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Choosing a behavioral therapy platform for pharmacotherapy of substance users

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Abstract

Behavioral therapy platforms have become virtual requirements in pharmacotherapy trials due to their utility in reducing noise variability, preventing differential medication adherence and protocol attrition, enhancing statistical power and addressing ethical issues in placebo-controlled trials. Selecting an appropriate behavioral platform for a particular trial requires study-specific tailoring, taking into account both the stage of development of the medication being evaluated, as well as the specific strengths and weaknesses of a broad array of available empirically supported behavioral therapies and the range of their possible targets (e.g., enhancing medication adherence, preventing attrition, addressing co-morbid problems, fostering abstinence, and targeting specific weaknesses of the pharmacologic agent). Choosing a suitable behavioral platform also requires consideration of the characteristics of the population to be treated, stage of scientific knowledge regarding the medication's effects, appropriate balance of internal and external validity, and consideration of potential ceiling effects. Available manualized behavioral treatments are reviewed, noting their strengths and limitations as behavioral therapy platforms for pharmacotherapy trials and as potential concomitant therapies in clinical practice.

Keywords

Behavioral therapies; Pharmacotherapy trials; Adherence; Treatment

1. Introduction

We have previously described the benefits of providing a standardized behavioral therapy “platform” for clinical trials testing the efficacy of pharmacotherapies for mental disorders (Carroll, 1997). These include enhancing statistical power by restricting variability associated with protocol deviation (e.g., through attrition and non-compliance) by defining and controlling non-pharmacologic aspects of the protocol, as well as addressing ethical concerns through providing adequate psychosocial support and monitoring when utilizing placebo or medications of unknown efficacy.

Although the general concept of a behavioral platform is now widely accepted in pharmacologic trials, the selection of an appropriate platform is a complex issue that has not yet been addressed in the substance abuse literature. There are now available a growing number of empirically supported, manual-guided behavioral therapies (National Institute on Drug Abuse, NIDA, 2000), a number of which may be suitable choices as “platforms” for pharmacotherapy efficacy research. Thus, in this manuscript, we will articulate a series of

issues for investigators to consider in choosing a behavioral intervention that will best enable the study to provide a valid test of a drug's efficacy as treatment for substance abuse.

For the purposes of this manuscript, we use a broad definition of 'behavioral therapy', referring to any adequately specified (usually manualized) protocol defining the nature, frequency, and content of non-pharmacologic contact and support offered to patients in the context of a pharmacologic trial. Our central point is that no single behavioral "platform" is likely to meet the design needs for studies evaluating different types of pharmacotherapies at different stages of development. Rather, the behavioral platform must be tailored to address the particular research questions and challenges inherent in each trial. To guide this tailoring, we suggest that investigators consider the following questions, which will be explored in detail below: (1) What are the targets for the behavioral platform? (2) What are the specific strengths and weaknesses of specific behavioral therapies as platforms? (3) Will the study primarily address pharmacotherapy efficacy issues or psychotherapy/pharmacotherapy interactions? (4) What is the optimal intensity of the behavioral "platform"? (5) How will the behavioral platform affect generalizability of findings and potential treatment dissemination? These guidelines are applicable principally to Phase II randomized controlled trials and Phase III effectiveness trials, but are applicable to some extent to earlier Phase I trials as well.

2. What are the targets for the behavioral therapy platform?

In the context of pharmacotherapy clinical trials, the fundamental goal of including a standardized behavioral therapy platform is to increase the likelihood of detecting a true difference (if any exists) between contrasting medications. Some major threats to the integrity of substance abuse pharmacotherapy trials include (a) bias and excessive error variance resulting from uncontrolled behavioral treatments, (b) insufficient treatment retention to permit detection of medication effects, (c) inadequate medication adherence to permit delivery of an effective medication dose, (d) continued uncontrolled drug use that undercuts trial participation, and (e) medication-specific weaknesses that must be addressed to permit effects to be detected. Any or all of these validity threats can be chosen as the targets for the behavioral platform.

2.1. Reducing bias and error variance

Without systematic control through study-specific training, behavioral therapies delivered in the context of pharmacotherapy trials can vary widely in quantity and quality with, at minimum, a resultant increase of random effects ("noise" variance) which will reduce the precision of the analysis of the cross-cell treatment effects (Feinstein et al., 1979; Lavori, 1992). A more troubling possibility is the introduction of systematic bias that results from delivering more intensive treatment to patients who are deriving little beneficial pharmacotherapy effect (e.g., patients on placebo or an ineffective agent) and less intensive treatment to those who are faring well due to positive medication effects (Carroll, 1997). This tendency of clinicians to "grease the squeaky wheel" has a net effect of reducing the possibility of detecting a true medication effect by improving the prognosis of those in placebo or ineffective medication groups. Thus, the behavioral therapy selected needs to describe both the lower bounds and the upper bounds of treatment intensity so that the study clinicians offer a relatively consistent amount of behavioral intervention to all study participants. The range of treatment intensity as well as mean 'dose' of behavioral intervention provided to participants should be monitored over the course of the trial and significant variation from protocol guidelines should be evaluated in the data analysis as a potential source of outcome variability.

2.2. Enhancing treatment retention

Treatment retention is crucial in pharmacotherapy clinical trials to ensure that patients on active medications sustain treatment long enough to detect medication effects, to obtain outcome ratings and data for all treatment groups for intention to treat analyses, and to ensure the safety of study participants through continued monitoring. The major behavioral treatment goal in this regard is to foster the patient's expectation that treatment benefit can be obtained, regardless of whether or not the medication is effective. Ethical standards dictate the delivery of a behavioral treatment that at least meets minimal standards of care for patients on placebo or medications of unknown efficacy (Freedman, 1987; Levine, 1985; Miller, 2000a; Miller and Brody, 2002a). However, achieving this level of care does not necessarily require intensive behavioral treatment, as there is a large literature documenting the efficacy of brief and minimal treatments, particularly for substance abusers with less severe conditions (Babor, 1994; Miller, 2000b; Wilk et al., 1997).

