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Personalized Treatment of Alcohol Dependence

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Abstract

Pharmacogenetic and adaptive treatment approaches can be used to personalize care for alcohol-dependent patients. Preliminary evidence shows that variation in the gene encoding the μ-opioid receptor moderates the response to naltrexone when used to treat alcohol dependence. Studies have also shown moderating effects of variation in the gene encoding the serotonin transporter on response to serotonergic treatment of alcohol dependence. Adaptive algorithms that modify alcohol treatment based on patients' progress have also shown promise. Initial response to outpatient treatment appears to be a particularly important in the selection of optimal continuing care interventions. In addition, stepped-care algorithms can reduce the cost and burden of treatment while maintaining good outcomes. Finally, matching treatment to specific problems present at intake or that emerge during treatment can also improve outcomes. Although all of these effects require replication and further refinement, the future of personalized care for alcohol dependence appears bright.

Keywords

Substance use; Alcohol dependence; Pharmacogenetics; OPRM1; Asn40Asp; A118G; Naltrexone; Nalmefene; Genetic moderation; 5-HTTLPR; Ondansetron; Sertraline; Adaptive trial designs; Adaptive protocol; Stepped care; Treatment algorithm

Introduction

Traditionally, diagnostic tests and medical treatments have been developed and evaluated using group data, a "one-size fits all" approach that leaves little room for individual variation [1]. Personalized medicine, which uses individual features to diagnose and treat disease, is of growing interest, having produced notable successes in oncology and cardiology [2•, 3]. To date, there have been fewer advances in the personalized diagnosis and treatment of

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addictive disorders. However, ongoing developments in genetics and pharmacogenetics and in the use of adaptive trial designs offer great potential to extend these advances to the treatment of addiction, including alcohol dependence, the focus of this review [4–6].

Studies of adaptive trial designs have examined their utility in personalizing both pharmacological and behavioral therapies. In these studies, randomization is used at one or more points to determine the optimal treatment modifications for patients who are not responding adequately to the treatment they are receiving at that point [7]. The goal of adaptive trials is to develop algorithms for evidence-based treatment protocols to ensure the greatest likelihood of turning non-responders into responders. Thus, the growing use of adaptive study designs is highly relevant to personalized alcohol dependence treatment.

Adaptive treatment models, which specify when and how treatment should be modified for non-responders, can be generated by adaptive trials. However, adaptive treatments may also be developed by a consideration of research-based practice guidelines and the work of consensus panels [8•]. These models, which have also been referred to as “stepped care,” “dynamic treatment regimes,” “tailored interventions,” and “treatment algorithms,” are designed to improve outcomes by providing flexible care that is adjusted over time on the basis of patient response to treatment, according to clearly operationalized, empirically-derived decision rules [7, 8•, 9].

Adaptive research trials and adaptive treatment protocols are relatively new. Most of the analytic and evaluative methods in this area come from prevention studies, cancer screening, and studies of hypertension, depression, and opioid addiction treatments [9–13].

Pharmacogenetics of Alcohol Dependence Treatment

Although there is a growing literature on genetic risk factors for alcohol dependence [14], we will focus on studies of genetic moderators of the pharmacotherapy of alcohol dependence. Here we extend a prior review [15] and focus on the genes encoding the μ-opioid receptor and the serotonin transporter, the best studied genetic moderators of alcohol dependence treatment.

The Opioidergic System

Three types of opioid receptors μ, κ, and δ, bind opioid peptides to produce their biological effects [16]. The human genes encoding the μ-opioid receptor (MOR; locus name *OPRM1),* the δ opioid receptor (*OPRD1),* and the κ-opioid receptor (*OPRK1)* are all expressed in the brain. Effects at the μ-opioid receptor mediate the effects of many opioid agonists [17].

