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Review article

Pharmacogenomics of Alcohol Addiction: Personalizing Pharmacologic Treatment of Alcohol Dependence

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SUMMARY

Alcohol dependence is a serious psychiatric disorder with harmful physical, mental and social consequences, and a high probability of a chronic relapsing course. The field of pharmacologic treatment of alcohol dependence and craving is expanding rapidly; the drugs that have been found to reduce relapse rates or drinking in alcohol-dependent patients and are approved for treatment of alcohol dependence are naltrexone, acamprosate and disulfiram, whereas also topiramate appears as a promising therapy. For many patients, however, these treatments are not effective. Evidence from a number of different studies suggests that genetic variation is a significant contributor to interindividual variation of clinical presentation of alcohol problems and response to a given treatment. The aim of the present review is to summarize and discuss the findings on the association between gene polymorphisms and the response to alcohol dependence treatment medications. It is anticipated that future implementation of pharmacogenomics in clinical practice will help personalize alcohol dependence drug treatment, and development personalized hospital pharmacology.

Keywords: Alcohol, addiction, naltrexone, topiramate, disulfiram, acamprosate, pharmacogenetics, personalized drug treatment, hospital pharmacology

INTRODUCTION

Alcohol dependence is a serious psychiatric disorder with harmful physical, mental and social consequences, and a high probability of a chronic relapsing course. According to the 2014 global status report on alcohol and health by the World Health Organization, in 2012, about 3.3 million deaths, or 5.9% of all global deaths, and 5.1% of the global burden of disease and injury, were attributable to alcohol consumption [1]. Globally, Europe is the region with the highest consumption of alcohol per capita [1]. Alcohol dependence is associated with psychiatric conditions such as major depression, dysthymia, mania, hypomania, panic disorder, phobias, generalized anxiety disorder, personality disorders, any drug

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use disorder, schizophrenia, and suicide [2]. On the other hand, psychiatric comorbidity is associated with alcohol-related symptoms of greater severity [2]. Long-term relapse prevention in alcohol-dependent patients is based on psychotherapy and pharmacotherapy. Although psychotherapy is in some cases effective in reducing alcohol consumption and in maintaining abstinence, without a pharmacological adjunct to psychosocial therapy, the clinical outcome is poor, with up to 70% of patients resuming drinking within 1 year [3-5].

The field of pharmacologic treatment of alcohol dependence and craving is expanding rapidly [6]. To date, the drugs that have been found to reduce relapse rates or drinking in alcohol-dependent patients and are approved for treatment of alcohol dependence are naltrexone, acamprosate and disulfiram, whereas also topiramate appears as a promising therapy [7]. For many patients, however, these treatments are not effective. Evidence from a number of different studies suggests that genetic variation is a significant contributor to interindividual variation of clinical presentation of alcohol problems and response to a given treatment.

Pharmacogenomics is the area of medicine that studies the genetic factors that influence drug response and toxicity [8, 9]. In this context, pharmacogenomics paves the path to personalized medicine. The rapidly advancing field of pharmacogenomics is a promising area of investigation, focusing on genetic variations in components that affect drug pharmacokinetics and pharmacodynamics [10-17] or that are involved in their therapeutic mechanisms and/or cause of their adverse events [18, 19]. Application of pharmacogenomics explains some of the interindividual variable response to various classes of drugs, such as psychiatric drugs [20, 21], antidiabetics [22] and oral coumarinic anticoagulants [23]. Efforts are now focusing on the development of genotype-based guidelines that will help clinicians in incorporating pharmacogenomic knowledge in their routine clinical practice. Among the most solid and recent pharmacogenomic applications is the genotype-guided dosing algorithm of oral coumarinic anticoagulants; results of two large randomised clinical trials conducted in European populations showed that patients who received genotype-guided dosing of the oral coumarinic anticoagulants acenocoumarol, phenprocoumon and warfarin had increased percentage of time in the therapeutic range compared to controls [24, 25].

In view of these developments in several pharmacotherapeutic areas it was inevitable that also the field of personalization of alcohol dependence treatment would get a boost from pharmacogenomics. The choice of alcohol-dependence treatment may improve by identifying genetic variations that predict individual responses to therapeutic interventions. Data has accumulated suggesting that specific genetic polymorphisms govern the therapeutic response, the dose requirements and the risk of experiencing adverse effects to the respective therapy [26]. Therefore, pharmacogenomics of alcohol dependence treatment is an emerging field with promising application in psychiatry. Below we discuss evidence for genetic variation in the effect of the 4 anti-craving drugs.

Information of all gene polymorphisms that have been studied in association with drug response – their chromosome location, effect on encoded protein, and the medication they affect - is presented in Table 1. To further help the reader in easily assessing the published studies, all currently available data on gene polymorphisms associated with alcohol dependence drug response are briefly listed in three tables: Table 2 presents gene polymorphisms studied in association with the opioid antagonists naltrexone, nalmofene and naloxone response, Table 4 presents gene polymorphisms studied in association with acamprosate response, Table 5 presents gene polymorphisms studied in association with disulfiram response and Table 6 presents gene polymorphisms studied in association with topiramate response. Furthermore, given the significance of clinical trials assessing implementation of pharmacogenomics in routine clinical practice, completed and ongoing clinical trials on alcohol addiction pharmacogenomics are listed in Table 3.

PHARMACOGENOMICS OF MEDICATIONS USED TO TREAT ALCOHOL DEPENDENCE

Opioid antagonists: Naltrexone, nalmofene and naloxone

Naltrexone is a specific opioid antagonist targeting endogenous opioid receptors, particularly μ-receptors. Blocking opioid receptors with naltrexone leads to less alcohol-induced