2.3. Enhancing medication adherence

True differences in efficacy of different pharmacotherapies are more likely to be detected if adherence is high and comparable across treatment conditions. While cross-treatment differences in adherence may be a powerful indicator of differential treatment acceptance (e.g., through intolerable side effects), substance abusers may show poor medication adherence for reasons other than lack of efficacy or side effects. For example, some agents, such as naltrexone for opioid dependence or disulfiram for alcohol dependence, are associated with limited patient acceptance and adherence (Fuller et al., 1986; Modesto-Lowe and Van Kirk, 2002; O'Brien, 1997; Rounsaville, 1995) in part because they are too powerful in preventing relapse to substance use if taken properly. Unless combined with some type of targeted behavioral intervention, ranging from family assisted compliance contracting (O'Farrell et al., 1992a), to direct monitoring of medication compliance (Rigsby et al., 2000), to providing incentives for adherence (Preston et al., 1999), the pharmacologic efficacy of these agents may not translate into treatment efficacy in the context of clinical trials. In general, the limited treatment adherence in many pharmacotherapy trials for substance abusers (de Lima et al., 2002; Rohsenow et al., 2000) requires the incorporation of medication adherence strategies into any behavioral platform chosen. Such strategies are particularly necessary when clinical trials evaluate agents with delayed effects, partial effects, troublesome side effects and/or complex dosing schedules.

2.4. Managing problems other than drug use

No pharmacotherapies for substance use disorders are sufficiently comprehensive in their effects to be a sole treatment because substance abusers frequently enter treatment with co-morbid mental disorders and multiple functional impairments (Leshner, 1999; McLellan et al., 1993; O'Brien, 1997). Behavioral treatments may be needed to address these ancillary problems so that study subjects have a sufficient level of symptom control or stability to participate and/or hope to achieve benefit from the pharmacotherapy treatments being evaluated. For example, in studies of pharmacologic treatments for substance abusers with co-morbid psychiatric conditions (e.g., depressed cocaine abusers, schizophrenic cigarette smokers), the behavioral therapy platform should aim for an adequate and consistent level symptom control for the psychiatric disorder to enable the patient to participate in the trial (George et al., 2000; McDowell et al., 2000; Nunes et al., 1998; Schmitz et al., 2001a).

2.5. Achieving at least minimal control of drug use

Most pharmacotherapies for substance use disorders yield only partial effects and many require patients to achieve an initial period of abstinence prior to treatment onset. In only few instances is it advisable to provide study medications to patients in the context of heavy

or uncontrolled substance use. Moreover, as noted above, in placebo-controlled trials the behavioral therapies platform treatment provided to patients assigned to placebo must equal minimal requirements for standard care. For these reasons, abstinence or reduced substance use is a target for all behavioral therapy platforms. As elaborated below, the intensity of these behavioral therapy treatments must be considered on a trial-by-trial basis to achieve a level of reduction in substance use that is sufficient to meet study requirements while avoiding ceiling effects that would obscure or prohibit detection of medication effects.

2.6. Addressing medication-specific weaknesses

Even the newest medication being considered for substance abuse clinical trials has gone through prior Phase I and II human studies to determine safety and to evaluate its pharmacokinetic and pharmacodynamic properties. Many other medications to be evaluated as new substance abuse treatments are already approved and marketed for other treatment indications. Hence, investigators typically design substance abuse pharmacotherapy trials with considerable foreknowledge about an agent's weaknesses that may need to be addressed with a behavioral therapy in order to enable any potential beneficial medication effects to be detected. We will discuss approaches to dealing with (a) moderate/weak medication effects, (b) strong and potentially too powerful medication effects, (c) delayed medication effects, (d) unpleasant side effects and (e) medications requiring frequent or complex methods of delivery. Anticipating and dealing with these weaknesses is the single most important consideration in choosing a behavioral platform for pharmacotherapy clinical trials.

2.6.1. Moderate/weak medication effects—With few exceptions (e.g., disulfiram for alcohol, naltrexone for opioids), most substance abuse medications have variable or partial effects on the target symptoms of craving (e.g., naltrexone or acamprosate for alcohol dependence), attenuation of drug reward (e.g., cocaine or nicotine vaccines, methadone for opioids), reduction of withdrawal symptoms (e.g., clonidine for opioid withdrawal) or treatment of co-morbid medical or psychiatric disorders (e.g., SSRI's for depression, HIV vaccine). Even partial effects can make an important difference in helping motivated, medication compliant patients to achieve treatment goals. At the same time, partial effects can be readily overridden by continued heavy drug use by patients with limited ability or desire to stop or cut down. For clinical trials of such agents, behavioral treatments that foster motivation to become abstinent or provide behavioral coping strategies may be analogous to catalysts that permit chemical reactions to take place (Anton et al., 1999).

Particular challenges are presented by weak/moderate medications that have sustained effects and require relatively infrequent administration (e.g., LAAM). Sustained effect agents that might need to be given only once a month or less often have been considered the ideal pharmacotherapy for addictive disorders. However, they can pose interesting challenges since the patients are likely to consider them "magic bullets" that negate any need for the patient to exert much effort in his or her rehabilitation. An example of an agent with both a partial effect and requiring infrequent administration is a vaccine for cocaine or nicotine. Most vaccines are not likely to be complete blockers of these drugs and will probably be relatively easily overridden by modest increases in the usual doses that an abuser would take (Kosten and Biegel, 2002a). The vaccines are more likely to attenuate the priming effects of a slip to drug use and thereby facilitate a relapse prevention behavioral approach in patients who have already attained some measure of abstinence.

