

Pharmacotherapy of Alcohol Use Disorders: Seventy-Five Years of Progress

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ABSTRACT. Modern pharmacotherapy for alcohol dependence has its roots in the failure of National Prohibition in the United States and the rise of the disease model of alcoholism (embodied in Alcoholics Anonymous). In 1948, disulfiram was the first medication approved by the U.S. Food and Drug Administration (FDA) to treat alcohol dependence, but its efficacy has not been supported by randomized controlled trials. In the 1960s, benzodiazepines replaced older treatments for alcohol withdrawal, but sedative and dependence-producing effects limit their utility in the postwithdrawal period. In the 1980s, the focus shifted to the treatment of co-occurring psychiatric disorders and medications that modify negative mood states, which contribute to relapse to heavy drinking. In the 1990s, developments in neurobiology implicated specific neurotransmitter systems underlying alcohol's effects, culminating in the 1994 approval by the FDA of the opioid antagonist naltrexone to

treat alcohol dependence. In 2006, the FDA approved a long-acting formulation of naltrexone. Recently, nalmefene, another opioid receptor antagonist, was approved in Europe for as-needed use to reduce heavy drinking. Acamprosate, an amino acid derivative, first approved in France in 1989, received FDA approval in 2004. However, the beneficial effects of the approved medications are only modestly greater than those of placebo, and their use is limited. Topiramate, currently under investigation for alcohol dependence, has greater efficacy but a variety of adverse effects. In addition to the identification of novel compounds, the future of alcohol dependence pharmacotherapy will depend on developments in pharmacogenetics, in which genetic variation that moderates treatment efficacy and adverse effects is used to personalize treatment. (*J. Stud. Alcohol Drugs, Supplement 17*, 79–88, 2014)

MODERN PHARMACOTHERAPY FOR ALCOHOL use disorders had its genesis in two seminal events: the repeal of National Prohibition in the United States in 1933 and the establishment of Alcoholics Anonymous (AA) in 1935. Although these events did not lead directly to the use of medications (and, in fact, AA has opposed the use of medications that can potentially cause dependence or that are intended to help heavy drinkers reduce, rather than stop, drinking), they contributed to the view that alcoholism is a treatable disease that may be amenable to pharmacotherapy (Levine, 1984).

Prohibition's advocates had argued that the elimination of alcoholic beverages would end alcoholism and all its associated evils. The external control on the availability of distilled spirits reduced overall per capita alcohol consumption, but it failed to end alcoholism. Although the repeal of Prohibition was the result of many factors unrelated to drinking (Levine, 1984), passage of the Twenty-First Amendment (U.S. Const. amend. XXI) was an acknowledgment that external controls limiting access to alcoholic beverages were not sufficient to prevent alcohol misuse.

The establishment of AA, shortly after Prohibition's repeal, solidified this view. It re-established the theory, prevalent among those in the early Temperance Movement, that alcoholism was a progressive disease. Early support of AA by the Yale Center of Alcohol Studies (now the Center of Alcohol Studies at Rutgers University) lent the self-help organization scientific credibility. Although AA continues to oppose any therapeutic approach that does not endorse abstinence as its goal, its disease construct remains highly influential and has indirectly supported biological approaches to alcohol treatment (Levine, 1984).

In the pages that follow, we review chronologically the main foci of medications development for alcohol dependence. Of necessity, this review is not exhaustive; rather, it aims to highlight the changes that have occurred in medications development and guide further developments in the field. A recent review provides more detailed information on the medications for which efficacy has been demonstrated and the preclinical basis for their use (Kranzler et al., 2013).

Conditioned reflex treatment

In the 1930s, psychotherapy was the dominant mode of alcoholism treatment. The few drug therapies available were not supported by scientific data and were of questionable value. Many of these remedies relied on the concept of aversive conditioning or "conditioned reflex treatment." Investigators attempted to create disgust toward alcohol by adding agents with emetic qualities to alcoholic beverages

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or by pairing these agents with the consumption of alcoholic drinks (Bowman and Jellinek, 1941).

In 1936, Galant attempted to create an aversion to alcohol by injecting patients with apomorphine while they drank a glass of vodka (described in Bowman and Jellinek, 1941). The treatment was repeated 10–20 times for each of 22 patients, with only 2 patients remaining abstinent beyond 6 months. In 1940, Voegtlin claimed to have achieved a 64% 4-year cure rate in 685 patients treated with an emetine administration protocol that included the reduction of extraneous stimuli, the use of a variety of beverages to allow the subject to discriminate between noxious and allowable drinks, and reinforcement sessions to prevent the extinction of the conditioned response (Voegtlin, 1940; see also the description in Bowman and Jellinek, 1941). Despite limited evidence of the efficacy of aversion therapy, it remains a central element of alcoholism treatment at Schick Shadel Hospital in Seattle, WA (Smith and Frawley, 1990).

Another early pharmacologic approach to alcoholism treatment used psychostimulants to create a feeling of well-being and obviate the euphoric effects of alcohol. Bloomberg (1939) administered amphetamine to 21 alcoholic patients, who became more alert and energetic and reported no desire to drink (see also Bowman and Jellinek, 1941). Reifenshtein and Davidoff (1940) found that amphetamine was of benefit in cases of acute alcohol intoxication and recommended it to treat depression in institutionalized alcoholics (see also Bowman and Jellinek, 1941).

Disulfiram

It was not until the discovery of disulfiram for relapse prevention and benzodiazepines for alcohol withdrawal that specific pharmacologic treatments for alcoholism became a promising therapeutic area. Disulfiram's aversive properties were discovered serendipitously. In 1948, two Danish scientists, Jacobsen and Hald, became violently ill shortly after consuming cocktails at a party. Earlier, both had ingested disulfiram, a potential antihelminthic, which they were testing for safety. This experience of the acetaldehyde syndrome led them to suggest that disulfiram could be used to "sensitize" individuals to alcohol and treat their alcoholism (Dale and Ebaugh, 1950; Hald and Jacobsen, 1948).

Disulfiram's efficacy depends on its ability to block the activity of acetaldehyde dehydrogenases, which with alcohol ingestion sharply increases the blood concentration of acetaldehyde. Elevated concentrations of acetaldehyde cause vasodilation and facial flushing, headache, and nausea and vomiting, among other signs and symptoms (Fuller et al., 1986). In 1948, the U.S. Food and Drug Administration (FDA) approved disulfiram to treat alcoholism. It remains in use to prevent relapse in abstinent alcoholics.

Although some clinicians attest to the beneficial effects of disulfiram, few studies have systemically assessed its

efficacy. A notable exception is the multicenter Veterans Affairs (VA) Cooperative study of disulfiram (Fuller et al., 1986). Its publication represented a watershed event in the pharmacotherapy of alcoholism. In that study, 605 patients were randomly assigned to receive disulfiram 250 mg/day, disulfiram 1 mg/day (i.e., an "active" control for the threat of a disulfiram reaction), or riboflavin 50 mg per day. Greater adherence to the study medication and visits scheduled was associated with a robust beneficial effect on abstinence during the 1-year treatment period. There were no significant medication-group differences on drinking outcomes, employment, or social stability. However, in participants who drank during the treatment period, those receiving disulfiram 250 mg reported significantly fewer drinking days than those assigned to the other groups.