Gene (protein)	Genomic locus	SNP ID*	SNP gene location	Amino acid substitution	Effect on encoded product	MAF*	Drug studied in association with
OPRM1	6q25.2	rs1799971A>G (c.A118G)	Exon 1, missense, non synonymous amino acid substitution	Asn40Asp	Increased binding of ß-endorphin	0.19	Naltrexone
OPRK1	8q11.2	rs997917T>C (c.258-4707A>G, g.7312553T>C)	Intron 1	-	Unknown	0.429	Naltrexone
OPRD1	1p36.1-p34.3	rs4654327A>G (c.*343G>A, g.28277638G>A)	3' UTR	-	Potential effect on transcription levels	0.431	Naltrexone
SLC6A3 (DAT)	5p15.3	rs28363170 (c.*987_*988ins ACT GGA GCG TGT ACT ACC CCA GGA CGC ATG CAG GGC CCC C) 3 to 11 repeats, most common alleles are 9 and 10 repeats	3' UTR	-	Regulation of DAT gene expression potential effect on transcription levels	NA	Naltrexone
GABRA6	5q34	rs3219151T>C (c.*135C>T, g. 5940584C>T)	3' UTR	-	Potential effect on transcription levels	0.544	Acamprosate
GABRB2	5q34	rs2229944C>T (c.1194C>T, g.5532988G>A)	Exon 10, synonymous amino acid substitution	Ala436=	Unknown	0.109	Acamprosate
DRD2 (actual ANKK1)	11q23.2	rs1800497 C>T (c.2137G>A, g.25397210G>A)	Exon 8, missense, non synonymous amino acid substitution	Glu713Lys	Reduced number of DRD2 molecules and receptor binding	0.296	Acamprosate
DBH	9q34.2	rs1611115C>T (c.-979T>C, g. C1021T)	Promoter, effect on transcription level	-	Reduced transcription	0.208	Disulfiram
GRIK1	21q22.11	rs2832407A>C (c.1251+1338A>C)	Intron 9, unknown	-	Unknown	0.448	Topiramate

Table 1. Summary of the genetic locus and gene polymorphisms that have been examined in association with response to alcohol dependence medications

MAF: Minor Allele Frequency
***** as reported in dbSNP Short Genetic Variations database (www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs)

pleasure and, ultimately, less craving and relapse. μ-opioid receptors primarily bind β-endorphin and diffuse this binding via G-protein signaling that alters neuronal firing and leads to neuroadaptive changes [27]. Other opioid receptor antagonists with similar to naltrexone properties are naloxone and nalefene, however, naltrexone is more commonly prescribed in alcohol addiction therapy. A missense polymorphism in μ-opioid receptor (*OPRM1*) gene, *118A>G* (*Asn40Asp*), leads to altered β-endorphin binding, function, and receptor levels. This substitution has been reported to increase binding of β-endorphin and increase functional activity *in vitro*. Carriers of *118G* (*40Asp*) allele have 3-fold higher affinity for β-endorphin binding compared to *118AA* (*40AsnAsn*) individuals (Table 1) [28].

Since naltrexone targets the μ-opioid receptor, *OPRM1 118A>G* gene polymorphism is an attractive candidate to assess the interindividual differential response to naltrexone [27]. Indeed, results of several studies suggest that *118G* carriers respond better to naltrexone treatment. For consistency, throughout the manuscript we refer to *OPRM1* polymorphism with nucleotide substitution nomenclature.

Several studies have assessed the potential effect of *OPRM1A118G* polymorphism on altered endogenous response associated with response to alcohol pharmacotherapy (Table 2). Wand and colleagues have tested the hypothesis that *OPRM1 A118G* polymorphism influences the hypothalamic-pituitary-adrenal (HPA) axis activation induced by opioid receptor blockage; opioid receptor antagonists such as naloxone, nalmefene and naltrexone affect disinhibition of HPA axis leading to cortisol and adrenocorticotropin hormones release [29]. A total of 39 healthy men receiving five doses of naloxone were included in the study. The authors have found that carriers of *118G* allele had greater cortisol response to receptor blockage and different increase (between 30-90 minutes) and decrease (after 90 minutes) rate of adrenocorticotropin [29]. Similar results were obtained by Hernandez-Avila and colleagues who also estimated cortisol and adrenocorticotropin response to intravenous naloxone or placebo [30]. In a total of 30 healthy participants, carriage of *118G* allele was associated with higher cortisol concentration both at baseline and after naloxone infusion, with greater peak cortisol response and greater area under the cortisol time curve [30]. The increased cortisol response to naloxone in *118G* carriers was also replicated in the study of Chong and colleagues in a total of 74 participants who received five doses of naloxone [31]. In the latter studies, no effect on plasma adrenocorticotropin was noticed. In a different study, Ray and colleagues found an association of *OPRM1 118G* allele with increase of allopregnanolole levels in 32 naltrexone treated heavy drinkers; allopregnanolole is a GABAergic neuroactive steroid that has been associated with naltrexone pharmacotherapy [32]. Naltrexone increased allopregnanolole in *OPRM1 118G* cariers but not in *118AA* homozygotes, whereas no effect on cortisol levels was present. Based on these results the authors proposed that the enhanced therapeutic response of *118G* carriers to naltrexone could be attributed in part to the ability of the drug to increase allopregnanolole levels at least in these individuals [32]. These results suggest that *OPRM1 A118G* polymorphism is associated with differential response to physiological processes that are mainly regulated via activation of opioid receptors.

A different approach was followed by Ray and colleagues who have tested the hypothesis that individuals who have a genetic predisposition to greater feelings of euphoria after consuming alcohol due to *OPRM1 A118G* polymorphism also present with more successful response to the medication that reduces feelings euphoria [33]. In 38 students with a moderate or heavier drinking pattern who intravenously received alcohol, feelings of euphoria were recorded. Carriers of *118G* allele reported greater feelings of intoxication, higher increases in alcohol-induced stimulation and higher increases in state happiness compared to *118AA* homozygotes [33]. Results were replicated by the same research team in 40 participants who underwent the same alcohol challenge [34].Similarly to their previous report, carriers of *118G* allele reported higher alcohol-induced euphoria compared to *118AA* homozygotes [34].

Studies that assess the potential association of *OPRM1 A118G* polymorphism with naltrexone response, analyze several drinking outcomes such as craving, relapse and abstinence, and recruit participants who are alcohol-dependent, treatment- or non-treatment seeking. First *in vivo* evidence on association of *OPRM1 A118G* polymorphism with naltrexone response was published in 2003. Oslin and colleagues have analyzed the association between *OPRM1 A118G* genotype and drinking outcomesin 71 alcohol-dependent individuals of European descent [35]. Additionally to naltrexone treated individuals (treated with naltrexone 50 or 100 mg for 12 weeks), a placebo treated group of 59 individuals was also included in the study. The authors have shown that, compared to *118AA* individuals, carriers of *118G* allele had a greater chance not to return to heavy drinking (OR=3.52) and also had significantly longer time to first relapse (OR=2.79) [35]. Ray and colleagues have tested the hypothesis that *OPRM1 A118G* polymorphism acts as modulator of naltrexone effects on alcohol sensitivity and have found that naltrexone reduced self-reported alcohol-induced euphoria in participants with at least one *118G*

allele [34]. Similarly, in the pharmacogenetic arm of the clinical trial NCT00006206, the researchers examined the role of *OPRM1 A118G* polymorphism as a predictor of naltrexone treatment response [36]. Among individuals initially recruited, 300 were randomized on naltrexone therapy. Alcohol dependent patients who were treated with naltrexone and had at least one *118G* allele showed an increasing trend in abstinent days over time and fewer heavy drinking days over time, while additionally they also had the best outcome [36].