An extreme example of the challenge in keeping patients engaged in treatment involves using a monoclonal antibody to reverse overdoses of an hallucinogen such as phencyclidine (PCP) (Owens, 1997). These monoclonal antibodies may last several months after

administration and if the abuser leaves the emergency room without ongoing treatment engagement, his attempts to override the antibody blockade could lead to a fatal overdose. Thus, matching an appropriate behavioral intervention to the pharmacotherapy study such as a study of overdose reversal with monoclonal antibodies can have critical importance, for the safety of individual patients as well as for the outcome of the study.

2.6.2. Strong or potentially excessively powerful medication effects—Potent pharmacotherapies that retain patients well, such as opioid agonists, or agents where substance use is unlikely if adherence is assured (e.g., depot preparations of naltrexone for opioid dependence) generally require less intensive behavioral treatment platforms than those with partial or moderate effects. However, as noted above, lack of patient acceptance and adherence has produced disappointing results from agents with exquisitely powerful pharmacologic efficacy in the laboratory, such as disulfiram for alcohol dependence (Fuller et al., 1986) and naltrexone for opioid dependence (Rounsaville, 1995). Because these highly powerful agents require a sustained commitment to complete abstinence and frequent administration, potent behavioral interventions have been required to enable pharmacologic efficacy to translate into clinical effectiveness. For example, involving a spouse or significant other greatly improved disulfiram adherence and outcomes; similarly, providing incentives for naltrexone compliance also enhances compliance and hence outcome in naltrexone treatment of opioid dependence (Carroll et al., 2001; Chick et al., 1992; O'Farrell and Litten, 1992b; Preston et al., 1999).

2.6.3. Delayed medication effects—Before beneficial medication effects occur, patients are, effectively, receiving only behavioral treatment. In addition to receiving no initial positive benefit from medications with delayed actions, patients also frequently must tolerate unpleasant side effects that may occur immediately. When medication effects are known to be delayed, treatment should commence with a comparatively intensive behavioral treatment to keep patients engaged in treatment, manage aversive medication effects and foster abstinence or reduced drug use. This approach has been used successfully in antidepressant studies with substance abusers (Covey et al., 2002; Mason et al., 1999; McDowell et al., 2000; Petrakis et al., 1998; Schmitz et al., 2001a). The intensity of the behavioral approach can then be reduced following the optimal titration of medication dose. For example, contingency management might be used to initiate abstinence (through providing high-value incentives for abstinence) prior to the start of the randomized medication phase, and at the point of randomization, the contingencies could be changed such that medication compliance rather than abstinence would be reinforced to foster retention and adherence in the trial. A delayed and partial treatment effect is a particular limitation of the cocaine vaccine, which requires many weeks in order for sufficient antibody titers to be achieved and has cocaine elimination properties that can be readily overridden if patients relapse to uncontrolled heavy use prior achieving effective titer levels.

2.6.4. Medications requiring complex or frequent modes of delivery—When medication regimens are complex and require multiple daily dosing, behavioral therapies may need to target the medication-taking behaviors themselves while placing less emphasis on other salient issues such as reduction of drug use. For example, adherence with the complex multi-drug highly active retroviral treatment (HART) for HIV infection can be enhanced with electronically monitored dispensing and contingent rewards for timely self-administration (Rigsby et al., 2000), and compliance with the hepatitis B vaccine can likewise be enhanced with monetary incentives (Seal et al., 2003).

3. Strengths and limitations of potential behavioral therapies platforms

In the sections below and in Table 1, we evaluate several empirically supported behavioral therapies for substance use in terms of (1) their utility and specific strengths as behavioral platforms (e.g., producing abstinence, fostering compliance) and (2) their potential limitations as platforms (e.g., cost, generalizability, patient burden, compatibility with pharmacotherapy). While the range of behavioral approaches reviewed here is necessarily limited, we describe some of the most commonly used approaches currently used as platforms in medication trials. In many cases these reflect the authors' judgment derived from experience with these approaches in clinical trials; empirical support for many of these statements is lacking due to the relative rarity of medication trials with systematically evaluated the efficacy of behavioral platforms (e.g., 2×2 factorial designs). Moreover, the handful of studies that have used factorial designs to evaluate the level or type of behavioral therapy on medication compliance or effects uniformly indicate better outcomes for participants assigned to the higher intensity behavioral therapy (usually CBT) over the less intensive approach, either through main or interaction effects (Carroll et al., 2004; Carroll et al., 1998a; Carroll et al., 2000; Carroll et al., 1994b; Hall et al., 2002; Hall et al., 1998; Heinala et al., 2001; O'Malley et al., 1996; O'Malley et al., 1992; O'Malley et al., 2003; Schmitz et al., 2001b).

3.1. Low intensity treatments

Consisting of supportive approaches that emphasize medication adherence, low intensity treatments are typically administered by health care professionals (e.g., physicians, nurses) and in some cases by trained counselors. Sessions are typically brief (e.g., 15–30 min). Examples include Clinical Management from the NIMH Treatment of Depression Collaborative Research Program (Fawcett et al., 1987), the BRENDA approach (Pettinati et al., 2000; Volpicelli et al., 2001), the Medical Management used in Project Combine (Pettinati et al., in press) and in many smoking trials (Hall et al., 2002), primary care management models (O'Malley et al., 2003), and Compliance Enhancement (Carroll et al., 1998b). The strengths of these approaches as platforms include that they are of comparatively low cost, easy to learn and monitor, focus on medication adherence as a mechanism of change, and impose limited burdens on patient and staff in terms of time. Through offering patient support as well as opportunity for regular assessment of patient status, low intensity approaches can in many cases satisfy ethical considerations in placebo-controlled trials (Freedman, 1987; Levine, 1985; Street and Luoma, 2002).

