Pharmacogenomics of Alcohol Addiction: Personalizing Pharmacologic Treatment of Alcohol Dependence

Georgia Ragia1,2, Vangelis G. Manolopoulos1,3

1 Laboratory of Pharmacology, Medical School, Democritus University of Thrace, Alexandroupolis, Greece
2 DNALEX S.A., Leontaridou 2, Alexandroupolis, Greece
3 Clinical Pharmacology Unit, Academic General Hospital of Evros, Alexandroupolis, Greece

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...
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
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 nalmefene, 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].

<table>
<thead>
<tr>
<th>Gene (protein)</th>
<th>Genomic locus</th>
<th>SNP ID*</th>
<th>SNP gene location</th>
<th>Amino acid substitution</th>
<th>Effect on encoded product</th>
<th>MAF*</th>
<th>Drug studied in association with</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPRM1</td>
<td>6q25.2</td>
<td>rs1799971A&gt;G (c.A118G)</td>
<td>Exon 1, missense, non synonymous amino acid substitution</td>
<td>Asn40Sp</td>
<td>Increased binding of β-endorphin</td>
<td>0.19</td>
<td>Naltrexone</td>
</tr>
<tr>
<td>OPRK1</td>
<td>8q11.2</td>
<td>rs997917T&gt;C (c.258-4707A&gt;G, g.7312553T&gt;C)</td>
<td>Intron 1</td>
<td>-</td>
<td>Unknown</td>
<td>0.429</td>
<td>Naltrexone</td>
</tr>
<tr>
<td>OPRD1</td>
<td>1p36.1-p34.3</td>
<td>rs4654327A&gt;G (c.343G&gt;A, g.28277638G&gt;A)</td>
<td>3' UTR</td>
<td>-</td>
<td>Potential effect on transcription levels</td>
<td>0.431</td>
<td>Naltrexone</td>
</tr>
<tr>
<td>SLC6A3 (DAT)</td>
<td>5p15.3</td>
<td>rs283631700 (c.<em>887_</em>988ins ACT GGA GCG TGT ACT ACC CCA GGA GCC ATG CAG GCC CCC C)</td>
<td>3' UTR</td>
<td>-</td>
<td>Regulation of DAT gene expression potential effect on transcription levels</td>
<td>NA</td>
<td>Naltrexone</td>
</tr>
<tr>
<td>GABRA6</td>
<td>5q34</td>
<td>rs3219151T&gt;C (c.135C&gt;T, g.5940584C&gt;T)</td>
<td>3' UTR</td>
<td>-</td>
<td>Potential effect on transcription levels</td>
<td>0.544</td>
<td>Acamprosate</td>
</tr>
<tr>
<td>GABRB2</td>
<td>5q34</td>
<td>rs2229944C&gt;T (c.1194C&gt;T, g.5532988G&gt;A)</td>
<td>Exon 10, synonymous amino acid substitution</td>
<td>Ala436=</td>
<td>Unknown</td>
<td>0.109</td>
<td>Acamprosate</td>
</tr>
<tr>
<td>DRD2 (actual ANKK1)</td>
<td>11q23.2</td>
<td>rs1800497 C&gt;T (c.2137G&gt;A, g.25397210G&gt;A)</td>
<td>Exon 8, missense, non synonymous amino acid substitution</td>
<td>Glu713Lys</td>
<td>Reduced number of DRD2 molecules and receptor binding</td>
<td>0.296</td>
<td>Acamprosate</td>
</tr>
<tr>
<td>DBH</td>
<td>9q34.2</td>
<td>rs1611115C&gt;T (c.-979T&gt;C, g.1021T)</td>
<td>Promoter, effect on transcription level</td>
<td>-</td>
<td>Reduced transcription</td>
<td>0.208</td>
<td>Disulfiram</td>
</tr>
<tr>
<td>GRIK1</td>
<td>21q22.11</td>
<td>rs2832407A&gt;C (c.1251+1338A&gt;C)</td>
<td>Intron 9, unknown</td>
<td>-</td>
<td>Unknown</td>
<td>0.448</td>
<td>Topiramate</td>
</tr>
</tbody>
</table>