During the last five years, there has been an increase in publications on the association of *OPRM1 A118G* polymorphism with naltrexone response, and the majority of the studies support the hypothesis that carriers of *118G* allele have enhanced response to naltrexone. In 2009, Ooteman and colleagues have tested the hypothesis that naltrexone primarily exerts its effects in patients characterized by genetic variation in opioidergic system whereas acamprosate primarily exerts its effects in patients characterized by variations in glutamatergic system [37]. A total of 52 naltrexone treated and 56 acamprosate treated alcohol dependent patientswere included in genetic analyses. The authors have found that naltrexone outperformed acamprosate in *OPRM1 118G* allele carriers, whereas acamprosate outperformed naltrexone in the *OPRM1 118AA* group [37]. These results support a role of *OPRM1 A118G* genotyping prior of therapy choice. Results on the association of genetic factors with acamprosate response are discussed in detail in *Acamprosate* section that follows. Oroszi and colleagues have also found an association of *118G* allele and good clinical response to naltrexone [38]. In 146 alcohol dependent patients the authors have used a haplotype-based procedure and have showed that higher percentage of naltrexone-treated patients carrying the haplotype consisted by *118G* allele had good clinical outcome compared to non-carriers [38]. It should be noted that the sole haplotype that was associated with naltrexone response was the one carrying the *118G* allele. In a different prospective study in 63 alcohol-dependent Korean patients treated with naltrexone 25mg/day for first 3 days and 50mg/day for the remaining days ofa 12-week treatment, Kim and colleagues have found that patients with at least one *118G* allele took significantly longer time to relapse than *118AA* homozygotes [39]. These results highlight that the association of *OPRM1 A118G* polymorphism with naltrexone responseoutscales potential ethnic differences. In a following study in 40 social drinkers administered naltrexone 25mg for first day and 50mg for the rest 5 days of the 6-days follow-up, Setiawan and colleagues analyzed the association of *OPRM1 A118G* polymorphism with subjective effects of alcohol [40]. Carriers of *118G* allele reported experiencing decreased euphoria during naltrexone treatment after seeing and drinking alcohol [40]. Results of a double-blinded, randomized, placebo-controlled laboratory trial on naltrexone that included 35 non-treatment seeking Asian Americans heavy drinkers have also showed that *118G* carriers experience greater alcohol-induced sedation and subjective intoxication, and lower alcohol craving compared to *118AA* [41]. *OPRM1 118G* allele was also associated with increased percentage of non-hazardous drinking in a study that included 112 European problem drinkers treated with naltrexone 100mg/day for 12 weeks [42].

Urge to drink has also been analyzed as an outcome of naltrexone response. McGeary and colleagues have analyzed the association of *OPRM1 A118G* polymoprhism with the urge to drink alcohol in a total of 90 individuals consisting a mixed of population of non treatment seeking alcohol dependent individuals and non alcohol dependent individuals; 42 of them were treated with naltrexone 50mg/day for 3 weeks [43]. The authors have found that *OPRM1 118G* carriers showed greater urge to drink when receiving naltrexone compared with placebo. Urge to drink alcohol may become more salient when one is attempting to avoid drinking and may be a marker for the effort required to abstain from drinking. Since this urge may be more predictive of drinking among treatment seekers, the authors mention that their results cannot be generalized to alcohol dependent individuals in treatment [43]. Similar results were presented by Kranzler and colleages, who analyzed the association of *OPRM1 A118G* polymorphism with desire to drink in 81 problem drinkers who received naltrexone 50mg/day [44]. In this study, registered as NCT00369408 in ClinicalTrials.gov, carriers of *118G* allele showed a stronger evening drinking desire and were at greater risk of drinking more than *118AA* homozygotes, which was attenuated by naltrexone [44].

It is widely recognized that, in all fields of medicine, pharmacogenomic applica-

tion has the greater possible impact on clinical practice when multiple gene analyses are carried out and that once a gene has been documented to be clearly associated with a drug response, then studies of other genes should include the previous genes in analyses [16, 45]. This approach has been applied by Ashenhurst and colleagues; in 40 heavy drinkers who underwent an intravenous alcohol challenge paradigm after receiving 50mg of naltrexone, the researchers analyzed the pharmacogenetic effect of delta and kappa opioid receptor gene polymorphisms on subjective responses to alcohol after controlling for *OPRM1 A118G* polymorphism [46]. The authors have found that *OPRK1 rs997917* and *OPRD1 rs4654327* gene polymorphisms were associated with response to alcohol and this effect remained significant after controlling for *OPRM1 A118G* polymorphism [46]. Anton and colleagues have analyzed both *OPRM1 A118G* and dopamine transporter (DAT) 9 and 10 VNTRs in 83 nontreatment seeking alcohol dependent individuals receiving either placebo or naltrexone 25mg for 2 days and 50mg for 5 days for a week [47]. The authors did not find a role of *OPRM1 A118G* polymorphism alone with response to naltrexone, but they report an epistasis between *OPRM1* and *DAT* genes. In non-carriers of *118G* allele, carriers of *DAT* 9 VNTR had more stimulation to alcohol or medication treatment and in these individuals naltrexone reduced the number of drinks consumed per day [47]. Schacht and colleagues have also reported a similar interaction of *OPRM1* and *DAT* genes [48]. In the study, a total of 74 non treatment seeking alcohol dependent individuals treated with naltrexone 50mg or placebo for 1 week were included. Results of fMRI alcohol cue reactivity task performed on day 6 showed that *OPRM1 A118G* polymorphism did not have a main effect on medication, however, *118G* carriers who also carried *DAT* 10VNTR had less stimulation than 9 VNTR carriers [48]. More recently, in a cohort of 43 alcohol dependent individuals, the interaction of *OPRM1* with *DAT* was replicated [49]. *OPRM1 118G* carriers and *DAT* 10 VNTR homozygotes reported steeper increase in stimulation and positive mood across rising alcohol concentration [49]. The consistency in *OPRM1-DAT* interaction results suggests that opioidergic and dopaminergic systems interact and determine the reinforcing properties of alcohol.