The weaknesses of low intensity approaches include their comparatively low potency for treatment engagement, abstinence initiation or long-term relapse prevention. Because they typically do not offer 'active ingredients' of other behavioral therapies, these approaches typically do not exert a large effect on adherence or retention and may be difficult to implement over longer periods of time. Thus, they are most applicable in trials where the medication is expected to provide the bulk of the therapeutic effect, either because the severity of substance dependence or related problems is comparatively low or the effect of the medication is expected to be comparatively powerful. Because of these limitations, low-intensity treatments may be inappropriate for some placebo-controlled trials evaluating new agents of unknown efficacy, particularly for less stable populations (e.g., those with co-morbid psychiatric disorders).

3.2. Manualized drug counseling approaches

These approaches are based on traditional counseling strategies and emphasize the importance of abstinence as a treatment goal as well as involvement of self-help groups. These approaches are grounded in disease models of addiction and can be delivered in either

group or individual formats. Because they are manualized approximations of the counseling approach typical of many drug abuse treatment settings (e.g., 'treatment as usual'), these approaches have the additional advantage of being offering a less variable platform than typical 'treatment as usual' platforms, a critical consideration in the selection of an appropriate behavioral platform, particularly in large multisite studies. Examples of this type of approach include Individualized and Group Drug Counseling (Daley et al., 2002; Mercer and Woody, 1999) and Twelve Step Facilitation (Nowinski et al., 1992). Strengths of manualized counseling approaches include their high level of generalizability, familiarity to counselors and hence comparative ease of training, as well as their ability to target a range of patient concerns (e.g., abstinence, social issues). These approaches, which are intended to foster involvement in self-help groups, also can link patients to important, inexpensive, and enduring sources of community support. Moreover, recent trials have provided some evidence for their efficacy as stand-alone treatments (Crits-Christoph et al., 1999; Project MATCH Research Group, 1997) as well as their utility as behavioral platforms (Carroll et al., 1998a; Krystal et al., 2001).

Relative weaknesses of these approaches include their low to moderate potency and that there is as yet comparatively little evidence for the durability of their effects following treatment cessation. Because these approaches do not specifically address the role of medication in recovery or medication adherence, investigators must typically develop some alternate means of addressing medication adherence, for example through scheduling additional meetings with study physicians or other medical staff. Moreover, it is important to recognize that acceptance of pharmacotherapy, while increasing, remains variable in self-help groups (Rychtarik et al., 2000; Swift et al., 1998).

Thus, these approaches are most appropriate as platforms for potent or moderately effective non-agonist pharmacotherapies and may be more appropriate for more severely dependent populations. Manualized drug counseling approaches are also well-suited for effectiveness trials (Krystal et al., 2001) or trials where abstinence is desirable (e.g., evaluations of relapse prevention agents), and may also enhance durability of treatment effects if patients become firmly engaged in self-help groups.

3.3. Cognitive-behavioral approaches

Cognitive-behavioral approaches (CBT) are short-term approaches which attempt to foster abstinence by increasing patients' skills for coping with high risk situations and associated problems (Marlatt and Gordon, 1985). Several manualized CBT approaches are available for a range of substance-using populations (Annis and Davis, 1989; Carroll, 1998; Hall et al., 2002; Kadden et al., 1992; Monti et al., 1989; Rawson et al., 1995) and also offer a range of different intensities. Relative strengths of CBT as a behavioral platform includes its established efficacy (DeRubeis and Crits-Christoph, 1998; Irvin et al., 1999; Miller and Wilbourne, 2002c; Morgenstern and Longabaugh, 2000), its durability beyond the active treatment period (Carroll et al., 2000; Carroll et al., 1994b; Rawson et al., 2002) as well as emerging evidence that it may have a complementary role with some pharmacotherapies (Anton et al., 1999; Carroll et al., 2004; Carroll et al., 1998a; Hall et al., 2002; Heinala et al., 2001; O'Malley et al., 1996; O'Malley et al., 2003). CBT's efficacy across a range of different psychiatric disorders (DeRubeis and Crits-Christoph, 1998) also makes this approach attractive for trials targeting populations with dual disorders (Brown et al., 1997; George et al., 2000; Mason et al., 1999; McDowell et al., 2000; Nunes et al., 1998; Patten et al., 1998; Schmitz et al., 2001a). Relative weaknesses of CBT are that comparatively extensive staff training is needed to learn to implement CBT effectively (Morgenstern et al., 2001; Sholomskas et al., 2002). CBT can also be comparatively demanding on patients and may be particularly challenging for patients with cognitive limitations due to intoxication or substance-induced neuropsychologic impairment (Aharonovich et al., 2003).

Thus, CBT is most appropriate for trials where the experimental agent is expected to yield moderate to weak effects and for trials involving complex co-morbid populations. CBT can be used in both efficacy and effectiveness studies, and may be particularly useful in studies where the experimental medication may not directly affect drug use (e.g., medications that target co-morbid conditions).