The most widely studied genetic moderator of alcohol treatment response is a variant identified in exon 1 of *OPRM1* [18]. This common single nucleotide polymorphism (SNP), A118G, encodes an amino acid substitution (Asn40Asp) in the extracellular domain of the receptor. The frequency of the Asp40 (118G) allele varies widely by population, with the lowest frequency in African-Americans (<5 %), an intermediate frequency in those of European ancestry (2.5 %201315.5 %), and the highest frequency in Asians (25 %–47 %)

[19]. The effect of the variant allele on MOR function in human brain is controversial, with evidence for both loss of function and gain of function [15].

Human Laboratory Studies

Following intravenous alcohol administration, Asp40-allele carriers reported experiencing a more intense “high” and greater subjective intoxication, stimulation, sedation, and happiness than Asn40 homozygotes [20]. In an alcohol cue-exposure study, male heavy drinkers with an Asp40 allele reported higher levels of craving than did Asn40 homozygotes [21].

Human laboratory studies have also been used to examine naltrexone’s effects on the subjective response to alcohol or alcohol-related cues. A within-subject, double-blind study examined the effects of pre-treatment with naltrexone or placebo on the response to intravenous alcohol in a sample of non-treatment-seeking heavy drinkers [22]. Although Asp40-allele carriers experienced lower levels of alcohol craving and greater alcohol-induced “high” as the breath alcohol concentration was increased, naltrexone blunted the positive response to alcohol, most robustly in individuals Asp40 carriers. In contrast, McGeary et al. [23] found that naltrexone pretreatment paradoxically was associated with greater cue-elicited craving than placebo in heavy drinkers with an Asp40 allele. No such difference was seen in Asn40-allele homozygotes.

Clinical Trials of Opioid Receptor Antagonists to Treat Alcohol Dependence

Although meta-analyses of alcohol dependence treatment [24, 25] show that naltrexone is superior to placebo on a number of drinking outcomes, there is considerable variability in efficacy among studies, suggesting that the medication is not efficacious for all patients. The finding that individuals with a greater percentage of alcoholic family members show a more robust treatment response [26–28] has led to an effort to identify genetic variants that can be used as biomarkers in alcohol-dependent individuals to identify who is most likely to benefit from opioid antagonist treatment.

The first report of differential naltrexone response to carriers of the Asp40 allele was by Oslin et al. [5], in a secondary analysis of data from 130 European-American (EA) participants in 3 placebo-controlled trials of naltrexone. In that study, patients with 1 or 2 Asp40 alleles were significantly less likely than Asn40 homozygotes to relapse to heavy drinking when treated with naltrexone. Although a formal interaction was not detected, there was no effect of the SNP in placebo-treated subjects. Gelernter, et al. [29] examined the moderating effect of 3 *OPRM1* SNPs (including Asn40Asp), 3 polymorphisms in *OPRD1*, and 1 poly- morphism in *OPRK1* on treatment outcome in 215 patients from the VA Cooperative Study of Naltrexone Treatment [30]. They found no evidence of genetic moderation of the response to naltrexone treatment. Anton, et al. examined the Asn40Asp SNP in 911 participants in the COMBINE Study [31]. Using genotype information for EAs who were randomly assigned to naltrexone or placebo, they found a moderating effect of the Asp40 allele in the subjects who received naltrexone and medical management, but not in those that received naltrexone and a more intensive psychotherapy.

Open-label studies of naltrexone in alcohol-dependent individuals have also yielded equivocal findings. In a study of naltrexone treatment of Korean alcoholics [32], analysis of

the moderating effect of the Asn40Asp SNP was limited to participants who were treatment adherent. Carriers of the Asp40 allele showed a longer time to relapse than Asn40homozygotes. An Australian study of naltrexone in 100 alcohol-dependent individuals [33] was associated with decreases in self-reported and objective indicators of alcohol use and craving from pretreatment levels. However, there was no evidence of a significant effect of the Asn40Asp SNP on a variety of drinking outcomes.

