

Neurobiology, Genetics and Treatment of Alcohol Craving

Cem Sengul¹, Nesrin Dilbaz²

¹Assoc. Prof. Dr., Pamukkale University,
Department of Psychiatry, Denizli - Turkey
²Prof. Dr., Uskudar University,
Department of Psychiatry, Istanbul - Turkey



ABSTRACT

Neurobiology, genetics and treatment of alcohol craving

Alcohol craving has increasingly been considered an important issue in alcohol use disorders in the last decade. Biologic studies on alcohol craving were mainly focused on neurobiology, genetics and pharmacological treatment of this condition. In this report, we started from receptor systems, than we explained genetics and epigenetics of alcohol craving. At last, we described the main drugs currently used in the treatment of alcohol craving. Other potential drugs and future choices for treating alcohol craving were also described.

Key words: Alcohol craving, genetic, neurobiology, treatment

ÖZET

Alkol aşermesinin nörobiyolojisi, genetiği ve tedavisi

Alkol aşermesi son 10 yılda, giderek artan bir şekilde, alkol kullanım bozukluklarında önemli bir sorun olarak kabul edilmektedir. Alkol aşermesi ile ilgili yapılan biyolojik çalışmalar, daha çok nörobiyoloji, genetik ve bu durumun farmakolojik tedavisi üzerine odaklanmaktadır. Biz bu yazımızda, reseptör sistemlerinden başlayarak, alkol aşermesinin genetiği ve epigenetiğini gözden geçirdik. Son olarak da, alkol aşermesinde kullanılan ana ilaçlardan başlayarak, alkol aşermesinde kullanılması muhtemel diğer ilaçları ve gelecekteki olası tedavi seçeneklerini açıklamaya çalıştık.

Anahtar kelimeler: Alkol aşermesi, genetik, nörobiyoloji, tedavi

Address reprint requests to / Yazışma adresi:

Assoc. Prof. Dr. Cem Sengul
Pamukkale University, Faculty of Medicine,
Department of Psychiatry, Denizli - Turkey

Phone / Telefon: +90-258-444-0728/5019

E-mail address / Elektronik posta adresi:
acemsen@gmail.com

Date of receipt / Geliş tarihi:
August 15, 2012 / 15 Ağustos 2012

Date of acceptance / Kabul tarihi:
October 30, 2012 / 30 Ekim 2012

INTRODUCTION

Alcohol craving is an uncontrollable desire to take alcohol and symptoms including anxiety, asthenia, anorexia and insomnia, when this desire is not fulfilled (1). There are several counterparts of the term "craving", which is described as "a strong desire" in Oxford Dictionary, in Turkish, such as "arzu", "istek" and "aşerme"; we preferred the last one since we believe it is more appropriate. When the individual start drinking alcohol, a very strong desire to use alcohol develops and this desire continues for a long time. This results in continued use of alcohol by the individual in spite of serious side effects and important negative outcomes (1,2).

Brain reward system, reinforcing effect of the substance and craving forms the trivet of dependence neurobiology (3). First of all, a substance has to induce euphoria in order to cause dependence. Therefore, it has been hypothesized that dependence equals to brain

reward system. Indeed, research has shown that nucleus accumbens and dopamine as a neurotransmitter have a role in emergence of dependence, but this hypothesis is insufficient to explain all processes associated with dependence (4). Following this, it has been argued that reward can not be the only reason for dependence since non-dependent individuals experience same level of pleasure when using these substances. In this context, need to focus on processes other than reward have been increasingly stressed. Concept of craving came in this process; first it was taken on as a symptom of withdrawal, later, it was reported in patients who stopped using the substance several years ago and it has been taken on as a separate phenomenon. Thus, during 1990s and 2000s, different aspects of craving became a research topic. In the recent years, with the advent of technology, it has become possible to study changes leading to craving at cell nucleus and DNA levels (5,6).