Benzodiazepines and the treatment of alcohol withdrawal

The first benzodiazepine, chlordiazepoxide, received FDA approval in 1960 as an anxiolytic. Because of their greater safety, the benzodiazepines have replaced older drugs to treat alcohol withdrawal, including paraldehyde, chloral hydrate, and meprobamate (Thimann and Gauthier, 1956). Benzodiazepines positively modulate activity at the GABA_A (gamma-aminobutyric acid-type A) receptor complex and have sedative, hypnotic, and anticonvulsant effects. In an early, randomized controlled trial (RCT) for alcohol withdrawal, Sereny and Kalant (1965) randomly assigned 58 men to receive chlordiazepoxide, the phenothiazine promazine, or placebo. Chlordiazepoxide-treated patients had fewer severe withdrawal symptoms, but the drug was only moderately better than promazine in reducing other symptoms, including sleep difficulties and diaphoresis.

In the intervening years, many studies were published on the use of various medications to treat the alcohol withdrawal syndrome. A review of 14 of the most rigorous of these trials (Williams and McBride, 1998) evaluated the safety and efficacy of benzodiazepines, chlormethiazole (a thiamine derivative that is not approved for use in the United States), beta-blockers, and anticonvulsants for this indication. The authors concluded that some of these agents, particularly the anticonvulsant carbamazepine, may be useful in selected populations of alcoholics, but that the most consistently robust data supported the use of benzodiazepines.

Benzodiazepines were also studied to treat alcoholism after withdrawal. In early studies (reviewed by Kissin, 1975), chlordiazepoxide was efficacious in the long-term outpatient maintenance of alcoholics. However, the extended use of benzodiazepines is limited by their potential for additive central nervous system depression in combination with alcohol and by the tolerance and dependence that these agents produce, especially in individuals susceptible to dependence (Schuster and Humphries, 1981). Jaffe and colleagues (1983) suggested that some benzodiazepines were less likely than

others to induce dependence and that dependence on benzodiazepines could be preferable to dependence on alcohol, a more toxic agent (Jaffe and Ciraulo, 1985). However, the general view among experts in the field at the time, which continues today, was that the use of benzodiazepines in alcoholics is best limited to the detoxification period (Meyer, 1986a).

Medications to treat comorbid psychiatric disorders and reduce relapse risk

Other than the developments seen with the benzodiazepines, the 1950s and 1960s saw little progress in the development of medications to treat alcohol use disorders. Medication use was also strongly opposed by AA, whose members viewed tranquilizers as a chemical crutch and an impediment to sobriety (Murray and Swegan, 1958). There was a growing recognition at this time, however, based on family, adoption, and twin studies, that alcohol dependence is strongly influenced by genetic factors (Goodwin, 1975), which implied that alcoholism might be amenable to pharmacologic intervention.

In the 1960s, lysergide (lysergic acid diethylamide; LSD) was tested as “psychedelic therapy,” which was thought to enhance the effects of psychotherapy. Canadian investigators reported impressive improvements in alcoholics following a single dose of lysergide (MacLean et al., 1961; Smith, 1958). However, in an open-label study in 99 inpatient female alcoholics (Van Dusen et al., 1967), lysergide-treated patients were no more likely to be abstinent at 18 months than historic controls. The investigators noted that although the lysergide-treated subjects achieved the “transcendent” state, they did not decrease their drinking more than controls, despite having gained greater insight into their condition.

In 1972, a national survey (Jones and Helrich, 1972) reported that 90% of physicians in private practice prescribed medications to treat alcoholism, despite a lack of data supporting their efficacy. These medications included anticonvulsants and phenothiazines for acute conditions and disulfiram and antidepressants for chronic therapy. Sellers and colleagues (1981) forecast that medications would never play a major role in alcohol rehabilitation but could potentially aid behavioral and social therapies. Central to the problem of medications development was the recognition that alcoholism was heterogeneous and the expression of a variety of pathologies. Thus, it was thought that no one treatment could be effective for all alcoholic individuals.

By the mid-1980s, a new research paradigm emerged that focused on the diagnosis and treatment of psychiatric disorders commonly associated with alcohol dependence (Meyer, 1986b). Underlying this effort was the belief that psychiatric disorders and the negative emotional states associated with them contributed to the development and persistence of heavy drinking and the precipitation of relapse in

abstinent individuals. Prominent negative emotional states that were identified as precipitating relapse were frustration, anger, anxiety, depression, and boredom (Marlatt, 1985). This conceptual framework facilitated the examination of medications to modify the negative states and thereby enhance psychosocial efforts to prevent relapse. This period was also characterized by an increasing scientific rigor and the ascension of the RCT as the “gold standard” of clinical research.

Tricyclic antidepressants. Ciraulo and Jaffe (1981) reported that the preponderance of evidence from RCTs showed the treatment of depressed alcoholics with tricyclic antidepressants to be of little benefit beyond early abstinence, when negative emotional states predominate. They identified important methodological confounds in the published studies: a failure to distinguish primary from secondary depression, the conflation of symptoms related to withdrawal with those of enduring disorders, and lack of attention to family history of depression as a potential moderator of treatment response. Dorus et al. (1987) later reported that, although depressive symptoms commonly occur during withdrawal, they often improve spontaneously with abstinence from alcohol, which was supported by the findings of Brown and Schuckit (1988). Subsequently, there were many studies of antidepressants (both tricyclic antidepressants and selective serotonin reuptake inhibitors [SSRIs]) to treat depression in alcoholic patients. In a meta-analysis of 14 RCTs in depressed patients with alcohol or other drug dependence, Nunes and Levin (2004) found that antidepressant medication exerted a modest beneficial effect for patients. They concluded that antidepressants are not stand-alone treatments for these co-occurring conditions and should be accompanied by treatments directly targeting the dependence. This conclusion was subsequently borne out in an RCT in alcohol-dependent patients with co-occurring major depression in which a combination of sertraline and naltrexone yielded greater reductions in both depressive symptoms and alcohol consumption than either medication alone or double placebo (Pettinati et al., 2010).

Lithium carbonate. Lithium carbonate has been evaluated both to treat affective symptoms presumed to contribute to the risk of heavy drinking and for its direct effects on drinking behavior (Kline et al., 1974; Merry et al., 1976; Pond et al., 1981). Although lithium did not appear to relieve depressive symptoms, two studies (Kline et al., 1974; Merry et al., 1976) showed that it decreased the incapacitating symptoms of alcohol dependence. A study by Fawcett et al. (1987) suggested that lithium could have a direct effect on drinking behavior. However, a large, 52-week, multicenter RCT of lithium in 171 depressed and 286 nondepressed alcoholic veterans (Dorus et al., 1989) showed no differential effect of the medication on the likelihood of abstinence, number of days drinking, number of hospitalizations, or change in the severity of alcoholism or depression.

Buspirone. This nonbenzodiazepine anxiolytic became an attractive treatment for anxiety in alcoholics because it is less sedating than benzodiazepines, does not add to alcohol's impairment of psychomotor functions, and has no apparent abuse potential (Goa and Ward 1986). In a double-blind study in patients with a mild-to-moderate alcohol use disorder (Bruno, 1989), buspirone-treated subjects showed a greater reduction in anxiety and a higher rate of retention in treatment than those assigned to placebo, but at 8 weeks alcohol consumption did not differ significantly between the groups. In a trial in abstinent alcoholics with co-occurring generalized anxiety disorder (Tollefson et al., 1992), there was greater treatment retention and anxiety reduction with buspirone than placebo. Buspirone-treated patients also showed greater improvement on a subjective, global measure of drinking outcome. Kranzler et al. (1994) found that buspirone was more effective than placebo in retaining anxious alcoholics in treatment, delaying relapse to heavy drinking, and, during a 6-month posttreatment follow-up period, reducing the number of drinking days. In contrast, a study of an anxious, severely alcohol-dependent patient sample, Malcolm et al. (1992) showed that buspirone was no better than placebo in reducing either anxiety or drinking.