The need to draw firm conclusions on the association of gene polymorphisms with response to a given pharmacotherapy has led to a type of studies called meta-analysis; a statistical procedure that integrates the results of several independent studies that were conducted analyzing the same outcome [50]. Currently, only one meta-analysis on the effect of *OPRM1 A118G* polymorphism on naltrexone response has been published [51]. Meta-analysis included a total of 6 studies that assessed the pharmacogenetic effect of *OPRM1 A118G* polymorphism on naltrexone response in alcohol-dependent patients. Overall the results support the evidence that naltrexone treated patients carrying *118G* allele have lower relapse rates than those who are *118AA* homozygous (OR=1.97), but similar abstinence rates [51].

The abovementioned results on the association of *OPRM1 A118G* polymorphism with naltrexone response were not replicated in all studies. Gelernter and colleagues have assessed the association of *OPRM1 A118G* polymorphism with naltrexone response in 215 alcohol-dependent male subjects treated with naltrexone 50mg/day for 3 to 12 months [52]. The authors did not find an association of *OPRM1* polymorphisms with rate of and time to relapse [52]. Similarly, Mitchell and colleagues did not find a contribution of *OPRM1* gene polymorphism on naltrexone effect estimated by self reported ethanol consumption [53]. This study included a total of 25 subjects treated with naltrexone 50mg/day [53]. O'Malley and colleagues have also analyzed the association of *OPRM1 A118G* polymorphism with naltrexone response in 101 alcohol-dependent Alaskians treated for 16 weeks with placebo, naltrexone 50mg monotherapy or naltrexone 50mg and sertraline 100mg combined therapy [54]. *OPRM1* genotyping was successful for 92 participants, however, all further analyses were restricted in 75 participants who were *118AA* homozygous, of whom 52 were treated with naltrexone as monotherapy or combined therapy. When the effect of treatments were compared within this subgroup, the pattern of *OPRM1* polymorphism association was similar to the results in the total sample, suggesting that *OPRM1* polymorphism is not associated with enhanced response to naltrexone [54]. In 2008, Tidey and colleagues analyzed the association of *OPRM1 A118G* polymorphism with drink data, urge levels and subjective effects on alcohol consumption in

180 heavy drinkers, 63% of whom were alcohol-dependent [55]. 88 individuals received naltrexone 50mg/day for 3 weeks. Naltrexone significantly decreased percent drinking days, however, *OPRM1 A118G* polymorphism was not a moderator of naltrexone response [55]. Similarly, Coller and colleagues examined prospectively in 100 alcohol dependent patients treated with naltrexone 50mg for 12 weeks the association of *OPRM1 A118G* polymorphism with several clinical outcomes of naltrexone treatment, such as time to first relapse and craving [56]. The authors found no evidence of association of *OPRM1 A118G* polymorphism and treatment success on any of the outcome measures [56]. Similar results were reported by Arias and colleagues in a cohort of alcohol dependent patients treated with nalmefene, a specific and potent opioid receptor antagonist that has affinity for the three opioid receptor subtypes (OPRM1, OPRD1 and OPRK1) [57]. In a total of 166 nalmefene treated alcohol dependent patiemts, the authors found no association of genetic variants, including *OPRM1 A118G*, with moderated response to nalmefene [57]. The lack of association reported in the latter study could be attributed to the fact that even though nalmefene is structurally similar to naltrexone, it differs in binding affinity for opioid receptors.

Drug	Gene polymorphisms	Subject population	Investigated parameter	Primary outcome	Reference
Naloxone	*OPRM1 A118G*	39 healthy men treated with five doses of naloxone (0, 50, 100, 200 and 400 μg/kg, incremental doses per 30 minutes)	Cortisol and adrenocorticotropin release	Carriers of *OPRM1 118G* allele had: - greater cortisol response - different increase adrenocorticotropin rate (between 30 - 90 minutes) - different decrease adrenocorticotropin rate (after 90 minutes)	[29]
		30 healthy individuals treated with intravenous naloxone 125 μg/kg	Cortisol and adrenocorticotropin release	Carriers of *OPRM1 118G* allele had: - higher cortisol concentration (baseline and after naloxone infusion) - greater peak cortisol response - greater area under the cortisol time curve	[30]
		74 individuals receiving five increasing doses of naloxone (0, 50, 100, 200 and 400 μg/kg, incremental doses per 30 minutes)	Cortisol and adrenocorticotropin release	Carriers of *OPRM1 118G* allele had: - increased cortisol response	[31]
		32 non-treatment seeking hazardous drinkers receiving 50mg naltrexone	Allopregnanolole and cortisol levels	Carriers of *OPRM1 118G* allele had: - increased allopregnanolole levels	[32]
		38 students with moderate or heavier drinking pattern intravenously receiving alcohol	Alcohol induced sedation, stimulation, subjective response, mood alterations	Carriers of *OPRM1 118G* allele had: -greater feelings of intoxication - higher increases in alcohol induced stimulation - higher increases in state happiness	[33]

Table 2. Human studies on the association of genetic polymorphisms with response to the opioid receptor antagonists naloxone and naltrexone.

Naltrexone		40 non-treatment seeking heavy drinkers receiving naltrexone 50mg for three days and intravenously administered alcohol	Alcohol sensitivity, subjective response to alcohol, craving	Carriers of *OPRM1 118G* allele had: - higher increases in alcohol induced euphoria - reduced alcohol induced euphoria when receiving naltrexone	[34]
		71 naltrexone treated (50 or 100 mg/day for 12 weeks) alcohol dependent individuals 59 placebo treated individuals	Clinical response to naltrexone (relapse, abstinence)	Carriers of *OPRM1 118G* allele had: - greater chance not to return to heavy drinking - longer time to first relapse	[35]
		300 alcohol dependent patients treated with naltrexone 50 or 100mg/day for 16 weeks	Clinical response to naltrexone (abstinence, heavy drinking days, adverse events)	Carriers of *OPRM1 118G* allele had: - an increasing trend in abstinent days - fewer heavy drinking days - the best clinical outcome	[36]
	OPRM1 A118G, DRD1 D2/D1, DRD2 TaqI A2/A1, GRIN2B C2664T, GABRA6T1519C, GABRB2 C1421T, GABRG2 G3145A	- 56 acamprosate treated and - 52 naltrexone treated - 30 placebo treated alcohol dependent patients	Subjective craving, physiological cue reactivity outcome (heart rate)	In carriers of *OPRM1 118G* allele: - naltrexone outperformed acamprosate	[37]
	OPRM1 A118G	146 alcohol dependent patients treated with naltrexone 100mg/day for 16 weeks	Clinical response to naltrexone (abstinence, heavy drinking days, adverse events)	Carriers of *OPRM1 118G* allele had: - good clinical outcome	[38]
		63 alcohol dependent patients treated with naltrexone 25mg/day for first 3 days and 50mg/day for remaining days of a 12 week treatment	Clinical response to naltrexone (abstinence rate, relapse rate, time to relapse)	Carriers of *OPRM1 118G* allele had: - longer time to relapse	[39]
		40 social drinkers treated with naltrexone 25mg/day for first day and 50mg/day for remaining 5 days	Subjective effects of alcohol	Carriers of *OPRM1 118G* allele had: - decreased euphoria during naltrexone treatment after seeing and drinking alcohol	[40]

