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Editorial

Alcohol Craving, Glutamate and Acamprosate

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INTRODUCTION

Alcohol dependence is a common disorder. Globally and in the U.S.A, alcohol dependence ranks 5th and 3rd, respectively, on the list of preventable causes of morbidity and mortality (1). Alcohol dependence is characterized by cycles of excessive alcohol consumption, interspersed with intervals of abstinence. Notwithstanding its psychological and social ramifications, once established, alcohol dependence is essentially a brain disorder that bears many of the characteristics of other medical relapsing disorders such as diabetes and hypertension. Indeed, without a pharmacological adjunct to psychosocial therapy, the clinical outcome is poor, with up to 70% of patients resuming drinking within one year (2,3).

Relapse, which may be defined as return to uncontrolled alcohol use following abstinence, is a key element of the disease, and therefore an important target for novel treatments. Over the last 20 years, the role of pharmacotherapy in relapse prevention has become increasingly evident (4). Alcohol dependence is a chronic relapsing disorder with craving and loss of control over intake as key phenomena. Thus, recent developments in the pharmacotherapy of alcohol dependence have targeted the phenomenon of craving in order to improve abstinence rates.

Neurobiology of Addiction and Glutamate

Research into the neurobiological substrates that underlie the rewarding and reinforcing effects of drugs of abuse has focused on the mesolimbic dopamine reward circuitry, comprised primarily of dopaminergic neurons in the ventral tegmental area that project rostrally to forebrain and limbic regions such as the nucleus accumbens, amygdala and frontal cortex (5).

Other nerotransmitter systems are also involved in the process of addiction, such as opioid, GABA, serotonin and glutamate. The past two decades have witnessed a dramatic accumulation of evidence indicating that the excitatory amino acid glutamate plays an important role in drug addiction and alcoholism among others. All drugs of abuse appear to modulate glutamatergic transmission, albeit by different mechanisms, and this modulation of glutamate transmission is believed to result in long-lasting neuroplastic changes in the brain that may contribute to the perseveration of drug-seeking behavior and drug associated memories. In general, attenuation of glutamatergic transmission reduces drug reward, reinforcement, and relapse-like behavior. On the other hand, potentiation of glutamatergic transmission appears to facilitate the extinction of drug-seeking behavior (6).

Acamprosate and Mechanism of Action

One of the substances currently used in treatment of alcoholism is acamprosate. Acamprosate is a synthetic glutamate receptor agonist that has been prescribed in Europe for more than 20 years and was approved by the Turkish Ministry of Health in 2003, whereas by the U.S. Food and Drug Administration (FDA) in 2004.

Acamprosate's principal neurochemical effects have

been attributed to antagonism of NMDA glutamate receptors (7,8), which restore the balance between excitatory and inhibitory neurotransmission that is dysregulated following chronic alcohol consumption (9). Recently, however, it also has been proposed that acamprosate modulates glutamate neurotransmission at metabotropic-5 glutamate receptors (mGluR5) (10). Acamprosate has been shown to decrease dopamine hyperexcitability in the nucleus accumbens during alcohol withdrawal (11,12) and general neuronal hyperexcitability (13,14). Evidence from a human magnetic resonance imaging study support acamprosate's ability to modulate glutamate neurotransmission as it decreases activity in brain regions rich in N-acetylaspartate and glutamate (15). Studies on neuronal networks in vivo suggest that acamprosate may have differential effects on glutamate/NMDA receptors at low concentrations, with effects on GABA-A receptors at higher concentrations (16). Nevertheless, although there is a general consensus that acamprosate is a NMDA receptor modulator and it seems to rectify imbalance in the GABA and glutamate systems, acamprosate may have different actions at different concentrations or in different brain areas dependent on receptor distribution and/or subtype (9).

Daily Dose, Side Effects and Contraindication

Due to its poor oral bioavailability, large doses of acamprosate (typically in the 2–3 g per day range) are needed in order to observe efficacy. Human laboratory studies in both volunteers (17) and alcohol-dependent individuals (18) have shown that acamprosate is relatively safe, with the most important adverse events being diarrhea, nervousness, and fatigue, especially at a relatively high dose (3 g/day). Since acamprosate is excreted unchanged in the kidneys, there is no risk of hepatotoxicity, but it should be used with caution in those with renal impairment (17,18) and contraindicated for patients with serum creatinine above 120 µmol/L. Since there are no sufficient clinical data, use in pediatric (age below 18), geriatric (age above 65) and pregnant (Pregnancy category B) patients is not suggested.