Antipsychotics. RCTs have failed to define a role for phenothiazines for any of the symptoms that frequently trouble patients in the postdetoxification period, including anxiety, tension, and depression (Jaffe and Ciraulo, 1985). Similarly, the atypical antipsychotics, first introduced in the mid-1990s, have failed to show efficacy in the treatment of alcoholism. For example, in an RTC of 224 heavy-drinking alcohol-dependent patients (Litten et al., 2012), the atypical antipsychotic quetiapine showed no advantage over placebo in decreasing alcohol consumption. However, the antipsychotic tiapride achieved sufficient success in clinical trials to gain regulatory approval in Europe for alcoholism treatment. This selective dopaminergic blocker reportedly decreases anxiety and depression without the dyskinesias or sedative effects of other antipsychotics. An initial trial of tiapride showed that it was superior to placebo in reducing the amount of drinking and increasing the duration of abstinence in 32 anxious or depressed alcoholics (Shaw et al., 1987). In a subsequent RCT of 100 alcohol-dependent patients following detoxification, tiapride was again better than placebo at promoting abstinence and reducing alcohol consumption, although the study was limited by a high dropout rate (Shaw et al., 1994).

Medications that directly reduce alcohol consumption

The 1990s was a period of renewed research on craving, a symptom originally recognized by Jellinek (1955) as a key component of alcoholism. More recently, craving has been viewed as an important contributor to relapse in abstinent individuals, and therapies based on both cognitive and be-

havioral conceptualizations and classical conditioning were developed to reduce craving. New psychometric instruments to measure craving were developed and numerous biological models of craving elaborated. The neuroadaptive model, perhaps the most prominent among the many models of craving, posited that brain cell function adapts over time to the persistent presence of alcohol. Once neuroadaptation develops, the absence of alcohol disturbs the homeostatic balance and produces craving (Anton, 1999). Alcohol-related cues and stressful events, both of which elicit memories of alcohol-induced relief, also contribute to craving and relapse (Anton, 1999).

Interest in medications to prevent relapse in abstinent alcoholics was promoted by experimental evidence that alcohol interacts with several neurotransmitter systems, including the endogenous opioid system, catecholamines (especially dopamine), serotonin, and excitatory amino acids, such as glutamate (Kranzler, 1995). Medications that directly reduce alcohol consumption are thought to work by decreasing the urge or craving for alcohol or by reducing its reinforcing effects.

Serotonergic medications. Preclinical studies showed that alcohol consumption is modulated by serotonergic neurotransmission (LeMarquand et al. 1994). Clinical studies, however, demonstrated that serotonergic medications—the most studied of which are the SSRIs—have only a modest, inconsistent effect on drinking behavior (Kranzler and Anton, 1994). The 5-HT₃ (5-hydroxytryptamine-3) antagonist, ondansetron, has also been studied for this purpose (Johnson et al., 2000, 2011).

(A) *FLUOXETINE:* Naranjo et al. (1990) reported a 17% decrease in daily alcohol consumption from baseline levels in heavy drinkers assigned to receive fluoxetine 60 mg/day but no effect in subjects treated with fluoxetine 40 mg/day or placebo. Subsequently, inpatient alcoholics pretreated with fluoxetine 80 mg/day and given access to alcohol reduced their intake only during the first week of treatment (Gorelick and Paredes, 1992). Gerra et al. (1992) compared the effects of fluoxetine 40 mg/day, acamprosate, and placebo in family history–positive (FHP) and family history–negative (FHN) alcoholics using a crossover design. Both active medications were superior to placebo in reducing the number of drinks consumed, but only FHP patients responded to fluoxetine and only FHN patients responded to acamprosate. In outpatient alcoholics treated with coping skills psychotherapy and fluoxetine 60 mg/day or placebo, Kranzler et al. (1995) found no advantage to active medication on drinking outcomes. A secondary analysis of these data (Kranzler et al., 1996) identified a subgroup of patients with premorbid vulnerability and alcohol-related difficulties (i.e., the higher risk/severity, earlier-onset subtype, identified as Type B by Babor et al., 1992), in which fluoxetine was associated with poorer treatment outcomes than placebo.

(B) *CITALOPRAM*: Naranjo and colleagues studied citalopram extensively. They first reported that in early-stage problem drinkers without depression, citalopram 40 mg/day but not citalopram 20 mg/day reduced the number of drinks per day and increased the number of days abstinent (Naranjo et al., 1987). In a later crossover study, Naranjo et al. (1992) found that when subjects received citalopram 40 mg/day, they drank less and had more abstinent days than when treated with placebo. Subsequently, they found that citalopram 40 mg/day in combination with a brief psychosocial intervention showed an advantage over placebo that was limited to the first week of treatment (Naranjo et al., 1995).

(C) *SERTRALINE*: Subsequent studies of serotonergic medications focused largely on the stratification of subjects by clinical features. Pettinati and colleagues (2000) showed that in alcoholics with lower risk/severity and later disease onset (i.e., Type A of Babor et al. [1992]), treatment with sertraline resulted in fewer drinking days and a greater likelihood of abstinence at 12 weeks than placebo. In contrast, among alcoholics with greater risk and severity and an earlier onset of alcoholism (i.e., Type B of Babor et al. [1992]), placebo-treated patients had better outcomes, although not significantly so. In a 6-month follow-up of these patients, Dundon and colleagues (2004) found that Type A patients treated with sertraline maintained the initial beneficial effect of the medication, whereas the Type B alcoholics treated with sertraline increased their heavy drinking more than placebo-treated patients.

(D) *ONDANSETRON*: This 5-HT₃ receptor antagonist is FDA approved to treat chemotherapy and postsurgical nausea and vomiting, but the dosage of ondansetron used to treat alcohol dependence is appreciably lower than that used for these indications. In the first study of ondansetron to treat alcohol dependence, a dosage of 4 µg/kg twice daily was superior to placebo among early-onset alcoholics (i.e., individuals with an onset of problem drinking before age 25), both on the proportion of days abstinent and on the intensity of drinking (Johnson et al., 2000). In late-onset alcoholics, however, the effects of the active medication did not differ from those of placebo.

Opioid antagonists. The theoretical basis for the use of opioid antagonists to treat alcohol dependence dates from the 1980s, when preclinical studies first showed an interaction between alcohol and opioid receptors, implying a role for the endogenous opioid system as a mediator of the reinforcing effects of alcohol (Hiller et al., 1981; Lucchi et al., 1982). Preclinical studies also demonstrated opioidergic regulation of drinking behavior (Reid et al., 1986). The opioid antagonist naltrexone was shown to decrease voluntary alcohol consumption in macaques (Myers et al 1986), supporting the potential utility of opioid antagonists to treat alcohol dependence.

(A) *NALTREXONE*: Naltrexone was first approved to treat opioid dependence in 1984. Ten years later, it was also ap-

proved to treat alcohol dependence, based on the results of two publicly funded RCTs. The first study, by Volpicelli et al. (1992), showed that naltrexone reduced craving for alcohol and decreased the risk of relapse to heavy drinking in alcohol-dependent veterans enrolled in a 12-week intensive day treatment program. The second study, by O'Malley and colleagues (1992), which was initiated based on Volpicelli et al.'s unpublished findings, replicated the beneficial effects of naltrexone in a placebo-controlled trial of weekly outpatient care. This coordinated effort made it possible for naltrexone, with its demonstrated safety, to receive FDA approval.

