Pharmacogenetics of alcohol use disorders and comorbid psychiatric disorders

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**ABSTRACT**

Alcohol use disorders (AUDs) represent a significant health burden worldwide. Currently, there are three medications approved by the U.S. Food and Drug Administration for the treatment of AUDs, and other drugs are being prescribed off-label for this purpose. However, response rates for pharmacologic treatment are low, and extant research suggests that treatment effects may partially depend on genetic factors. Personalized medicine, or using a patient’s genetics and/or personal history to determine efficacy of treatment prior to prescription, is an emerging tool that will help clinicians treat their patients more effectively and safely. This review systematically discusses current findings from AUD pharmacotherapy trials examining disulfiram, acamprosate, naltrexone, the injectable naltrexone, and topiramate. Furthermore, it presents pharmacogenetics findings associated with these medications in an attempt to further the field of personalized medicine. Research from trials examining AUDs and comorbid major depressive disorder and anxiety disorders is also presented, and pharmacogenetic findings for these treatments are discussed. Lastly, the authors comment on the present and future states of the field of personalized medicine for AUD.

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1. Introduction

In the United States, alcohol use disorders (AUDs) (alcohol abuse and dependence) have a lifetime prevalence of 30%
predict a patient tool that can identify and develop genetic biomarkers that can side effect pro
million for the clinicians in creating personalized treatment plans for each of the treatment of alcoholism: disul
nritic, behavioral, or pharmacological interventions, oftentimes resulting in combinations. Currently, there are three oral medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcoholism: disulfiram, acamprosate and naltrexone. An injectable version of naltrexone is also approved by the FDA for the treatment of alcohol dependence. In addition, there are other drugs such as topiramate (discussed below), ondansetron, baclofen, gabapentin and varenicline that are currently being prescribed off-label to treat alcohol dependence; however, it should be noted that these drugs are not FDA approved to treat alcohol dependence. With the exception of topiramate (Blodgett et al., 2014), none of these medications systematically exhibit superior treatment response compared to placebo (Anton et al., 2014; Muller et al., 2014). In fact, reviews of placebo-control trials of naltrexone and acamprosate, arguably two of the most efficacious pharmacotherapies, show that roughly 40–70% of individuals taking either of these medications fail to respond positively (Rosner et al., 2010a, 2010b; Srisurapanont and Jarusuraisin, 2005). Furthermore, response is heterogeneous; individual patients can exhibit divergent treatment responses and side effects for the same drug, and even at the same dose, with some patients responding favorably to one treatment but not another. Multiple factors influence drug response rates, including clinical, environmental and social factors, as well as genetic factors.

2. Pharmacogenetics

Pharmacogenetics involves the investigation of how genetic variation can influence the pharmacokinetic and pharmacodynamic processes of a given drug. Pharmacokinetics refers to the absorption, distribution, metabolism and excretion of a drug. Pharmacodynamic studies focus on the effects of the drug on the body, such as how drugs interact with receptors, transporters and downstream targets. Understanding these processes, particularly from a genetic basis, would allow clinicians to utilize a medication with greater certainty of effectiveness by allowing them to predict a patient’s optimal therapeutic response to a particular drug based on his or her unique genetic makeup.

Although there is strong evidence for a genetic role in alcohol dependence, with heritability estimates between 50% and 60% (Heath et al., 1997; Prescott and Kendler, 1999; Sullivan et al., 2012), it remains unclear to what degree genetic variation influences individual differences in treatment response (Anton et al., 2014). However, similar to the complex phenotype of AUD for which a multitude of genes might play a role (Goldman et al., 2005), “drug response” can also be considered a complex phenotype, with likely multiple genes contributing to the efficacy and side effect profile of a given drug (Weinshilboum, 2003).

Nevertheless, the promise of pharmacogenetics as a prognostic tool that can identify and develop genetic biomarkers that can predict a patient’s therapeutic response and risk of side effects has gained recent attention. Recently, President Obama requested $215 million for the “Precision Medicine Initiative,” a plan to assist clinicians in creating personalized treatment plans for each of their patients. While other fields, such as oncology and diabetes, are currently spearheading this innovative direction of personalized medicine, several attempts have also been made for the pharmacotherapy of AUD.