In parallel to these developments in the world, by 2000s articles investigating different aspects of craving

have begun to be published in our country. In those articles, different models explaining craving were described and their reflections in treatment were discussed (1,7,8), and reliability and validity of scales which have been used widely in the world, such as obsessive compulsive desire to drink and Penn alcohol craving scale, were investigated (9-11).

In this article, our aim was to review new developments in this field by searching for full text articles in Pubmed and Turkish Psychiatric Index data bases by using craving, neurobiology, genetics, epigenetics and different drug names as key words.

Neurobiology of Alcohol Craving

Dopamine has an important role in regulation of brain reward system and is also closely associated with craving. Association of dopaminergic system and craving was first shown in animal studies. Brain imaging and drug studies following these found that dopamine has a role in craving. In brain imaging studies, mesolimbic dopaminergic alterations resulting from chronic use of several different substances, from nicotine to cocaine, are shown to be associated with craving. Besides, there are several studies and case series which indicates that antidopaminergic drugs decrease craving while dopaminergic agents increase it (12,13).

Since every neurotransmitter system in the brain is interrelated, serotonergic, glutamatergic, noradrenergic, GABAergic, and endogen opioid systems are also related with craving. Anton grouped craving into three. He argued that, GABAergic and glutamatergic systems were responsible for abstinence related craving, while dopaminergic, glutamatergic and endogen opioid systems were responsible for craving related with memories on rewarding effects of alcohol and serotonergic system was responsible for stress related craving (14).

Along with neurotransmitters, association of craving with molecules like leptin, ghrelin, adiponectin and BDNF (brain derived neurotrophic factor) have been investigated. It has been reported that particularly peptides, which effect appetite, such as leptin and ghrelin, are connected with craving (15). Hillemecher et

al. (16), reported an association between leptin level and craving in both male and female patients with alcohol dependence; Addolorato et al. (17) compared ghrelin level and obsessive compulsive drinking scale scores and found that in those with high ghrelin level craving was more severe. On the other hand, Hilburn et al. (18) found association between serum BDNF and alcohol, cocaine and metaphetamine craving. Hillemecher et al. (19), investigated the relation of adiponectin, resistin and craving and found decreased adiponectin level during craving periods and that adiponectin was associated with craving while resistin was not. All these findings suggest that neuroendocrinological mechanisms are effective to a large degree in craving and that more detailed investigations are necessary.

Genetics of Alcohol Craving

In recent years, a significant part of the studies on craving are genetic studies. In these studies, findings from neurobiology of craving have been utilized and effects of genetic variations among people on craving have been investigated. Particularly, the effects of genetic variations of dopaminergic, serotonergic and opioid systems on craving have been studied along with other genetic variations observed in genes that were thought to be related with craving (5,20).

Genetic polymorphisms of enzymes related with dopamine synthesis and degradation have been shown to be associated with alcohol dependence (20). Researchers also investigated the relation of craving and genetic polymorphisms in dopaminergic system. Agrawal et al. (5), investigated the association of DRD1, DRD2, DRD3 and DRD4 dopamine receptor gene polymorphisms and dopamine transporter gene (DAT) SLC6A3 polymorphism with craving and found an association between some polymorphisms in DRD3 gene and craving. Serotonergic system has also been investigated. In serotonergic system, particular attention has been paid to genetic polymorphisms in the serotonin transporter (5HTT) gene. Association of 5HTT gene long-short (l/s) polymorphism and craving has been examined and individuals with l allele were found to

show more severe craving (21). Individuals with TT genotype of rs1042173 polymorphism on the same gene show higher craving (22). On the other hand, Thompson et al. (23) did not find any association between 5HTT gene polymorphisms and craving. In a study investigating the association between Asn40Asp polymorphism on opiate 1 receptor (OPRM1) and craving, individuals carrying Asp40 allele showed more craving (24). There are also other studies which reported associations between sex steroids, alpha synuclein, cannabinoid receptors and GABAergic system genes and craving (25-27).

