some authors have reported a significantly favorable effect of acamprosate on craving (Chick et al., 2000; Paille et al., 1995; Sass et al., 1996), others have failed to observe any significant effects at 12 months of treatment (Gual and Lehert, 2001). Tentative identification of treatment responders in Europe using the Lesch typology (Lesch et al., 1988) has shown that alcoholic individuals categorized as Lesch types I and II (Lesch et al., 2001) benefit the most from acamprosate.

γ-Hydroxybutyric Acid. γ-Hydroxybutyric acid (GHB) is a naturally occurring short-chain fatty acid found in the human brain and is formed primarily from the precursor GABA. Its mechanism of action is not completely known. Intake of GHB saturates GHB receptors and produces $GABA_B$ effects, explaining its alcohol-mimetic effect on the central nervous system. Clinical trials found GHB (50 mg/kg t.i.d.) to be effective at reducing alcohol craving as measured by the alcohol craving scale (Caputo et al., 2003), presumably by reproducing the rewarding effects of alcohol (Agabio et al., 1998; Gessa et al., 2000). The side effects of GHB include dizziness, hyporeflexia, and somnolence, which are usually well tolerated. However, there is a serious risk of abuse and dependence associated with using GHB, thus limiting its usefulness.

Baclofen. Baclofen is a $GABA_B$ agonist currently used to treat muscle spasticity. There are a limited number of randomized clinical trials assessing the role of baclofen in alcohol dependence. A small published study ($N = 39$) reported that baclofen (15–30 mg/d) was superior to placebo at reducing drinking and craving, as evidenced by a reduction in total OCDS score and the obsessive and

compulsive subscale (Addolorato et al., 2002b). It is possible that the suppressing effect of baclofen on alcohol withdrawal symptoms and the reduction of obsessive craving may aid patients in achieving and maintaining abstinence (Addolorato et al., 2000, 2002c). Baclofen is usually well tolerated and without any risk of abuse, making it an ideal treatment for relief and/or obsessive craving. Larger randomized clinical trials are needed, however, to corroborate such positive results (Addolorato et al., 2002a).

Topiramate. Topiramate is an antiepileptic drug that acts as a $GABA_A$ receptor agonist at a nonbenzodiazepine site. Based on its effects on GABAergic and glutamatergic systems, topiramate is hypothesized to be effective in treating patients with relief craving. In a randomized clinical trial with 150 subjects, Johnson et al. (2003a) were the first to show that topiramate is effective in reducing drinking, increasing abstinence, and improving overall quality of life and impulsivity among currently drinking, alcohol-dependent individuals. Craving was assessed at baseline and at every treatment week for the duration of the study using the OCDS. Topiramate $\leq$ 300 mg/d, compared with placebo, reduced all subscale measures of craving. Craving reductions were predictive and consistent with decreases in drinking outcomes. The implications of these findings are unclear and raise consideration of the bidirectionality of craving and drinking. For instance, could these findings be due to the fact that the significant reductions in drinking diminished craving response rather than the other way around? Could it be that, because of its multiplicity of pharmacological action, topiramate might have an effect on different types of craving? Obviously, further research studies in controlled settings such as the human laboratory are needed to find responses to these questions. Recently, an inpatient study found that topiramate 50 mg/d ($N = 25$) was as effective as lorazepam up to 4 mg/d ($N = 27$) in treating alcohol withdrawal (Choi et al., 2005). These results are consistent with our impression that alcohol withdrawal symptoms did not increase when subjects were asked to cut back on or cease active drinking while on topiramate (Johnson et al., 2003a). Taken together, these data suggest that topiramate appears to be effective at suppressing alcohol withdrawal symptoms and, in this way, might have a particular benefit of decreasing relief craving.