3.4. Contingency management

Contingency management (CM) approaches provide rewards or incentives for verifiable, targeted behaviors, such as abstinence as verified by drug-free urine toxicology screens. Examples include take-home doses for methadone maintained patients who abstain from substance use (Stitzer et al., 1986; Stitzer et al., 1992), vouchers redeemable for goods and services to patients who provide drug free urine samples (Higgins et al., 1993; Silverman et al., 1998), and variable-ratio reinforcement of abstinence (low-cost contingency management) where patients can earn the opportunity to draw lots for prizes contingent on abstinence (Petry and Martin, 2002; Petry et al., 2000).

Strengths of CM as a behavioral platform include, in particular, compelling evidence for its potency in a number of populations, and settings (DeRubeis and Crits-Christoph, 1998; Griffith et al., 2000), as well as its flexibility and specificity. That is, CM has the unique advantage in that it can be used to target very specific goals and thus can be used in pharmacotherapy trials to address specific weaknesses of medications. For example, in a trial where adherence is expected to be problematic, incentives can be used specifically to target medication adherence (Preston et al., 1999). In extended trials where it may be difficult to encourage patients to continue to attend data collection sessions, CM might be used specifically to patients reward patients for attending assessment sessions (for example, patients might receive cash bonuses for attending consecutive assessment sessions or for completing all scheduled follow-up evaluations).

Weaknesses of CM include the cost of the incentives, the need for specialized personnel to deliver contingencies effectively, and as-yet limited acceptance of CM in general clinical practice (Petry, 2000; Petry et al., 2001). This consideration in turn limits the potential generalizability of trials utilizing CM as a platform. Moreover, when abstinence is targeted by incentives, CM's potency may lead to ceiling effects that can obscure detection of medication effects. Thus, CM as a behavioral platform is best suited to efficacy, rather than effectiveness trials. Nevertheless, CM's potency, as well as the specificity and precision with which contingencies can be targeted makes CM an appealing choice for trials that require attention to particular weaknesses of an agent, such as need for sustained abstinence, abstinence initiation, or medication adherence issues.

3.5. Motivational interviewing

Motivational interviewing (MI) (Miller and Rollnick, 2002b) is a brief approach which seeks to bring about rapid commitment to change problem behaviors. MI has achieved a high level of empirical support in alcohol-dependent populations (Bien et al., 1993; Miller and Wilbourne, 2002c; Wilk et al., 1997) and more recently in a range of other substance-abusing populations (Dunn et al., 2001). MI's strengths as a behavioral platform include its high level of acceptability to patients and staff and its applicability to a broad range of populations, settings, and problems. MI techniques may be crucial to deal with treatment engagement issues, particularly for pharmacotherapies that entail major patient burden or side effects.

In terms of weakness, MI's brevity may render it difficult to implement over extended trials. Thus, it may be best suited to enhance treatment engagement in shorter trials. Recent data

also suggests that it may be challenging to training line clinicians to use MI effectively (Miller and Mount, 2001; Rubel et al., 2000). Finally, because patients are free to select their own goals for treatment, MI may not be compatible for trials where abstinence is essential and thus MI's efficacy and role in fostering medication adherence is not yet clear.

3.6. Family and couples approaches

Family and couples approaches encompass a broad range of treatment approaches and modalities which share the common feature that at least one member of the patient's family is directly involved in treatment. Although level of efficacy varies with the specific type of family/couples intervention, empirical support for several types of family/couples treatment is strong (Stanton and Shadish, 1997) and there is evidence that involving the patient's spouse in treatment can foster medication adherence, particularly where compliance contracts are used (Carroll et al., 2001; Chick et al., 1992; Fals-Stewart et al., 1997; O'Farrell et al., 1992a; O'Farrell and Litten, 1992b).

Strengths of family/couples approaches as behavioral platforms include that family members can be powerful advocates of treatment compliance and that family involvement in treatment may foster enduring benefits. Moreover, family involvement may be essential to successful medication adherence and treatment retention with some specialized populations, including adolescents (Huey et al., 2000). Weaknesses include limited generalizability, in that studies which require the involvement of significant others will necessarily be limited to the subset of patients who have comparatively strong social supports and family members who are willing to participate in treatment. Also, family-based approaches are comparatively complex and typically require extensive counselor training (Henggeler et al., 1997; Szapocznik et al., 1988).

4. Will the study address pharmacotherapy efficacy or psychotherapy/ pharmacotherapy interactions?

The choice of a two-cell or factorial (2×2) design where level of pharmacotherapy (e.g., experimental medication versus placebo) is crossed with more than one level of behavioral therapy often rests upon considerations such as whether the medication is anticipated to be a stand-alone treatment or whether complementary behavioral therapies are hypothesized to be necessary to detect a drug effect. Stage of scientific knowledge regarding the medication is also a consideration. That is, initial trials of new agents typically use a 2-cell design where the medication is compared with placebo or a reference pharmacotherapy in the context of a single behavioral platform. Follow-up or replication trials may include two intensities or types of behavior therapy to explore, for example, the minimal intensity of platform within which medication effects can be detected versus whether medication effects can be maximized in the context of a more potent behavioral therapy. Phase III 'effectiveness' studies often attempt to replicate the very low anticipated levels of psychosocial support and intervention available in usual clinical practice. However, those Phase III trials that have specified and monitored the behavioral support patients receive (Krystal et al., 2001) have typically had higher rates of adherence and retention than those that have not (Fudala et al., 2003).

While factorial designs are inherently more complicated, expensive, and require larger sample sizes, and hence are comparatively infrequent in the substance abuse treatment literature, such designs are the sole means of efficiently determining whether a medication's effects vary with the behavioral context in which it is delivered. Questions such as 'What is the minimum level of behavioral support with which this medication can be administered effectively?' and 'To what extent can additional behavioral therapies maximize this

medication's therapeutic effect?' require factorial designs. Moreover, failure to examine the effect of different intensities of behavioral platforms on a medication's effects may lead to restrictions in FDA labeling once the medication is approved, as was the case with naltrexone for alcohol dependence.