In all of these studies, which investigated single nucleotide polymorphisms, indicated that craving is associated with genetic factors in general. However, a single nucleotide polymorphism is not expected to explain whole craving pathophysiology. This is because results are controversial and craving is a very complex process, which can not be explained with a single neurotransmitter or receptor gene polymorphism. Therefore, studies, which investigate the whole genome simultaneously, have begun to come forward. Agrawal et al. (5) reported that Integrin alpha D (ITGAD) gene on chromosome 7 was associated with craving. However, this is a new technique and more studies in this field are necessary.

Epigenetic Studies

With technological progress, it is now possible to observe changes, which take place in nucleus of the cells. Epigenetics studies changes in gene activation with mechanisms such as methylation, acetylation, phosphorylation, which do not change DNA code in cell nucleus (28). Best example to understand epigenetics comes from functional differences of cells localized in different parts of the body, although the genetic structure is the same (27). In all psychiatry, most of the epigenetics studies have been conducted in dependence field. Epigenetic changes including histone acetylation, demethylation are shown to be evident both during acute effects of the substance and abstinence periods (29). Particularly, Eric Nestler and his team's studies on change of transcription factors, which effect RNA

synthesis from DNA in cell nucleus, during substance use, are quite interesting. Cocaine was given to rats and effects of cocaine on transcription factors in cell nucleus were investigated. When cocaine was given to animals, changes in transcription factors such as CREB (cAMP response element binding protein) and Δ fosB are detected. In the first days of exposure to cocaine, CREB increases extremely and return to normal in a short time. But increased Δ fosB activity continues long after exposure to cocaine. Maintenance of increased Δ fosB levels even after cessation of the substance after chronic exposure to substance is important to show change in gene expression due to long term substance use. It has been argued that this may also be useful to explain craving. In some substances, individuals show craving symptoms long after cessation of the substance (30,31). All these studies stress the importance of epigenetics on substance-induced conditions including withdrawal, intoxication and craving. Thus, researchers have begun studies targeting treating impaired epigenetic mechanisms and these give hope for future treatment of craving.

Treatment of Craving

Along with studies on neurobiology and genetics, treatment studies form an important aspect of studies on craving. Effects of both currently available pharmacological agents and new agents developed with information from neurobiology and genetic studies on craving have been investigated (32).

Treatment of alcohol withdrawal (detoxification) has been done with success in the whole world by using fluids, vitamin support, and benzodiazepines. However, detoxification treatment is never sufficient alone and effective drugs are necessary to prevent recurrence. Since craving is an important factor for recurrence, if drugs used for maintenance decrease craving, that will be an important contribution to prevention (33).

Drugs currently indicated for alcohol maintenance treatment are disulfiram, naltrexone and acamprosate. Long acting injectable form of naltrexone is available in some countries. Phase 2 and 3 studies are continuing for

several drugs, but only one antiepileptic drug, topiramate, is currently in approval stage by Food and Drug Administration (FDA) (34). Disulfiram has been used to avert alcohol use. While there are some results in the recent years suggesting that disulfiram might be effective in decreasing cocaine craving by inhibiting beta hydroxylase, it has been accepted that it has no effect on alcohol craving (35). Naltrexone is an opioid antagonist; it decreases alcohol related pleasure, positive reinforcement and craving by blocking endorphine receptors. Evidence for naltrexone related decrease in craving include longer periods of abstinence in patients taking naltrexone when compared with placebo, fewer sudden impulse to drink alcohol in people taking naltrexone and statement of individuals taking naltrexone that they enjoy less when they drink. Studies also showed that, opiod antagonist nalmefene, which is structurally similar to naltrexone, is effective in decreasing craving (36).