Serotonergic Agents. The activity profile of selective serotonin reuptake inhibitors (SSRIs) should make this class of drugs an ideal treatment for the obsessive craving associated with alcohol dependence. In general, however, there is no strong evidence supporting the effectiveness of SSRIs for the treatment of alcohol dependence (Chick et al., 2004). Some clinical studies have shown the efficacy of fluoxetine (20 mg/d) in depressed, alcohol-dependent patients but did not report its effects on craving (Cornelius et al., 1997; Janiri et al., 1996). Fluoxetine was found first to decrease depressive symptoms and then to reduce drinking in alcohol-dependent patients. Therefore, fluoxetine can be an ideal drug for patients who self-medicate their depression with alcohol and for those who do not have alcohol dependence as their primary diagnosis. However, it is important to take into consideration the difficulty in segregating primary from secondary diagnoses when treating depressed alcoholic individuals. Whereas 1 study indicated some efficacy of SSRIs in treating late-onset alcoholic individuals (Pettinati et al., 2000), another found that SSRIs can make symptoms worse in early-onset alcoholic individuals (Kranzler et al., 1996).

Ondansetron is a $5\text{-}HT_3$ antagonist that can reduce corticomesolimbic dopaminergic activity and thereby reduce the rewarding effects of alcohol. A recent double-blind clinical study ($N = 20$) of ondansetron (4 μg/kg b.i.d.) as adjunctive treatment to cognitive behavioral therapy showed that it was superior to placebo in reducing drinking and increasing abstinence in early-onset but not late-onset alcoholic individuals (Johnson et al., 2000b). Of interest, ondansetron was also found to decrease reward craving, as measured by the VAS in early-onset but not late-onset alcoholic individuals, therefore correlating with the drinking reduction (Johnson et al., 2002).

Combining Medications

Combining medications is another way to increase the effectiveness of pharmacological agents. This is important because the same individual can often experience different types of craving on the same day. Targeting multiple neurotransmitter systems, therefore, may further enhance a reduction in craving. In a small, preliminary, randomized clinical trial ($N = 20$), the combination of ondansetron 4 μg/kg b.i.d. and naltrexone 25 mg b.i.d., compared with placebo, was effective at reducing drinking and automaticity of drinking on the OCDS in early-onset alcoholic individuals (Johnson et al., 2000a). A reduction in automaticity of drinking was strongly correlated with reduced drinking and increased abstinence, and the effect size of combined ondansetron and naltrexone treatment was large (Ait-Daoud et al., 2001). These findings suggest that combining different pharmacological agents with complementary mechanisms of action may be a strategy for developing effective alcohol dependence treatments in the future.

New Vistas

Excessive alcohol consumption affects plasma levels of hormones of the HPA system (Brady and Sonne, 1999). Attempts to better delineate some of these effects have yielded promising yet contradictory results. For example, cortisol secretion stimulated by corticotropin-releasing hormone was found to be decreased in actively drinking alcoholic individuals, increased during withdrawal (Adinoff et al., 1991), and at normal levels during early abstinence (Adinoff et al., 1990; Inder et al., 1995). In another study, results showed a correlation between baseline craving and the activity of the HPA axis in

alcohol-dependent subjects treated with naltrexone, such that lower cortisol levels were associated with higher levels of craving. The plasma cortisol and adrenocorticotropic hormone levels were higher in the naltrexone group compared with placebo during treatment (O'Malley et al., 2002). Studies have shown that other factors might also influence the HPA axis and craving. Whereas the HPA axis peptides, such as cortisol or adrenocorticotropic hormone, might decrease craving in alcoholic individuals, peptides with an inhibitory action, such as leptin, tend to be associated with increased craving (Kiefer et al., 2002). Further investigation to better understand the role of the HPA axis in alcohol drinking and craving will provide a promising tool for the fight against alcohol dependence.

Summary

Craving is not yet well understood in alcohol dependence; however, through research, our understanding may lead to the development of effective pharmacotherapeutic tools. The role of craving in the maintenance of drinking behavior has been proven through numerous clinical trials reporting its correlation with increased drinking. More tools are needed to identify and subtype craving, such as specific assays that can provide an objective measure of treatment response. Finally, educating clinicians and patients about the importance of recognizing craving in everyday life would be useful for patients to gain control over their drinking.