Acamprosate has no significant clinical interaction with alcohol. Recently, it was shown that acamprosate can reduce heart rate response but not the increase in cortisol or subjective craving following the presentation of alcohol cues. This finding suggests utility for acamprosate in managing autonomic dysregulation in abstinent alcoholics exposed to a high risk for relapse situations (4).

Craving Types and Effect of Acomprasate on Craving

Alcohol seeking and relapse can be conceptualized as being driven by positive reinforcement, and the related phenomenon of 'reward craving', or by negative reinforcement, related to 'relief craving' (19). Reward craving, involves those people who consume because of a desire for the positive effects of alcohol. They are not generally extroverts, novelty seekers, or sensation seekers, but rather they seek the neurotransmitter chemical reward involving the opioidergic/dopaminergic system. Verheul et al. (20) suggested that this category might continually seek rewards to compensate for a low level of cortical arousal.

The relief craving involves those people who consume to relieve tension or arousal. Verheul et al. (20) described the personality style associated with this type as stress reactive, defined as possessing "the anxious sensitivity to both external stressful events and internal physiological arousal". These individuals are hypothesized, in neurobiological terms, to manifest neural hyper-excitability due to increased excitatory or glutamatergic neurotransmission, decreased inhibitory or GABAergic neurotransmission, or both (20). Although neither of the two approved alcoholism medications with central actions, naltrexone and acamprosate, directly targets stress-induced craving, the latter has been postulated to target 'relief craving' (21).

Weinstein et al. (22) presented some preliminary results of an uncontrolled pilot study suggesting that acamprosate does alter cue-induced self-reported craving and reaction time to an alcohol-related stimulus. In addition, Agelink et al. (23) showed improved autonomic neurocardial balance in abstinent alcoholics treated with acamprosate, i.e. following treatment with

acamprosate patients showed less disturbances in neurocardiac vagal function.

There is converging evidence that mesolimbic activation following alcohol intake (first drink) and conditioned alcohol cues represent a major pathway into relapse (24). Clinical data now provide evidence for reduced alcohol craving following an alcoholic drink when subjects are pre-treated with acamprosate (25). The results showed that acamprosate attenuated the subjective craving induced by alcohol ingestion (i.e., "alcohol priming") in comparison to placebo-treated patients. Furthermore, acamprosate reduced alcohol-induced elevation in blood-cortisol levels. Lastly, there was a negative correlation between acamprosate plasma levels and alcohol craving following a priming drink. No effects of acamprosate on cue reactivity, or on the acute rewarding and sedating effects of the priming drink, were observed. These results suggest a potential mechanism by which acamprosate mediates its therapeutic effect in the treatment of alcoholism, by attenuating the urge to drink following an alcohol slip. Additionally, a clinical study applying cue-exposure to abstinent alcohol dependent subjects showed a reduction of cue-induced physiological cue-reactivity (i.e. heart rate) in subjects following treatment with acamprosate (4).

Some investigators hypothesize that acamprosate specifically acts on craving that is mediated through glutamatergic and GABA-ergic dysregulations of stress, anxiety or withdrawal systems (relief craving), and is thus accompanied by autonomic nervous system reactions (20, 26). Stress is a major factor contributing to relapse in abstinent drug and alcohol abuse patients. Growing evidence supports a role of metabotropic glutamate receptors (mGluRs) in stress-associated drug use and drug seeking (27).

Clinical Studies for Efficacy

The first demonstration of the clinical efficacy of acamprosate in reducing the incidence of relapse in alcoholics was published in the mid-1980s (28). Most of the clinical evidence for the efficacy of acamprosate in the treatment of alcohol dependence comes from a series of European studies. In 2004, Mann et al. (29) wrote a meta-analysis of 17 published studies that included 4087 alcohol dependent individuals. In that report, continuous abstinence rates at 6 months were greater than for those who got placebo (acamprosate, 36.1%; placebo, 23.4%; relative benefit, 1.47; 95%CI = 1.29–1.69; $p<0.001$). The overall pooled difference in success rates between acamprosate and placebo was 13.3% (95%CI = 7.8–18.7%), and the number needed to treat was 7.5. Similar results were obtained from another meta-analysis conducted at about the same time (30). Generally, the effect size of acamprosate is small (0.14) for increasing the percentage of non-heavy drinking days (31) and 0.23 for reducing the relapse to heavy drinking (32). Early studies also had some methodological problems, including nonstandardization of diagnostic criteria and the psychosocial adjunct to the medication, which were resolved in later trials.