In this review we discuss recent, clinically relevant findings pertaining to the utilization and pharmacogenetics of the three FDA-approved oral medications for the treatment of alcohol dependence. We also include a discussion of the utility of the injectable naltrexone, as well as the non-FDA approved drug topiramate. We additionally summarize the current pharmacotherapies and pharmacogenetics of comorbid AUD/MDD and AUD/anxiety disorders. Lastly, we discuss both the current state and future of the field of personalized medicine, citing its implications and where we believe the field should go.

3. Disulfiram

Although disulfiram was approved by the FDA in 1951 for the treatment of alcohol dependence (De Sousa, 2010), it is not often prescribed clinically (Swift, 1999), and up to 80% of patients discontinue disulfiram treatment (Fuller et al., 1986). Disulfiram causes “acetaldelyde syndrome” via inhibiting the aldehyde-dehydrogenase enzyme and increasing the presence of acetaldehyde in the body. When consumed with alcohol, it can produce the side effects of flushing, rash, tachycardia, hypertension, headaches, nausea, vomiting, and diarrhea. These symptoms typically begin around 5–15 min after alcohol consumption and subside anywhere from 30 min to a couple of hours after alcohol intake has stopped (Caputo et al., 2014).

Findings pertaining to the clinical effectiveness of disulfiram compared to other pharmacotherapy interventions or placebo have been inconsistent. A recent meta-analysis looking at the efficacy of disulfiram reported that in open-label drug trials, disulfiram showed superior efficacy over any other control group (Skinner et al., 2014). However, this effect was not seen in blinded trials. Importantly, the authors reported that in the double-blind placebo-control trials included in their meta-analysis, there was no benefit of prescribing disulfiram for alcohol relapse prevention. In fact, patients prescribed disulfiram reported significantly more adverse events than controls (Skinner et al., 2014). According to Krampe and Ehrenreich (2010), the mechanism behind disulfiram’s reported effectiveness comes from the psychological effect of taking this medication; when alcohol-dependent patients know the physiological effects of consuming alcohol while taking this drug, the efficacy of disulfiram is greater than when the risks of the drug are not explained.

3.1. Pharmacogenetics of disulfiram

Because of disulfiram’s limited clinical utility, few studies examining the moderating effects of genetic variation on treatment response have been conducted. However, due to evidence that disulfiram inhibits the dopamine-beta-hydroxylase (DBH) enzyme, an enzyme implicated in alcohol dependence (Kohnke et al., 2002), Mutschler et al. (2012) investigated genetic variation in the DBH gene and response to disulfiram. Specifically, they examined the single nucleotide polymorphism (SNP) rs1611115 (C-1021T) in the DBH gene, a SNP that is functionally related to DBH activity (Kohnke et al., 2002). Their study included 66 participants recruited from a specialized disulfiram outpatient clinic. They found no association between genotype and disulfiram treatment response in their sample. However, they did demonstrate that T-allele carriers had an increased risk of adverse events when taking disulfiram (Mutschler et al., 2012). In summary, due to the dearth of pharmacogenetic studies examining disulfiram, changing clinical prescribing patterns of this drug based on individuals’ genotypes is unjustified. Instead, decisions to prescribe disulfiram...
should be based on clinical features of patients, and side effects should be monitored closely. Furthermore, potential side effects of consuming alcohol while taking this drug should be thoroughly explained to all patients considering disulfiram as a treatment.

4. Acamprosate

Acamprosate was approved by the FDA in 2004 to treat alcohol dependence through preventing relapse and promoting abstinence. Clinically, it appears to have utility for patients seeking to remain abstinent as opposed to reducing their drinking levels (Bouza et al., 2004). Although the exact mechanisms of action behind this drug are not completely understood, it is believed to exert antagonistic effects on N-methyl-D-aspartic acid (NMDA) receptors while indirectly affecting γ-aminobutyric acid type A (GABA<sub>A</sub>) transmission (Kalk and Lingford-Hughes, 2014). Side effects of this drug typically include diarrhea, dizziness, and headaches (Caputo et al., 2014).

