

Pharmacological treatment of alcohol use disorder. Scientific evidence

Trattamento farmacologico del disturbo da uso di alcol. Evidenze scientifiche

FABIO ATTILIA^{1*}, ROBERTA PERCIBALLI¹, CLAUDIA ROTONDO¹, IDA CAPRIGLIONE¹,
SILVIA IANNUZZI¹, MARIA LUISA ATTILIA¹, MARIO VITALI², GIOVANNI ALESSANDRINI³,
MARIA CONCETTA MARCELLA SCAMPORRINO¹, MARCO FIORE⁴, MAURO CECCANTI¹;
INTERDISCIPLINARY STUDY GROUP CRARL, SITAC, SIPaD, SITD, SIPDip**

*E-mail: fabio_attilia@libero.it

¹Centro di Riferimento Alcolologico della Regione Lazio (CRARL), Sapienza University of Rome, Italy

²ASUR Marche-AV4, Italy

³ASL Viterbo, General Medicine, Viterbo, Italy

⁴Institute of Cell Biology and Neurobiology (IBCN-CNR), Rome, Italy

SUMMARY. Pharmacological treatment of alcohol use disorder represents an essential core of the therapeutic project in a multidisciplinary approach. While non-drug treatment is evolving, from a medical perspective few pharmacotherapies are available; in particular acamprosate, naltrexone and more recently nalmefene among anticraving drugs, disulfiram as an antidipsotropic medication. New studies are focusing on off-label drugs. Moreover, scientific evidence has to support any therapeutic indication which should be tailored on patient needs and comorbidity by considering the individual bio-psycho-social profile. Follow-up is essential in order to assess patient compliance to treatment and monitoring outcomes.

KEY WORDS: alcohol use disorder, anticraving drugs, follow-up.

RIASSUNTO. La terapia farmacologica nei pazienti con disturbo da uso di alcol riveste un ruolo centrale nel progetto terapeutico, altamente contestualizzato in un approccio multidisciplinare. Sebbene i trattamenti non farmacologici per la dipendenza da alcol risultino ben strutturati e in continua evoluzione, dal punto di vista medico le possibilità di intervento sono realmente ristrette, con poche molecole a disposizione approvate per il disturbo da uso di alcol: nello specifico, l'acamprostatato, il naltrexone e, più recentemente, il nalmefene tra gli anticraving; il disulfiram tra gli avversivanti. Nuovi approcci sperimentali stanno cercando di ampliare tale gamma attraverso l'utilizzo di farmaci off-label. Evidenze scientifiche devono supportare l'indicazione terapeutica, quest'ultima deve dimostrarsi "cucita" sulle esigenze del paziente e sulle comorbilità presenti tenendo conto del profilo bio-psyco-sociale individuale. Fondamentale risulta il follow-up per valutare la ritenzione in trattamento e il monitoraggio degli outcome alcolologici.

PAROLE CHIAVE: disordine da uso di alcol, terapia anticraving, follow-up.

INTRODUCTION

The goal of drug treatment, during the rehabilitation phase, is the maintenance of abstinence, by preventing relapse or decreasing the number of relapses, to reduce organic damage. A multidisciplinary approach to alcoholism consists of a combination of pharmacotherapy (namely anti-craving drugs and psychiatric drugs when necessary) and psychological support to create the most suitable therapy for each individual bio-psycho-social profile¹. Thus, the new concept of "tailor-made" therapy responds to these needs. Developments in genetics and the use of off-label drugs are expanding the range of available drugs resulting in new alternative therapies and an improvement of the effectiveness of traditional drugs.

ANTICRAVING DRUGS

Acamprosate

Acamprosate (ACA) is used in alcohol dependence due to its modulation of glutamatergic transmission via its effects on NMDA receptors. Owing to its tolerability and safe profile, Acamprosate is extremely versatile^{2,3}. ACA is administered at the dosage of 666 mg three times per day. Dosage reductions are required for patients weighing <60 kg and for those with renal impairment⁴. Since ACA is cleared by the kidneys, where there is a severe renal failure, the drug is contraindicated. Studies on pregnancy and Child-Pugh class C cirrhosis do not exist⁵.