In multi-site trial in the U.S.A., there was no overall clinical evidence that acamprosate was superior to placebo among a heterogeneous cohort of alcohol-dependent individuals (33). Further, in 2006, the multi-site COMBINE (Combined Medications and Behavioral Interventions) project also failed to find any therapeutic benefit of acamprosate compared with placebo on any drinking outcome measures in a medically managed setting (34). Other studies have also demonstrated a lack of efficacy of acamprosate in reducing alcohol consumption or craving, or promoting abstinence (35-38).

The reasons for these negative findings, especially in light of numerous previous positive findings, are still being debated. There are some possible explanations for the discrepancy between U.S.A. and European studies. First, the populations sampled differ, with European, compared with U.S.A, studies having alcohol-dependent individuals with more prolonged drinking histories and alcohol-related neurological and psychosocial impairments. Thus, it is tempting to speculate that European studies might have included individuals with greater neuroplasticity and, therefore, higher response to the ameliorating effects of anti-glutamatergic agents such as acamprosate. Kiefer and Mann (39) have hypothesized that the COMBINE study, by enrolling individuals who were able to achieve 4 days of

pretreatment abstinence without detoxification, may have selected a less dependent sample that would not be responsive to acamprosate. Others have suggested that initiation of acamprosate treatment following detoxification produces reductions in alcohol craving as opposed to when given during active alcohol consumption (40), as was done in the COMBINE study. Second, U.S.A., compared with European, studies have tended to have higher levels of standardized psychosocial intervention as an adjunct to acamprosate, thereby masking the effect of the medication. Some investigators have suggested that a significant "placebo effect" in the COMBINE study might have masked any beneficial effects of acamprosate (41), and that improvements in nondrinking related outcomes measures such as quality of life were in fact superior in acamprosate- versus placebo-treated patients in the COMBINE study (42). Nevertheless, over the years, acamprosate has demonstrated effect sizes ranging from small to moderate in reducing overall alcohol consumption, subjective measures of alcohol craving, and promoting abstinence, as reviewed in recent meta-analyses (43-49).

One of the latest study that evaluated the effectiveness and tolerability of acamprosate for helping patients dependent on alcohol to maintain abstinence was Cochrane review (50). Among patients taking acamprosate in the 24 trials, risk of return to any drinking was 86 percent that of patients treated with placebo (i.e., 14 percent less risk in treatment group compared with placebo). Based on statistical weighting of trials, the authors calculated a number needed to treat of 9 to prevent one additional patient from returning to drinking. Patients treated with acamprosate also maintained cumulative abstinence (i.e., total days without alcohol use, whether or not the patient had periodic return to drinking) for 11 percent longer than patients taking placebo. The only adverse effect of acamprosate that reached statistical significance compared with placebo was diarrhea (the authors calculated a weighted number needed to harm of 9), but this adverse effect did not affect adherence to treatment. Overall trial dropout because of adverse effects or any other cause was actually greater in patients taking placebo.

Three of the studies also compared acamprosate versus naltrexone; two studies compared combination treatment of acamprosate and naltrexone versus placebo; and two studies compared combination treatment of acamprosate and naltrexone versus acamprosate alone (50). None of these comparisons demonstrated statistically significant treatment benefits among interventions. However, these comparisons showed that acamprosate carried a higher risk of diarrhea, and that the combination of acamprosate and naltrexone led to a markedly higher rate of withdrawal because of adverse events compared with placebo or acamprosate alone. Ten trials reported posttreatment follow-up. They found that treatment effects for return to drinking and for cumulative abstinence remained statistically significant 3 to 12 months after study conclusion, indicating that benefits of acamprosate may persist beyond the treatment period. Thus, a recent Cochrane review of 24 randomized controlled trials (RCTs) found the anti-craving drug acamprosate to be an effective and safe treatment strategy for supporting continuous abstinence after detoxification in alcohol-dependent patients (50).

Acamprosate Use in Adolescents

Similarly to other agents, there is a dearth of clinical data for its use in youth. One double-blind, placebo-controlled study recruited 26 adolescents, aged 16 to 19 years, with chronic or episodic alcohol dependence, who were randomly assigned to acamprosate (1332 mg daily) or placebo for 90 days. Time to first occurrence of relapse was the primary outcome measure, and cumulative abstinence duration was the secondary outcome measure. The authors observed (at 90 days) that the proportion of subjects who remained abstinent was statistically higher in the acamprosate group compared with the placebo group (7 of 13 vs 2 of 13; p=0.0076). Also, the mean cumulative abstinence duration was statistically greater in the acamprosate group versus placebo (79.8 [SD=37.5] vs 32.8 [SD=19.0] days; p=0.012). The most common reason for study withdrawal was relapse in both groups. The drug was well tolerated with no significant differences in adverse effects between the two groups (51).