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)
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 OPRM1 A118G 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 blockade; 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 blockade 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 allopregnanolone levels in 32 naltrexone treated heavy drinkers; allopregnanolone is a GABAergic neuroactive steroid that has been associated with naltrexone pharmacotherapy [32]. Naltrexone increased allopregnanolone in OPRM1 118G carriers but not in 118A 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 allopregnanolone 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 outcomes in 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
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 patients were 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 to 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 shown 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 response outscapes 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. McGee and colleagues have analyzed the association of OPRM1 A118G polymorphism 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 colleagues, 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 Ashen-hurst 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-analyses; 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. Gelner 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 patients, 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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene polymorphisms</th>
<th>Subject population</th>
<th>Investigated parameter</th>
<th>Primary outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxone</td>
<td>OPRM1 A118G</td>
<td>39 healthy men treated with five doses of naloxone (0, 50, 100, 200 and 400 μg/kg, incremental doses per 30 minutes)</td>
<td>Cortisol and adrenocorticotropic release</td>
<td>Carriers of OPRM1 118G allele had: - greater cortisol response - different increase adrenocorticotropic rate (between 30 - 90 minutes) - different decrease adrenocorticotropic rate (after 90 minutes)</td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 healthy individuals treated with intravenous naloxone 125 μg/kg</td>
<td>Cortisol and adrenocorticotropic release</td>
<td>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</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>74 individuals receiving five increasing doses of naloxone (0, 50, 100, 200 and 400 μg/ kg, incremental doses per 30 minutes)</td>
<td>Cortisol and adrenocorticotropic release</td>
<td>Carriers of OPRM1 118G allele had: - increased cortisol response</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32 non-treatment seeking hazardous drinkers receiving 50mg naltrexone</td>
<td>Allopregnanolone and cortisol levels</td>
<td>Carriers of OPRM1 118G allele had: - increased allopregnanolone levels</td>
<td>[32]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38 students with moderate or heavier drinking pattern intravenously receiving alcohol</td>
<td>Alcohol induced sedation, stimulation, subjective response, mood alterations</td>
<td>Carriers of OPRM1 118G allele had: - greater feelings of intoxication - higher increases in alcohol induced stimulation - higher increases in state happiness</td>
<td>[33]</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>40 non-treatment seeking heavy drinkers receiving naltrexone 50mg for three days and intravenously administered alcohol</td>
<td>Alcohol sensitivity, subjective response to alcohol, craving</td>
<td>Carriers of OPRM1 118G allele had: - higher increases in alcohol induced euphoria - reduced alcohol induced euphoria when receiving naltrexone [34]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>71 naltrexone treated (50 or 100mg/day for 12 weeks) alcohol dependent individuals 59 placebo treated individuals</td>
<td>Clinical response to naltrexone (relapse, abstinence)</td>
<td>Carriers of OPRM1 118G allele had: - greater chance not to return to heavy drinking - longer time to first relapse [35]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>300 alcohol dependent patients treated with naltrexone 50 or 100mg/day for 16 weeks</td>
<td>Clinical response to naltrexone (abstinence, heavy drinking days, adverse events)</td>