The first U.S. study examining the efficacy of acamprosate initially reported that the percentage of days abstinent from alcohol was not significantly different between acamprosate-treated alcohol-dependent patients and patients receiving placebo. However, a secondary analysis of this study showed that acamprosate was more effective than placebo in patients who had an initial goal of abstinence (Mason et al., 2006). A 2008 report on the efficacy of acamprosate examined results from three European double-blind placebo-control trials and found that complete abstinence from alcohol was significantly higher in alcohol-dependent patients treated with acamprosate than patients treated with placebo. Furthermore, those taking acamprosate reported a longer time to first drink than those receiving placebo (Kranzler and Gage, 2008). A 2010 meta-analysis looked at 17 clinical trials and determined that acamprosate was significantly associated with continuous abstinence compared with placebo. Furthermore, they determined that this drug was also safe and effective in reducing risk of drinking following detoxification in alcohol-dependent individuals (Rosner et al., 2010a). More recently, a 2013 meta-analysis comparing naltrexone and acamprosate examined when these medications were most beneficial and what outcome measures were impacted. Acamprosate was shown to be more efficacious than naltrexone in maintaining abstinence. Additionally, acamprosate demonstrated larger effect sizes than placebo on measures of abstinence in individuals who were detoxified prior to medication administration (Maisel et al., 2013).

Despite these positive findings of the efficacy of acamprosate, some studies have not reported a beneficial treatment response. The COMBINE study (discussed below) compared treatment response to naltrexone, acamprosate, placebo, behavioral therapies, or a combination of therapies in individuals with alcohol dependence. Their findings did not support the efficacy of acamprosate in the treatment of alcohol dependence (Anton et al., 2006). Additionally, an Australian double-blind placebo-control study by Morley et al. (2006) failed to find a significant effect of acamprosate on time to first drink, time to relapse, and continued abstinence.

4.1. Pharmacogenetics of acamprosate

Recently, various studies have shown an association between the intronic SNP rs13273672 in the GATA4 gene, a gene located on chromosome 8, and alcohol dependence (Edenberg et al., 2010; Treutlein et al., 2009), although other studies did not confirm this association (Karpuyk et al., 2014b). GATA4 encodes GATA4 binding protein type 4, a transcription factor that regulates the expression of atrial natriuretic peptide (ANP) (McBride and Nemer, 2001). It has been suggested that reduced ANP expression in the central nervous system is associated with the dysregulation of stress and anxiety mechanisms in the brain, a possible link between ANP and alcohol dependence (Jorde et al., 2014). In a randomized, double-blind placebo-control study, Kiefer et al. (2011) showed that alcohol-dependent individuals with the rs13273672 G allele were more likely to have decreased time to relapse following acamprosate treatment than alcohol-dependent individuals with the AA genotype. This genetic effect was not seen in patients treated with naltrexone or placebo.

Length of abstinence following treatment with acamprosate has also been demonstrated to be associated with genetic variants in GRIN2B, the gene that encodes the GluN2B subunit of NMDA receptors (Karpuyk et al., 2014a). In the discovery sample of this study, 225 alcohol-dependent participants were administered acamprosate for three months in an open label trial. To replicate the initial findings, a replication sample of 110 alcohol-dependent men treated with acamprosate from the PREDICT study was used (Mann et al., 2009). Genetic analyses from the discovery sample showed that the minor allele (A) of SNP rs2058878 in GRIN2B was associated with a longer period of abstinence. Interestingly, in the replication sample, this association was marginally significant. Additionally, the minor allele (G) of rs2300272, a SNP in high linkage disequilibrium with rs2058878, was found to be significantly associated with a shorter abstinence period in the independent replication sample. Although these findings implicate a relationship between genetic variation in GRIN2B and response to acamprosate, it should be noted that interpretations of these data are limited due to the fact that this study did not use a placebo arm (Karpuyk et al., 2014a).

Thus, data suggest that acamprosate could be clinically effective for patients who have an initial desire to remain abstinent. Acamprosate treatment efficacy may be partially moderated by genetic variation of SNP rs13273672 in GATA4 or SNPs rs2058878 and rs2300272 in GRIN2B.

5. Naltrexone

The FDA approved naltrexone in 1994 for the treatment of alcohol dependence following independent studies showing that it reduced craving and relapse rates in alcoholics (O’Malley et al., 1992; Volpicelli et al., 1992). Naltrexone is a mu opioid receptor antagonist that reduces alcohol’s reinforcing and rewarding effects while simultaneously reducing the craving associated with environmental cues (Anton et al., 2014). One of the most influential studies showing the efficacy of naltrexone for the treatment of alcohol dependence was the COMBINE study, a multisite randomized clinical trial funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (Anton et al., 2006). This trial demonstrated that subjects with alcohol dependence administered daily oral naltrexone were more likely to have a higher percentage of days abstinent from alcohol and a longer time to first heavy drinking episode than patients treated with behavioral therapies, placebo, acamprosate, or a combination of therapies. Interestingly, receiving daily naltrexone plus daily acamprosate did not result in an increased treatment benefit over taking naltrexone alone (Anton et al., 2006). The Maisel et al. (2013) meta-analyses comparing naltrexone and acamprosate showed naltrexone to be more efficacious than acamprosate in reducing heavy drinking and craving. Furthermore, in trials mandating abstinence before the trial start date, naltrexone was demonstrated to exhibit larger effect sizes than placebo for maintenance of abstinence and reduction of heavy drinking.