Neuroprotective Effects of Acamprosate

The hyperglutamatergic syndrome occurring during alcohol withdrawal was not only associated with craving and relapse to renewed alcohol intake, but also with glutamate-induced toxicity mediated via Ca^{2+} entry (52). Acamprosate reduced Ca^{2+} related neurotoxicity observed during ethanol withdrawal (52). It was suggested that protection against the neurotoxic effects of acamprosate was mediated via an action on mGluRs modulating NMDA receptor function. Moreover, acamprosate inhibited the neurotoxic effects of the mGluR agonist (10,53). In summary, acamprosate carries the potential to have neuroprotective effects in ethanol withdrawal by causing indirect inhibition of NMDA receptors, possibly via action on mGluRs even if other actions of acamprosate, including anti-oxidant effects (54) cannot be excluded.

Using Acamprosate During Withdrawal

The FDA approved the following indication for acamprosate: "The maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation". It is recommended that acamprosate should be started as soon as possible after detoxification. However, since there is pre-clinical evidence that acamprosate may be neuroprotective and since it can be safely prescribed during alcohol withdrawal, consideration should be given to prescribing it earlier (9). In addition, one controlled study of acamprosate showed that acamprosate given during the alcohol detoxification period did not cause any unwanted effects, and might possibly be an advantage in successfully achieving abstinence in the rehabilitation (post-detoxification) period of treatment (55).

In a study to test the comparison of initiating acamprosate in the detoxification versus post-detoxification period, there were no significant outcome differences between acamprosate and placebo-treated patients for starting acamprosate during detoxification. Starting acamprosate after detoxification was completed, was associated with better drinking outcomes during subsequent alcohol rehabilitation treatment (40). It may be that the activity of acamprosate at NMDA receptors is different in the presence of very recent alcohol use compared to after patients have been detoxified and free from alcohol for several days.

Predictors of Treatment Success

It is likely that, as with any psychotropic medication, specific subsets of patients may respond better to acamprosate than others. Because acamprosate is a drug taken three times a day, compliance is harder to establish than with drugs taken once a day. In addition, side effects like diarrhea may cause (temporal) noncompliance. Motivational interventions directed toward full abstinence motivation and abstinence at the start of treatment are crucial for both compliance with acamprosate and successful treatment outcome (56). Multi-site trial conducted in the U.S.A. showed that, while there was no overall clinical evidence that acamprosate was superior to placebo among a heterogeneous cohort of alcohol-dependent individuals, post-hoc analysis suggested that a subgroup of alcoholics with a treatment goal of abstinence might derive benefit (33). Decreased motivation to initiate treatment among depressed as compared to non-depressed alcoholics significantly affects treatment compliance in acamprosate-treated patients (57). From the European studies, acamprosate appears to benefit alcohol-dependent individuals with increased levels of anxiety, physiological dependence, negative family history, late age of onset, and female gender (58). Finally, acamprosate benefited very frequent drinkers and contrary to expectations, was associated with poorer response compared to placebo for consistent daily drinkers who had longer durations of pretreatment abstinence (e.g., ≤14 days) (59).

Anxiety and Depressive Symptoms

Several randomized, placebo-controlled trials of acamprosate have been conducted that use standardized assessment tools to document symptoms of anxiety (60) or depression (61,62) in alcohol-dependent patients. The analyses of these psychiatric subgroups have been

very limited in terms of reporting alcoholism treatment outcomes, but they do suggest that acamprosate can be safely used in patients with psychiatric symptoms. The safety of using acamprosate in patients with psychiatric symptoms is further supported by pharmacokinetic studies demonstrating that acamprosate does not interact with psychiatric medications, including antidepressants, antipsychotics, and sedative-hypnotics (63), as well as the results from 10 clinical trials indicating that the incidence of adverse events is similar for acamprosate versus placebo in patients taking concomitant medications (64).

