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Adding Individual Psychotherapy after Relapse in a Pharmacotherapy Trial: Commentary on the PREDICT Study

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Abstract

Background—With few exceptions there has been a dearth of research evaluating the independent and combined effects of a promising medication and an effective behavioral intervention for alcohol problems. Few studies have incorporated both theory and empirical findings to ascertain how the combination of medication and behavioral intervention interact or work synergistically to produce better outcomes or why a particular combination of pharmacological and behavioral treatment works better than another combination or either of the interventions employed alone.

Methods—The PREDICT Study is one of the few pharmacotherapy trials that has utilized a behavioral intervention to reduce/delay relapse to heavy drinking. The findings in the PREDICT Study were reviewed to gain a better understanding of how the combination of pharmacotherapy and behavioral intervention can be employed to manage the course of recovery for individuals with AUD.

Results—Findings in the PREDICT study show that behavioral interventions and pharmacotherapies have complementary functions that can be utilized to address the differential needs, capabilities, and resource associated with AUD. However, researchers were forced to rely mainly on their own clinical experiences rather than an overarching conceptual model in determining how the approach should be employed with AUD patients, thereby limiting the conclusions that could be drawn from the study findings.

Conclusions—Different vulnerabilities underlying AUD should be considered in determining what kinds of behavioral interventions should be paired with particular medications. At the same time, we need to have a better understanding of the clinical course of pharmacobehavioral treatment to deal with the array of problems/situations that arise over the course of combination therapy.

Keywords

Alcohol Use Disorders; Mechanisms of Action; Pharmacobehavioral Treatment; Patient-Treatment Matching; Clinical Decision Making

There are four alcohol medications that have received FDA approval, naltrexone, injectable naltrexone, disulfiram and acamprosate. Despite the available of these medications, they are

not widely utilized or prescribed. In a recent article, Litten and colleagues (2014) reported that \$1.6 billion more is expended for an antidepressive medication such as Lexipro than all alcohol medications even though the number of individuals afflicted with alcohol use disorders are comparable to those suffering from a major depressive disorder. It has been estimated that only 12% of specialty settings use alcohol medications (Abrahams, 2010). Conflicting findings, modest effect sizes of alcohol medications, and the additional costs of monitoring and managing alcohol medications have served as barriers in incorporating medications in clinical settings where AUD patients are typically seen. It is conceivable that more providers would be ready and willing to offer medication assisted behavioral treatment if the added benefits of the combination could be demonstrated.

Unfortunately, with few exceptions there has been a dearth of research evaluating the independent and combined effects of a promising medication and an effective behavioral intervention for alcohol problems (See Anton et al., 2001; Anton et al. 2006; Carroll and Kilack, 2011; O'Malley et al., 2001; Penberthy et al., 2011). More often than not, pharmacotherapy trials employ a low intensity, weak impact behavioral intervention as a platform treatment so as not to mask the benefits of the alcohol medication.

With this background in mind, I read with interest the article by Bernier and colleagues (2014) on the PREDICT Study. The PREDICT Study is one of the few pharmacotherapy trials that has utilized a behavioral intervention as a stepped care approach to facilitate abstinence or reduce/delay relapse to heavy drinking. This interesting study was aimed at determining whether AUD patients would benefit from receiving additional AUD psychotherapy after relapsing while receiving an anti-craving medications (acamprosate 2 g. and naltrexone 50 mg) or placebo. Those relapsed were randomly assigned to either to an intensive psychotherapy termed "alcoholism specific therapy (ASP)" or a control group in which no additional psychotherapy was provided. ASP is an adapted German version of combined behavioral intervention (CBI) that was utilized in the NIAAA-funded COMBINE Study. Regardless of whether they received intensive psychotherapy or not, all patients continued with the active medications or placebo and medical management (MM). MM is a primary care type intervention, also employed in COMBINE, to manage side effects and facilitate compliance with the medication regime.

Findings in this study revealed that patients who received additional psychotherapy remained abstinent longer than those who continued with the pharmacotherapy (along with MM) alone. However, a sizeable proportion of patients assigned to the additional therapy declined to participate even though they relapsed to heavy drinking while receiving the MM and medications. In other words, the benefits of additional psychotherapy (ASP) only extended to patients that were committed to or preferred additional psychotherapy leaving the researchers to conclude that the level of severity of the alcohol problems may be a less important consideration than patients' preferences in referring relapsed patients to additional psychotherapy.

Several questions or issues can be raised about the study findings which are discussed below.

First, patients migrating from step 1 (i.e., medication plus medical management) to step 2 (i.e., medication, medical management and ASP) were required to undergo a brief period of abstinence prior to taking part in the psychotherapy. Under these circumstances, patients might have preferred to remain in MM than deal with inherent difficulties (e.g., craving) in stopping drinking. At the same time, MM, although focused on medication adherence issues, may have given patients sufficient support so that did not feel the need to go elsewhere to fulfill their treatment needs.