The effectiveness of the drug is evident in relapse but not in the case of heavy drinking². (Recommendation A1 of Table 1)⁵.

Naltrexone

Naltrexone (NTX) is an opioid antagonist, blocking mu-opioid receptors located in brain areas that have been implicated in reward pathways associated with alcohol. Its effectiveness is related to the reduction of the number of days of alcohol consumption and alcoholic drinks consumed in one drinking episode⁶. NTX has been found to be superior to a placebo in maintaining abstinence and in preventing relapse^{3,7}. Its effectiveness increases if combined with psychotherapy⁸. NTX is contraindicated in liver failure while it is used with caution in case of liver disorders, even in mild forms⁵. Furthermore, NTX is contraindicated in patients who use opioids since it may cause withdrawal symptoms. The initial dose is 25 mg for the first 4-5 days, then 50 mg daily. Doses may be increased to 100-150 mg daily³. NTX is particularly effective in patients presenting a family history of alcohol use disorder (AUD)⁹, and /or those presenting with early onset and antisocial behavior¹⁰. In individuals presenting the genetic polymorphism G, which codes for the mu opioid receptor (OPRM1), this drug has been found to be more effective at a dosage of 100 mg/day¹¹. (Recommendation A1 of Table 1).

Nalmefene

Nalmefene is an antagonist at mu- and delta-opioid receptors and a partial agonist to the kappa receptors^{12,13}. It decreases reinforcing effects of alcohol, thus helping reduce consumption by modulating the opioid system^{14,15}: nalmefene is the first drug to have been approved in Europe with the goal to reduce consumption in heavy alcohol drinkers¹². Nalmefene represents the “as needed approach” in which the drug must be administered 1-2 hours before the expected alcohol consumption. The maximum dosage is one pill per day. Contraindications are a recent history of opioid use, renal and liver failures, recent episodes of alcohol withdrawal syndrome (AWS) or hallucinations^{16,17}. (Recommendation A2 of Table 1).

ANTIDIPSOTROPIC MEDICATIONS

Disulfiram

Disulfiram exhibits an antidipsotropic effect. It has been the first drug available for AUD treatment and still represents the drug of choice in some countries. It inhibits the conversion of acetaldehyde in acetic acid by blocking the aldehyde dehydrogenase 2 (ALDH2) in the liver and in the brain, resulting in an accumulation of acetaldehyde¹⁸. This compound, in high concentrations, creates a specific reaction characterized by nausea, vomiting, headache, flushing on the face and neck and more rarely vertigo, blurred vision, hypotension and syncope¹⁹. Disulfiram is contraindicated in the case of hepatic impairment, cardiovascular diseases, psychosis, or cognitive impairment, pregnancy or in patients who plan to have children. Absolute abstinence is required some days before the start of treatment and patients must sign the informed consent. The administration of the drug should have placed under the supervision of a relative. Because of its contraindications and its lack of convenience Disulfiram is not commonly used^{20,21}. (Recommendation A2 of Table 1).

OTHER DRUGS

Baclofen

Baclofen is an agonist of GABA-B receptors. It inhibits dopaminergic activity and it is used for spasticity²². In recent years, studies have been conducted to assess the effectiveness in reducing alcohol cravings in patients presenting AUD; however, data require confirmation for its use²³. (Recommendation B2 of Table 1).

Varenicline

Varenicline is a partial agonist of $\alpha 4\beta 2$ nicotinic receptors exhibiting high affinity and high selectivity. It is used in nicotine dependence²⁴⁻²⁶ and it has been used in AUD only recently²⁷. It activates acetylcholine nicotinic receptor $\alpha 7$ which is implicated in the reward pathway associated with alcohol²⁸.

Table 1. Treatments’ efficacy grading of both evidence and recommendations (adapted from EASL⁵).