Secondary analysis of the first U.S.A acamprosate trial (N = 601) for alcohol dependence examined the effects of subsyndromal psychiatric symptoms or history of severe psychopathology on alcoholism treatment outcomes and any mitigating effects of acamprosate. Subsyndromal anxiety and the presence of ≥1 psychiatric antecedent were significant negative predictors of good response, whereas lower pretreatment drinking intensity, baseline motivation to have abstinence as a goal, and treatment with acamprosate were significant positive predictors of good response. Thus, the beneficial effects of acamprosate treatment in combination with motivational therapy may offset the liabilities for alcoholism recovery that are associated with current anxiety symptoms and/or a significant past psychiatric history (65). Finally, in human laboratory trials, acamprosate ameliorated sleep disturbances associated with alcohol withdrawal and reduced brain hyperexcitability associated with alcohol withdrawal (66,67).

CONCLUSION

Relapse prevention in alcohol dependence relies on psychosocial or pharmacological treatment or both, with the primary goal of long-term or lifelong abstinence (68). Whereas psychosocial interventions may be offered as the sole treatment option, current treatment guidelines like the international WFSBP (World Federation of Societies of Biological Psychiatry) guidelines (68) recommend offering pharmacological treatment with anti-craving medication only in combination with some kind of professional psychosocial support or psychosocial therapy (69).

Although treatment of alcohol abuse is complicated and can be associated with high relapse rates, use of acamprosate in addition to psychosocial interventions for patients who have already been detoxified is associated with reduced return to drinking and increased cumulative abstinence during treatment and for up to one year afterward. The balance of evidence suggests that acamprosate is an inhibitory modulator of the NMDA receptor by a mechanism not fully understood up to now, perhaps involving mGluR5. This may be relevant to effects on protracted withdrawal which may in turn be relevant to relapse. Craving because of alcohol-associated stimuli and the so-called "withdrawal relief craving" going along with conditioned hyperglutamatergic states might be a relevant target for acamprosate treatment.

It is likely that, as with any psychotropic medication, specific subsets of patients may respond better to acamprosate than others. Individualized treatment of the "right" patient with the "right" drug would then markedly increase effects size. This is no surprise since addictive behavior results from a complex interaction of genes, environment, and alcohol effects over time. They lead to clinical heterogeneity in terms of symptomatology, severity of the disorder, and most importantly of treatment response. Additional research is clearly needed to determine precisely what these beneficial motivational, methodological, outcome measure, or perhaps genetic factors are in order to identify alcoholics that are most likely to exhibit a positive response to acamprosate.

KAYNAKLAR

1. U.S. Department of Health and Human Services. 10th Special report to the U.S. Congress on alcohol and health. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism; 2000.
2. Swift RM. Drug therapy for alcohol dependence. N Engl J Med 1999; 340:1482-1490.

3. Finney JW, Hahn AC, Moos RH. The effectiveness of inpatient and outpatient treatment for alcohol abuse: the need to focus on mediators and moderators of setting effects. Addiction 1996; 91:1773-1796.

4. Ooteman W, Koeter MW, Verheul R, Schippers GM, van den Brink W. The effect of naltrexone and acamprosate on cue-induced craving, autonomic nervous system and neuroendocrine reactions to alcohol-related cues in alcoholics. Eur Neuropsychopharmacol 2007; 17:558-566.

5. Bjorklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. Trends Neurosci 2007; 30:194-202.

6. Gass JT, Olive MF. Glutamatergic substrates of drug addiction and alcoholism. Biochem Pharmacol 2008; 75:218-265.

7. Zieglgansberger W, Hauser C, Wetzel C, Putzke J, Siggins GR, Spanagel R. Actions of acamprosate on neurons of the central nervous system. In: Soyka M, editor. Acamprosate in relapse prevention of alcoholism. Berlin: Springer; 1996, 65-70.

8. De Witte P, Bachteler D, Spanagel R. Acamprosate: preclinical data. In: Spanagel R, Mann KF, editors. Drugs for relapse prevention of alcoholism. Basel, Switzerland: Birkha¨user Verlag; 2005, 73-83.

9. De Witte P, Littleton J, Parot P, Koob G. Neuroprotective and abstinence-promoting effects of acamprosate: elucidating the mechanism of action. CNS Drugs 2005; 19:517-537.

10. Harris BR, Prendergast MA, Gibson DA, Rogers DT, Blanchard JA, Holley RC, Fu MC, Hart SR, Pedigo NW, Littleton JM. Acamprosate inhibits the binding and neurotoxic effects of trans-ACPD, suggesting a novel site of action at metabotropic glutamate receptors. Alcohol Clin Exp Res 2002; 26:1779-1793.