		35 non treatment seeking heavy drinkers treated with naltrexone 25mg for 2 days and 50mg for 2 days)	Clinical response to naltrexone (intoxication, craving)	Carriers of *OPRM1 118G* allele had: - greater alcohol induced sedation and intoxication - lower craving for alcohol	[41]
		112 problem drinkers treated with naltrexone 100mg/day for 12 weeks	Clinical response to naltrexone (non hazardous drinking)	Carriers of *OPRM1 118G* allele had: - increased percentage of non-hazardous drinking	[42]
		90 individuals (mixed population of non treatment seeking alcohol dependent individuals and non alcohol dependent individuals), 42 of them treated with naltrexone 50mg/day for 3 weeks and 48 on placebo	Urge to drink	Carriers of *OPRM1 118G* allele had: - increased urge to drink when receiving naltrexone compared to placebo	[43]
		81 problem drinkers receiving naltrexone 50mg/day for 2 weeks	Drinking attenuation by naltrexone (desire to drink, subsequent drinking)	Carriers of *OPRM1 118G* allele had: - stronger evening desire to drink - greater risk of drinking more	[44]
	OPRM1 A118G, OPRK1 rs997917 & rs6985606, OPRD1 rs4654327, rs2236856, rs499062, rs678849& rs508448	40 heavy drinkers receiving 50mg naltrexone for 3 days and undergoing intravenous alcohol challenge	Subjective response to alcohol, craving	*OPRK1 rs997919* and *OPRD1 rs4654327* polymorphisms were associated with response to alcohol after controlling for *OPRM1 A118G* polymorphism	[46]
	OPRM1 A118G, DAT 9 VNTR	83 non treatment seeking alcohol dependent individuals receiving placebo or naltrexone 25mg/day for 2 days and 50mg/day for 5 days	Response to naltrexone (number of drinks, heavy drinking days, alcohol stimulation)	Non carriers of *OPRM1 118G* allele and carriers of *DAT* 9 VNTR had: - more stimulation to alcohol - reduced number of drinks when on naltrexone treatment	[47]
		74 non treatment seeking alcohol dependent individuals receiving placebo or naltrexone 50mg/day for 1 week	Alcohol cue elicited rain activation	Carriers of *OPRM1 118G* allele and carriers of *DAT* 10 VNTR had: - less stimulation to alcohol	[48]

		43 non treatment seeking alcohol dependent individuals	Subjective response to alcohol	Carriers of *OPRM1 118G* allele and carriers of *DAT* 10 VNTR had: - steeper increase in stimulation to alcohol - steeper increase in positive mood	[49]
	OPRM1 A118G (Meta analysis)	6 studies: 453 naltrexone treated alcohol dependent patients	Response to naltrexone (relapse rate, abstienence rate	Carriers of *OPRM1 118G* allele had: - lower relapse rate	[51]
	OPRM1 A118G	215 alcohol dependent male patients treated with naltrexone 50mg/day for 3 to 12 months	Naltrexone response (relapse rate, time to relapse, drinks per drinking day)	No association of *OPRM1 118G* polymorphism with investigated parameter	[52]
		25 alcohol dependent patients treated with naltrexone 50mg/day	Self reported ethanol consumption	No association of *OPRM1 118G* polymorphism with investigated parameter	[53]
		101 alcohol dependent patients treated with naltrexone monotherapy 50mg/day or naltrexone and 50mg/day and sertraline 100mg combined therapy or placebo for 16 weeks	Naltrexone response (drinking behavior, craving)	No association of *OPRM1 118G* polymorphism with investigated parameter, analyses were restricted in *OPRM1 118AA* individuals	[54]
		180 heavy drinkers (63% alcohol dependent), 88 treated with naltrexone 50mg/day for 3 weeks	Naltrexone response (urge for alcohol, time between drinks, alcohol effects)	No association of *OPRM1 118G* polymorphism with investigated parameter	[55]
		100 alcohol dependent patients treated with naltrexone 50mg/day for 12 weeks	Naltrexone response (relapse rate, time to relapse, craving, adverse events, treatment retention)	No association of *OPRM1 A118G* polymorphism with investigated parameter	[56]
Nalmefene	*OPRM1 A118G*	166 alcohol dependent patients with nalmefene 28 weeks20 or 40 mg/day for	Nalmefene efficacy and safety	No association of *OPRM1 A118G* polymorphism with investigated parameter	[57]

The association of *OPRM1* gene polymorphisms with naltrexone response is the subject of several clinical trials (Table 3). Clinical trial NCT00920829 assesses the effect of *OPRM1 A118G* gene polymorphism on treatment response to naltrexone in treatment-seeking alcohol dependent patients treated with 25 or 50 mg naltrexone. Response will be measured by the percent of heavy drinking days and days of abstinence. Additional primary outcome is the potential difference in the naltrexone dampening of the alcohol cue-induced brain activation dependent on *OPRM1* genotype. Medication compliance and side effects based on *OPRM1* genotype will also be assessed.In clinical trial NCT02026011 the pharmacogenomic effects of *OPRM1 A118G* genepolymorphism on biobehavioral and neural markers of response to naltrexone (50mg/day) in individuals of East Asian descent is assessed. Clinical trials NCT01738867 and NCT00817089 have been completed but results have not been annotated yet. In clinical trial NCT01738867 at least 48 healthy subjects with a history of social drinking would be recruited and genetically be stratified to result in equal numbers of *A118G'AA'* homozygotes and *A118G'G'* carriers for a 5 days treatment with placebo, naltrexone or GSK1521498, a novel opioid antagonist being investigated as a candidate treatment for behavioral and substance addictions. In naltrexone treatment arm, individuals would receive 25mg for the first two days and 50mg for the rest 3 days. Outcomes include functional brain response to alcohol, plasma cortisol and subjective response to an ethanol challenge. In clinical trial NCT00817089, males of European or Asian decent following two inpatient alcohol challenge sessions along with 12 weeks of outpatient treatment using random assignment to either naltrexone (100mg/day) or placebo, were recruited. The relationship between *OPRM1 A118G* polymorphism and the subjective/objective measures to alcohol among alcohol dependent patients treated with naltrexone was