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect and clinical practice	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate and clinical practice	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate and clinical practice. Any estimate of effect is uncertain	C
Grading of recommendation	Notes	Symbol
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost or resource consumption	2

Pharmacological treatment of alcohol use disorder. Scientific evidence

Some studies have detected the effectiveness of Varenicline but further studies are required to assess its therapeutic use²⁹. (Recommendation B2 of Table 1).

Sodium oxybate

Sodium oxybate, besides being a medication for AWS treatment, is approved in Italy and Austria in preventing relapse and decreasing craving. Despite its effectiveness, studies conducted thus far are not reliable because of their small sample sizes.

Therefore, future studies should use random sampling and employ large sample sizes with standardized assessment scales to be valid. Moreover, it is important to monitor for abuse in multi-drug abusers and in patients presenting dual diagnosis³⁰⁻³². (Recommendation B2 of Table 1).

NEW APPROACHES OF PHARMACOGENETICS IN THE TREATMENT OF ALCOHOL USE DISORDER

Alcohol addiction is a complex disease that results from a variety of genetic and environmental influences. The variety of factors activates several individual pathophysiological mechanisms leading to the development and progression of AUD. In support of this hypothesis, numerous studies have been conducted demonstrating the existence of slight differences in the population at the genetic level (i.e., polymorphisms) that may increase the vulnerability in developing dependence or determining some characteristics of the disease such as severity of drinking, craving, the age of onset, etc. After such genetic variations were identified, they were used to study the best response to treatment with drugs in terms of therapeutic efficacy and tolerability. Studies have been conducted on both the main drugs used in alcohol dependence (NTX and ACA) and on the off-label drugs (topiramate, ondansetron, sertraline and olanzapine).

Naltrexone

Studies conducted on alcohol dependence and treatment with NTX have shown that some individuals having alcohol problems present a deficit of endogenous opioids³³ along with genetic markers (i.e., polymorphisms) predictive of pharmacological response. In particular, studies have focused on the single-nucleotide polymorphism (SNP) rs1799971 concerning OPRM1 gene, which determines the A118G variation at the nucleotide level³⁴ resulting in the amino acid substitution Asn40Asp at the protein level. The presence of the G allele is associated with: an increased binding capacity for β -endorphin, a reduction in mRNA levels and in the synthesis of the protein-receptor^{35,36}, as well as a more efficient response to NTX at a dose of 100 mg/day³⁷.

Other studies have investigated whether NTX is effective in some patients at a dosage of 50 mg/day and they showed that a response was possible in individuals presenting the variable number of tandem repeat polymorphism (VNTR from 7 to 11) of DRD4 gene⁴⁴. To summarize, since the G allele is more common among Caucasian and Asiatic people, the use of NTX would be most beneficial in these populations.

Acamprosate

It was FDA approved for AUD treatment in 2004. Researchers studying populations have identified polymorphisms able to predict response to treatment with ACA, in particular: the C1412T polymorphism of GABRB2 gene, the SNP rs13273672 polymorphism of GATA4 gene and the PER2Brdm1 mutation of PER2 gene. The first two are associated with the physiological response to alcohol, the latter is associated with the response to ACA. A preclinical study on mice carriers of the gene mutation PER2 showed a reduction of alcohol consumption following the administration of ACA³⁷. The same study focused on alcohol consumption in a population of Caucasian individuals treated with ACA, showing that the individual carriers of at least one mutated allele, within a regulatory region of PER2, showed a lower alcohol intake (<300 g/die) than those who do not carry the mutated allele. However, these findings need to be replicated in independent studies to validate the importance of pharmacogenetics to treatment.

Ondansetron

Ondansetron was FDA approved for the treatment of nausea, postoperatively and in chemotherapy. This drug has a high affinity for the 5-HT₃ receptors which regulate the release of dopamine. While alcohol induces an increase of dopamine, ondansetron reduces the release of the neurotransmitter by blocking the 5-HT₃ receptors. Several studies³⁸ investigated the effectiveness of ondansetron by dividing alcoholic individuals into two subgroups based on their genotype for the promoter region of the SLC6A4 gene coding for the serotonin transporter (5-HTTLPR L/S polymorphism). The study showed that the patients with the LL genotype treated with ondansetron responded better in terms of alcohol amount and days of abstinence, compared to the other subgroups. Based on these results, researchers have further investigated genotype LL carriers, by analyzing the role of a functional polymorphism of the SLC6A4 gene (rs1042173 [T/G] SNP). The result was that individuals who carry both 5-HTTLPR LL polymorphism and rs1042173 TT polymorphism, treated with ondansetron at the dosage of 0.5 mg/die, present a more effective response to the drug. Unfortunately, the sample of this exploratory study was too small to be validated.