11. Dahchour A, De Witte P, Bolo N, Ne´de´lec JF, Muzet M, Durbin P, Macher JP. Central effects of acamprosate. Part 1. Acamprosate blocks the glutamate increase in the nucleus accumbens microdialysate in ethanol withdrawn rats. Psychiatry Res 1998; 82:107-114.

12. Rossetti ZL, Carboni S. Ethanol withdrawal is associated with increased extracellular glutamate in the rat striatum. Eur J Pharmacol 1995; 283:177-183.

13. Gewiss M, Heidbreder C, Opsomer L, Durbin P, De Witte P. Acamprosate and diazepam differentially modulate alcohol-induced behavioural and cortical alterations in rats following chronic inhalation of ethanol vapour. Alcohol Alcohol 1991; 26:129-137.

14. Spanagel R, Putzke J, Stefferl A, Schobitz B, Zieglgansberger W. Acamprosate and alcohol. II. Effects on alcohol withdrawal in the rat. Eur J Pharmacol 1996; 305:45-50.

15. Bolo N, Ne´de´lec JF, Muzet M, De Witte P, Dahchour A, Durbin P, Macher JP. Central effects of acamprosate. Part 2. Acamprosate modifies the brain in-vivo proton magnetic resonance spectrum in healthy young male volunteers. Psychiatry Res 1998; 82:115-127.

16. Pierrefiche O, Daoust M, Naassila M. Biphasic effect of acamprosate on NMDA but not on GABAA receptors in spontaneous rhythmic activity from the isolated neonatal rat respiratory network. Neuropharmacology 2004; 47:35-45.

17. Mason BJ, Goodman AM, Dixon RM, Hameed MH, Hulot T, Wesnes K, Hunter JA, Boyeson MG. A pharmacokinetic and pharmacodynamic drug interaction study of acamprosate and naltrexone. Neuropsychopharmacology 2002; 27:596-606.

18. Johnson BA, O'Malley SS, Ciraulo DA, Roache JD, Chambers RA, Sarid-Segal O, Couper D. Dose-ranging kinetics and behavioral pharmacology of naltrexone and acamprosate, both alone and combined, in alcoholdependent subjects. J Clin Psychopharmacol 2003; 23:281-293.

19. Heinz A, Lober S, Georgi A, Wrase J, Hermann D, Rey ER, Wellek S, Mann K. Reward craving and withdrawal relief craving: assessment of different motivational pathways to alcohol intake. Alcohol Alcohol 2003; 38: 35-39.

20. Verheul R, Van Den Brink W, Geerlings P. A three-pathway psychobiological model of craving for alcohol. Alcohol Alcohol 1999; 34: 197-222.

21. Littleton J, Zieglgansberger W. Pharmacological mechanisms of naltrexone and acamprosate in the prevention of relapse in alcohol dependence. Am J Addict 2003; 12 (Suppl.1): 3-11.

22. Weinstein A, Feldtkeller B, Feeney A, Lingford-Hughes A, Nutt D. A pilot study on the effects of treatment with acamprosate on craving for alcohol in alcohol-dependent patients. Addict Biol 2003; 8:229-232.

23. Agelink MW, Lemmer W, Malessa R, Zeit T, Majewski T, Klieser E. Improved autonomic neurocardial balance in short-term abstinent alcoholics treated with acamprosate. Alcohol Alcohol 1998; 33:602-605.

24. Heilig M, Egli M. Pharmacological treatment of alcohol dependence: target symptoms and target mechanisms. Pharmacol Ther 2006; 111: 855-876.

25. Hammarberg A, Jayaram-Lindstrom N, Beck O, Franck J, Reid MS. The effects of acamprosate on alcohol-cue reactivity and alcohol priming in dependent patients: a randomized controlled trial. Psychopharmacology (Berl) 2009; 205: 53-62.

26. Koob GF, Le Moal M. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat Neurosci 2005; 8:1442-1444.

27. Mason BJ, Shaham Y, Weiss F, Le AD. Stress, alcohol craving, and relapse risk: mechanisms and viable treatment targets. Alcohol 2009; 43:541-543.

28. Lhuintre JP, Daoust M, Moore ND, Chretien P, Saligaut C, Tran G, Bosimare F, Hillemand B. Ability of calcium bis acetyl homotaurine, a GABA agonist, to prevent relapse in weaned alcoholics. Lancet 1985; 1:1014-6.

29. Mann K, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol dependent individuals: results of a meta-analysis. Alcohol Clin Exp Res 2004; 28:51-63.

30. Bouza C, Angeles M, Munoz A, Amate JM. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. Addiction 2004; 99:811-828.