Kranzler et al. [34] examined the moderating effect of the Asn40Asp SNP on medication response in a placebo-controlled trial of daily or targeted naltrexone in problem drinkers who sought to reduce their drinking. In the aggregate, the SNP did not significantly moderate the effect of naltrexone on drinking behavior. However, by using a daily diary method in which patients reported by telephone each evening their current desire to drink and their drinking during the preceding day they were able successfully to show that genotype, medication, desire to drink and their interactions predicted the number of nighttime drinks consumed. Interesting, when the evening level of desire to drink was relatively high, Asp40 allele carriers were at greater risk than Asn40 homozygotes to drink more, which was attenuated by naltrexone. This is consistent with a modest effect of the Asn40Asp SNP and appeared to depend on the greater statistical power resulting from the "micro-longitudinal" study design.

There is also one study [35] of the moderating effects of genetic variation on treatment response in a sub-sample of alcohol-dependent patients from a placebo-controlled trial of nalmefene [36], an opioid antagonist with partial agonist effects at the κ receptor [37]. Although nalmefene significantly reduced the weekly number of heavy drinking and very heavy drinking days, there was no evidence of moderation by 2 SNPs in *OPRM1* (including Asn40Asp), 2 SNPs in *OPRD1*, or 1 SNP in *OPRK1*.

Trials of Naltrexone in Non-Treatment-Seeking Heavy Drinkers

In a placebo-controlled, cross-over trial of naltrexone in 30 non-treatment-seeking individuals, 1 week of naltrexone treatment reduced drinking behavior more than 1 week of placebo treatment [38]. However, there was no moderating effect of the Asp40 allele on the response to naltrexone. Tidey et al. [39] found no moderating effect of the Asp40 allele on drinking outcomes in a 3-week, placebo-controlled trial of naltrexone in 173 heavy drinkers.

Summary

The moderating effect of the *OPRM1* Asn40Asp SNP on the efficacy of naltrexone in reducing heavy drinking is, overall, modest. The considerable differences among studies may reflect variation in study populations and methods. In addition to small sample sizes in some studies, the imbalance in the frequency of the alleles being studied limits the statistical power of these retrospective comparisons. Although a preliminary meta-analysis showed evidence of significant moderation of the effects of naltrexone on risk of heavy drinking by the Asn40Asp polymorphism [40], large, prospective studies are needed to estimate more accurately the magnitude of the moderating effect of the Asn40Asp SNP on the efficacy of naltrexone. Although the only published pharmacogenetic study of nalmefene failed to show evidence of a moderating effect of the Asn40Asp SNP, because this medication is being

developed for use in the European Union, additional studies of nalmefene appear warranted. Variants in other opioid-related genes (both receptors and peptide ligands) should also be considered as potential moderators of treatment with naltrexone and nalmefene.

The Serotonergic System

Medications that modify serotonin (5-HT) neurotransmission, including selective serotonin reuptake inhibitors (SSRIs) and specific 5-HT receptor blockers have been studied as potential treatments for alcohol dependence. Although in rodents, manipulations that increase 5-HT consistently reduce drinking [41], 5-HT agonists have yielded inconsistent effects on drinking in humans [42]. This suggests that phenotypic or genotypic subtypes of alcohol dependence could affect the response to serotonergic medications [42].

Studies of phenotypic variation in this response have focused on age of onset and risk/vulnerability subtypes [43–46]. Two studies showed that early-onset or high vulnerability participants treated with fluoxetine or fluvoxamine had poorer outcomes than those receiving placebo [43, 44], whereas 1 study [45] showed a significant advantage of sertraline in late-onset low-risk/vulnerability patients. Ondansetron, a 5-HT_3 antagonist, was shown in a placebo-controlled trial [46] to reduce drinking among early-onset alcoholics. In this study early-onset alcoholics treated with low-dose ondansetron (ie, 1, 4, or 16 mg/kg/day) had significantly more abstinent days and significantly less alcohol consumption than the placebo group. In alcoholics with a later onset of problem drinking, the effects of ondansetron did not differ from those of placebo.