Topiramate

Topiramate was FDA approved for the treatment of epilepsy in 1996 and for the treatment of migraine in 2004. It has been tested in multiple clinical trials since it could be promising in AUD treatment. Topiramate decreases reinforcing effects of alcohol and craving³⁹. A meta-analysis⁴⁰, based on data from seven random studies (2003-2014), suggested that topiramate might have beneficial effects in AUD treatment but because of its many side effects, the use is limited. The most common side effects are cognitive dysfunction⁴¹, paresthesia⁴², and taste abnormalities⁴³. Pharmacogenetics studies were conducted on an SNP for the GRIK1 gene coding for one of the main receptors of topiramate: the Gluk1 receptor. The rs2832407 polymorphism is a substitution of the nucleotide C/A. Rav et al.⁴⁴ suggested that patients with at least one copy of A allele (AC or AA) treated with 300 mg of

Attilia F et al.

topiramate, presented an increased risk of experiencing adverse events compared to patients with two copies of the C allele (CC). Furthermore, in 2014 Kranzler et al.⁴⁵, by dividing patients based on their genetic profile (CC, AA, or AC), compared the efficacy of 200 mg of topiramate versus placebo. This study has shown that only CC patients received a real benefit from topiramate, while no difference was found between the drug and placebo in patients with at least one A allele.

Sertraline

Sertraline was FDA approved for the treatment of depression in 2002 and for the treatment of generalized anxiety disorder in 2003. Sertraline belongs to the selective serotonin reuptake inhibitors (SSRI) drug classification. In 2009 Kenna et al.⁴⁶, by randomly administering a placebo, ondansetron and sertraline to 21 patients at a dose of 200 mg/die for three weeks, suggesting beneficial effects resulted from sertraline on some individuals carrying the 5-HTTLPR LL polymorphism. These individuals were the subject of further studies for the investigation of an SNP, a rs25531 substitution of the nucleotide A/G in the upstream promoter region of the SLC6A4 gene. The study showed that patients who responded to the administration with sertraline carried the LALA profile, that exhibits a totally functional serotonin transporter and a late onset of AUD⁴⁷. These individuals showed a good response up to 3 months after the discontinuation of the drug.

Olanzapine

Olanzapine was FDA approved for the treatment of schizophrenia and bipolar disorder only. It is an atypical antagonist of D2 and D4 receptors which determines a decrease in craving for alcohol⁴⁸. The DRD4 gene of dopamine presents a VN-TR polymorphism, with a number of repetitions that varies from 2 to 11 which allows for the division of individuals in two subgroups: those with a number of repetitions between 2 and 6, classified as DRD4 S and those with more than 7 repetitions, classified as DRD4 L. Association studies between this variation and AUD have showed that individuals who carry the L allele exhibit greater craving after alcohol intake^{49,50}. Another study has investigated the association olanzapine-DRD4 showing that olanzapine reduces craving to the L allele carriers only, while no benefits were observed in S allele carriers⁵¹.

CONCLUSIONS

Scientific evidence must support therapeutic indications appropriate to the needs of each patient and their comorbidities by considering the individual bio-psycho-social profile⁵²⁻⁵⁷. Thus, the combination of pharmacotherapy, psychological and psychiatric support is necessary, as are the follow-up and the monitoring of clinical outcomes.

Conflict of interests: the authors have no conflict of interests to declare.