Although various studies have established the efficacy of naltrexone, other studies have reported negative findings (Chick et al., 2008).
Similarly, another study showed that heavy drinkers demonstrated that Asp40-allele carriers treated with naltrexone placebo group (Anton et al., 2008). Recently, Kranzler et al. (2013a) naltrexone-treated individuals with the Asn40Asn variant or either who received naltrexone had a lower percentage of heavy drinking in the study, it was also shown that individuals with the Asp40 allele for personal use only. No other uses without permission. Copyright ©2017. Elsevier Inc. All rights reserved.
due to the infrequency of injections (only once a month), it offers a
greater chance of increasing compliance among this population,
ultimately increasing the beneficial treatment response. However,
with this injection, injection-site related side effects, such as ne-
crosis, infection, or inflammation, can occur, and the drug is con-
traindicated in individuals who take opioid analgesics (Johnson,
2007).

An initial randomized double-blind placebo-control study by
Johnson et al. (2004) reported that the injectable naltrexone was
more efficacious than placebo in decreasing percentage of heavy
drinking days among alcohol-dependent individuals. However, both
groups demonstrated a decrease in heavy drinking during the
study, but it should be noted that the study consisted of an un-
balanced cell design, with 25 individuals receiving a naltrexone
injection and only 5 receiving placebo. Additionally, this study
showed that the injectable naltrexone was well-tolerated, and side
effects included headaches, injection-site pain, nausea, and ab-
domininal pain. A subsequent, highly influential study by Garbutt
et al. (2005) looked at treatment response to injectable naltrexone
among alcohol-dependent individuals over a six-month period. In
this study, participants were divided into four groups: 380 mg of
long-acting naltrexone injection, 190 mg of long-acting naltrexone
injection, and matching-volume placebo injections. All injections
were given monthly. According to this study, the long-acting nal-
trexone reduced heavy drinking compared to placebo, and the
380 mg dose offered a significant reduction in heavy drinking over
placebo. However, adverse events, including nausea, injection-site
pain, fatigue, dizziness, and decreased appetite, were reported
more in the high-dose naltrexone group compared to the low-dose
naltrexone group and both placebo groups. Despite these effects,
the medication was well-tolerated. Interestingly, a gender analysis
showed that in the high-dose naltrexone group, only men ex-
perienced a decrease in drinking; women in the high-dose group
actually reported an increase in drinking.

A follow-up analysis of the Garbutt et al. (2005) study revealed
additional findings pertaining to the efficacy of the injectable naltrexone
(O’Malley et al., 2007). For individuals who reported four
days or greater of abstinence prior to treatment, the high-
dose naltrexone was significantly associated with more patients
who sustained complete abstinence for the entirety of the trial
compared to placebo. Additionally, high-dose naltrexone patients
significantly reported an increased time to first drink and first
heavy drinking episode and a lower number of drinking days and
heavy drinking days per month compared to individuals receiving
placebo.

Clinically, the injectable naltrexone appears to be well-toler-
ated, easy to administer, more likely to increase compliance in
patients, and efficacious for men. Additionally, injectable naltrex-
one is ideal for individuals who are already prescribed other oral
medications, as an injection would reduce the number of pills
taken (Johnson, 2006, 2007).

6.1. Pharmacogenetics of injectable naltrexone

There are currently no pharmacogenetic studies of injectable
naltrexone.

7. Topiramate

Although topiramate is not currently FDA-approved for the
treatment of alcohol dependence, it is sometimes prescribed off-
label for this purpose. It is an anticonvulsant medication (Arbazi
et al., 2010) that increases the transmission of gamma-aminobu-
tyric acid (GABA) and inhibits transmission of glutamate (Shinn
and Greenfield, 2010). Although it is prescribed clinically, an
estimated 20% of patients taking topiramate have dropped out of
alcoholism-related clinical trials of this drug due to its side effects
(Johnson et al., 2007).

