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REVIEW

Pharmacogenetics of alcohol addiction: current perspectives

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Abstract: Genetics of alcohol addiction is currently a contradictive and complex field, where data in the most studies reflect methods' limitations rather than meaningful and complementary results. In our review, we focus on the genetics of alcohol addiction, leaving genetics of acute alcohol intoxication out of the scope. A review of the literature on pharmacogenetic biomarkers development for the pharmacotherapy personalization reveals that today the evidence base concerning these biomarkers is still insufficient. In particular, now the researches with the design of randomized controlled trials and meta-analysis investigating the effect of the SNPs as biomarkers on the therapy efficacy are available for naltrexone only. For other medications, there are only a few studies in small samples. It decreases the possibilities to implement the pharmacogenetic algorithms for the pharmacotherapy personalization in patients with alcohol use disorders (AUD). In view of the importance of the precision approaches development not in addiction medicine only, but in other fields of medicine also to increase the efficacy and safety of the therapy, studies on pharmacogenetic biomarkers development for the medications used in patients with AUD (eg, naltrexone, disulfiram, nalmefene, acamprosate, etc.) remain relevant to this day.

Keywords: pharmacogenetics, pharmacogenomics, alcohol use disorder, naltrexone, acamprosate, nalmefene

Introduction

According to the latest data, harmful alcohol use resulted in an estimated 3 million deaths or 5.3% of all global deaths.[1] Their leading causes are digestive diseases (21.3%), unintentional injuries (20.9%), cardiovascular diseases and diabetes (19.0%), infectious diseases (12.9%) and malignant neoplasms (12.6%).[1]

As with other addictive disorders, genetics influence alcohol use disorder (AUD) to a considerable degree, with heritability estimates of more than 60%.[2,3] Previous reviews on the subject[4,5] demonstrated that the advances in the field of pharmacogenetics in AUD are slow due to many difficulties and it is important to advance the precision medicine approaches for the treatment of AUD. According to available data of meta-analyses and systematic reviews, the following medications showed their efficacy in comparison with placebo: disulfiram,[6] naltrexone,[7] extended-release injectable naltrexone,[7] acamprosate,[7] nalmefene,[8] baclofen,[9] gabapentin,[10] and topiramate.[11] We may now consider the available scientific evidence bearing on the effects of single nucleotide polymorphisms (SNPs) on pharmacokinetics, pharmacodynamics, as well as on clinical efficacy and safety of the alcohol addiction treatment.

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Disulfiram

Disulfiram exhibits an antidipsotropic effect. It inhibits the conversion of acetaldehyde, a toxic metabolite of alcohol, in acetic acid by blocking the aldehyde dehydrogenase 2 (ALDH2) in the liver and the brain, resulting in an accumulation of acetaldehyde.[12] In addition, disulfiram inhibits dopamine β-hydroxylase (DβH) converting dopamine to norepinephrine.[13] The DβH genetic polymorphism can affect the level of protein of the same name. In particular, *1021C>T* polymorphism lowers the expression of DβH resulting in the reduced plasma DβH level.[14] Thus, it was assumed that patients carrying this polymorphic marker would have a reduced plasma DβH level, which is likely to alter the efficacy of disulfiram in such patients: a lower baseline DβH level should enhance the disulfiram effect. Unfortunately, the only clinical trial enrolling 66 patients with alcohol addiction has not revealed any statistically significant difference neither in the efficacy level nor in the risk of adverse effects across the patients carrying T and C alleles.[15] We also found another study conducted in patients with cocaine addiction that demonstrates a statistically significant effect of the polymorphism of the ankyrin repeat and kinase domain-containing 1 (*ANKK1*) genes and dopamine receptor D2 (*DRD2*) genes on disulfiram efficacy level.[16] The investigation of these markers would probably allow developing recommendations on the personalized treatment of alcohol addiction with disulfiram to increase its efficacy and safety.

Thus, although disulfiram is included in the guidelines as a drug recommended for the alcohol addiction treatment, today there is no data on the pharmacogenetics of this medication. Further studies are required to develop the pharmacogenetic biomarkers affecting the efficacy and safety of disulfiram in patients suffering from alcohol addiction.