Studies of the pharmacogenetics of serotonergic medications have focused on *SLC6A4*, the gene encoding the 5-HT transporter (5-HTT), which regulates 5-HT tone. A 44-bp repeat insertion in the 5-HTT linked promoter region (5-HTTLPR) of *SLC6A4* results in long (L) and short (S) alleles [47]. Due to different transcriptional activity these alleles encode higher-activity and lower-activity 5-HTT proteins, respectively [48]. An A-to-G SNP (rs25531) in the L-specific repeat of the gene also affects function, such that the L_G allele is functionally similar to the lower-activity S allele [49, 50]. Two placebo-controlled trials have shown moderating effects of variation in *SLC6A4* on the response to serotonergic medications.

Johnson et al. [51•] randomly assigned alcohol-dependent patients to receive 11 weeks of double-blind treatment with ondansetron or placebo. Individuals with the 5-HTTLPR LL genotype who were treated with ondansetron drank significantly fewer drinks per drinking day and had a significantly higher percentage of abstinent days than those who received placebo. Further, ondansetron patients with the LL genotype reported significantly better outcomes on both of these measures than individuals with an S allele. There was also an interaction between the 5'-HTTLPR and 3'-UTR polymorphisms: ondansetron-treated patients with both the LL 5-HTTLPR genotype and the TT 3' UTR genotype drank significantly fewer drinks per drinking day and had a higher percentage of days abstinent than all other genotype and treatment groups combined.

Kranzler et al. [52], in a 12-week, placebo-controlled trial of sertraline, examined the moderating effects of both age of onset of alcohol dependence and 5-HTTLPR genotype on

drinking behavior in alcohol-dependent subjects. Whereas, in late-onset alcoholics, sertraline treatment reduced drinking behavior more than placebo, in early-onset alcoholics, greater reductions were seen with placebo treatment. This interaction effect occurred only in high-activity-allele (ie, L'-allele) homozygotes. Follow-up of these patients showed that the effect of sertraline remained significant during the 3-month post-treatment period for L'/L' late-onset alcoholics, with the sertraline group having significantly fewer drinking days than the placebo group, with no other significant effects of at 3-month or 6-month follow-up visits.

The findings that the effects of ondansetron and sertraline, which are different neuropharmacologically, are both moderated by high-activity alleles of 5-HTTLPR may reflect a shared underlying mechanism for these medications. That is, the synaptic availability of 5-HT, which is influenced by both SSRI treatment and 5-HTTLPR, can determine the extent to which the predominantly post-synaptic 5-HT_3 receptors, which are the primary target of ondansetron, are stimulated. Efforts to replicate these findings is needed, as is further examination of variation in *SLC6A4* that may affect expression of the 5-HTT and augment the moderating effects observed to date.

Adaptive Treatment Approaches

Patient progress while in treatment can also be used to personalize interventions for alcohol use disorders. Approaches to the treatment of medical and behavioral disorders in which changes in symptoms or status are monitored over time and used to adjust the treatment protocol according to well-specified guidelines are referred to as "adaptive" treatment protocols [7, 8•]. Adaptive treatments can also incorporate tailoring on the basis of patient characteristics assessed at intake—such as genetics—to further personalize care.

The main components of an adaptive treatment are tailoring variables, therapeutic components, and decision rules [7]. Tailoring variables are the measures that are used to monitor patient progress. In the case of alcohol dependence, alcohol use will often be used as a tailoring variable. How-ever, measures such as attendance in treatment sessions or self-help groups, self-efficacy, coping behavior, or motivation could also be used as tailoring variables [8•]. For example, decisions to increase or decrease the intensity of treatment over time might be driven by changes in the patient's perceived ability to cope with various problems without drinking (ie abstinence self-efficacy).