31. Kranzler HR, Van Kirk J. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcohol Clin Exp Res 2001; 25:1335-1341.

32. Chick J, Lehert P, Landron F, Plinius Maior Society. Does acamprosate improve reduction of drinking as well as aiding abstinence? J Psychopharmacol 2003; 17:397-402.

33. Mason BJ, Goodman AM, Chabac S, Lehert P. Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: the role of patient motivation. J Psychiatr Res 2006; 40:383-393.

34. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift R, Weiss RD, Williams LD, Zweben A; COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence – The COMBINE Study: a randomized controlled trial. J Am Med Assoc 2006; 295:2003-2017.

35. Donovan DM, Anton RF, Miller WR, Longabaugh R, Hosking JD, Youngblood M; COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence (The COMBINE Study): examination of posttreatment drinking outcomes. J Stud Alcohol Drugs 2008; 69:5-13.

36. Laaksonen E, Koski-Jannes A, Salaspuro M, Ahtinen H, Alho H. A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. Alcohol Alcohol 2008; 43:53-61.

37. Morley KC, Teesson M, Reid SC, Sannibale C, Thomson C, Phung N, Weltman M, Bell JR, Richardson K, Haber PS. Naltrexone versus acamprosate in the treatment of alcohol dependence: a multi-centre, randomized, double-blind, placebo-controlled trial. Addiction 2006; 101:1451-1462.

38. Richardson K, Baillie A, Reid S, Morley K, Teesson M, Sannibale C, Weltman M, Haber P. Do acamprosate or naltrexone have an effect on daily drinking by reducing craving for alcohol? Addiction 2008; 103:953-959.

39. Kiefer F, Mann K. Pharmacotherapy and behavioral intervention for alcohol dependence. JAMA 2006; 296:1727-1728.

40. Kampman KM, Pettinati HM, Lynch KG, Xie H, Dackis C, Oslin DW, Sparkman T, Sharkoski T, O'Brien CP. Initiating acamprosate within-detoxification versus post-detoxification in the treatment of alcohol dependence. Addict Behav 2009; 34:581-586.

41. Weiss RD, O'Malley SS, Hosking JD, Locastro JS, Swift R. Do patients with alcohol dependence respond to placebo? Results from the COMBINE Study. J Stud Alcohol Drugs 2008; 69:878-884.

42. LoCastro JS, Youngblood M, Cisler RA, Mattson ME, Zweben A, Anton RF, Donovan DM. Alcohol treatment effects on secondary nondrinking outcomes and quality of life: the COMBINE study. J Stud Alcohol Drugs 2009; 70:186-196.

43. Kennedy WK, Leloux M, Kutscher EC, Price PL, Morstad AE, Carnahan RM. Acamprosate. Expert Opin Drug Metab Toxicol 2010; 6:363-80.

44. Kiefer F, Mann K. Acamprosate: how, where, and for whom does it work? Mechanism of action, treatment targets, and individualized therapy. Curr Pharm Des 2010; 16: 2098-2102.

45. Kranzler HR, Gage A. Acamprosate efficacy in alcohol-dependent patients: summary of results from three pivotal trials. Am J Addict 2008; 17:70-76.

46. Mann K, Kiefer F, Spanagel R, Littleton J. Acamprosate: recent findings and future research directions. Alcohol Clin Exp Res 2008; 32:1105-1110.

47. Mason BJ, Heyser CJ. Acamprosate: a prototypic neuromodulator in the treatment of alcohol dependence. CNS Neurol Disord Drug Targets 2010; 9:23-32.

48. Mason BJ, Heyser CJ. The neurobiology, clinical efficacy and safety of acamprosate in the treatment of alcohol dependence. Expert Opin Drug Saf 2010; 9:177-188.

49. Snyder JL, Bowers TG. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence: a relative benefits analysis of randomized controlled trials. Am J Drug Alcohol Abuse 2008; 34:449-461.

50. Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database Syst Rev 2010; (9):CD004332.

51. Niederhofer H, Staffen W. Acamprosate and its efficacy in treating alcohol dependent adolescents. Eur Child Adolesc Psychiatry 2003; 12:144-148.

52. Al Qatari M, Khan S, Harris B, Littleton J. Acamprosate is neuroprotective against glutamate-induced excitotoxicity when enhanced by ethanol withdrawal in neocortical cultures of fetal rat brain. Alcohol Clin Exp Res 2001; 25: 1276-1283.