Naltrexone

Synthesized in 1963 by Endo laboratories, naltrexone is a nonspecific competitive opioid antagonist approved by The US Food and Drug Administration (FDA) for the treatment of alcohol addiction in 1994. It alters the subjective effects of ethanol intoxication and attenuates craving.[17]

Previous studies have suggested that genetic polymorphisms encoding μ-opioid receptors (OPRM1) may moderate the effect of naltrexone in patients suffering from alcohol addiction. Several works describe this gene as a predictor of both alcohol addiction and the efficacy of naltrexone treatment.[18–23]

There is the mixed evidence regarding the influence of the *118A>G* functional polymorphism in the *OPRM1* gene resulting in adenine (*A*) to guanine (*G*) substitution at the gene sequence position 118.[24] Several studies[19,25–31] demonstrated greater efficacy of naltrexone among the carriers of this polymorphism which has been associated with the increased binding affinity of the endogenous ligand β-endorphin for μ-opioid receptors.[32] Meanwhile, other randomized clinical trials[33–35] revealed no such pharmacogenetic effect. In addition, a recent systematic review that meta-analyzed eight eligible clinical studies found no significant difference between *A* allele homozygotes and those with at least one *G* allele.[36] Hence, the effect of the *118A>G* functional polymorphism on naltrexone response rates remains debatable.[24]

A study performed by Kranzler et al.[37] showed that patients carrying *GG* genotype who are prone to the use of alcohol in the evenings and at night, against the background of naltrexone treatment, experienced a more pronounced reduction of craving at that time than the wild-type carriers did. According to a research conducted by Chen,[31] patients carrying *GG* genotype who abuse alcohol and receive naltrexone, consume less alcohol after the treatment course in comparison with the patients who receive placebo or homozygous carriers of the wild-type allele *A* who also receive naltrexone.

However, the randomized clinical trial conducted by Schacht et al.[24] demonstrated that the *OPRM1* genotype did not significantly moderate the effects of naltrexone on drinking, but *G*-allele carriers who received naltrexone had an accelerated return to heavy drinking after the medication was stopped.

Evidence demonstrating the naltrexone efficacy in patients from various ethnic groups and of both genders is essential for practice. Setiawan et al.[38] investigated the effect of 6-days treatment with naltrexone in 40 volunteers (20 males and 20 females) who were social drinkers aged 18–50. At the end of each treatment period, all patients received a single dose of their preferred alcoholic beverage with the opportunity to work for the additional alcohol units using a progressive ratio breakpoint paradigm. The results showed that naltrexone use resulted in the reduced stimulant and euphorigenic effects of the priming dose of alcohol, especially in women and carriers of the *A118G* polymorphism of the *OPRM1* gene; the participants with both of these traits were considered the most sensitive.

Data on the frequency of genetic polymorphisms in different ethnic groups are of particular interest. Among whites, Bond et al.[32] revealed that the expected frequencies of homozygous *G118* and heterozygous subjects are 2% and 20%, respectively, with the allelic frequency of the *G118* variant of 11.5%, regardless of gender. In Asians, the frequency of the *G118* variant is higher and varies from 35 to 47%: 35% in Chinese, 44% in Thais, 45% in Malays, 47% in Indians,[39] and more than 49% in Japanese.[40]

Pharmacogenetic aspects of naltrexone use in patients carrying the functional polymorphisms of *OPRK1* (*rs997917*) and *OPRD1* (*rs4654327*) genes, as well as the combination of the *A118G* polymorphism of the *OPRM1* gene and the *VNTR* polymorphism of the human dopamine transporter (*DAT1*) gene, are not investigated sufficiently. Several studies indicate the potential of further research investigating the joint effect of these two systems on the intensity of subjective feelings of alcohol intoxication.[17,34,41,42]

A correlation between the functional polymorphisms of *OPRK1* (*rs997917*) and *OPRD1* (*rs4654327*) genes and the efficacy of naltrexone treatment (versus placebo) was revealed. The study conducted by Ashenhurst demonstrated the changes in subjective response to alcohol and the rate of alcohol craving.[43] Of the two *OPRK1* SNPs examined, *rs997917* demonstrated a significant effect on the alcohol-induced sedation. The *TT* homozygous patients reported the reduced feelings of alcohol sedation during the naltrexone use as compared to the *C* allele-carriers. Moreover, pharmacogenetic effects were also observed for a SNP in the *OPRD1* gene: carriers of the *A* allele at this locus reported greater naltrexone-induced blunting of alcohol stimulation and craving in comparison with the *G*-allele homozygous patients.