Examined drug	Gene polymorphisms	Clinical trial Assession number	Status	Population	Clinical trial examined Outcome	Published results
Naltrexone	*OPRM1 A118G*	NCT00006206	Completed	300 alcohol dependent patients randomized on naltrexone	Percent days abstinent, time to relapse to heavy drinking, measures of drinking outcomes and adverse exoesirences, psychological assessments and quality of life	Carriers of *OPRM1 118G* allele showed an increasing trend in abstinent days over time, fewer heavy drinking days over time and the best outcome [36]
		NCT00369408	Completed	81 problem drinkers on naltrexone 50mg/day	Drinking days, heavy drinking days, alcohol-related problems and biological measures of alcohol consumption	Carriers of *OPRM1 118G* allele showed a stronger evening drinking desire and were at greater risk of drinking more than *118AA* homozygotes [44]

Table 3. Clinical trials assessing the pharmacogenomics of alcohol dependence drugs

		NCT00920829	Recruiting	Treatment seeking alcoholic patients treated with 25 or 50mg naltrexone	Percent heavy drinking days, adverse effects, drinks per drinking day and percent days abstinent	N.A.
		NCT02026011	Recruiting	Individuals of East Asian descent treated with naltrexone 50mg/day	Subjective effects of alcohol, neural response to alcohol cues, time to first drink and total number of drinks	N.A.
		NCT01738867	Completed	A total of at least 48 healthy subjects with a history of social drinking treated with naltrexone 25 mg orally once daily for the first two days and 50 mg once daily for 3 days	Brain activation within the reward circuitry in response to consumption of food and alcohol cues, adverse events, safety and tolerability, plasma cortisol concentrations, subjective responses to i.v. doses of ethanol	N.A.
		NCT00817089	Completed	Alcohol dependent males of European or Asian decent treated with naltrexone 50mg/day for 12 weeks	Differences between the peak cortisol response and subjective response, improvement in quality of life, biological markers of heavy drinking	N.A.
Acamprosate	*GRIN1, GRIN2A, GRIN2B, mGluR5*	NCT00662571	Completed			N.A.
Topiramate	Candidate genes are not defined	NCT00884884	Unknown	216 non-treatment seeking, alcohol dependent individuals treated with topiramate 100mg/day or 200mg/day alone or in combination with aripiprazole 7.5mg/day or 115mg/day	Drinking and safety, clinical and behavioral effects	N.A.

N.A.: Non Applicable

tested.

OPRM1 A118G polymorphism is associated with naltrexone response with a high degree of reproducibility and has emerged as a useful genetic marker in personalizing naltrexone treatment. Results from prospective, randomized clinical trials on the association of *OPRM1 A118G* polymorphism with naltrexone response will enable the clinical application of naltrexone pharmacogenomics in routine clinical practice.

Acamprosate

Acamprosate has been approved to maintain abstinence in alcohol dependent individuals who have quit drinking. Acamprosate does not prevent the withdrawal symptoms people may experience when they stop drinking alcohol, but reduces craving for alcohol and relapse after quitting drinking. The exact mechanism of action of acamprosate is still unknown, however, it has been suggested that it interferes with the glutamate system, leading to neurotransmitter balance restoration that is disturbed after chronic alcohol abuse [58]. Overall, the adoption of acamprosate in alcohol addiction treatment is limited [59]. This might be the major factor that even though only one third of individuals receiving acamprosate remain alcohol abstinent for more than six months, data on acamprosate pharmacogenomics are scarce.

The potential association of genetic variations with acamprosate response has been assessed only in one study (Table 4); Ooteman and colleagues have tested the differential effects on acamprosate and naltrexone on reductions in cue-induced craving and physiological cue reactivity for different polymorphisms on the opioid, dopamine, glutamate and γ-aminobutyric acid (GABA) receptors [37]. The authors have found that acamprosate efficacy was enhanced in *GABRA6 1519C* allele carriers and that in *GABRB2 1412TT* homozygous individuals acamprosate outperformed naltrexone with respect to physiological cue reactivity (heart rate), and in *DRD2 A1A1* homozygous acamprosate outperformed naltrexone with respect to craving as measured with a visual analogue scale [37]. The minor allele frequency of the described gene polymorphisms and their effect on protein are presented in Table 1.

Table 4. Human studies on the association of genetic polymorphisms with response to acamprosate

Drug	Gene polymorphisms	Subject population	Investigated parameter	Primary outcome	Reference
Acamprosate	*OPRM1 A118G, DRD1 D2/D1, DRD2 TaqI A2/A1, GRIN2B C2664T, GABRA6T1519C, GABRB2 C1421T, GABRG2 G3145A*	- 56 acamprosate treated and - 52 naltrexone treated - 30 placebo treated alcohol dependent patients	Subjective craving, physiological cue reactivity outcome (heart rate)	- Acamprosate efficacy was enhanced in *GABRA6 1519C* allele carriers - In *GABRB2 1412TT* individuals acamprosate outperformed naltrexone (parameter measured: physiological cue reactivity - heart rate) - In *DRD2 A1A1* individuals, acamprosate outperformed naltrexone (parameter measured: craving)	[37]

Currently, one clinical trial assessing the effect of genetic variations on acamprosate response is registered on the ClinicalTrials.gov website (listed in Table 3). Clinical trial NCT00662571, assessing the effect of polymorphisms in *GRIN1*, *GRIN2A* and *GRIN2B* genes coding for N-methyl-D-aspartate receptor (NMDA) and type 5 metabotropic glutamate receptor (mGluR5) on acamprosate response has been completed; however, the results have not been published yet.