Although not all studies of alcohol dependence have shown naltrexone to be efficacious, meta-analyses over more than a decade have shown it to be superior to placebo, primarily in reducing the risk of heavy drinking (Bouza et al., 2004; Kranzler and Van Kirk, 2001; Rösner et al. 2010b; Srisurapanont and Jarusuraisin, 2005). In the most recent analysis, Rösner et al. (2010b) examined data from 50 RCTs and nearly 8,000 participants. They found that, compared with placebo, naltrexone significantly reduced the risk of heavy drinking by about 17% and decreased drinking days by about 4%, a nonsignificant effect. Naltrexone also produced significant reductions in the number of heavy drinking days, amount of alcohol consumed, and levels of GGT (gamma-glutamyltransferase), a liver enzyme whose concentration increases with heavy drinking.

The time-limited nature of the naltrexone trials has generally not coincided with the chronic, relapsing nature of alcohol dependence; most naltrexone studies have been of 4 months' duration or less. A notable exception to this was the VA Cooperative Study (Krystal et al., 2001), which showed no advantage for naltrexone over placebo during either a 12-week or a 52-week treatment period. In follow-up studies of patients who had received naltrexone for up to 4 months, the relapse rate, number of drinking days, and number of heavy drinking days increased gradually following the cessation of treatment (Anton et al., 2001, 2006; O'Malley et al., 1996). The optimal duration of naltrexone treatment remains to be determined.

Given its modest efficacy, there have been a number of efforts to enhance the clinical benefits of naltrexone. The first of these used a targeted approach as an alternative to daily medication (Kranzler et al., 1997). In an 8-week study of problem drinkers, Kranzler et al. (2003) randomly assigned heavy drinkers to either naltrexone or placebo and either daily medication or medication targeted to high-risk drinking situations. The targeted naltrexone group showed an initial decline in the frequency of heavy drinking, which increased during the last 3 weeks of the treatment period, when the medication available to patients was limited by the study design. In the daily naltrexone group, the early decline in heavy drinking persisted throughout the trial. A subsequent study of heavy drinkers (Kranzler et al., 2009b), also using a four-cell design (naltrexone vs. placebo and daily vs.

targeted treatment), showed that, by the end of the 12-week study, men in the targeted naltrexone group consumed fewer drinks per drinking day than patients in the other treatment groups.

Because poor compliance with oral naltrexone may reduce the benefits of the medication, a second approach to enhancing outcomes with naltrexone is the use of a long-acting injectable formulation. In a 1-month pilot study, alcoholics treated with a depot formulation showed greater reductions in the frequency of heavy drinking than placebo-treated patients (Kranzler et al., 1998). A 12-week RCT of a different depot naltrexone formulation in 315 patients showed that, although it did not reduce the risk of heavy drinking, it delayed the onset of any drinking, increased the total number of days of abstinence, and doubled the likelihood of subjects remaining abstinent throughout the study period (Kranzler et al., 2004). A multicenter study of a third long-acting formulation served as the basis for its approval by the FDA to treat alcohol dependence (Garbutt et al., 2005). In that trial, more than 600 alcohol-dependent subjects were randomly assigned to receive six monthly injections of naltrexone 380 mg, naltrexone 190 mg, or placebo. The 380 mg dosage reduced the number of heavy drinking days by 25%, which was significantly better than placebo. Although the naltrexone 190 mg dosage reduced heavy drinking days by 17%, it was not significantly better than placebo.

(B) *NALMEFENE*: Mason and colleagues (1994) found that nalmefene, another opioid antagonist, at a dosage of 40 mg/day, was superior to nalmefene 10 mg/day or placebo in preventing relapse to heavy drinking. Mason et al. (1999) subsequently found no difference between nalmefene 20 mg/day and 80 mg/day. However, when grouped together, the nalmefene-treated subjects were significantly less likely to relapse to heavy drinking than was the placebo group. In a 12-week, multisite study in recently abstinent outpatient alcoholics (Anton et al., 2004), participants received 5 mg, 20 mg, or 40 mg of nalmefene or placebo daily. All groups reduced the frequency of heavy drinking days equally.

Recently, based on the results of three European studies, the European Medicines Agency approved nalmefene 18 mg for as-needed treatment to reduce heavy drinking in alcohol-dependent patients. In the first of these studies, Mann et al. (2013) randomly assigned 598 subjects to 6 months of treatment with nalmefene or placebo. Nalmefene treatment significantly reduced heavy drinking by 2.3 days per month and total alcohol consumption by about one standard drink per day more than placebo treatment. In a 6-month study of 718 patients with alcohol dependence (Gual et al., 2012), nalmefene-treated subjects reported a significantly greater reduction in the number of heavy drinking days and total alcohol consumption than the placebo group. In a 12-month study of 665 patients (van den Brink et al., 2012), nalmefene reduced the number of heavy drinking days and total alcohol

consumption throughout the treatment period. Except for the study midpoint, this reduction was statistically significant.

Acamprosate. In 2004, the FDA approved the amino acid derivative acamprosate to treat alcohol dependence, based on the results of three pivotal European studies (reviewed in Kranzler and Gage, 2008). Acamprosate appears to exert its effects through a weak antagonism of N-methyl-D-aspartate (NMDA) receptor activity and inhibition of the metabotropic glutamate receptor 5 (Blednov and Harris, 2008; Mann et al., 2008).

In a meta-analysis of 24 RCTs enrolling a total of 6,915 subjects, mostly participants in the European studies conducted by the company that owns the drug (Rösner et al. 2010a), acamprosate significantly reduced the risk of drinking and significantly increased the duration of abstinence. However, in four large studies, including two multicenter trials in the United States (Anton et al., 2006; Mason et al., 2006), a European study (Mann et al., 2012), and an Australian study (Morley, 2006), patients treated with acamprosate had outcomes comparable to those receiving placebo. In the COMBINE study (Anton et al., 2006), acamprosate failed to reduce alcohol consumption either alone or when combined with naltrexone.

Topiramate. Topiramate affects multiple enzyme and neurotransmitter systems. First approved as an anticonvulsant in 1996, it was subsequently approved to prevent migraine and, in combination with phentermine, for weight loss. Three RCTs have shown topiramate to be efficacious in reducing alcohol consumption. In both single-site and multi-site trials, Johnson et al. (2003, 2007) found that topiramate 300 mg/day resulted in large, significant reductions in both self-reported drinking and GGT concentration. Miranda et al. (2008) compared the effects of topiramate 200 mg/day, topiramate 300 mg/day, and placebo in heavy drinkers. In this study, topiramate was titrated to the target dosage over a 32-day period, where it was maintained for 1 week. During the titration period, the frequency of heavy drinking was significantly lower in both topiramate groups than in the placebo group, with no significant difference between the topiramate groups.

Together with its effects to reduce drinking, topiramate produces a variety of adverse effects that limit its clinical utility. The most common adverse effects include paresthesia, anorexia (with weight loss), difficulties with memory or concentration, and mild-to-moderate taste disturbances (Markind, 1998). Rarely, topiramate causes serious ophthalmologic effects.

Baclofen. Because of its activity as a GABA_B agonist, the antispasmodic baclofen has generated interest as a treatment for alcohol dependence. In a 30-day RCT of 39 patients with alcohol dependence, 70% of baclofen-treated patients remained abstinent compared with 21% of those in the placebo group (Addolorato et al., 2002). A subsequent 12-week study of 84 patients with hepatic cirrhosis (Addo-

lorato et al., 2007) yielded a similar advantage for baclofen over placebo. However, Garbutt and colleagues (2005) found no effect of baclofen on drinking outcomes in an RCT of 80 subjects with alcohol dependence. Muzyk et al. (2012) concluded that, although the evidence did not support the use of baclofen as a first-line agent, it could be of value in patients with cirrhosis.