Various studies have demonstrated the efficacy of topiramate
over placebo for the treatment of alcoholism. A 12-week ran-
mized double-blind placebo-control study by Johnson et al. (2003)
showed that topiramate-treated alcohol-dependent individuals
reduced drinks per day on average, reduced drinks per drinking
day on average, and decreased the percentage of heavy drinking
days compared to individuals receiving placebo. However, com-
monly reported side effects of topiramate included dizziness,
paresthesia, weight loss, concentration and memory difficulties,
and psychomotor slowing. A subsequent 14-week randomized
double-blind placebo-control study of topiramate demonstrated
that alcohol-dependent patients receiving the drug were sig-
ificantly more likely to have a decreased percentage of heavy
drinking days than the placebo group. The topiramate group ad-
ditionally reported more days abstinent from alcohol and fewer
drinks per drinking day compared to the placebo group. However,
individuals receiving topiramate had significantly greater reports
of the following side effects: paresthesia, taste perversion, anor-
exia, difficulty with concentration/attention, nervousness, dizzii-
ness, and pruritus (Johnson et al., 2007). A recent, comprehensive
meta-analysis of seven placebo-control clinical trials showed that
topiramate is significantly better than placebo in both decreasing
aggregate measures of heavy drinking days and increasing ag-
gregate measures of abstinence for alcohol-dependent patients.
However, the overall effect of this drug is moderate. Surprisingly,
this meta-analyses further showed that on measures of abstinence,
heavy drinking, and craving, topiramate demonstrated larger ef-
fect sizes than both naltrexone and acamprosate, suggesting fur-
ther studies into the efficacy of topiramate are warranted (Blodgett
et al., 2014). Conversely, a study by De Sousa et al. (2008) de-
monstrated that disulfiram is more efficacious than topiramate at
preventing relapse and increasing time to first relapse in alcohol-
dependent participants, but only in an open-label trial.

7.1. Pharmacogenetics of topiramate

Pharmacogenetic studies of topiramate have focused on an
intronic SNP (rs2832407) in the GRIK1 gene due to previous data
demonstrating an association between GRIK1 and alcohol depen-
dence (Kranzler et al., 2009a). GRIK1 encodes GluK1, a glutamate
receptor, and it has been shown that receptors with this particular
subunit bind topiramate (Kranzler et al., 2009a). A placebo-control
12-week study of 138 heavy drinkers demonstrated that topir-
amate was significantly associated with a decrease in heavy
drinking days and an increase in days abstinent from alcohol
compared to placebo. Among European Americans (N = 122 sub-
sample), only the topiramate-treated individuals who were C-al-
lele homozygous for SNP rs2832407 showed a significant decrease
in heavy drinking days relative to placebo (Kranzler et al., 2014b).
A validation and extension study of these findings further de-
monstrated the association between genetic variation in the GRIK1
gene and topiramate response. Kranzler et al. (2014a) not only
confirmed their initial findings but also showed that rs2832407C
homozygote individuals treated with topiramate reported a de-
crease in positive alcohol expectancies and desire to drink, an
effect that was not seen in A-allele individuals.

An interesting study by Ray et al. (2009) in non-treatment
seeking heavy drinkers examined the effect of genotype on se-
verity of side effects. They showed a significant interaction be-
tween genetic variation of SNP rs2832407 and medication such
that A-allele individuals treated with topiramate reported higher
side-effect severity in comparison to participants with the CC
genotype receiving topiramate.
In summary, topiramate is currently not FDA approved for the treatment of alcohol dependence; however, there is evidence that topiramate is more efficacious than placebo in treating alcohol dependence, and one meta-analyses has demonstrated that it has larger effect sizes than both naltrexone and acamprosate. Side effects can be troublesome and are more likely to occur with this drug than with placebo. Furthermore, C-allele homozygous individuals for SNP rs2832407 in GRIK1 are not only more likely to respond beneficially to topiramate than their A-allele counterparts, but also experience a lower rate of side effects when receiving topiramate. These findings suggest that this SNP moderates treatment efficacy of topiramate. Clinically, given previous data and the fact that topiramate is not FDA approved, if prescribed physicians should proceed cautiously and closely monitor potential side effects.