***Interdisciplinary Study Group - Centro Riferimento Alcológico Regione Lazio (CRARL), Società Italiana per Il Trattamento dell'Alcolismo e delle sue Complicanze (SITAC), Società Italiana Patologie da Dipendenza (SIPaD), Società Italiana delle Tossicodipendenze (SITD),*

Società Italiana di Psichiatria e delle Dipendenze (SIPDip): Giovanni Addolorato, Vincenzo Aliotta, Giuseppe Barletta, Egidio Battaglia, Gemma Battagliese, Valentina Carito, Onofrio Casciani, Pietro Casella, Fernando Cesarini, Mauro Cibir, Rosaria Ciccarelli, Paola Ciolli, Giovanna Coriale, Angela Di Prinzi, Roberto Fagetti, Emanuela Falconi, Michele Federico, Giampiero Ferraguti, Daniela Fiorentino, Simona Gencarelli, Angelo Giuliani, Antonio Greco, Guido Intaschi, Luigi Janiri, Angela Lagrutta, Giuseppe La Torre, Giovanni Laviola, Roberta Ledda, Lorenzo Leggio, Claudio Leonardi, Anna Loffreda, Fabio Lugoboni, Simone Macri, Rosanna Mancinelli, Massimo Marconi, Icro Maremmani, Marcello Maviglia, Marisa Patrizia Messina, Martino Mistretta, Franco Montesano, Michele Parisi, Esterina Pascale, Fabiola Pisciotta, Giampaolo Spinnato, Alessandro Valchera, Valeria Zavan.

REFERENCES

1. Soyka M, Lieb M. Recent developments in pharmacotherapy of alcoholism. *Pharmacopsychiatry* 2015; 48: 123-35.
2. Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. *Cochrane Database Syst Rev* 2010; (9):CD004332.
3. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA* 2014; 311: 1889-900.
4. Plosker GL. Acamprosate: a review of its use in alcohol dependence. *Drugs* 2015; 75: 1255-68.
5. European Association for the Study of Liver. EASL Clinical practical guidelines: management of alcoholic liver disease. *J Hepatol* 2012; 57: 399-420.
6. Rösner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisuranont M, Soyka M. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev* 2010; (12): CD001867.
7. Maisel NC, Blodgett JC, Wilbourne PL, et al. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction* 2013; 108: 275-93.
8. Jarosz J, Miernik K, Wachal M, et al. Naltrexone (50 mg) plus psychotherapy in alcohol-dependent patients: a meta-analysis of randomized controlled trials. *Am J Drug Alcohol Abuse* 2013; 39: 144-60.
9. Krishnan-Sarin S, Krystal JH, Shi J, Pittman B, O'Malley SS. Family history of alcoholism influences naltrexone-induced reduction in alcohol drinking. *Biol Psychiatry* 2007; 62: 694-7.
10. Kiefer F, Jiménez-Arriero MA, Klein O, Diehl A, Rubio G. Cloninger's typology and treatment outcome in alcohol-dependent subjects during pharmacotherapy with naltrexone. *Addict Biol* 2008; 13: 124-9.
11. Oslin DW, Berrettini W, Kranzler HR, et al. A functional polymorphism of the mu-opioid receptor gene is associated with Naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology* 2003; 28: 1546-52.
12. Keating GM. Nalmefene: a review of its use in the treatment of alcohol dependence. *CNS Drugs* 2013; 27: 761-72.
13. Gianoulakis C. Influence of the endogenous opioid system on high alcohol consumption and genetic predisposition to alcoholism. *J Psychiatry Neurosci* 2001; 26: 304-18.
14. Walker BM, Valdez GR, McLaughlin JP, Bakalkin G. Targeting dynorphin/kappa opioid receptor systems to treat alcohol abuse and dependence. *Alcohol* 2012; 46: 359-70.
15. Nealy KA, Smith AW, Davis SM, Smith DG, Walker BM. κ -opioid receptors are implicated in the increased potency of intracumbens nalmefene in ethanol-dependent rats. *Neuropharmacology* 2011; 61: 35-42.
16. Paille F, Martini H. Nalmefene: a new approach to the treatment of alcohol dependence. *Subst Abuse Rehabil* 2014; 5: 87-94.
17. Van den Brink W, Sørensen P, Torup L, Mann K, Gual A; SENSE Study Group. Long-term efficacy, tolerability and safety of nalme-