Pharmacogenetic approaches

Based on advances in human genetics, in the past decade there have been a number of studies examining genetic variants as potential moderators of the effects of medications to treat alcohol dependence, which have led to the identification of specific genotypes associated with treatment response. In some naltrexone studies, for example, carriers of a variant (118G or Asp40) allele in *OPRM1*, the gene encoding the μ -opioid receptor, had a better clinical response to naltrexone than 118A (or Asn40) allele homozygotes (Anton et al., 2008; Oslin et al. 2003). A recent meta-analysis of this effect in six published studies showed that naltrexone-treated patients with one or two Asp40 alleles were more than twice as likely not to relapse to heavy drinking as Asn40-allele homozygotes (Chamorro et al., 2012).

Similarly, studies of serotonergic medications have examined the moderating effects of a functional polymorphism (5-HTTLPR) in *SLC6A4*, which encodes the serotonin transporter. Kranzler et al. (2011) reported that the tri-allelic 5-HTTLPR polymorphism moderated the effects of sertraline and age at onset of alcohol dependence on the frequency of drinking and heavy drinking. Specifically, in individuals with the $L_A L_A$ genotype, sertraline decreased drinking significantly in late-onset alcoholics, whereas in early-onset alcoholics, placebo treatment was associated with fewer drinking and heavy drinking days.

Johnson et al. (2011) subsequently found that variants in *SLC6A4* influenced the response to ondansetron: The medication reduced drinking only in alcohol-dependent individuals with the 5-HTTLPR LL genotype. Further, a single nucleotide polymorphism in the 3' untranslated region (3'UTR) of the serotonin transporter gene (Seneviratne et al., 2009) interacted with the 5-HTTLPR polymorphism to moderate the response to ondansetron. The greatest reductions in drinking were in L-allele homozygotes that were also homozygous for the T allele of the 3'UTR single nucleotide polymorphism.

As discussed above, the major limiting feature of topiramate is its adverse event profile. A secondary analysis of data from Miranda et al. (2008) showed that the severity of topiramate-related adverse effects in heavy drinkers was moderated by a polymorphism in *GRIK1*, the gene encoding the kainate receptor GluK1 (previously called the GluR5) subunit (Ray et al. 2009), which was chosen based on a preliminary association with alcohol dependence (Kranzler

et al., 2009a). Despite the fact that the polymorphism is not functional, the finding is of interest because the GluK1 subunit binds topiramate preferentially (Gryder and Rogawski, 2003). Independent validation of these findings is needed to determine whether genotyping could help to identify individuals most susceptible to the adverse effects of topiramate treatment.

Future directions

The disease model of alcoholism, first proposed by advocates of the Temperance Movement, is now firmly established and serves as the basis for much of the alcohol treatment in the United States. Since 1948, four medications have been approved in the United States to treat alcoholism; other medications have been approved exclusively in Europe. Unfortunately, none of these medications is widely prescribed, in part because of their modest efficacy. Going forward, the aim of research in neuropharmacology will be to identify novel compounds to treat alcohol dependence. Together with the ongoing adaptation of medications approved to treat other disorders, these advances should yield more robust treatment effects. Research in genetics can be expected to enhance the identification of variants that affect the risk of developing alcohol dependence, providing potential targets for medications development and potential moderators of medication response. However, the application of pharmacogenetics to the treatment of alcohol dependence is still in its infancy, with most studies based on comparatively small samples of convenience. Prospective studies of large samples are essential to advance this field. This will ensure that pharmacogenetics plays a key role in the personalized treatment of alcohol dependence by matching specific medications to individuals based on their genetic and epigenetic features, thereby enhancing treatment effects and reducing the risk of adverse events.

References

- Addolorato, G., Caputo, F., Capristo, E., Domenicali, M., Bernardi, M., Janiri L., . . . Gasbarrini, G. (2011). Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. *Alcohol & Alcoholism, 37*, 504–508.
- Addolorato, G., Leggio, L., Ferrulli, A., Cardone, S., Vonghia, L., Mirijello, A., Abenavoli, L., D'Angelo, C., Caputo, F., Zambon, A., Haber, P. S., & Gasbarrini, G. (2007). Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: Randomised, double-blind controlled study. *Lancet, 370*, 1915–1922.
- Anton, R. F. (1999). What is craving? Models and implications for treatment. *Alcohol Research & Health, 23*, 165–173.
- Anton, R. F., Moak, D. H., Latham, P. K., Waid, L. R., Malcolm, R. J., Dias, J. K., & Roberts, J. S. (2001). Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. *Journal of Clinical Psychopharmacology, 21*, 72–77.
- Anton, R. F., O'Malley, S. S., Ciraulo, D. A., Cisler, R. A., Couper, D., Donovan, D. M., . . . Zweben, A., & the COMBINE Study Research Group.