Krupitsky et al revealed that the efficacy of naltrexone treatment in patients suffering from opioid addiction was different across the patients carrying different allelic variants of the opioid receptor genes and dopaminergic system genes.[44] Thus, patients carrying the combination of *CC* or *CT* genotypes of *OPRK1* and *TT* genotype of *DRD2* demonstrated better response to treatment, whereas a combination of the *A118G* polymorphism of the *OPRM1* gene and the *VNTR* polymorphism of the *DAT1* gene showed a significant effect on the subjective feelings of alcohol intoxication.

Although numerous studies demonstrate the efficacy of the extended-release injectable naltrexone for the alcohol addiction treatment (in comparison with placebo),[45–48] at the moment the effects of genetic factors on the extended-release injectable naltrexone efficacy are not investigated sufficiently.[49]

Due to the contradictory results of the studies investigating the efficacy of naltrexone in patients suffering from AUD,[33,50] genetic testing is not commonly used in clinical practice today. Hence, there is a need to strengthen the evidence base.

Acamprosate

FDA has approved acamprosate for the alcohol addiction treatment in 2004. Although the results of numerous studies confirm the efficacy of acamprosate in the treatment of AUD,[7] its exact mechanism of action is still uncertain. It seems to modulate NMDA receptor transmission and $GABA_A$ transmission.[51]

Adverse effects registered in clinical trials included diarrhea, dizziness, and headaches.[52]

A double-blind, placebo-controlled trial conducted by Kiefer[53] demonstrated a statistically significant effect of the *GATA4 rs13273672* SNP on the duration of remission in patients with alcohol addiction who receive acamprosate. It was found that patients with the mutant allele *G* show the reduced time to relapse in comparison with those carrying the *AA* genotype. No such effect was revealed in the groups of patients who received naltrexone or placebo.

This effect probably results from the fact that *GATA4* encodes a transcription factor of atrial natriuretic peptide (ANP).[54] It was confirmed in a study conducted by Kiefer who investigated the plasma level of the ANP.[53] Research suggests that the reduced ANP levels contribute to the dysregulation of the stress and anxiogenic systems of the brain, which is commonly found in patients with alcohol addiction.[55] It was assumed that acamprosate has a more pronounced effect on the duration of remission in patients carrying the *A* allele due to the differences in the ANP level across the patients with different genotypes.

Moreover, studies demonstrate the effect of *GRIN2B* encoding the NMDA receptor *GluN2B* subunit on the duration of remission in patients who receive acamprosate.[56] This study included 225 patients with alcohol addiction. It revealed that the minor allele *A* of the *rs2058878* polymorphism is associated with the longer remission in comparison with the *G* allele. Unfortunately, this study had a serious limitation due to the absence of a placebo group. Therefore, the study results were inconclusive regarding the effect of the *GRIN2B* polymorphism on the efficacy of acamprosate.

Thus, despite the lack of data on acamprosate pharmacogenetics, this medication is considered effective and safe for the treatment of patients with alcohol addiction.

Nalmefene

Nalmefene is a selective opioid receptor antagonist acting as a μ- and δ- receptor antagonist and a partial κ receptor agonist.[57,58] Although structurally nalmefene is similar to naltrexone, it exhibits a higher bioavailability rate and a longer plasma half-life, with a lower risk of liver toxicity.[59]

FDA has approved nalmefene for opioid overdose only (www.fda.org). Several clinical trials conducted in the US have not demonstrated a higher efficacy of nalmefene in the treatment of patients with AUD as an anticraving therapy in comparison with placebo.[60,61] At the same time, three multisite clinical trials conducted in Europe, where nalmefene was approved for the treatment of patients with AUD by the European Medicines Agency in February 2013,[58,60] showed its efficacy in alcohol consumption reduction across patients suffering from alcohol addiction with high levels of consumption (more than 60 grams/daily for men and more than 40 grams/daily for women).