5. How intensive should the behavioral platform be?

An additional consideration in the selection of a behavioral platform is the appropriate intensity of the therapy so that the effects of the behavioral therapy do not overwhelm or obscure medication effects. Again, this requires consideration of the target of the behavioral platform, the needs of the population to be treated, the anticipated size of the medication effect, and the level of the medication's development.

Ceiling effects are most likely when both the behavioral platform and the medication have the same target, such as reduced substance use. For example, medication effects could easily be overwhelmed in a trial that used as a platform contingency management with incentives of high value for abstinence, but ceiling effects would be less likely if the contingencies were used solely to reward medication adherence or treatment retention. Lower-intensity platforms should reduce the likelihood of ceiling effects. However, the complexity and severity of the population to be treated is also a consideration, in that a low-intensity platform would be appropriate for mildly depressed, low-severity alcohol abusers but would clearly be inadequate for drug-abusing schizophrenics.

Ceiling effects of behavioral platforms have been cited as obscuring detection of effects of medications of low- to moderate effect size (Covey et al., 2002), but at least three factors mitigate this concern. First, inclusion of a behavioral platform should affect both the experimental and control conditions equally in most cases (e.g., adding a constant to the determination of effect size). Second, a medication effect that is meaningful should be detectable in the context of low-to moderate behavioral therapies, which are also likely to be the standard of care in clinical practice. Third, the costs in statistical power and the threats to internal validity associated with uncontrolled behavioral treatments may be more likely than ceiling effects of carefully selected behavioral platforms to overwhelm medication effects (Carroll, 1997).

6. Generalizability considerations

All clinical trials represent a trade-off between internal and external validity, and selection of a behavioral platform must be considered in striving for the appropriate balance of these issues. Generally, initial efficacy testing of a novel medication might utilize a behavioral platform that optimizes the ability to detect a hypothesized drug effect. However, inclusion of a behavioral platform that exceeds any reasonable bounds (e.g., initial 28 day hospitalization before starting medications, contingency management that involves thousands of dollars in incentives, requirement of full scale psychoanalysis as the behavioral treatment) may so limit generalizability that the goals of the pharmacotherapy efficacy testing are undermined. If extensive, non-standard behavioral platforms are included, some assessment of cost effectiveness issues should be incorporated into the study design to provide data around possible benefits that justify the more extensive treatment. Later Phase III effectiveness trials might use low intensity approaches which more closely approximate 'treatment as usual' but which impose some guidelines to reduce variability across sites (e.g., restrictions on number and type of behavioral sessions).

7. Examples

7.1. Cocaine vaccine trials and behavioral platforms of CBT and CM

As noted above, CBT has demonstrated efficacy in treating cocaine or alcohol dependence relative to other psychotherapies and in enhancing the effects of the pharmacotherapy employed (Carroll et al., 1998a; Carroll et al., 1994a; Hall et al., 2002; Hall et al., 1998). Several studies demonstrate that when examined at 1-year follow-up, many more of the CBT treated patients had sustained abstinence than patients assigned to supportive clinical management. This delayed efficacy of CBT has been found with either desipramine (Carroll et al., 1994b) or disulfiram for cocaine dependence (Carroll et al., 2000), and with naltrexone for alcohol dependence (O'Malley et al., 1996). All three of these medications are thought to be effective due to a reduction in the priming effect of the abused substance, but this reduction in priming is indirect. A vaccine can reduce the priming effect directly and relatively potently, since the vaccine prevents the rapid entry of cocaine into the brain, where priming occurs. Thus, this synergism between CBT and an antipriming medication should be particularly powerful with this vaccine. Furthermore, CBT might have sustained efficacy for relapse prevention even after the antibody levels decline.

Thus, the limitations of a vaccine may be well addressed by a synergism between the vaccine and CBT. One aspect of this synergism is that CBT's short-term, focused approach may help cocaine-dependent individuals cope with specific situations and stimuli that can trigger "slips" and lead to full relapses. The vaccine's target of slips that occur in spite of avoiding these triggers also addresses a potential limitation of CBT. A second synergism is CBT's ability to sustain long-term abstinence over 6–12 months, which appears better than other therapies and which addresses the vaccine's limitation of declining antibody levels after 9–12 months. A specific choice of CBT is based on its strength to hold patients in treatment, but it is not so strong as to eliminate the possibility for any medication effects. As counter examples, low intensity clinical management approaches may be too weak to hold patients, while CM tends to produce very high rates of abstinence without any medications. Thus, CM serves as an excellent means to induce initial abstinence and may be very helpful during the induction phase of active vaccination, where it takes up to 8 weeks of repeated vaccination in order to attain therapeutic antibody levels (Kosten et al., 2002b). Thus, behavioral platforms may also change during the course of a clinical trial in order to have optimal efficacy with the medication being tested.

7.2. CM and Bupropion for depressed cocaine abusing methadone patients

We have demonstrated a significant synergism between contingency management (CM) and the antidepressant desipramine (DMI) in reducing cocaine use in an opioid-maintained population (Kosten et al., 2004). In that study we showed that a particular strength of CM may be in establishing initial cocaine abstinence, because initial abstinence has been an important prognostic factor for pharmacotherapy for cocaine abuse (Sofuoglu et al., 2002, under review). Similarly, in a study of mazindol for cocaine abusing methadone maintained patients, we found that those patients with 2 weeks of abstinence before entering this trial had a substantially better reduction in cocaine use (Margolin et al., 1997). Similar findings on initial abstinence predictors of success have been shown with other cocaine pharmacotherapies (Alterman et al., 1997; Kampman et al., 2001; Mulvaney et al., 1999). Alterman found across four studies that patients with a urine indicative of recent cocaine use at intake to the treatment study were less than half as likely to complete treatment or achieve initial abstinence. This concept of initial abstinence also appears important for the pharmacotherapy of other abused substances such as alcohol, where naltrexone is best at reducing relapse after an initial alcohol free period through detoxification, for example (O'Malley et al., 1992; Volpicelli et al., 1992). Thus, the synergism between CM and

bupropion may include establishing initial abstinence as an enhancing effect on medication efficacy.