- (2006). Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. *Journal of the American Medical Association*, 295, 2003–2017.
- Anton, R. F., Oroszi, G., O'Malley, S., Couper, D., Swift, R., Pettinati, H., & Goldman, D. (2008). An evaluation of μ -opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: Results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. *Archives of General Psychiatry*, 65, 135–144.
- Anton, R. F., Pettinati, H., Zweben, A., Kranzler, H. R., Johnson, B., Bohn, M. J., . . . Karhuvaara, S. (2004). A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. *Journal of Clinical Psychopharmacology*, 24, 421–428.
- Babor, T. F., Hofmann, M., DelBoca, F. K., Hesselbrock, V., Meyer, R. E., Dolinsky, Z. S., & Rounsaville, B. (1992). Types of alcoholics, I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. *Archives of General Psychiatry*, 49, 599–608.
- Blednov, Y. A., & Harris, R. A. (2008). Metabotropic glutamate receptor 5 (mGluR5) regulation of ethanol sedation, dependence and consumption: Relationship to acamprosate actions. *International Journal of Neuropsychopharmacology*, 11, 775–793.
- Bloomberg, W. (1939). Treatment of chronic alcoholism with amphetamine (Benzedrine) sulfate. *New England Journal of Medicine*, 220, 129–135.
- Bouza, C., Angeles, M., Muñoz, A., & Amate, J. M. (2004). Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: A systematic review. *Addiction*, 99, 811–828.
- Bowman, K. M., & Jellinek, E. M. (1941). Alcohol addiction and its treatment. *Quarterly Journal of Studies on Alcohol*, 2, 98–176.
- Brown, S. A., & Schuckit, M. A. (1988). Changes in depression among abstinent alcoholics. *Journal of Studies on Alcohol*, 49, 412–417.
- Bruno, F. (1989). Buspirone in the treatment of alcoholic patients. *Psychopathology*, 22, Supplement 1, 49–59.
- Chamorro, A.-J., Marcos, M., Mirón-Canelo, J.-A., Pastor, I., González-Sarmiento, R., & Laso, F.-J. (2012). Association of μ -opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: A systematic review and meta-analysis. *Addiction Biology*, 17, 505–512.
- Ciraulo, D. A., Jaffe, J. H. (1981). Tricyclic antidepressants in the treatment of depression associated with alcoholism. *Journal of Clinical Psychopharmacology*, 1, 146–150.
- Dale, P. W., & Ebaugh, F. G. (1950). Antabuse therapy in chronic alcoholism. *American Journal of the Medical Sciences*, 220, 103–109.
- Dorus, W., Kennedy, J., Gibbons, R. D., & Ravi, S. D. (1987). Symptoms and diagnosis of depression in alcoholics. *Alcoholism: Clinical and Experimental Research*, 11, 150–154.
- Dorus, W., Ostrow, D. G., Anton, R., Cushman, P., Collins, J. F., Schaefer, M., . . . Sather, M. R. (1989). Lithium treatment of depressed and nondepressed alcoholics. *Journal of the American Medical Association*, 262, 1646–1652.
- Dundon, W., Lynch, K. G., Pettinati, H. M., & Lipkin, C. (2004). Treatment outcomes in type A and B alcohol dependence 6 months after serotonergic pharmacotherapy. *Alcoholism: Clinical and Experimental Research*, 28, 1065–1073.
- Fawcett, J., Clark, D. C., Aagesen, C. A., Pisani, V. D., Tilkin, J. M., Sellers, D., . . . Gibbons, R. D. (1987). A double-blind, placebo-controlled trial of lithium carbonate therapy for alcoholism. *Archives of General Psychiatry*, 44, 248–256.
- Fuller, R. K., Branchey, L., Brightwell, D. R., Derman, R. M., Emrick, C. D., Iber, F. L., . . . Shaw, S. (1986). Disulfiram treatment of alcoholism: A Veterans Administration cooperative study. *Journal of the American Medical Association*, 256, 1449–1455.
- Garbutt, J. C., Kranzler, H. R., O'Malley, S. S., Gastfriend, D. R., Pettinati, H. M., Silverman, B. L., . . . Ehrlich, E. W., & the Vivitrex Study Group. (2005). Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. *Journal of the American Medical Association*, 293, 1617–1625.
- Gerra, G., Caccavari, R., Delsignore, R., Bocchi, R., Fertonani, G., & Passeri, M. (1992). Effects of fluoxetine and ca-acetyl-homotaurinate on alcohol intake in familial and nonfamilial alcoholic patients. *Current Therapeutic Research*, 52, 291–295.
- Goa, K. L., & Ward, A. (1986). Buspirone. A preliminary review of its pharmacological properties and therapeutic efficacy as an anxiolytic. *Drugs*, 32, 114–129.
- Goodwin, D. W. (1975). Genetic determinants of alcohol addiction. *Advances in Experimental Medicine and Biology*, 56, 339–355.
- Gorelick, D. A., & Paredes, A. (1992). Effect of fluoxetine on alcohol consumption in male alcoholics. *Alcoholism: Clinical and Experimental Research*, 16, 261–265.
- Gryder, D. S., & Rogawski, M. A. (2003). Selective antagonism of GluR5 kainate-receptor-mediated synaptic currents by topiramate in rat basolateral amygdala neurons. *Journal of Neuroscience*, 23, 7069–7074.
- Gual, A., He, Y., Torup, L., van den Brink, W., & Mann, K. (2012, June). *ESENSE 2: A randomized, double-blind, placebo-controlled study of nalmefene, as-needed use in alcohol dependence patients*. Poster presented at the 35th Annual RSA Scientific Meeting, San Francisco, CA.
- Hald, J., & Jacobsen, E. (1948). A drug sensitising the organism to ethyl alcohol. *The Lancet*, 252(6539), 1001–1004.
- Hiller, J. M., Angel, L. M., & Simon, E. J. (1981). Multiple opiate receptors: Alcohol selectively inhibits binding to delta receptors. *Science*, 214, 468–469.
- Jaffe, J., & Ciraulo, D. (1985). Drugs used in the treatment of alcoholism. In J. Mendelson & N. Mello (Eds.), *The diagnosis and treatment of alcoholism* (2nd ed., pp. 355–389). New York, NY: McGraw-Hill.
- Jaffe, J. H., Ciraulo, D. A., Nies, A., Dixon, R. B., & Monroe, L. L. (1983). Abuse potential of halazepam and of diazepam in patients recently treated for acute alcohol withdrawal. *Clinical Pharmacology and Therapeutics*, 34, 623–630.
- Jellinek, E. M. (1955). The “craving” for alcohol. *Quarterly Journal of Studies on Alcohol*, 16, 35–38.
- Johnson, B. A., Ait-Daoud, N., Bowden, C. L., DiClemente, C. C., Roache, J. D., Lawson, K., . . . Ma, J. Z. (2003). Oral topiramate for treatment of alcohol dependence: A randomized controlled trial. *The Lancet*, 361(9370), 1677–1685.
- Johnson, B. A., Ait-Daoud, N., Seneviratne, C., Roache, J. D., Javors, M. A., Wang, X.-Q., . . . Li, M. D. (2011). Pharmacogenetic approach at the serotonin transporter gene as a method of reducing the severity of alcohol drinking. *American Journal of Psychiatry*, 168, 265–275.
- Johnson, B. A., Roache, J. D., Javors, M. A., DiClemente, C. C., Cloninger, C. R., Prihoda, T. J., . . . Hensler, J. (2000). Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: A randomized controlled trial. *Journal of the American Medical Association*, 284, 963–971.
- Johnson, B. A., Rosenthal, N., Capece, J. A., Wiegand, F., Mao, L., Beyers, K., . . . Swift, R. M., & the Topiramate for Alcoholism Advisory Board, & the Topiramate for Alcoholism Study Group. (2007). Topiramate for treating alcohol dependence: A randomized controlled trial. *Journal of the American Medical Association*, 298, 1641–1651.
- Jones, R. W., & Helrich, A. R. (1972). Treatment of alcoholism by physicians in private practice: A national survey. *Quarterly Journal of Studies on Alcohol*, 33, 117–131.
- Kissin, B. (1975). The use of psychoactive drugs in the long-term treatment of chronic alcoholics. *Annals of the New York Academy of Sciences*, 252, 385–395.
- Kline, N. S., Wren, J. C., Cooper, T. B., Varga, E., & Canal, O. (1974). Evaluation of lithium therapy in chronic and periodic alcoholism. *American Journal of the Medical Sciences*, 268, 15–22.