8. Pharmacogenetics of comorbid AUD and psychiatric disorders

In addition to AUD being a complex disorder, it is highly comorbid with other complex psychiatric disorders, such as major depressive disorder (MDD) and anxiety disorders (Buckley and Brown, 2006; Grant and Harford, 1995; Jane-Llopis and Matysins, 2006). For example, Martins and Gorelick (2011) showed that a diagnosis of MDD or an anxiety disorder increases the probability of developing a diagnosis of alcohol dependence. It is believed that there are common biological and/or genetic underlying factors that associate MDD and anxiety disorders with substance dependence, and that this underlying vulnerability explains the high rates of co-occurrence among these disorders. Determining the genetic factors associated with a comorbid diagnosis of AUD/MDD and AUD/anxiety disorders is critical for the development of pharmacotherapy interventions that address both diagnoses and provide better treatment outcomes.

8.1. Pharmacogenetics of AUD and comorbid MDD

Approximately one-third of alcohol-dependent individuals exhibit depressive symptoms (Bradizza et al., 2006). Although selective serotonin reuptake inhibitors (SSRIs) are widely prescribed for the treatment of depression, clinical trials examining the efficacy of SSRIs in treating comorbid alcohol dependence and depression have shown few promising results, and there are few pharmacogenetic studies of these drugs. One example is sertraline, an approved SRI medication for the treatment of depression. A 12-week randomized placebo-control trial demonstrated that in currently depressed alcohol-dependent patients, sertraline treatment was associated with individuals consuming fewer drinks per drinking day than individuals receiving placebo. However, there was no difference in other drinking measures between the two groups. Interestingly, female participants receiving sertraline reported less depressive symptoms than female participants taking placebo (Moak et al., 2003). A later study by Kranzler et al. (2006) reported no significant difference in either placebo or sertraline group measures of depression and alcohol dependence, with both groups showing a decrease in depression symptoms and alcohol consumption.

In contrast to SSRI monotherapy for the treatment of co-occurring alcohol dependence and depression, a combination treatment of sertraline and naltrexone may provide more treatment benefits. A study of 170 individuals with comorbid alcohol and alcohol dependence randomly assigned individuals into either a sertraline alone, naltrexone alone, naltrexone+sertraline, or a double placebo condition. The combination treatment group showed an increased rate of abstinence from alcohol and an increase in time to relapse to heavy drinking compared to other treatment groups. Furthermore, this group showed less depressive symptoms than other groups, as well as reporting fewer adverse events (Pettinati et al., 2010).

The pharmacogenetics of comorbid AUDs and MDD has not been studied extensively. One study by Su et al. (2011) examined the association between genetic variation in the BDNF gene and alcohol dependence-related depression. The BDNF gene encodes BDNF, or brain-derived neurotrophic factor, a growth factor in the brain whose concentration is changed by alcohol. Genetic variation at SNP rs6265 in BDNF was correlated with alcohol dependence-related depression, with higher rates of the A allele being seen in depressed alcoholics versus non-depressed alcoholics. Furthermore, A-allele individuals had higher rates of remission following treatment with sertraline.

For the practitioner, there is evidence to suggest that combination (naltrexone+sertraline) pharmacotherapy is more promising for the treatment of co-occurring AUD and MDD than simply prescribing sertraline alone. However, female patients may see a reduction in symptoms while taking only sertraline. Genetic variation of SNP rs6265 may moderate medication response to sertraline in depressed alcoholics, but further studies are needed to validate these findings.

8.2. Pharmacogenetics of AUD and comorbid anxiety disorders

Alcoholism and anxiety disorders are also highly comorbid. Despite this high comorbidity, however, there is currently limited pharmacogenetics data available. Comorbid anxiety disorders, including generalized anxiety disorder (GAD), panic disorder (PD), social phobia, specific phobia, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD), occur in approximately 5–30% of AUD patients. Conversely, among anxiety disorder patients, the prevalence of AUD ranges from 7% to 10%, with approximately 50% of patients using alcohol to self-medicate their anxiety symptoms (Vorspan et al., 2015). Additionally, a current diagnosis of an anxiety disorder is predictive of converting from alcohol abuse to alcohol dependence within a 10 year span, and a diagnosis of alcohol dependence is predictive of generalized anxiety disorder (GAD), social phobia (SP), and panic disorder (PD) occurring (Vorspan et al., 2015). To complicate matters further, benzodiazepines, medications often prescribed for the treatment of anxiety disorders, should not be prescribed for alcoholics; these drugs negatively interact with alcohol in the body, and they are associated with a risk of developing dependence (Anton et al., 2014). As a result, SSRIs have been studied as a pharmacotherapy alternative for treating co-occurring alcoholism and anxiety.