This synergism may also be based on the limitations of CM. Griffith et al. (Griffith et al., 2000) conducted a meta-analysis of the CM studies done in methadone treatment settings focusing on urine toxicology outcomes and found a modest effect size of 0.25 based on 30 studies. This effect size is smaller than that reported for CM studies with primary cocaine dependence. Data from Higgins (Higgins et al., 1994; Higgins et al., 1993; Higgins et al., 1991), and others suggest that CM effects tend to be poorly sustained after the contingencies are discontinued (Higgins et al., 2000a; Higgins et al., 2000b; Petry and Martin, 2002; Silverman et al., 1998). However, a synergy between CM and medications such as the antidepressant bupropion may facilitate successful abstinence, because these two approaches act through different mechanisms with the intensity of intervention changing along different dimensions. For instance, CM procedures act by reinforcing and learning non-drug-taking behaviors, but learning these behaviors can be impaired by depressive symptoms as well as neurobiologic abnormalities induced by the cocaine such as the up-regulated dopamine transporter. As an example of the neurobiologic abnormalities, neuroimaging studies using PET have demonstrated a marked reduction in dopamine D2 receptor binding, while SPECT analyses have shown an increase in the dopamine transporter (DAT) which persisted for weeks after cessation of cocaine intake (Best et al., 1994; Little et al., 1999; Malison et al., 1998; Volkow et al., 1990). Thus, neurobiologic abnormalities might be addressed by medications such as bupropion, which can normalize the 25% DAT upregulation that has been described in these patients, and thereby complement the behavioral interventions (Malison et al., 1998).

8. Summary

In clinical practice and in clinical trials, the best outcomes tend to be associated with combinations of pharmacotherapies and behavioral therapies, rather than either form of treatment delivered alone. However, in neither case should the selection of the behavioral approach be arbitrary. Because behavioral therapies can broaden, strengthen and enhance the durability of pharmacotherapies like methadone, disulfiram, and naltrexone, the judicious selection of an appropriate behavioral platform can facilitate more efficient and less costly medication trials with drug users.

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References

- Aharonovich E, Nunes EV, Hasin D. Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. *Drug Alcohol Depend.* 2003; 71:207–211. [PubMed: 12927659]
- Alterman AI, Kampman KM, Boardman C, Cacciola JS, Rutherford MJ, McKay JR, Maany I. A cocaine-positive baseline urine predicts outpatient treatment attrition and failure to attain initial abstinence. *Drug Alcohol Depend.* 1997; 46:79–85. [PubMed: 9246555]
- Annis, HM.; Davis, CS. Relapse prevention. In: Hester, RK.; Miller, WR., editors. *Handbook of Alcoholism Treatment Approaches*. Pergamon Press; New York: 1989. p. 170-182.
- Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK. Naltrexone and cognitive-behavioral therapy for the treatment of outpatient alcoholics: Results of a placebo-controlled trial. *Am J Psychiatry.* 1999; 156:1758–1764. [PubMed: 10553740]