Due to the structural similarity to naltrexone, the use of nalmefene is associated with similar common adverse effects. Similarly to naltrexone, nalmefene can induce nausea and vomiting, when compared with placebo.[7] At present, studies to evaluate if gastrointestinal side effects could lead to treatment interruption are lacking.[62] Insomnia, dizziness, headache, decreased attention and paresthesia have also been reported in association with nalmefene use.[63]

Nalmefene is mostly metabolized in the liver to nalmephene 3-O-glucuronide by the UGT2B7 enzyme (mainly) and by the UGT1A3 and UGT1A8 enzymes.[64] CYP3A4 isoenzyme also partly converts nalmephene into 3-O-sulphate nalmefene and nornalmefene, which do not show any pharmacological effect.

No relevant pharmacokinetic interactions have been reported in clinical trials, but possible interactions with the potent UGT2B7 inhibitors, such as diclofenac and naproxene,[65] ketoconazole,[66] and low concentrations of amitriptyline,[67] cannot be excluded. Contrarily, the concomitant use of the UGT2B7 inducer, such as different chemotherapeutic agents[68] or dihydroartethmisine,[69] may result in a decrease of plasma drug concentrations to the sub-therapeutic ranges.

Topiramate

Topiramate is a derivative of D-fructose, a naturally occurring monosaccharide.[70] FDA has approved topiramate for the treatment of seizure disorder, migraine prevention, and chronic weight management (along with phentermine).[61] Although the FDA has not currently approved topiramate for the AUD therapy, this medication is also a useful option for the AUD treatment.[71] A randomized, double-blind, placebo-controlled trial revealed the anticraving properties of topiramate.[72] Similar to other drugs used for the alcohol addiction treatment, it is thought to reduce mesolimbic dopaminergic activity.[73]

The use of topiramate is associated with the common adverse effects, such as paresthesia, dysgeusia, anorexia, difficulty with concentration or attention, nervousness, dizziness, and pruritus.[74] The detailed analysis demonstrated that this medication causes the dose-related transient cognitive impairment including mental slowing and modest reductions in verbal fluency and working memory.[75]

Topiramate exerts effects through AMPA/kainate receptors containing the GluK1 and GluK2 subunits, which are encoded by genes GRIK1 and GRIK2, respectively.[76] Kranzler et al revealed that the efficacy of topiramate is modulated by the SNP *rs2832407* in *GRIK1*, the gene encoding the GluK1 receptor subunit.[77,78] This provided the basis for studies of *rs2832407* as a moderator of the response to topiramate. In addition, a previous pharmacogenetic analysis of the human laboratory pilot study[79] showed that *rs2832407* was associated with the severity of topiramate-induced side effects.[80] The randomized clinical trial by Kranzler et al have not found an effect of the SNP on adverse events, suggesting that the kainate receptor does not play a unique role in mediating topiramate-related adverse effects.[81]

Topiramate may be a potential substrate for cytochrome P450 (CYP) 2C9, a CYP3A4 inducer and a CYP2C19 weak inhibitor.[70] According to the package insert (Topina, Kyowa Hakko Kirin, Japan), this drug is chiefly metabolized by CYP3A4. Stiripentol is a potent inhibitor of CYP3A4, but interactions between topiramate and stiripentol have not been studied.[82]

Ondansetron

Ondansetron is a competitive serotonin 5-HT_3 receptor antagonist.[83] FDA has approved this medication for the prevention of nausea and vomiting caused by cancer chemotherapy, radiation therapy and surgery.[84]

The randomized controlled trial by Johnson et al demonstrated the efficacy of ondansetron in self-reported drinking reduction across the patients with the early-onset alcoholism.[85] In this trial, patients who received ondansetron at low dosages (1 and 4 μg) have been found to reduce alcohol consumption and have increased abstinence.[85] In the prospective, open-label study conducted by Kranzler et al, ondansetron given at

a dose of 4 μg twice per day decreased the number of drinks per day, drinks per drinking day and alcohol-related problems in the early-onset alcohol-dependent patients, but not in the late-onset ones.[86] However, according to the meta-analysis of seven trials performed by Torrens et al, selective serotonin reuptake inhibitors are not effective in the treatment of AUD in patients without comorbid depression.[87] Similarly, recent American Psychiatric Association (APA) practice guideline for the pharmacological treatment of patients with AUD do not recommend the use of any antidepressants unless the patient has a comorbid depression.[88]