CONCLUSIONS

Multiple neurotransmitter systems have been implicated in the acute reinforcing effects of alcohol, including GABA, opioid peptides, dopamine, serotonin, and glutamate. These neurochemical interactions have been localized to circuitry in the corticomesolimbic system and extended amygdala, with focal points in the VTA, NAc, and central nucleus of the amygdala. Neuroadaptive changes within this circuitry regulate the transition from alcohol taking to alcohol dependence through the reward system. In contrast, during alcohol withdrawal and protracted abstinence, there is recruitment of brain stress (i.e., antireward) systems. Therefore, a greater understanding of these neurochemical and neurohormonal adaptive responses would enable progress in identifying biological (including molecular) targets associated with disease pathophysiology, as well as viable targets for pharmacotherapeutic treatment.

The development and pathophysiology of alcohol dependence are influenced by complex genetic interactions with environmental factors to define particular behavioral endophenotypes or disease subtypes. These behavioral endophenotypes can be conceptualized as the building blocks that assemble to express the full-blown disease. Genetic studies of these behavioral endophenotypes have established the contribution of genetic factors to the pathophysiology of the disease and, ultimately, might aid in identification of vulnerability factors. Ongoing research is using the concept of alcohol subtypes to examine how polymorphic differences (e.g., at the serotonin transporter) not only might contribute to differential behavioral responses to alcohol but could also be used to target specific medication to a particular subtype for optimal therapeutic response.

In the past decade, 2 medications have been approved by the US FDA for the treatment of alcohol dependence. Interestingly, however, acamprosate and naltrexone appear to act on different behavioral aspects of alcohol dependence; acamprosate is more likely to increase abstinence, whereas naltrexone's prominent effect is to decrease heavy drinking. Further, whereas alcohol-dependent individuals who are motivated highly toward abstinence benefit most from acamprosate, those who are highly compliant with taking their medication experience the greatest treatment gains from naltrexone. As both treatments for alcohol dependence are effective on different behavioral aspects of the alcoholism disorder, the risk–benefit analysis and treatment goals should be considered when determining the appropriate treatment for a particular patient. Notably, additional refinement in identifying which patient would benefit most from naltrexone or acamprosate has been investigated actively in recent clinical trials that have incorporated analysis of therapeutic response by alcoholism subtype.

Novel medications that have anticonvulsant-type properties or that modulate GABA/glutamate function appear to be a promising avenue in medications development for treating a spectrum of alcohol use–related disorders. This is because these classes of compounds could have efficacy in treating either the alcohol dependence or alcohol withdrawal symptoms or both. For example, in small-sample clinical studies, gabapentin, valproate, and topiramate all appear to ameliorate alcohol withdrawal symptoms; therefore, the results of larger confirmatory studies are awaited eagerly. Some of these agents have shown clinical utility at improving the drinking outcomes of alcohol-dependent individuals. For instance, valproate has been shown to be efficacious in treating alcohol dependence among individuals with comorbid bipolar disorder. Additionally, topiramate has been shown to be efficacious in treating alcohol dependence and, when topiramate is combined with ondansetron, these therapeutic effects might be magnified.

Notwithstanding the conceptual approach of directing pharmacotherapeutic strategies toward reducing craving for alcohol, this phenomenon is not well understood and, at times, has been controversial. This is because although numerous clinical trials have demonstrated a relationship between craving and drinking, others, particularly those trials studying naltrexone, have not demonstrated such a relationship or have been equivocal. As different behavioral components of craving have been associated with

various neurobiological processes, understanding which medication(s) might be most efficacious at ameliorating a particular type of craving could enable optimization of pharmacotherapeutic strategy. At its core, this approach could also underlie the essence of differential pharmacogenomic response. Although speculative, it is tempting to note that medications modulating glutamate function, such as acamprosate and topiramate, seem best to target postcessation or relief craving; medications modulating GABA function, such as baclofen, might reduce obsessive craving; and the 5-HT_3 antagonist, ondansetron, appears to decrease reward craving. Further studies are needed to understand the pathophysiological (i.e., biological and environmental) and treatment implications of this differential effect of class of medication on various types of craving.

Further studies are also needed to elucidate more fully the complex biological and environmental interactions that occur to define vulnerability, pathophysiology, and differential response to various medications in treating the spectrum of alcohol dependence and withdrawal-related disorders.

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