<td>Carriers of OPRM1 118G allele had: - an increasing trend in abstinent days - fewer heavy drinking days - the best clinical outcome [36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPRM1 A118G, DRD1 D2/D1, DRD2 Taq1 A2/ A1, GRIN2B C2664T, GABRA6 T1519C, GABRB2 C1421T, GABRG2 G3145A</td>
<td>- 56 acamprosate treated and - 52 naltrexone treated - 30 placebo treated alcohol dependent patients</td>
<td>Subjective craving, physiological cue reactivity outcome (heart rate)</td>
<td>In carriers of OPRM1 118G allele: - naltrexone outperformed acamprosate [37]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPRM1 A118G</td>
<td>146 alcohol dependent patients treated with naltrexone 100mg/day for 16 weeks</td>
<td>Clinical response to naltrexone (abstinence, heavy drinking days, adverse events)</td>
<td>Carriers of OPRM1 118G allele had: - good clinical outcome [38]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPRM1 A118G</td>
<td>63 alcohol dependent patients treated with naltrexone 25mg/day for first 3 days and 50mg/day for remaining days of a 12 weeks treatment</td>
<td>Clinical response to naltrexone (abstinence rate, relapse rate, time to relapse)</td>
<td>Carriers of OPRM1 118G allele had: - longer time to relapse [39]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPRM1 A118G</td>
<td>40 social drinkers treated with naltrexone 25mg/day for first day and 50mg/day for remaining 5 days</td>
<td>Subjective effects of alcohol</td>
<td>Carriers of OPRM1 118G allele had: - decreased euphoria during naltrexone treatment after seeing and drinking alcohol [40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Intervention</td>
<td>Outcome Measures</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>--------------</td>
<td>------------------</td>
<td>----------</td>
<td></td>
</tr>
</tbody>
</table>
| Georgia R et al | 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, rs4654327 & rs508448 | Subjective response to alcohol, craving | OPRK1 rs997919 and OPRD1 rs4654327 polymorphisms were associated with response to alcohol after controlling for OPRM1 A118G polymorphism | [46] |
| | 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] |
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Naltrexone response (investigated parameter)</th>
<th>OPRM1 A118G polymorphism association</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 studies: 453 naltrexone treated alcohol dependent patients</td>
<td>Response to naltrexone (relapse rate, abstention rate)</td>
<td>No association of OPRM1 A118G polymorphism with investigated parameter [51]</td>
</tr>
<tr>
<td>215 alcohol dependent male patients treated with naltrexone 50mg/day for 3 to 12 months</td>
<td>Naltrexone response (relapse rate, time to relapse, drinks per drinking day)</td>
<td>No association of OPRM1 A118G polymorphism with investigated parameter [52]</td>
</tr>
<tr>
<td>25 alcohol dependent patients treated with naltrexone 50mg/day</td>
<td>Self reported ethanol consumption</td>
<td>No association of OPRM1 A118G polymorphism with investigated parameter [53]</td>
</tr>
<tr>
<td>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</td>
<td>Naltrexone response (drinking behavior, craving)</td>
<td>No association of OPRM1 A118G polymorphism with investigated parameter, analyses were restricted in OPRM1 118AA individuals [54]</td>
</tr>
<tr>
<td>180 heavy drinkers (63% alcohol dependent), 88 treated with naltrexone 50mg/day for 3 weeks</td>
<td>Naltrexone response (urge for alcohol, time between drinks, alcohol effects)</td>
<td>No association of OPRM1 A118G polymorphism with investigated parameter [55]</td>
</tr>
<tr>
<td>100 alcohol dependent patients treated with naltrexone 50mg/day for 12 weeks</td>
<td>Naltrexone response (relapse rate, time to relapse, craving, adverse events, treatment retention)</td>
<td>No association of OPRM1 A118G polymorphism with investigated parameter [56]</td>
</tr>
<tr>
<td>Nalmefene</td>
<td>Nalmefene efficacy and safety</td>
<td>No association of OPRM1 A118G polymorphism with investigated parameter [57]</td>
</tr>
</tbody>
</table>
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 gene polymorphism 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 A118GAA homozygotes and A118GG 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