Second, in the PREDICT study the behavioral intervention was initiated after patients had relapsed. The authors indicate that it might have been preferable to reverse of the order of the two approaches by providing only psychotherapy in step 1 and the medication in step 2 (i.e. for nonresponses). Such an approach might be more amenable to patients since undergoing a medication regime appeared to be a more preferable or attractive alternative to nonresponses than intensive psychotherapy. (The adherence rates were higher in the medications plus MM only group than those who received intensive psychotherapy along with MM and medications). What is apparent here is that we know little about how medication and behavioral interventions interact or work synergistically to produce better outcomes. Should the medication be employed together, sequentially or in adapted manner as in the PREDICT study?

Third, what is missing from the PREDICT Study is a conceptual model that explains how and why the particular combination of pharmacological intervention might work better than another combination or pharmacological and behavioral intervention. In the PREDICT Study the researchers adopted the combination from the COMBINE Study which also lacked an overarching model in pairing the particular medications with the particular psychotherapy (Unfortunately the findings from the COMBINE Study were unavailable when the German study was initiated). At the same time, we know little about how to choose particular combinations of pharmacological and behavioral interventions to maximize the benefits of alcohol treatment. What is specific about the medication and behavioral intervention that would make it more effective than another combination or either approach employed alone? Or for that matter, how do different combinations work synergistically to improve alcohol treatment? What are the mechanisms of action that explain how the combination helped to reduce drinking levels and related problems? Lacking a strong conceptual model or empirical findings, these researchers were forced to rely mainly upon by their own clinical experiences in managing the course of recovery for PREDICT study patients.

In future research, different vulnerabilities underlying AUD must be considered such as the reinforcement effects, severe craving and resulting distress, along with impaired decision-making to ascertain what kinds of behavioral interventions should be paired with particular medications. A medication such as naltrexone may impact on specific receptors in the brain that decrease the reinforcing value/effects of drinking while a behavioral intervention such as cognitive behavioral therapy (CBT) can deal with aspects of the AUD not addressed directly by the medication such as strengthening coping skills to reduce cravings, enhancing network for support for sobriety, managing moods, and finding alternate ways of reducing stress associated with drinking. Some medications such as disulfiram may enable the

individual to sustain a period of abstinence to permit therapeutic engagement in behavioral treatment. The behavioral intervention can capitalize on the benefits accrued from the medication by strengthening motivation as well as support decision-making for change. In short, psychosocial and pharmacotherapy have complementary functions that can address the differential needs capabilities and resources of individuals with AUD.

We also need to have a better understanding of clinical course of medication assisted treatment. How do we address the array of problems or situations occurring over the course of medication-assisted interventions? Often these issues stem from a change in expectations or preferences about their own conditions and/or the circumstances associated with changes or lack of changes in the drinking behavior. If not addressed, these issues can precipitate a full blown relapse and/or lead to premature termination from treatment. Individuals who fully comply in the initial phases of treatment and reduce or abstain from drinking, may later decide to stop taking their medication because they believe that the problem has been resolved and does not require further “chemical” assistance. They may make this decision on their own, without consulting a clinician and without knowledge of why continuing a medication may be necessary. In contrast, others who continuing to drink while taking the medication, may feel that treatment is ineffective and decide to drop-out without fully realizing that the effects of the medication have not had sufficient time to work. Another group may stop taking the medication to see if they could handle drinking on their own without the medication. In such cases, behavioral interventions such as motivational interviewing can be useful in addressing the above medication adherence issues and at the same time, provide requisite support to remain fully engaged (i.e., taking the medication and attending the sessions). This would afford a greater opportunity to obtain the benefits from the medication and pursue activities that might offer benefits extending beyond the current treatment situation, such as solidifying family relationships, finding new employment opportunities, improving physical and mental health, reducing everyday hardships, and in general, improving their overall quality of life.

We need to design combination studies incorporating both theory and empirical findings would enable us to match the pharmacological and behavioral components with biological, psychological, economic and social factors associated with different AUD populations. In this way, we may discover that certain populations (e.g. low level of AUD) may benefit from psychotherapy alone (i.e., without medication) and other populations (e.g., co-occurring disorders) may need regimen of alcohol medications along with intensive interventions (i.e. intensive case management and coping skills training, and twelve-step facilitation). Such studies would enable us to formulate algorithms aimed at different patient subgroups and later support the development of tailor-made AUD treatment (Litten et al., 2013).

In sum, behavioral interventions and pharmacotherapy have complementary functions that can be integrated to address the differential needs, capabilities and resources of individuals with AUD to optimize the benefits of treatment.

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