Pharmacological treatment of alcohol use disorder. Scientific evidence

- fene as-needed in patients with alcohol dependence: a 1-year, randomized controlled study. *J Psychopharmacol* 2014; 28: 733-44.
18. Vasiliou V, Malamas M, Marselos M. The mechanism of alcohol intolerance produced by various therapeutic agents. *Acta Pharmacol Toxicol* 1986; 58: 305-10.
 19. McMahon FG. Disulfiram-like reaction to a cephalosporin. *JAMA* 1980; 243: 2397.
 20. Jørgensen CH, Pedersen B, Tønnesen H. The efficacy of disulfiram for the treatment of alcohol use disorder. *Alcohol Clin Exp Res* 2011; 35: 1749-58.
 21. Spithoff S, Kahan M. Primary care management of alcohol use disorder and at-risk drinking: Part 2: counsel, prescribe, connect. *Can Fam Physician* 2015; 61: 515-21.
 22. Imbert B, Alvarez JC, Simon N. Anticraving effect of baclofen in alcohol-dependent patients. *Alcohol Clin Exp Res* 2015; 39: 1602-8.
 23. Leggio L, Garbutt JC, Addolorato G. Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. *CNS Neurol Disord Drug Targets* 2010; 9: 33-44.
 24. Oncken C, Gonzales, Nides M, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med* 2006; 166: 1571-7.
 25. Nides M, Oncken C, Gonzales D, et al. Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo and bupropion-controlled trial with 1-year follow-up. *Arch Intern Med* 2006; 166: 1561-8.
 26. Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves KR; Varenicline Phase 3 Study Group. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006; 296: 64-71.
 27. McKee SA, Harrison EL, O'Malley SS, et al. Varenicline reduces alcohol self-administration in heavy-drinking smokers. *Biol Psychiatry* 2009; 66: 185-90.
 28. Bowers BJ, McClure-Begley TD, Keller JJ, Paylor R, Collins AC, Wehner JM. Deletion of the alpha7 nicotinic receptor subunit gene results in increased sensitivity to several behavioral effects produced by alcohol. *Alcohol Clin Exp Res* 2005; 29: 295-302.
 29. Plebani JG, Lynch KG, Rennert L, Pettinati HM, O'Brien CP, Kampman KM. Results from a pilot clinical trial of varenicline for the treatment of alcohol dependence. *Drug Alcohol Depend* 2013; 133: 754-8.
 30. Leone MA, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. *Cochrane Database Syst Rev* 2010; (2): CD006266.
 31. Brambilla R, Vigna-Taglianti F, Avanzi G, Faggiano F, Leone M, et al. [Gamma-hydroxybutyrate (GHB) for mid/long term treatment of alcohol dependence: a systematic review]. *Riv Psichiatr* 2012; 47: 269-80.
 32. Skala K, Caputo F, Mirijello A, et al. Sodium oxybate in the treatment of alcohol dependence: from the alcohol withdrawal syndrome to the alcohol relapse prevention. *Expert Opin Pharmacother* 2014; 15: 245-57.
 33. Oslin DW, Berrettini W, Kranzler HR, et al. A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology* 2003; 28: 1546-52.
 34. Anton RF, Oroszi G, O'Malley S, et al. An evaluation of mu-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. *Arch Gen Psychiatry* 2008; 65: 135-44.
 35. Bond C, LaForge KS, Tian M, et al. Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. *Proc Natl Acad Sci U S A* 1998; 95: 9608-13.
 36. Mague SD, Isiegas C, Huang P, et al. Mouse model of OPRM1 (A118G) polymorphism has sex-specific effects on drug-mediated behavior. *Proc Natl Acad Sci U S A* 2009; 106: 10847-52.
 37. Spanagel R, Pendyala G, Abarca C, et al. The clock gene *Per2* influences the glutamatergic system and modulates alcohol consumption. *Nat Med* 2005; 11: 35-42.