<table>
<thead>
<tr>
<th>Examined drug</th>
<th>Gene polymorphisms</th>
<th>Clinical trial Assessment number</th>
<th>Status</th>
<th>Population</th>
<th>Clinical trial examined Outcome</th>
<th>Published results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone</td>
<td>OPRM1 A118G</td>
<td>NCT00006206</td>
<td>Completed</td>
<td>300 alcohol dependent patients randomized on naltrexone</td>
<td>Percent days abstinent, time to relapse to heavy drinking, measures of drinking outcomes and adverse exoexperiences, psychological assessments and quality of life</td>
<td>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]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT00369408</td>
<td>Completed</td>
<td>81 problem drinkers on naltrexone 50mg/day</td>
<td>Drinking days, heavy drinking days, alcohol-related problems and biological measures of alcohol consumption</td>
<td>Carriers of OPRM1 118G allele showed a stronger evening drinking desire and were at greater risk of drinking more than 118AA homozygotes [44]</td>
</tr>
<tr>
<td>Study ID</td>
<td>Status</td>
<td>Description</td>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00920829</td>
<td>Recruiting</td>
<td>Treatment seeking alcoholic patients treated with 25 or 50mg naltrexone</td>
<td>Percent heavy drinking days, adverse effects, drinks per drinking day and percent days abstinent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02026011</td>
<td>Recruiting</td>
<td>Individuals of East Asian descent treated with naltrexone 50mg/day</td>
<td>Subjective effects of alcohol, neural response to alcohol cues, time to first drink and total number of drinks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01738867</td>
<td>Completed</td>
<td>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</td>
<td>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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00817089</td>
<td>Completed</td>
<td>Alcohol dependent males of European or Asian decent treated with naltrexone 50mg/day for 12 weeks</td>
<td>Differences between the peak cortisol response and subjective response, improvement in quality of life, biological markers of heavy drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00662571</td>
<td>Completed</td>
<td>Topiramate GRIN1, GRIN2A, GRIN2B, mGlur5</td>
<td>N.A.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00884884</td>
<td>Unknown</td>
<td>Topiramate Candidate genes are not defined</td>
<td>N.A.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Drug</th>
<th>Gene polymorphisms</th>
<th>Subject population</th>
<th>Investigated parameter</th>
<th>Primary outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate</td>
<td>OPRM1 A118G, DRD1 D2/D1, DRD2 TaqI A2/A1,</td>
<td>- 56 acamprosate treated and - 52 naltrexone treated</td>
<td>Subjective craving, physiological cue reactivity outcome (heart rate)</td>
<td>- Acamprosate efficacy was enhanced in GABRA6 1519C allele carriers</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td>GRIN2B C2664T, GABRA6T1519C, GABRB2 C1421T</td>
<td>- 30 placebo treated alcohol dependent patients</td>
<td></td>
<td>- In GABRB2 1412TT individuals acamprosate outperformed naltrexone (parameter measured: physiological cue reactivity - heart rate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GABRG2 G3145A</td>
<td></td>
<td></td>
<td>- In DRD2 A1A1 individuals, acamprosate outperformed naltrexone (parameter measured: craving)</td>
<td></td>
</tr>
</tbody>
</table>