Acamprosate is a NMDA receptor modulator, which has calcium acetylhomotaurinate structure, and structural analogue of the neurotransmitter taurin, which has an inhibitor effect in CNS. It modulates the impaired balance between glutamate and GABA (37). Experimental studies showed that craving is with glutamatergic system hyperactivity in animals and that acamprosate decreases this hyperactivity. After strong effect of acamprosate on craving was shown in experimental models, clinical studies also indicated effectiveness (38). Relations between craving protection effects of drugs, which are used to treat recurrence in alcohol dependence and hypothalamus-hypophysis-adrenal axis, have been investigated. In one study, adrenocorticotrophic hormone (ACTH) and cortisole levels were lower in the placebo group than the naltrexone and acamprosate groups during early abstinence period. Kiefer et al. (39) argued that naltrexone and acamprosate decreased craving by inhibiting the decrease in ACTH and cortisole levels. Han et al. (40) suggested that the balance between inhibitor and excitator neurotransmission is associated with alcohol and food craving and that acamprosate showed anti craving effect by modulating the balance between GABA and glutamate. Mann et al. (41) investigated 17

studies conducted with acamprosate in a meta-analyses and reported that acamprosate extended the alcohol free period and decreased craving in patients with recently completed detoxification treatment. Another recently published meta-analysis examined gender effects on acamprosate effectiveness and found that acamprosate decreased heavy drinking both in men and women and that treatment compliance is high (42).

Effects of several drugs other than drugs indicated for maintainance treatment of alcohol dependence on craving have been investigated. Antidepressants, antipsychotics and antiepileptics are promising in craving treatment (36). There are conflicting results on effects of antidepressants on craving. They have been found to be very effective on decreasing craving in animal studies but this can not be shown in clinical studies. Nevertheless, it has been suggested that these drugs may be effective in patients with alcohol dependence who have comorbid depression and obsessive type craving (36,43).

Effects of typical and atypical antipsychotics have also been investigated. A typical antipsychotic, flupentixole, was reported to be effective on alcohol and cocaine craving, but these results could not be replicated (44). Results from atypical antipsychotics quetiapine and aripiprazole are more promising. Ray et al. (45), compared 400 mg quetiapine with placebo in patients with alcohol dependence and found that quetiapine was superior than placebo in decreasing craving. Martinotti et al. (46) compared partial dopamine agonist aripiprazole with naltrexone and found that aripiprazole was as effective as naltrexone in decreasing craving. Although particular studies with quetiapine and aripiprazole reported that these drugs are effective in decreasing craving, there are not enough studies to take treatment indications and results should be replicated in larger studies with bigger samples.

Antiepileptic drugs are commonly used in alcohol dependence to decrease withdrawal symptoms and epileptic seizures during detoxification phase. Possible effects of carbamazepine, oxcarbazepine, valproate, topiramate and lamotrigine are investigated and the most promising appears to be topiramate. Topiramate opens GABA dependent chlore channels and antagonize

glutamate by inhibiting AMPA and kainate receptors. Studies showed that topiramate decreases alcohol withdrawal symptoms, alcohol intake and craving. After obtaining positive results in replication studies, FDA approval process for maintenance period is going on (33,47).

Other drugs claimed to decrease craving are baclofen, gamma-hydroxybutyric acid (GHB) and some other drugs effective on serotonin receptors (41). Baclofen, a GABA B receptor agonist, was found to be effective both in open and double blind placebo controlled studies to decrease alcohol intake, increase alcohol free period and prevent recurrence (48). Effects of ritanserin, buspirone and ondansetron, which are effective on serotonin receptors, on craving was examined, 5HT₃ receptor antagonist ondansetron was found to be superior than placebo on decreasing craving in early onset alcohol dependence while 5HT_{1A} partial agonist buspirone and 5HT₂ receptor antagonist ritanserin were not different from placebo (33,43,49). GHB, an endogenous neuromodulator, is claimed to decrease alcohol withdrawal symptoms and craving (50). On the other hand, research on cannabinoid antagonists, corticotrophin releasing factor antagonists, neuropeptide Y and immunotherapies are continuing (51).