In an adaptive protocol, treatment can be modified by augmenting the current intervention or switching to another intervention altogether. The key concern here is for the other intervention to have a sufficiently different mechanism of action that it has a reasonable chance of success where the initial intervention failed. Decision rules are the "if—then" statements that link responses on the tailoring variables to specific changes in therapeutic components or procedures. An example of a decision rule might be: "If the patient has 3 or more heavy drinking days within a 7-day period, augment standard outpatient treatment with individual CBT sessions." Decision rules are clearly operationalized, and they involve specified cutting scores on the tailoring variables and specified treatment selections.

Adaptive Alcohol Treatment Studies

Bischof and colleagues [53] described an adaptive, telephone-based, stepped-care approach for problem drinkers in medical practices in Germany. Individuals with alcohol use disorders were randomly assigned to 1 of 3 conditions: usual care, full care, or stepped care. Both the full care and stepped care models included a computerized intervention plus 4 subsequent telephone-based intervention sessions. In the stepped care version, the number of telephone contacts was determined by response to the intervention. In the full care version, all 4 telephone contacts were delivered. Both active interventions produced better drinking outcomes at 12 months than standard care. Drinking outcomes in the stepped care and full care conditions did not differ, even though participants in the stepped care condition received about half as many treatment sessions. Thus, the stepped care algorithm reduced patient burden and cost to the system, with no compromise on effectiveness [8•].

McKay and colleagues have conducted a series of studies to determine whether initial progress in outpatient treatment can predict optimal continuing care interventions. The first study found that alcohol-dependent patients who did not achieve abstinence during a 4-week intensive outpatient program (IOP) had much worse drinking outcomes over a 24-month follow-up than those who stopped drinking. How-ever, individuals who failed to achieve abstinence benefited more from a CBT-based continuing care intervention than from standard group continuing care. In contrast, there were no treatment differences in patients who had stopped drinking while in IOP [54]. In a second study, IOP patients who did not achieve the majority of the goals of IOP during the first month of treatment had better substance use outcomes if they subsequently received more intensive, clinic-based continuing care, whereas for those who made better progress in IOP, telephone continuing care was superior to clinic treatment [55]. Of the goals examined, alcohol use in IOP was the strongest single predictor of optimal continuing care selection [56]. Finally, a recent study found that augmenting IOP with extended continuing care was particularly beneficial in comparison to IOP only for patients who had low motivation for change and poor social support for recovery at the one-month point in IOP. Women and patients with prior treatments for alcoholism also benefited to a greater degree from extended continuing care [57].

O’Malley and colleagues [58] conducted a study to determine optimal continuation treatments for alcohol-dependent patients who initially responded positively to naltrexone. Patients were randomized to receive naltrexone in a primary medical care setting or in an addiction specialty care setting that provided cognitive-behavioral therapy (CBT) for alcohol dependence. Patients who achieved a good response over the first 10 weeks were randomized for a second time to either extended naltrexone or placebo, along with continuation of the behavioral treatment they had received in Phase 1. The continuation treatments were provided for an additional 24 weeks [8•].

The the primary care and CBT conditions were equivalent on most drinking outcomes during the first 10 weeks of the study. However, in the continuation phase, patients receiving primary care-based treatment had better drinking outcomes if they received extended naltrexone (ie, 81 % of those in the naltrexone condition were responders, compared with only 52 % in the placebo condition). Conversely, those who received CBT did not benefit

from extended naltrexone [58]. This study illustrates how the effectiveness of later treatment interventions can vary as a function of which intervention patients received earlier in the protocol [8].

Friedmann and colleagues [59] conducted a large-scale study of services-to-needs matching, with a sample of over 3100 addiction treatment patients. The study focused on the degree to which reported needs in 5 domains—medical, mental health, family, vocational, and housing—were addressed with services, and whether better matching produced better substance use outcomes. Overall, higher rates of services-to-problems matching predicted better substance use outcomes. The effect was concentrated in patients who reported problems in at least 4 of the 5 domains, and matching of vocational and housing services was particularly important [59].