- Kranzler, H. (1995). The pharmacology of alcohol abuse: An introduction. In H. Kranzler (Ed.), *The pharmacology of alcohol abuse* (pp. 1–10). New York, NY: Springer-Verlag.
- Kranzler, H. R., & Anton, R. F. (1994). Implications of recent neuropsychopharmacologic research for understanding the etiology and development of alcoholism. *Journal of Consulting and Clinical Psychology, 62*, 1116–1126.
- Kranzler, H. R., Armeli, S., Tennen, H., Blomqvist, O., Oncken, C., Petry, N., & Feinn, R. (2003). Targeted naltrexone for early problem drinkers. *Journal of Clinical Psychopharmacology, 23*, 294–304.
- Kranzler, H. R., Armeli, S., Tennen, H., Covault, J., Feinn, R., Arias, A. J., . . . Oncken, C. (2011). A double-blind, randomized trial of sertraline for alcohol dependence: Moderation by age of onset and 5-hydroxytryptamine transporter-linked promoter region genotype. *Journal of Clinical Psychopharmacology, 31*, 22–30.
- Kranzler, H. R., Bursleson, J. A., Brown, J., & Babor, T. F. (1996). Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics. *Alcoholism: Clinical and Experimental Research, 20*, 1534–1541.
- Kranzler, H. R., Bursleson, J. A., Del Boca, F. K., Babor, T. F., Korner, P., Brown, J., & Bohn, M. J. (1994). Buspirone treatment of anxious alcoholics: A placebo-controlled trial. *Archives of General Psychiatry, 51*, 720–731.
- Kranzler, H. R., Bursleson, J. A., Korner, P., Del Boca, F. K., Bohn, M. J., Brown, J., & Liebowitz, N. (1995). Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. *American Journal of Psychiatry, 152*, 391–397.
- Kranzler, H. R., & Gage, A. (2008). Acamprosate efficacy in alcohol-dependent patients: Summary of results from three pivotal trials. *The American Journal on Addictions, 17*, 70–76.
- Kranzler, H. R., Gelernter, J., Anton, R. F., Arias, A. J., Herman, A., Zhao, H., . . . Covault, J. (2009a). Association of markers in the 3' region of the GluR5 kainate receptor subunit gene to alcohol dependence. *Alcoholism: Clinical and Experimental Research, 33*, 925–930.
- Kranzler, H. R., Knapp, C., & Ciraulo, D. A. (2013). Pharmacotherapy of alcoholism. In H. R. Kranzler, D. Ciraulo, & L. Zindel (Eds.), *Clinical manual of addiction psychopharmacology* (2nd ed.). Washington, DC: American Psychiatric Press.
- Kranzler, H. R., Modesto-Lowe, V., & Nuwayser, E. S. (1998). Sustained-release naltrexone for alcoholism treatment: A preliminary study. *Alcoholism: Clinical and Experimental Research, 22*, 1074–1079.
- Kranzler, H. R., Tennen, H., Armeli, S., Chan, G., Covault, J., Arias, A., & Oncken, C. (2009b). Targeted naltrexone for problem drinkers. *Journal of Clinical Psychopharmacology, 29*, 350–357.
- Kranzler, H. R., Tennen, H., Penta, C., & Bohn, M. J. (1997). Targeted naltrexone treatment of early problem drinkers. *Addictive Behaviors, 22*, 431–436.
- Kranzler, H. R., & Van Kirk, J. (2001). Efficacy of naltrexone and acamprosate for alcoholism treatment: A meta-analysis. *Alcoholism: Clinical and Experimental Research, 25*, 1335–1341.
- Kranzler, H. R., Wesson, D. R., & Billot, L., & the Drug Abuse Sciences Naltrexone Depot Study Group. (2004). Naltrexone depot for treatment of alcohol dependence: A multicenter, randomized, placebo-controlled clinical trial. *Alcoholism: Clinical and Experimental Research, 28*, 1051–1059.
- Krystal, J. H., Cramer, J. A., Krol, W. F., Kirk, G. F., & Rosenheck, R. A., & the Veterans Affairs Naltrexone Cooperative Study 425 Group. (2001). Naltrexone in the treatment of alcohol dependence. *The New England Journal of Medicine, 345*, 1734–1739.
- Levine, H. G. (1984). The alcohol problem in America: From temperance to alcoholism. *British Journal of Addiction, 79*, 109–119.
- LeMarquand, D., Pihl, R. O., & Benkelfat, C. (1994). Serotonin and alcohol intake, abuse, and dependence: findings of animal studies. *Biological Psychiatry, 36*, 395–421.
- Litten, R. Z., Fertig, J. B., Falk, D. E., Ryan, M. L., Mattson, M. E., Collins, J. F., . . . Stout, R., & NCI 001 Study Group. (2012). A double-blind, placebo-controlled trial to assess the efficacy of quetiapine fumarate XR in very heavy-drinking alcohol-dependent patients. *Alcoholism: Clinical and Experimental Research, 36*, 406–416.
- Lucchi, L., Bosio, A., Spano, P. F., & Trabucchi, M. (1982). Action of ethanol and salsolinol on opiate receptor function. *Brain Research, 232*, 506–510.
- MacLean, J. R., MacDonald, D. C., Byrne, U. P., & Hubbard, A. M. (1961). The use of LSD-25 in the treatment of alcoholism and other psychiatric problems. *Quarterly Journal of Studies on Alcohol, 22*, 34–45.
- Malcolm, R., Anton, R. F., Randall, C. L., Johnston, A., Brady, K., & Thevos, A. (1992). A placebo-controlled trial of buspirone in anxious inpatient alcoholics. *Alcoholism: Clinical and Experimental Research, 16*, 1007–1013.
- Markind, J. E. (1998). Topiramate: a new antiepileptic drug. *American Journal of Health-System Pharmacy, 55*, 554–562.
- Mann, K., Bladström, A., Torup, L., Gual, A., & van den Brink, W. (2013). Extending the treatment options in alcohol dependence: A randomized controlled study of as-needed nalmefene. *Biological Psychiatry, 73*, 706–713.
- Mann, K., Kiefer, F., Spanagel, R., & Littleton, J. (2008). Acamprosate: Recent findings and future research directions. *Alcoholism: Clinical and Experimental Research, 32*, 1105–1110.
- Mann, K., Lemenager, T., Hoffmann, S., Reinhard, I., Hermann, D., Batra, A., . . . Anton, R. F., & the PREDICT Study Team. (2012). Results of a double-blind, placebo-controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. *Addiction Biology*. Advance online publication. Retrieved from <http://onlinelibrary.wiley.com/doi/10.1111/adb.12012/full>
- Marlatt, G. (1985). Relapse prevention: Theoretical rationale and overview of the model. In G. Marlatt & J. Gordon (Eds.), *Relapse prevention* (pp. 3–67). New York, NY: Guilford Press.
- Mason, B. J., Goodman, A. M., Chabac, S., & Leher, P. (2006). Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: The role of patient motivation. *Journal of Psychiatric Research, 40*, 383–393.
- Mason, B. J., Ritvo, E. C., Morgan, R. O., Salvato, F. R., Goldberg, G., Welch, B., & Mantero-Atienza, E. (1994). A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. *Alcoholism: Clinical and Experimental Research, 18*, 1162–1167.
- Mason, B. J., Salvato, F. R., Williams, L. D., Ritvo, E. C., & Cutler, R. B. (1999). A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Archives of General Psychiatry, 56*, 719–724.
- Merry, J., Reynolds, C. M., Bailey, J., & Coppen, A. (1976). Prophylactic treatment of alcoholism by lithium carbonate: A controlled study. *The Lancet, 308*(7984), 481–482.
- Meyer, R. E. (1986a). Anxiolytics and the alcoholic patient. *Journal of Studies on Alcohol, 47*, 269–273.
- Meyer, R. E. (1986b). How to understand the relationship between psychopathology and addictive disorders: Another example of the chicken and the egg. In R. E. Meyer (Ed.), *Psychopathology and addictive disorders* (pp. 3–16). New York, NY: Guilford Press.
- Miranda, R., Jr., MacKillop, J., Monti, P. M., Rohsenow, D. J., Tidey, J., Gwaltney, C., . . . McGeary, J. (2008). Effects of topiramate on urge to drink and the subjective effects of alcohol: A preliminary laboratory study. *Alcoholism: Clinical and Experimental Research, 32*, 489–497.
- Morley, K. C., Teesson, M., Reid, S. C., Sannibale, C., Thomson, C., Phung, N., . . . Haber, P. S. (2006). Naltrexone versus acamprosate in the treatment of alcohol dependence: A multi-centre, randomized, double-blind, placebo-controlled trial. *Addiction, 101*, 1451–1462.
- Murray, N., & Swegan, W. (1958). Notes and comment: To tranquilize or not to tranquilize. *Quarterly Journal of Studies on Alcohol, 19*, 509–510.