A few studies have examined pharmacotherapy for comorbid AUD and PTSD. One randomized, placebo-control study showed that sertraline-treated individuals comorbid for alcohol dependence and PTSD reported a significant reduction in drinks per drinking day relative to placebo, but only if they had early-onset PTSD and less severe alcohol dependence. Alternatively, placebo-treated individuals with more severe alcohol dependence and later-onset PTSD reported significantly fewer drinks per drinking day and a lower average number of alcoholic beverages drank per day. It thus may be that sertraline provides beneficial treatment for a subset of PTSD/alcohol dependent individuals (Brady et al., 2005). A later study into comorbid AUD/PTSD in veterans compared the efficacy of paroxetine (SSRI) to that of desipramine (norepinephrine uptake inhibitor) in combination with naltrexone or placebo. Participants were divided into four groups: paroxetine + naltrexone, paroxetine + placebo, desipramine + naltrexone, and desipramine + placebo. Paroxetine was not significantly more efficacious than desipramine in reducing PTSD symptoms, but desipramine was associated with reduced alcohol consumption.
compared to paroxetine. Interestingly, naltrexone was not associated with reduced drinking outcomes, although it did reduce craving compared to placebo (Petrakis et al., 2012).

Studies have also looked at comorbid social anxiety and AUD. One double-blind placebo-control clinical trial examined the efficacy of paroxetine for the treatment of these co-occurring disorders. In this study, paroxetine was significantly more efficacious than placebo at reducing anxiety symptoms (Book et al., 2008), but there was no significant difference between the two treatments on number of drinks consumed or frequency of drinking (Thomas et al., 2008).

A study by Tolleson et al. (1992) examined comorbid AUDs and GAD. In this randomized, double-blind placebo-control trial, they determined that buspirone, a serotonin partial agonist, was superior to placebo in reducing anxiety symptoms and the number of days the participants reported a desire to drink alcohol.

One of the most widely studied genes in pharmacogenetic studies of antidepressant drugs is the serotonin transporter gene (SLC6A4) (Helton and Lohoff, 2015). One polymorphism in the promoter region of the gene (5-HT transporter gene linked polymorphic region: 5-HTTLPR) includes an insertion or deletion of a repetitive sequence, producing a short allele (S) or a long (L) allele (Lesch et al., 1996). The long version of this 5-HTTLPR has been shown to affect transporter function, resulting in higher serotonin reuptake by the transporter (Lesch et al., 1996). There is also an A/G SNP (rs25531) in the 5-HTTLPR tightly linked to the L allele producing in effect a tri-allelic genotype (La, Lg, and S) (Perroud et al., 2010). The Lg allele is similar in functionality to the S allele (Hu et al., 2007).

In a placebo-control trial of sertraline by Kranzler et al. (Kranzler et al., 2011), it was shown that age of onset of alcohol dependence and genetic variation of 5-HTTLPR had moderating effects on sertraline efficacy. In a follow-up analysis, they examined the moderating effect of evening negative mood on nighttime consumption of alcohol. Their study demonstrated that placebo-treated individuals who were early onset alcoholics and homozygous for the La allele reported less nighttime drinking after experiencing an increased level of anxiety during the day, implicating the moderating role of anxiety in pharmacogenetic outcomes (Kranzler et al., 2013b).

Clinically, a single drug that offers beneficial treatment response for co-occurring AUD and anxiety disorders does not currently exist. Although SSRIs have been studied for the treatment of these comorbid disorders, studies report conflicting results, with some studies reporting a decrease in anxiety symptoms and no change in alcohol outcomes or the reverse. Although there seems to be some genetic moderation of variation in 5-HTTLPR on SSRI efficacy in anxious alcoholics, at this time these findings have not been replicated and offer little clinical utility.

In light of the high rates of co-occurrence between AUD, MDD, and anxiety disorders, it becomes even more critical to not only find medications that can safely and effectively treat one or both disorders, but also determine prior to prescription who will beneficially respond to which medication.