In patients who do not respond to treatment, effect of transcranial magnetic stimulation treatment, an effective treatment in which neuronal cells are stimulated via magnetic fields, on craving has been investigated. In fortyfive patients with alcohol dependence in which high frequency repetitive transcranial magnetic stimulation (rTMS) application to right dorsolateral prefrontal cortex (DLPFC) was compared with sham treatment in a single-blind design, craving scores improved significantly in patients receiving rTMS. This suggested that rTMS application along with drugs effective on craving might be effective on decreasing both craving and recurrence of alcohol dependence (52).

CONCLUSIONS

Different aspects of craving have been investigated in the recent years on a molecular level. Slowly, data obtained from these studies are reflecting on treatment. Effects of current treatments on craving have been examined and together with known mechanisms, we begin to understand their effects on cell cytoplasm and nucleus. Together with developments in epigenetics, emergence of drugs directly effective on epigenetic mechanisms may be groundbreaking in craving in the next 10-20 years.

REFERENCES

1. Turkcan A. The mechanism of alcohol craving. *Journal of Addiction* 2002; 3:37-42. (Turkish)
2. Ulug B. Alkol ve Madde bagimlilikinin norobiyolojisi In Yuksel N (Editor). *Temel Psikofarmakoloji*. Ankara: Tuna Matbaacilik, 2010; 367-375. (Turkish)
3. Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology* 2010; 35:217-238.
4. Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl)* 2007; 191:391-431.
5. Agrawal A, Wetherill L, Bucholz KK, Kramer J, Kuperman S, Lynskey MT, Numberger JI Jr, Schuckit M, Tischfield JA, Edenberg HJ, Foroud T, Bierut LJ. Genetic influences on craving for alcohol. *Addict Behav* 2013;38:1501-1508.
6. Addolorato G, Leggio L, Abenavoli L, Gasbarrini G; Alcoholism Treatment Study Group. Neurobiochemical and clinical aspects of craving in alcohol addiction: a review. *Addict Behav* 2005; 30:1209-1224.
7. Gurpunar D, Tokucoglu D. Craving of addictive substances and the dreams related with these substances. *Journal of Addiction* 2006; 7:38-43. (Turkish).
8. Guveli H, Saatcioglu O. Craving in addiction. *Bulletin of clinical Psychopharmacology* 2008; 18:140-152. (Turkish)
9. Evren C, Celik S, Evren B, Aksoy R. Validation study of the Turkish version of the obsessive-compulsive drinking scale in male alcohol dependent inpatients. *Düşünen Adam: The Journal of Psychiatry and Neurological Sciences* 2011; 24:1-12.