- Muzyk, A. J., Rivelli, S. K., & Gagliardi, J. P. (2012). Defining the role of baclofen for the treatment of alcohol dependence: A systematic review of the evidence. *CNS Drugs*, *26*, 69–78.
- Myers, R. D., Borg, S., & Mossberg, R. (1986). Antagonism by naltrexone of voluntary alcohol selection in the chronically drinking macaque monkey. *Alcohol*, *3*, 383–388.
- Naranjo, C. A., Bremner, K. E., & Lanctôt, K. L. (1995). Effects of citalopram and a brief psycho-social intervention on alcohol intake, dependence and problems. *Addiction*, *90*, 87–99.
- Naranjo, C. A., Kadlec, K. E., Sanhueza, P., Woodley-Remus, D., & Sellers, E. M. (1990). Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. *Clinical Pharmacology and Therapeutics*, *47*, 490–498.
- Naranjo, C. A., Poulos, C. X., Bremner, K. E., & Lanctôt, K. L. (1992). Citalopram decreases desirability, liking, and consumption of alcohol in alcohol-dependent drinkers. *Clinical Pharmacology and Therapeutics*, *51*, 729–739.
- Naranjo, C. A., Sellers, E. M., Sullivan, J. T., Woodley, D. V., Kadlec, K., & Sykora, K. (1987). The serotonin uptake inhibitor citalopram attenuates ethanol intake. *Clinical Pharmacology and Therapeutics*, *41*, 266–274.
- Nunes, E. V., & Levin, F. R. (2004). Treatment of depression in patients with alcohol or other drug dependence: A meta-analysis. *Journal of the American Medical Association*, *291*, 1887–1896.
- O'Malley, S. S., Jaffe, A. J., Chang, G., Rode, S., Schottenfeld, R., Meyer, R. E., & Rounsaville, B. (1996). Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. *Archives of General Psychiatry*, *53*, 217–224.
- O'Malley, S. S., Jaffe, A. J., Chang, G., Schottenfeld, R. S., Meyer, R. E., & Rounsaville, B. (1992). Naltrexone and coping skills therapy for alcohol dependence: A controlled study. *Archives of General Psychiatry*, *49*, 881–887.
- Oslin, D. W., Berrettini, W., Kranzler, H. R., Pettinati, H., Gelernter, J., Volpicelli, J. R., & O'Brien, C. P. (2003). A functional polymorphism of the μ -opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology*, *28*, 1546–1552.
- Pettinati, H. M., Oslin, D. W., Kampman, K. M., Dundon, W. D., Xie, H., Gallis, T. L., . . . O'Brien, C. P. (2010). A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. *American Journal of Psychiatry*, *167*, 668–675.
- Pettinati, H. M., Volpicelli, J. R., Kranzler, H. R., Luck, G., Rukstalis, M. R., & Cnaan, A. (2000). Sertraline treatment for alcohol dependence: Interactive effects of medication and alcoholic subtype. *Alcoholism: Clinical and Experimental Research*, *24*, 1041–1049.
- Pond, S. M., Becker, C. E., Vandervoort, R., Phillips, M., Bowler, R. M., & Peck, C. C. (1981). An evaluation of the effects of lithium in the treatment of chronic alcoholism, clinical results. *Alcoholism: Clinical and Experimental Research*, *5*, 247–251.
- Ray, L. A., Miranda, R., Jr., MacKillop, J., McGeary, J., Tidey, J. W., Rohsenow, D. J., . . . Monti, P. M. (2009). A preliminary pharmacogenetic investigation of adverse events from topiramate in heavy drinkers. *Experimental and Clinical Psychopharmacology*, *17*, 122–129.
- Reid, L. D., Czirr, S. A., Milano, W. C., Hubbell, C. L., & Manha, N. A. (1986). Opioids and intake of alcoholic beverages. *NIDA Research Monograph*, *75*, 359–362.
- Reifenstein, Jr., E. C., & Davidoff, E. (1940). The treatment of alcoholic psychoses with benzedrine sulfate in alcoholism with and without psychosis. *New York State Journal of Medicine*, *40*(February 15), 247–254.
- Rösner, S., Hackl-Herrwerth, A., Leucht, S., Leher, P., Vecchi, S., & Soyka, M. (2010a). Acamprosate for alcohol dependence. *Cochrane Database of Systematic Reviews*, Issue 9, Article No. CD004332.
- Rösner, S., Hackl-Herrwerth, A., Leucht, S., Vecchi, S., Srisurapanont, M., & Soyka, M. (2010b). Opioid antagonists for alcohol dependence. *Cochrane Database of Systematic Reviews*, Issue 12, Article No. CD001867.
- Schuster, C. L., & Humphries, R. H. (1981). Benzodiazepine dependency in alcoholics. *Connecticut Medicine*, *45*, 11–13.
- Sellers, E. M., Naranjo, C. A., & Peachey, J. E. (1981). Drug therapy: Drugs to decrease alcohol consumption. *The New England Journal of Medicine*, *305*, 1255–1262.
- Seneviratne, C., Huang, W., Ait-Daoud, N., Li, M. D., & Johnson, B. A. (2009). Characterization of a functional polymorphism in the 3' UTR of SLC6A4 and its association with drinking intensity. *Alcoholism: Clinical and Experimental Research*, *33*, 332–339.
- Sereny, G., & Kalant, H. (1965). Comparative clinical evaluation of chlorthalidazepoxide and promazine in treatment of alcohol-withdrawal syndrome. *British Medical Journal*, *1*, 92–97.
- Shaw, G. K., Majumdar, S. K., Waller, S., MacGarvie, J., & Dunn, G. (1987). Tiapride in the long-term management of alcoholics of anxious or depressive temperament. *British Journal of Psychiatry*, *150*, 164–168.
- Shaw, G. K., Waller, S., Majumdar, S. K., Alberts, J. L., Latham, C. J., & Dunn, G. (1994). Tiapride in the prevention of relapse in recently detoxified alcoholics. *British Journal of Psychiatry*, *165*, 515–523.
- Smith, C. M. (1958). A new adjunct to the treatment of alcoholism: The hallucinogenic drugs. *Quarterly Journal of Studies on Alcohol*, *19*, 406–417.
- Smith, J. W., & Frawley, P. J. (1990). Long-term abstinence from alcohol in patients receiving counter conditioning as part of a multimodal inpatient program. *Journal of Substance Abuse Treatment*, *7*, 77–82.
- Srisurapanont, M., & Jarusuraisin, N. (2005). Opioid antagonists for alcohol dependence. *Cochrane Database of Systematic Reviews*, Issue 1, Article No. CD001867.
- Thimann, J., & Gauthier, J. W. (1956). Miltown as a tranquilizer in the treatment of alcohol addicts. *Quarterly Journal of Studies on Alcohol*, *17*, 19–23.
- Tollefson, G. D., Montague-Clouse, J., & Tollefson, S. L. (1992). Treatment of comorbid generalized anxiety in a recently detoxified alcoholic population with a selective serotonergic drug (buspirone). *Journal of Clinical Psychopharmacology*, *12*, 19–26.
- U.S. Const. amend. XXI.
- van den Brink, W., Sorensen, P., Torup, L., Mann, K., & Gual, A. (2012, June). *Long-term efficacy, tolerability, and safety of nalmefene as-needed in alcohol-dependence: A randomized, double-blind, placebo-controlled study*. Poster presented at the 35th Annual RSA Scientific Meeting, San Francisco, CA.
- Van Dusen, W., Wilson, W., Miners, W., & Hook, H. (1967). Treatment of alcoholism with lysergide. *Quarterly Journal of Studies on Alcohol*, *28*, 295–304.
- Voegtlin, W. L. (1940). The treatment of alcoholism by establishing a conditioned reflex. *American Journal of Medical Science*, *199*, 802–810.
- Volpicelli, J. R., Alterman, A. I., Hayashida, M., & O'Brien, C. P. (1992). Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry*, *49*, 876–880.
- Williams, D., & McBride, A. J. (1998). The drug treatment of alcohol withdrawal symptoms: A systematic review. *Alcohol and Alcoholism*, *33*, 103–115.