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.

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 mesocorticollimbic 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.

---

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene polymorphisms</th>
<th>Subject population</th>
<th>Investigated parameter</th>
<th>Primary outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disulfiram</td>
<td>DβH C-1021T</td>
<td>62 disulfiram treated alcohol dependent patients</td>
<td>Time until first relapse, accumulated time of abstinence, craving, adverse events, treatment safety and tolerability</td>
<td>Carriers of -1021T allele had: - increased risk of adverse events - a trend towards longer cumulative alcohol abstinence</td>
<td>[64]</td>
</tr>
</tbody>
</table>
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 polymorphism was 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>
<thead>
<tr>
<th>Drug</th>
<th>Gene polymorphisms</th>
<th>Subject population</th>
<th>Investigated parameter</th>
<th>Primary outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>GRIK1 rs2832407C&gt;A</td>
<td>32 non-treatment seeking heavy drinkers (75% alcohol dependent patients) treated with topiramate 200-300mg/day for 5 weeks</td>
<td>Severity of adverse events, topiramate serum levels, drinking behavior</td>
<td>Carriers of rs2832407A allele had: - Increased severity of adverse events - Higher mean percentage of heavy drinking days - Higher serum topiramate levels</td>
<td>[69]</td>
</tr>
<tr>
<td>Topiramate</td>
<td>GRIK1 rs2832407C&gt;A</td>
<td>67 individuals treated with topiramate 200mg for 12 weeks and 71 placebo treated individuals</td>
<td>Topiramate efficacy and tolerability</td>
<td>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</td>
<td>[70]</td>
</tr>
<tr>
<td>Topiramate</td>
<td>GRIK1 rs2832407C&gt;A</td>
<td>67 individuals treated with topiramate 200mg for 12 weeks and 71 placebo treated individuals</td>
<td>Topiramate effect on body mass index (BMI)</td>
<td>In a subsample of 122 individuals, no association of GRIK1 rs2832407C&gt;A polymorphism was found with investigated parameter</td>
<td>[71]</td>
</tr>
<tr>
<td>Topiramate</td>
<td>GRIK1 rs2832407C&gt;A</td>
<td>67 individuals treated with topiramate 200mg for 12 weeks and 71 placebo treated individuals</td>
<td>Topiramate response (reduction in drinking, desire to drink, positive alcohol expectancies)</td>
<td>In a subsample of 122 individuals, rs2832407CC homozygotes: - drank less during treatment - showed the largest decreases in positive alcohol expectancies and desire to drink</td>
<td>[72]</td>
</tr>
</tbody>
</table>

Table 6. Human studies on the association of genetic polymorphisms with response to topiramate
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 pharma-
cotherapy. It is hoped that incorporation of pharma-
genomics 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 pharmaco-
genomics in the field of alcohol dependence may lead to increased productivity of indi-
viduals who are currently addicted to alcohol. Overall, application of personalized medicine approaches on alcohol dependence therapy with the use of pharmacogenomics may pro-
vide 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 prac-
tice - 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 alco-
hol dependence.

REFERENCES

1. World Health Organization. Global Status report on Al-
cohol and Health. 2014.


4. Assanangkornchai S, Srisurapanont M. The treat-

5. Mann K, Hermann D. Individualised treatment in alco-
hol-dependent patients. Eur Arch Psychiatry Clin Neuro-

6. Edens E, Massa A, Petrakis I. Novel pharmacological ap-


10. Ragia G, Giannakopoulou E, Karaglani M, Karantza IM, Tavridou A, Manolopoulos VG. Frequency of CYP450 enzyme gene polymorphisms in the Greek population: review of the literature, original findings and clinical signifi-


13. Arvanitidis K, Ragia G, Iordanidou M, Kyriaki S, Xan-
thi A, Tavridou A, Manolopoulos VG. Genetic polymor-


15. Ragia G, Petridis I, Tavridou A, Christakidis D, Manol-

16. Ragia G, Tavridou A, Elens L, Van Schaik RH, Manolo-
poulos VG. CYP2C9*2 allele increases risk for hypoglyce-
mia in POR*1/*1 type 2 diabetic patients treated with sul-


19. Iordanidou M, Paraskakis E, Tavridou A, Paschou P, Chatzimichael A, Manolopoulos VG. GS94T polymor-
phism of eNOS gene is a predictor of response to com-


21. Manolopoulos VG, Ragia G, Alevizopoulou P. Phar-
macokinetic interactions of selective serotonin reuptake inhibitors with other commonly prescribed drugs in the era of pharmacogenomics. Drug Metabol Drug Interact


45. Johnson JA, Klein TE, Relling MV. Clinical implementation of pharmacogenetics: more than one gene at a time.


Farmakogenomika u alkoholizmu: personalizovani farmakološki tretman alkoholizma

Georgia Ragia1,2, Vangelis G. Manolopoulos1,3

1 Laboratory of Pharmacology, Medical School, Democritus University of Thrace, Alexandroupolis, Greece
2 DNALEX S.A., Leontaridou 2, Alexandroupolis, Greece
3 Clinical Pharmacology Unit, Academic General Hospital of Evros, Alexandroupolis, Greece

KRATAK SADRŽAJ


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

Received: July 1, 2014
Accepted: August 1, 2014