10. Evren C, Flannery B, Celik R, Durkaya M, Dalbudak E. Reliability and validity of Turkish version the Penn Alcohol Craving Scale (PACS) in male alcohol dependent inpatients. *Journal of Addiction* 2008; 9:128-134. (Turkish)
11. Evren C, Durkaya M, Celik R, Dalbudak E, Cakmak D, Flannery B. Relationship of alcohol craving with alexithymia and dissociation in male alcohol dependent inpatients. *Anatolian Journal of Psychiatry* 2009; 10:165-173. (Turkish)
12. Sengul C, Herken H. Dopaminerjik system and addiction. *Journal of Addiction* 2009; 10:155-161. (Turkish)
13. Volkow ND, Fowler JS, Wang GJ. The addicted human brain: insights from imaging studies. *J Clin Invest* 2003; 111:1444-1451.
14. Anton RF. Pharmacological approaches to the management of alcoholism. *Journal of Clinical Psychiatry* 2001; 62 (Suppl.20):11-17.
15. Wurst FM, Rasmussen DD, Hillemecher T, Kraus T, Ramskogler K, Lesch O, Bayerlein K, Schanze A, Wilhelm J, Junghanns K, Schulte T, Dammann G, Pridzun L, Wiesbeck G, Kornhuber J, Bleich S. Alcoholism, craving, and hormones: the role of leptin, ghrelin, prolactin, and the pro-opiomelanocortin system in modulating ethanol intake. *Alcohol Clin Exp Res* 2007; 31:1963-1967.
16. Hillemecher T, Kahl KG, Heberlein A, Muschler MA, Eberlein C, Frieling H, Bleich S. Appetite- and volume-regulating neuropeptides: role in treating alcohol dependence. *Curr Opin Investig Drugs* 2010; 11:1097-1106.
17. Addolorato G, Leggio L, Hillemecher T, Kraus T, Jerlhag E, Bleich S. Hormones and drinking behaviour: new findings on ghrelin, insulin, leptin and volume-regulating hormones. An ESBRA Symposium report. *Drug Alcohol Rev* 2009; 28:160-165.
18. Hilburn C, Nejtck VA, Underwood WA, Singh M, Patel G, Gangwani P, Forster MJ. Is serum brain-derived neurotrophic factor related to craving for or use of alcohol, cocaine, or methamphetamine? *Neuropsychiatr Dis Treat* 2011; 7:357-364.
19. Hillemecher T, Weinland C, Heberlein A, Gröschl M, Schanze A, Frieling H, Wilhelm J, Kornhuber J, Bleich S. Increased levels of adiponectin and resistin in alcohol dependence-possible link to craving. *Drug Alcohol Depend* 2009; 99:333-337.
20. Sengul C, Herken H. From genetics to epigenetics: alcohol addiction. *Anatolian Journal of Psychiatry* 2009; 10:239-245. (Turkish)
21. Ait-Daoud N, Roache JD, Dawes MA, Liu L, Wang XQ, Javors MA, Seneviratne C, Johnson BA. Can serotonin transporter genotype predict craving in alcoholism? *Alcohol Clin Exp Res* 2009; 33:1329-1335.
22. Ait-Daoud N, Seneviratne C, Smith JB, Roache JD, Dawes MA, Liu L, Wang XQ, Johnson BA. Preliminary evidence for cue-induced alcohol craving modulated by serotonin transporter gene polymorphism rs1042173. *Front Psychiatry* 2012;16;3:6.
23. Thompson RD, Heffner JL, Strong JA, Blom TJ, Anthenelli RM. Relationship between the serotonin transporter polymorphism and obsessive-compulsive alcohol craving in alcohol-dependent adults: a pilot study. *Alcohol* 2010; 44:401-406.
24. Ray LA. Stress-induced and cue-induced craving for alcohol in heavy drinkers: preliminary evidence of genetic moderation by the OPRM1 and CRH-BP genes. *Alcohol Clin Exp Res* 2011; 35:166-174.
25. Lenz B, Jacob C, Frieling H, Jacobi A, Hillemecher T, Muschler M, Watson K, Kornhuber J, Bleich S. Polymorphism of the long polyglutamine tract in the human androgen receptor influences craving of men in alcohol withdrawal. *Psychoneuroendocrinology* 2009; 34:968-971.
26. Foroud T, Wetherill LF, Liang T, Dick DM, Hesselbrock V, Kramer J, Nurnberger J, Schuckit M, Carr L, Porjesz B, Xuei X, Edenberg HJ. Association of alcohol craving with alpha-synuclein (SNCA). *Alcohol Clin Exp Res* 2007; 31:537-545.
27. Han DH, Bolo N, Daniels MA, Lyoo IK, Min KJ, Kim CH, Renshaw PF. Craving for alcohol and food during treatment for alcohol dependence: modulation by T allele of 1519T>C GABAAalpha6. *Alcohol Clin Exp Res* 2008; 32:1593-1599.
28. Sengül C, Herken H. From genetics to epigenetics: heritability in schizophrenia. *Türkiye Klinikleri Journal of Psychiatry Special Topics* 2010; 3:24-29. (Turkish)
29. Tsankova N, Renthal W, Kumar A, Nestler EJ. Epigenetic regulation in psychiatric disorders. *Nat Rev Neurosci* 2007; 8:355-367.
30. Kocak EE, Ertugrul A. Psychiatric disorders and epigenetics. *Türk Psikiyatri Derg* 2012; 23:130-140. (Turkish)
31. Nestler EJ. Molecular mechanisms of drug addiction. *Neuropharmacology* 2004; 47:24-32.
32. Soyka M, Roesner S. New pharmacological approaches for the treatment of alcoholism. *Expert Opin Pharmacother* 2006; 7:2341-2353.
33. Toker Ugurlu T, Balci Sengul C, Sengul C. Psychopharmacology of addiction. *Current Approaches in Psychiatry* 2012; 4:37-50. (Turkish)
34. Olive MF. Pharmacotherapies for alcoholism: the old and the new. *CNS Neurol Disord Drug Targets* 2010; 9:2-4.