Several studies demonstrated that genetic variations in the 5-HT transporter gene (*SLC6A4*) may modulate the severity of alcohol consumption and predict the treatment response to ondansetron.[89–91] Johnson et al identified three genotypes in the *HTR3A* and *HTR3B* genes that were significantly associated with the efficacy of ondansetron treatment for AUD in European patients and showed that polymorphisms in the *HTR3A-rs1150226-AG*, *HTR3A-rs1176713-GG*, and/or *HTR3B-rs17614942-AC* genotypes, along with the *SLC6A4-LL/TT* genotypes, are predictors of the reduced drinking in response to ondansetron.[90]

Table 1 includes the data from all studies with statistically significant associations between the individual drug response and genetic polymorphism.

Pharmacogenetics of alcohol withdrawal syndrome

Current researches strongly suggest that alcohol affects multiple neurotransmitter systems in the brain. It is well known that alcohol acts as a central nervous system (CNS) depressant since it enhances the activity of the major CNS inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), and antagonizes the activity of the major CNS excitatory neurotransmitter, glutamate.[92] When alcohol intake is abruptly reduced or discontinued, an overt hyperexcited state may follow. It manifests clinically by various symptoms and alcohol withdrawal syndrome (AWS) complications, ranging from mild tremor and anxiety to seizures, delirium tremens, and even death.[93] AWS symptoms occur in more than 50% of patients with alcohol-related problems who require pharmacological treatment.[94]

Benzodiazepines have been used for the AWS therapy for more than 50 years.[95] Benzodiazepines are effective due to the inhibitory GABA-signaling pathways stimulating, which is similar to the action of alcohol.[96,97] Hence, these medications decrease the symptoms of AWS and

Table 1 The statistically significant associations between the individual drug response and genetic polymorphism

Drug	Gene	Polymorphism	Brief Description of the Results	Reference
Disulfiram	*ANKK1*	*rs1800497*	Increase the efficacy of the therapy on patients with coccaine addiction. There is no data in patients with AUD.	16
Disulfiram	*DRD2*	*rs2283265*		
Naltrexone	*OPRM1*	*118A>G*	Greater efficacy of naltrexone among the carriers of this polymorphism	19, 25,26,27,28,29,30,31
Naltrexone	*OPRK1*	*rs997917*	Greater naltrexone-induced blunting of alcohol stimulation and craving	43
Naltrexone	*OPRD1*	*rs4654327*		
Acamprosate	*GATA4*	*rs13273672*	Decrease the duration of remission	53
Acamprosate	*GRIN2B*	*rs2058878*	Increase the duration of remission	56
Topiramate	*GRIK1*	*rs2832407*	Decrease the duration of remission	77,78,79,80
Ondansetron	*HTR3A*	*rs1150226, rs1176713*	Increase the efficacy of ondansetron (reduced drinking)	90
Ondansetron	*HTR3B*	*rs17614942*		
Diazepam	*CYP2C19*	*c.681G>A, c.636G>A*	Reduced clearance	108,109,110

shorten its course, along with the prevention of AWS-related seizures, delirium tremens, and death.[96–98]

There are currently 16 benzodiazepines licensed by the FDA. Diazepam was the second benzodiazepine to be used clinically (after chlordiazepoxide), after being approved for use in 1963.[99] Diazepam and desmethyldiazepam, its active metabolite, have the most extended elimination half-lives, meaning that the levels of these substances decrease in a gradual, self-tapering manner, resulting in a reduced incidence and severity rates of the breakthrough symptoms and rebound phenomena.[100] In the acute AWS, diazepam may provide symptomatic relief from agitation, tremor, delirium tremens, and hallucinations.