Pharmacogenomics may have the potential to guide therapy of acamprosate, by increasing drug therapeutic success and days of abstinence. However, data is still lacking. Therefore, more studies should be conducted

to assess the effect of genetic variations on acamprosate response.

Disulfiram

Disulfiram reduces alcohol dependence by inhibiting the enzyme aldehyde dehydrogenase leading to increased plasma levels of acetaldehyde upon drinking alcohol, a byproduct of alcohol metabolism that is aversive [60]. Disulfiram also inhibits dopamine beta-hydroxylase (DβH), the enzyme that converts dopamine into norepinephrine and is co-released with catecholamines [61]. Polymorphisms in DβH gene affect circulating DβH levels. Specifically, *C-1021T* polymorphism, positioned ~1 kb upstream from the initiation codon of the *DβH* gene, is associated with decreased DβH levels. Individuals that are *-1021T* allele homozygous have the lowest levels of plasma DβH activity [62]. One could speculate that, in individuals with already low levels of DβH enzyme due to *C-1021T* polymorphism, disulfiram would be more effective in increasing dopamine and decreasing norepinephrine, therefore carriage of *-1021T* allele can potentially be associated with increased response to disulfiram therapy.

It has been suggested that individuals carrying *DβH C-1021T TT* genotype would respond better to disulfiram treatment and would need less of a dose whereas *CT* individuals would need an intermediate dose and those with the *CC* genotype may need increased concentrations for maximum therapeutic effectiveness [63]. For disulfiram, only one study has assessed the effect of *DβH C-1021T* polymorphism on treatment response (Table 5) [64]. In this study, Mutschler and colleagues have recruited 62 alcohol-dependent patients from the specialized disulfiram outpatient treatment program in Mannheim, Germany. The authors have found that carrying *DβH-1021T* low activity allele is associated with an increased risk of adverse events, but not with disulfiram response, despite a trend of longer cumulative alcohol abstinence achieved in *CT/TT* individuals, compared to *CC* group [64]. It should be noted, however, that,currently,disulfiram is not a treatment of choice for alcohol dependence due to the increased number and fear of the severe and sometimes fatal reaction known as a disulfiram–alcohol reaction. Disulfiram–alcohol reaction is the result of the build up of a chemical from the alcohol in the body when patients take the medicine and drink alcohol at the same time.

Table 5. Human studies on the association of genetic polymorphisms with response to disulfiram.

Drug	Gene polymorphisms	Subject population	Investigated parameter	Primary outcome	Reference
Disulfiram	*DBH C-1021T*	- 62 disulfiram treated alcohol dependent patients	Time until first relapse, accumulated time of abstinence, craving, adverse events, treatment safety and tolerability	Carriers of *-1021T* allele had: - increased risk of adverse events - a trend towards longer cumulative alcohol abstinence	[64]

Currently, no clinical trials are registered at ClinicalTrials.gov on DβH genetic variations and disulfiram response in alcohol dependent patients.

Disulfiram is currently rarely used for the treatment of alcohol dependence. Further pharmacogenomic studies that will unravel the genetic factors affecting disulfiram response are needed.

Topiramate

Topiramate is an anticonvulsant medication that has recently been identified as a potent therapy of alcohol dependence. Even though topiramate has not yet gained approval for alcohol dependence treatment, several controlled clinical trials have shown its efficacy in the treatment of alcohol dependence and it has been used in several countries for the treatment of alcohol dependence [65, 66]. Topiramate may antagonize alcohol rewarding effects associated with abuse liability by inhibiting mesocorticolimbic dopamine release. Also, it has been suggested that it enhances the inhibitory function of GABA, antagonizes excitatory glutamate receptors, and inhibits dopamine release [67]. However, a major concern and limitation in the use of topiramate has been its adverse effects, which are prominent especially during the titration period, appear to be dose-related but usually subside

with continued treatment [66]. Recently it has been reported that the *rs2832407 C>A* intron 9 polymorphism of glutamate receptor GluR5 (*GRIK1*) gene is associated with the severity of topiramate-induced side effects and with serum levels of topiramate, thus making it an interesting candidate for therapy personalization [68].

First evidence on the association of *GRIK1* polymorphisms with topiramate pharmacokinetics and response were published on 2009 (Table 6). Ray and colleagues have shown that,in a total of 32 alcohol dependent patients treated with topiramate 200-300 mg/day for 5 weeks, *GRIK1 rs2832407C>A* polymorphismwas associated with topiramate serum levels and the severity of topiramate-induced side effects [69]. Carriers of *rs2832407A* allele had both higher serum topiramate levels and of greater severity topiramate side effects both when compared to placebo and to homozygous topiramate treated *CC* individuals. Additionally, carriers of *rs2832407A* allele reported higher mean percentage of heavy drinking days as compared to *CC* individuals (40.4% vs. 22.2%) [69]. More recently, Kranzler and colleagues have analyzed the association of *GRIK1 rs2832407C>A* polymorphism with topiramate effect on heavy drinking days [70]. In a total of 138 individuals treated either with topiramate at a maximal dose of 200mg for 12 weeks (67 individuals) or matching placebo (71 individuals), the authors have found that, in a subgroup of 122 European American individuals the effect of topiramate on heavy drinking days was significantly greater than

Table 6. Human studies on the association of genetic polymorphisms with response to topiramate

Drug	Gene polymorphisms	Subject population	Investigated parameter	Primary outcome	Reference
Topiramate	*GRIK1 rs2832407C>A*	32 non-treatment seeking heavy drinkers (75% alcohol dependent patients) treated with topiramate 200-300mg/day for 5 weeks	Severity of adverse events, topiramate serum levels, drinking behavior	Carriers of *rs2832407A* allele had: - Increased severity of adverse events - Higher mean percentage of heavy drinking days - Higher serum topiramate levels	[69]
		67 individuals treated with topiramate 200mg for 12 weeks and 71 placebo treated individuals	Topiramate efficacy and tolerability	In a subsample of 122 individuals, the effect of topiramate on heavy drinking days was significantly greater than that of placebo only in *rs2832407CC* homozygotes	[70]
		67 individuals treated with topiramate 200mg for 12 weeks and 71 placebo treated individuals	Topiramate effect on body mass index (BMI)	In a subsample of 122 individuals, no association of *GRIK1 rs2832407C>A* polymorphism was found with investigated parameter	[71]
		67 individuals treated with topiramate 200mg for 12 weeks and 71 placebo treated individuals	Topiramate response (reduction in drinking, desire to drink, positive alcohol expectancies)	In a subsample of 122 individuals, *rs2832407CC* homozygotes: - drank less during treatment - showed the largest decreases in positive alcohol expectancies and desire to drink	[72]

that for placebo only in *rs2832407CC* homozygotes [70]. The same research team have further analyzed in the subgroup of 122 European American individuals the potential association of *GRIK1 rs2832407C>A* polymorphism with topiramate effect on BMI, but no association was found [71]. Finally, Kranzler and colleagues have validated in the subgroup of 122 European American individuals the interactive effect of *GRIK1 rs2832407C>A* polymorphism and topiramate as predictors of drinking level [72]. The authors have found that topiramate-treated *rs2832407CC* homozygotes drank less during treatment than those receiving placebo, validating this way their earlier findings, and have also shown that *rs2832407CC* homozygotes showed the largest decreases in positive alcohol expectancies and desire to drink [72].