35. Barth KS, Malcolm RJ. Disulfiram: an old therapeutic with new applications. *CNS Neurol Disord Drug Targets* 2010; 9:5-12.
36. Johnson BA. Update on neuropharmacological treatments for alcoholism: scientific basis and clinical findings. *Biochem Pharmacol* 2008; 75:34-56.
37. Rezvani AH, Lawrence AJ, Arolfo MP, Levin ED, Overstreet DH. Novel medication targets for the treatment of alcoholism: preclinical studies. *Recent Pat CNS Drug Discov* 2012; 7:151-162.
38. 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.
39. Kiefer F, Jahn H, Otte C, Naber D, Wiedemann K. Hypothalamic-pituitary-adrenocortical axis activity: a target of pharmacological anticraving treatment? *Biol Psychiatry* 2006; 60:74-76.
40. Han DH, Lyool IK, Sung YH, Lee SH, Renshaw PF. The effect of acamprosate on alcohol and food craving in patients with alcohol dependence. *Drug Alcohol Depend* 2008; 93:279-283.
41. 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.
42. Mason BJ, Lehert P. Acamprosate for alcohol dependence: a sex-specific meta-analysis based on individual patient data. *Alcohol Clin Exp Res* 2012; 36:497-508.
43. Addolorato G, Abenavoli L, Leggio L, Gasbarrini G. How many cravings? Pharmacological aspects of craving treatment in alcohol addiction: a review. *Neuropsychobiology* 2005; 51:59-66.
44. Soyka M, De Vry J. Flupenthixol as a potential pharmacotreatment of alcohol and cocaine abuse/dependence. *Eur Neuropsychopharmacol* 2000; 10:325-332.
45. Ray LA, Chin PF, Heydari A, Miotto K. A human laboratory study of the effects of quetiapine on subjective intoxication and alcohol craving. *Psychopharmacology (Berl)* 2011; 217:341-351.
46. Martinotti G, Di Nicola M, Di Giannantonio M, Janiri L. Aripiprazole in the treatment of patients with alcohol dependence: a double-blind, comparison trial vs. naltrexone. *J Psychopharmacol* 2009; 23:123-129.
47. Kenna GA, Lomastro TL, Schiesl A, Leggio L, Swift RM. Review of topiramate: an antiepileptic for the treatment of alcohol dependence. *Curr Drug Abuse Rev* 2009; 2:135-142.
48. Gache P. Baclofen: the new miracle cure for alcoholism? *Rev Med Suisse* 2011; 13:1458-1461.
49. Johnson BA, Roache JD, Ait-Daoud N, Zanca NA, Velazquez M. Ondansetron reduces the craving of biologically predisposed alcoholics. *Psychopharmacology (Berl)* 2002; 160:408-413.
50. Addolorato G, Cibirin M, Capristo E, Beghè F, Gessa GL, Stefanini GF, Gasbarrini G. Maintaining abstinence from alcohol with gammahydroxybutyric acid. *Lancet* 1998; 351:38.
51. McGregor IS, Galloway JE. Rats on the grog: novel pharmacotherapies for alcohol craving. *Addict Behav* 2004; 29:1341-1357.
52. Mishra BR, Nizamie SH, Das B, Praharaj SK. Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: a sham-controlled study. *Addiction* 2010; 105:49-55.