Benzodiazepines taken in toxic doses without other coingestants rarely cause a significant toxidrome.[101] The classic presentation of an isolated benzodiazepine overdose consists of CNS depression with normal vital signs. At the same time, severe and fatal adverse events due to diazepam use are sporadic and are usually associated with interaction with other substances (such as opiates or alcohol).[102] Chronic use of diazepam may result in tolerance, addiction and withdrawal syndrome.[103]

Diazepam is metabolized via CYP2C19 and CYP3A4 to desmethyldiazepam, which is found in the plasma at concentrations equivalent to diazepam. CYP2C9, CYP2B, and CYP3A5 are other isoenzymes involved in diazepam metabolism.[104] It is thought that the variability in the clearance of many benzodiazepines, including diazepam, is due to the variability in *CYP2C19* and *CYP3A4* genotypes.[104,105]

The *CYP2C19* gene is highly polymorphic, as 35 variant star (*) alleles are currently catalogued at the Human Cytochrome P450 (CYP) Allele Nomenclature Database.[99] The *CYP2C19*1* wild-type allele is associated with normal enzyme activity and the "normal metabolizer" phenotype, whereas the *CYP2C19*17* allele is associated with increased enzyme activity and the "ultrarapid metabolizer" phenotype, respectively.[106] *CYP2C19*2* is the most common loss-of-function variant, containing a *c.681G>A* variant in exon 5. It results in an aberrant splice site and the production of a truncated, non-functioning protein. It is reported that the *CYP2C19*2* allele frequencies are approximately 15% in Caucasians and Africans, and about 29–35% in Asians.[106,107] *CYP2C19*3* is another commonly tested loss-of-function variant, containing a *c.636G>A* variant in exon 4, which causes a premature stop codon. The *CYP2C19*3* allele frequencies are about 2–9% in Asian populations, but rare in other racial groups. Other loss-of-function variants include *CYP2C19*4-*8* and occur in less than 1% of the general population.[106,107] "Intermediate *CYP2C19* metabolizers" carry one copy of an allele encoding the reduced or absent function (eg, **1/*2*), while "poor metabolizers" are homozygous or compound heterozygous for two loss-of-function alleles (eg, **2/*2, *2/*3*).[99] Studies have found that "poor metabolizers" have a lower plasma clearance of diazepam compared to "normal metabolizers", and that diazepam had a longer plasma half-life in those individuals.[108–110] One study found that *CYP2C19* "poor metabolizers" took a longer period to emerge from general anesthesia than "normal" ones. This study also found that the "slow emergers" had lower levels of *CYP3A4* mRNA.[111] Despite the fact that *CYP3A4* isoenzyme is also involved in the metabolism of diazepam, clinical studies investigating the effect of *CYP3A4* and *CYP3A5* variants on benzodiazepine metabolism show the conflicting results.[112–115]

Conclusion

A review of the literature on pharmacogenetic biomarkers development for the pharmacotherapy personalization reveals that today the evidence base concerning these biomarkers is still insufficient. In particular, now the researches with the design of randomized controlled trials and meta-analysis investigating the effect of the SNPs as biomarkers on the therapy efficacy are available for naltrexone only. For other medications, there are only a few studies. These studies are conducted on small cohorts of patients; sometime the placebo and/or control arms are missing; the design of the pharmacological study is not properly described, or the dose of the medication is not specific; different genetic variants can impact the treatment response. It strongly reduces the possibilities to implement the pharmacogenetic algorithms for the pharmacotherapy personalization in patients with AUD.

Thus, we believe that the low interest in the results of research in the field of pharmacogenetics of addictions could be increased by the following ways:

- Improve a research design according to higher levels of evidence by the Oxford CEBM Levels of Evidence so that it'll be prospective, include the main group and the comparison group, and include blinding and randomization;
- Use the advanced research methods: next-generation sequencing, including Roche/454 Life Sciences, Illumina/Solexa, SOLiD and others;

- Develop meta-analyzes and systematic reviews, but this requires the results of more evidence-based research;
- Conducting pharmacoeconomic studies in the field of pharmacogenetics of addictions.

We would like to emphasize the importance of developing the pharmacogenetic decision support systems, which will allow implementing the results of research in the field of pharmacogenetics into clinical practice, resulting in the risk reduction of the adverse drug reactions and pharmacoresistance.

Disclosure

The authors report no conflicts of interest in this work.

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