Adaptive Treatment Studies with Drug Dependent Patients

We describe here a number of adaptive trials conducted to treat drug dependence because of the limited number of such studies with alcohol-dependent individuals and the potential that findings from drug dependence studies can also improve alcohol treatment. Brooner and Kidorf [60] developed a stepped care treatment for methadone patients, in which movement between 3 levels of counseling intensity was determined by attendance and urine toxicology results. Failure to attend treatment sessions or drug-positive urines triggered increases in the intensity of counseling provided to patients. Studies by this group indicate that this stepped care approach works equally well in methadone clinics or at physicians' offices [61], can be adapted to increase employment rates in methadone patients [62], and can be combined with contingency management to further improve outcomes [63]. A stepped care algorithm for opiate dependent patients that first provides buprenorphine and steps non-responders up to methadone maintenance was shown to be as effective as starting patients on methadone [64]. Therefore, the stepped care algorithm reduced patient burden and increased safety, without sacrificing good substance use outcomes.

Finally, Marlowe and colleagues [65] conducted a study of an adaptive intervention for drug court participants. In this study, offenders were initially assigned to bi-weekly or "as needed" hearing schedules on the basis of whether they carried a diagnosis of Antisocial Personality Disorder or had a history of prior treatments for substance dependence. This initial hearing schedule could be further adapted on the basis of outcomes in drug court. Offenders who attended drug court but were using drugs were given intensive case management to provide them with additional skills needed to achieve abstinence. Conversely, for those who failed to attend scheduled drug court sessions, their hearings were increased in frequency to bi-weekly, or they were terminated from the program and sentenced on their original drug charges if they had been placed on the bi-weekly schedule at the start of the study. This adaptive algorithm produced better drug use outcomes than standard drug court. This study is a good example of how tailoring on the basis of patient characteristics at intake can be combined with an adaptive algorithm driven by progress during treatment [8•]. Furthermore, it illustrates that it is possible to adapt treatment using two tailoring variables (ie attendance and drug use), with different modifications for each

variable (ie increased frequency of sessions and augmentation with clinical care management).

Conclusion

Developments in the pharmacotherapy of alcoholism and in the genetics of alcohol dependence have informed studies that match medications to patients based on genotype. The literature in this area is, however, only beginning to develop and the vast majority of studies have used comparatively small samples of convenience, rather than employing prospective designs in adequately powered samples. Despite conflicting results of studies of the Asn40Asp SNP in *OPRM1* as a moderator of the effects of naltrexone, this remains the most clinically relevant observation to date. Prospective studies may help to resolve controversy in relation to this effect.

Both of the placebo-controlled trials of alcohol dependence treatment that examined the moderating effects of the 5-HTTLPR polymorphism on the response to serotonergic medications showed that L-allele homozygotes responded differentially to the active treatments, despite their different pharmacological mechanism of action. Additional prospective studies of ondansetron and other serotonergic agents are needed to validate the use of this polymorphism as a predictor of treatment response. An-other important question to be addressed is whether the tri-allelic polymorphism (L_A vs L_G or S) is a more robust moderator of treatment response in alcohol dependence than the bi-allelic polymorphism (L vs S).

To be highly successful financially,, medications are marketed to large portions of the population, irrespective of individual features. The identification of patient characteristics that would allow a medication to be targeted to individuals for whom it would be most efficacious and least toxic would limit the size of the market for that medication. A shift from this wholesale approach to medications development to one that personalizes medication choices could improve the treatment of alcohol dependence.

Recent research also indicates that treatments for alcohol and drug dependence can be personalized through the incorporation of adaptive algorithms that are designed to modify treatment on the basis of patient progress. Initial response to outpatient treatment—as indicated by whether the patient is able to stop using alcohol and other drugs— appears to be a particularly good predictor of the type of continuing care that will achieve the best substance use outcomes [54, 56, 65]. In addition, stepped-care algorithms that start at a lower intensity are able to reduce the cost and burden of treatment while maintaining good outcomes [53, 63, 64]. Finally, matching treatment to specific problems present at intake, or that emerge during treatment, such as poor social support and low motivation, homelessness, and employment problems, can also improve treatment [57, 59].

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