Several clinical trials are registered on Clinicaltrials.gov website and assess whether topiramate will improve drinking outcomes in alcohol dependent individuals, however, currently, only one clinical trial assesses the association of gene polymorphisms with topiramate effect on craving, subjective stimulation and other behavioral effects associated with alcohol consumption (Table 3). The clinical trial NCT00884884 will recruit 216 healthy, alcohol-dependent volunteers who are not currently seeking treatment for their alcohol dependence to learn more about how topiramate and alprazolam medications may work on alcohol dependence and how gene polymorphisms modulate their action.

Topiramate appears to be a promising therapy for alcohol dependence. Accumulated data implicate consistently *GRIK1 rs2832407C>A* as a predictor of topiramate response and adverse drug reactions incidence. Therefore, upon approval of topiramate as a therapy for alcohol dependence, GRIK1 polymorphisms may have an important role in personalizing topiramate therapy.

Other drugs

So far, as it was already extensively described, the only three drugs that have been approved by FDA for alcohol dependence are naltrexone, acamprosate and disulfiram, whereas topiramate appears as a promising therapy. Several other compounds have been experimented for the treatment of alcohol dependence and some of them are in clinical development. Describing the exact mechanism of action of these drugs and their potency is beyond the scopes of the present review, therefore we simply list the drugs that have been associated with positive outcomes of alcohol dependence.

In Italy and Austria, sodium oxybate is already approved for alcohol dependence and it is expected to will be soon introduced in Kazakhstan. Sodium oxybate is a short-chain fatty acid, structurally similar to the inhibitory neurotransmitter γ-amino-butyric acid, which exerts an ethanol-mimicking effect on GABAB receptors in the central nervous system. Baclofen is a GABAB receptor agonist currently used to control spasticity that was also shown to reduce alcohol consumption. Ondansetron is a 5-HT3 receptor antagonist that is thought to reduce the reward from alcohol. Additionally, other compounds clinically approved for different than alcohol addiction indications, such as pregabalin, oxcarbamazepine, gabapentin, valproic acid, aripiprazole, prazosin, vigabatrin, tiagabine, quetiapine and neurosteroids, seem to be able to reduce alcohol consumption, but further trials should be performed to confirm their efficacy in preventing relapse and maintaining complete abstinence [73-75].

CONCLUSIONS AND FUTURE PERSPECTIVES

It is anticipated that treating effectively alcohol dependence will decrease social and economic burden of this serious disorder. As it was extensively described in the present review, pharmacogenomics of alcohol dependence is a field in which several applications are mature and ready to be implemented in routine clinical practice. *OPRM1 A118G* polymorphism is highly associated with improved response to naltrexone. This gene polymorphism can serve a marker to distinguish individuals who will benefit the most from naltrexone or who could be administered an alternative drug, such as acamprosate. Additionally, even prior of FDA approval of topiramate for treating alcohol dependence, it has been consistently shown that topiramate response is affected by *GRIK1 rs2832407C>A* polymorphism. As for the other drugs used for alcohol dependence, further studies are needed before any conclusions can be drawn on their utility in personalizing alcohol addiction therapy.

It is expected that in the coming years alcohol dependence pharmacogenomics may be instrumental in personalizing drug addic-

tion therapy by guiding the choice of pharmacotherapy. It is hoped that incorporation of pharmacogenomics in routine clinical practice will lead to increased days of abstinence, lower relapse rates and days of heavy drinking, as well as lower incidence of drug adverse events. More importantly, application of pharmacogenomics in the field of alcohol dependence may lead to increased productivity of individuals who are currently addicted to alcohol. Overall, application of personalized medicine approaches on alcohol dependence therapy with the use of pharmacogenomics may provide with benefits all the players involved: the patients who may respond faster and more effectively to pharmacotherapy, the psychiatrists who - by integrating the latest and most updated scientific information in their practice - will increase therapy response rates, and the national health systems in each country as well as the society as a whole as it may help to reduce the financial and social burden of alcoholdependence.

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Farmakogenomika u alkoholizmu: personalizovani farmakološki tretman alkoholizma

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KRATAK SADRŽAJ

Zavisnost od alkohola je ozbiljan psihijatrijski poremećaj sa štetnim fizičkim, mentalnim i socijalnim posledicama, sa velikom verovatnoćom da ima hroničan tok. Mogućnosti farmakološkog tretmana zavisnosti od alkohola, kao i potrebe za pijenjem alkohola se rapidno proširuju.
Lekovi koji redukuju relapse kod alkoholičara kao i pijenje alkohola alkoholičara, dakle, lekovi koji se koriste za farmakološki tretman lečenja alkoholizma su: naltrekson, akamprosat i disulfiram, a topiramat je lek koji obećava kao efikasna terapija. Međutim, kod mnogih pacijente ova farmakoterapija nije efikasna. Rezultati iz brojnih različitih studija ukazuju da genetičke varijacije bitno doprinose interindividualnoj varijaciji kliničke prezentacije bolesti alkoholizam i terapijskog odgovora na primenjenu farmakoterapiju.
U ovom revijalnom radu sumiramo i razmotramo rezultate istraživanja o povezanosti genskog polimorfizma i terapijske odgovore na lekove protiv zavisnosti od alkohola. Pretpostavlja se da će buduća implementacija farmakogenomike u kliničku praksu pomoći da se personalizije lečenje od alkoholne zavisnosti, tj razvije personalizovana bolnička farmakologija.

Ključne reči: alkohol, zavisnost, naltrekson, topiramat, disulfiram, akamprosat, farmakogenetika, personalizovana bolnička farmakologija

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