9. Discussion

Although the field has made some progress in understanding and treating AUDs over the past few decades, limited data exist for the use of genetic and/or biomarker information to guide the prescribing clinician. One of the main obstacles in the development of effective pharmacotherapies for AUD is not only the limited number of novel compounds, but also the lack of standardized trial designs and outcome measures. As it stands currently, some studies determine treatment efficacy by the successful attainment of complete abstinence, while others report significant results if participants have simply reduced their total number of drinks per day from baseline. Recently, in an effort to direct future pharmacotherapy trials for the treatment of AUDs, the FDA released a draft of a guidance for industry entitled “Alcoholism: Developing Drugs for Treatment” (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation). According to the FDA, the goal of treatment is to permanently reduce the adverse physical and psychosocial effects of alcohol-related behavior, essentially a harm-reduction approach. However, long-term behavior modification is difficult to assess during a short randomized clinical trial. Therefore, drug trials should be designed in a way that demonstrates a current modification in drinking habits that will indicate future patterns that are healthier and safer. In light of this guidance, trials should allow a grace period for individuals to attain abstinence or reduce their drinking to below heavy drinking levels. A treatment could then be deemed efficacious if these individuals sustain these healthier drinking patterns for a minimum of 6 months as a result of this intervention. Ideally, standardizing outcome measures in this way will generate more consistent results pertaining to the efficacy of a given pharmacological intervention.

Another significant obstacle in treating AUDs is the lack of development of safe and effective novel compounds specifically for use in alcoholism. While efforts have been made to examine non-FDA approved compounds, such as topiramate, ondansetron, baclofen, gabapentin and varenicline, to our knowledge no a-priori drug discovery efforts based on the distinct underlying neurobiology of AUDs exist. Although research into the efficacy of off-label medications does hold some promise, it is not enough. The failure to develop new medications ultimately limits the use of the innovative strategies associated with personalized medicine, potentially slowing progress in treating and understanding AUDs.

Lastly, for research into the pharmacogenetics of AUDs to advance, prospective analyses, not retrospective analyses, should be conducted. This issue is highly salient in light of the recent attempt by Oslin et al. (2015) to show an effect of the OPRM1 variant Asp40Asp on treatment response to naltrexone. Previous retrospective pharmacogenetic analyses of this SNP have robustly demonstrated that the Asp40 allele was predictive of reduced relapse rates and lower drinking rates in alcohol-dependent individuals treated with naltrexone compared to the Asn40Asn group (Anton, 2008; Chen et al., 2013; Kranzler et al., 2013a; Oslin et al., 2003). However, Oslin et al. (2015) failed to find a significant genotype × treatment interaction in their sample, suggesting that “it is premature to use the Asn40Asp polymorphism as a biomarker to predict the response to naltrexone treatment of alcohol dependence” (Oslin et al., 2015). Thus, despite previous findings, there is currently limited clinical justification for physicians’ ordering of genotyping tests to predict naltrexone treatment response, although in the future this will ultimately be the ideal.

9.1. Future directions of personalized medicine in AUDs

Prospective pharmacogenetic studies of AUD should include the following elements. First, they should use the standardized set of outcome measures as advised by the FDA to evaluate the efficacy of treatment response. Much of the current controversy in assessing positive or negative findings derives from discrepant drinking measures between studies. Prospective studies therefore need to focus on consistently defining behavior-based outcome measures that will longitudinally reduce the negative consequences of drinking outside of a short-term trial. Second, trial designs should include a standardized assessment schedule for the assessment of all patients. This standardization will not only aid clinical management of patients, but also offer a more consistent method for reporting adverse side effects to medications. An additional problem with current pharmacogenetic studies is lack of
power, and future studies should use adequate sample sizes in order not to be underpowered. With larger sample sizes, it will be possible to control for population stratification, a further concern with current studies. Lastly, there should be standardized minimum gene coverage, and gene-x-environment interactions should be evaluated to strengthen potential genetic findings. Ultimately, large prospective clinical trials will be the ideal, but they must not demonstrate the same lack of standardization currently seen in the field of pharmacogenetics.

In summary, pharmacogenetics of the treatment of AUDs is a rapidly developing field that deserves greater attention in both future research and clinical practice. Consistently implementing the practices associated with personalized medicine would produce more beneficial treatment responses and minimal side effects for all individuals, potentially reducing the prominence and consequences of AUDs nationally and globally.

References
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