 38. Johnson BA, Ait-Daoud N, Seneviratne C, et al. Pharmacogenetic approach at the serotonin transporter gene as a method of reducing the severity of alcohol drinking. *Am J Psychiatry* 2011; 168: 265-75.
 39. Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 2007; 298: 1641-51.
 40. Blodgett JC, Del Re AC, Maisel NC, Finney JW. A meta-analysis of topiramate's effects for individuals with alcohol use disorders. *Alcoholism Clin Exp Res* 2014; 38: 1481-8.
 41. Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* 2003; 361: 1677-85.
 42. Kampman KM, Pettinati HM, Lynch KG, Spratt K, Wierzbicki MR, O'Brien CP. A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. *Drug Alcohol Depend* 2013; 133: 94-9.
 43. Johnson BA, Rosenthal N, Capece JA, et al.; Topiramate for Alcoholism Study Group. Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Arch Intern Med* 2008; 168: 1188-99.
 44. Ray LA, Miranda R Jr, MacKillop J, et al. A preliminary pharmacogenetics investigation of adverse events from topiramate in heavy drinkers. *Exp Clin Psychopharmacol* 2009; 17: 122-9.
 45. Kranzler HR, Covault J, Feinn R, et al. Topiramate treatment for heavy drinkers: Moderation by a GRIK1 polymorphism. *Am J Psychiatry* 2014; 171: 445-52.
 46. Kenna GA, Zywiak WH, McGeary JE, et al. A within-group design of nontreatment seeking 5-HTTLPR genotyped alcohol-dependent subjects receiving ondansetron and sertraline. *Alcohol Clin Exp Res* 2009; 33: 315-23.
 47. Kranzler HR, Armeli S, Tennen H, et al. A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age of onset [corrected] and 5 hydroxytryptamine transporter-linked promoter region genotype. *J Clin Psychopharmacol* 2011; 31: 22-30. Erratum in: *J Clin Psychopharmacol* 2011; 31: 576.
 48. Hutchison KE, Swift R, Rohsenow DJ, Monti PM, Davidson D, Almeida A. Olanzapine reduces urge to drink after drinking cues and a priming dose of alcohol. *Psychopharmacology (Berl)* 2001; 155: 27-34.
 49. Hutchison KE, McGeary J, Smolen A, Bryan A, Swift RM. The DRD4 VNTR polymorphism moderates craving after alcohol consumption. *Health Psychol* 2002; 21: 139-46.
 50. Ceccanti M, Inghilleri M, Attilia ML, et al. Deep TMS on alcoholics: effects on cortisolemia and dopamine pathway modulation. A pilot study. *Can J Physiol Pharmacol* 2015; 93: 283-90.
 51. Hutchison KE, Wooden A, Swift RM, et al. Olanzapine reduces craving for alcohol: a DRD4 VNTR polymorphism by pharmacotherapy interaction. *Neuropsychopharmacology* 2003; 28: 1882-8.
 52. Ciafrè S, Fiore M, Ceccanti M, et al. Role of Neuropeptide Tyrosine (NPY) in ethanol addiction. *Biomed Reviews* 2016; 27: 27-39.
 53. Ciafrè S, Carito V, Tirassa P, et al. Ethanol consumption and innate neuroimmunity. *Biomed Reviews* 2018; 28: 49-61.
 54. Ceccanti M, Hamilton D, Coriale G, et al. Spatial learning in men undergoing alcohol detoxification. *Physiol Behav* 2015; 149: 324-30.
 55. Ceccanti M, Carito V, Vitali M, et al. Serum BDNF and NGF modulation by olive polyphenols in alcoholics during withdrawal. *J Alcohol Drug Depend* 2015; 3: 214-9.
 56. Ceccanti M, Coriale G, Hamilton DA, et al. Virtual Morris Task Responses in individuals in an abstinence phase from alcohol. *Can J Physiol Pharmacol* 2018; 96: 128-36.
 57. Carito V, Ceccanti M, Ferraguti G, et al. NGF and BDNF alterations by prenatal alcohol exposure. *Curr Neuropharmacol* 2017 Aug 24.