53. Harris BR, Gibson DA, Prendergast MA, Blanchard JA, Holley RC, Hart SR, Scotland RL, Foster TC, Pedigo NW, Littleton JM. The neurotoxicity induced by ethanol withdrawal in mature oranotypic hippocampal slices might involve cross-talk between metabotropic glutamate type 5 receptors and N-methyl-D-aspartate receptors. Alcohol Clin Exp Res 2003; 27: 1724-1735.

54. Dahchour A, Lallemand F, Ward RJ, De Witte P. Production of reactive oxygen species following acute ethanol or acetaldehyde and its reduction by acamprosate in chronically alcoholized rats. Eur J Pharmacol 2005; 520: 51-58.

55. Gual A, Lehert P. Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. Alcohol Alcohol 2001; 36: 413-418.

56. Koeter MW, van den Brink W, Lehert P. Effect of early and late compliance on the effectiveness of acamprosate in the treatment of alcohol dependence. J Subst Abuse Treat 2010; 39:218-226.

57. Lejoyeux M, Lehert P. Alcohol-use disorders and depression: results from individual patient data meta-analysis of the acamprosate-controlled studies. Alcohol Alcohol 2011; 46:61-67.

58. Verheul R, Lehert P, Geerlings PJ, Koeter MW, van den Brink W. Predictors of acamprosate efficacy: results from a pooled analysis of seven European trials including 1485 alcohol-dependent patients. Psychopharmacology 2005; 178:167–173.

59. Gueorguieva R, Wu R, Donovan D, Rounsaville BJ, Couper D, Krystal JH, O'Malley SS. Baseline trajectories of heavy drinking and their effects on postrandomization drinking in the COMBINE Study: empirically derived predictors of drinking outcomes during treatment. Alcohol 2012; 46:121-131.

60. Chick J, Lehert P, Landron F. Does acamprosate improve reduction of drinking as well as aiding abstinence? J Psychopharmacol 2003; 17:397-402.

61. Tempesta E, Janiri L, Bignamini A, Chabac S, Potgieter A. Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo controlled study. Alcohol Alcohol 2000; 35:202-209.

62. Morley KC, Teesson M, Reid SC, Sannibale C, Thomson C, Phung N, Weltman M, Bell JR, Richardson K, Haber PS. Naltrexone versus acamprosate in the treatment of alcohol dependence: a multicentre, randomized, double-blind, placebo-controlled trial. Addiction 2006; 101:1451-1462.

63. Durbin P, Hulot T, Chabac S. Pharmacodynamics and pharmacokinetics of acamprsoate: An overview. In: Soyka M, ed. Acamprosate in Relapse Prevention of Alcoholism. Proceedings of the 1st Campral Symposium. Stuttgart, Germany: Springer; 1995:47-64.

64. Rosenthal RN, Gage A, Perhach JL, Goodman AM. Acamprosate: safety and tolerability in the treatment of alcohol dependence. J Addict Med 2008; 2:40-50.

65. Mason BJ, Lehert P. The effects of current subsyndromal psychiatric symptoms or past psychopathology on alcohol dependence treatment outcomes and acamprosate efficacy. Am J Addict 2010; 19:147-154.

66. Boeijinga PH, Parot P, Soufflet L, Landron F, Danel T, Gendre I, Muzet M, Demazières A, Luthringer R. Pharmacodynamic effects of acamprosate on markers of cerebral function in alcohol-dependent subjects administered as pretreatment and during alcohol abstinence. Neuropsychobiology 2004; 50:71-77.

67. Staner L, Boeijinga P, Danel T, Gendre I, Muzet M, Landron F, Luthringer R. Effects of acamprosate on sleep during alcohol withdrawal: a double-blind placebo-controlled polysomnographic study in alcohol-dependent subjects. Alcoholism: Clinical & Experimental Research 2006; 30:1492-1499.

68. Soyka M, Kranzler HR, Berglund M, Gorelick D, Hesselbrock V, Johnson BA, Moller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of substance use and related disorders, part 1: alcoholism. World J Biol Psychiatry 2008; 9:6-23.

69. Wölwer W, Frommann N, Jänner M, Franke PE, Scherbaum N, Lieb B, Falkai P, Wobrock T, Kuhlmann T, Radermacher M, Maier W, Schütz C, Ohmann C, Burtscheidt W, Gaebel W. The effects of combined acamprosate and integrative behaviour therapy in the outpatient treatment of alcohol dependence: a randomized controlled trial. Drug Alcohol Depend 2011; 118:417-422.