- Babor TF. Avoiding the horrid and beastly sin of drunkenness: Does dissuasion make a difference. *J Consult Clin Psychol*. 1994; 62:1127–1140. [PubMed: 7860811]
- Best, SE.; Malison, RT.; Wallace, EA.; Zoghbi, SS.; Zea-Ponce, Y.; Baldwin, RM.; Innis, RB.; Kosten, TR. SPECT imaging of the dopamine transporter in cocaine abstinence: preliminary studies using [¹²³I]b-CIT. In: Harris, LS., editor. *Problems of Drug Dependence, 1994*, National Institute on Drug Abuse Research Monograph. Vol. 153. NIDA; Washington, DC: 1994.
- Bien TH, Miller WR, Tonigan JS. Brief interventions for alcohol problems: a review. *Addiction*. 1993; 88:315–335. [PubMed: 8461850]
- Brown RA, Evans DM, Miller IW, Burgess ES, Mueller TI. Cognitive-behavioral treatment for depression in alcoholism. *J Consult Clin Psychol*. 1997; 65:715–726. [PubMed: 9337490]
- Carroll, KM. *Therapy Manuals for Drug Addiction*. NIDA; Rockville, Maryland: 1998. A cognitive-behavioral approach: treating cocaine addiction.
- Carroll KM. Manual guided psychosocial treatment: a new virtual requirement for pharmacotherapy trials. *Arch Gen Psychiatry*. 1997; 54:923–928. [PubMed: 9337772]
- Carroll KM, Ball SA, Nich C, O'Connor PG, Eagan D, Frankforter TL, Triffleman EG, Shi J, Rounsaville BJ. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: Efficacy of contingency management and significant other involvement. *Arch Gen Psychiatry*. 2001; 58:755–761. [PubMed: 11483141]
- Carroll KM, Fenton LR, Ball SA, Nich C, Frankforter TL, Shi J, Rounsaville BJ. Efficacy of disulfiram and cognitive-behavioral therapy in cocaine-dependent outpatients. A randomized placebo-controlled trial. *Arch Gen Psychiatry*. 2004; 61:264–272. [PubMed: 14993114]
- Carroll KM, Nich C, Ball SA, McCance-Katz E, Rounsaville BJ. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction*. 1998a; 93:713–728. [PubMed: 9692270]
- Carroll KM, Nich C, Ball SA, McCance-Katz EF, Frankforter TF, Rounsaville BJ. One year follow-up of disulfiram and psychotherapy for cocaine-alcohol abusers: Sustained effects of treatment. *Addiction*. 2000; 95:1335–1349. [PubMed: 11048353]
- Carroll, KM.; Nuro, KF.; Rounsaville, BJ.; Petrakis, I. *Compliance Enhancement: A Clinician's Manual for Pharmacotherapy Trials in the Addictions*: Unpublished manual. Yale University Psychotherapy Development Center; 1998b.
- Carroll KM, Rounsaville BJ, Gordon LT, Nich C, Jatlow PM, Bisighini RM, Gawin FH. Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Arch Gen Psychiatry*. 1994a; 51:177–197. [PubMed: 8122955]
- Carroll KM, Rounsaville BJ, Nich C, Gordon LT, Wirtz PW, Gawin FH. One year follow-up of psychotherapy and pharmacotherapy for cocaine dependence: delayed emergence of psychotherapy effects. *Arch Gen Psychiatry*. 1994b; 51:989–997. [PubMed: 7979888]
- Chick J, Gough K, Falkowski W, Kershaw P, Hore B, Mehta B, Ritson B, Ropner R, Torley D. Disulfiram treatment of alcoholism. *Br J Psychiatry*. 1992; 161:84–89. [PubMed: 1638335]
- Covey LS, Glassman AH, Stetner F, Rivelli S, Stage K. A randomized trial of sertraline as a cessation aid for smokers with a history of major depression. *Am J Psychiatry*. 2002; 159:1731–1737. [PubMed: 12359680]
- Crits-Christoph P, Siqueland L, Blaine JD, Frank A, Luborsky L, Onken LS, Muenz L, Thase ME, Weiss RD, Gastfriend DR, Woody G, Barber JP, Butler S, Dale D, Salloum I, Bishop S, Najavits L, Lis J. Psychosocial treatments for cocaine dependence: results of the National Institute on drug abuse collaborative cocaine study. *Arch Gen Psychiatry*. 1999; 56:495–502.
- Daley, DC.; Mercer, D.; Carpenter, G. *Therapy Manuals for Drug Addiction*. NIDA; Bethesda, MD: 2002. *Drug Counseling for Cocaine Addiction: The Collaborative Cocaine Treatment Study Model*.
- de Lima MS, de Oliveira Soares BG, Reisser AA, Farrell M. Pharmacological treatment of cocaine dependence: a systematic review. *Addiction*. 2002; 97:931–949. [PubMed: 12144591]
- DeRubeis RJ, Crits-Christoph P. Empirically supported individual and group psychological treatments for adult mental disorders. *J Consult Clin Psychol*. 1998; 66:37–52. [PubMed: 9489261]

- Dunn C, Deroo I, Rivara FP. The use of brief interventions adapted from motivational interviewing across behavioral domains: a systematic review. *Addiction*. 2001; 96:1725–1742. [PubMed: 11784466]
- Fals-Stewart W, O'Farrell TJ, Birchler GR. Behavioral couples therapy for male substance-abusing patients: A cost outcomes analysis. *J Consult Clin Psychol*. 1997; 65:789–802. [PubMed: 9337498]
- Fawcett J, Epstein P, Fiester SJ, Elkin I, Autry JH. Clinical management-imipramine/placebo administration manual: NIMH treatment of depression collaborative research program. *Psychopharmacol Bull*. 1987; 23:309–324. [PubMed: 3303100]
- Feinstein, AR. Compliance bias and the interpretation of therapeutic trials. In: Haynes, RB.; Taylor, DW.; Sackett, DL., editors. *Compliance in Healthcare*. Johns Hopkins Press; Baltimore, MD: 1979. p. 309-322.
- Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med*. 1987; 317:141–145. [PubMed: 3600702]
- Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiange CN, Jones K, Collins JF, Raisch D, Casadonte P, Goldsmith RJ, Ling W, Malkerneker U, McNicholas L, Renner J, Stine S, Tusel DJ. for the Buprenorphine/Naloxone Collaborative Study Group. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med*. 2003; 329:949–958. [PubMed: 12954743]
- Fuller RK, Branchey L, Brightwell DR, Derman RM, Emrick CD, Iber FL, James KE, Lacoursiere RB, Lee KK, Lowenstam I. Disulfiram treatment of alcoholism: a Veterans Administration cooperative study. *JAMA*. 1986; 256:1449–1455. [PubMed: 3528541]
- George TP, Ziedonis DM, Feingold A, Pepper WT, Satterburg CA, Winkel J, Rounsaville BJ, Kosten TR. Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenics. *Am J Psychiatry*. 2000; 157:1835–1842. [PubMed: 11058482]
- Griffith JD, Rowan-Szal GA, Roark RR, Simpson DD. Contingency management in outpatient methadone treatment: a meta-analysis. *Drug Alcohol Depend*. 2000; 58:55–66. [PubMed: 10669055]
- Hall SM, Humfleet GL, Reus VI, Munoz RF, Hartz DT, Maude-Griffin PM. Psychological intervention and antidepressant treatment in smoking cessation. *Arch Gen Psychiatry*. 2002; 59:930–936. [PubMed: 12365880]
- Hall SM, Reus VI, Munoz RF, Sees KL, Humfleet G, Hartz DT, Frederick S, Triffleman EG. Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. *Arch Gen Psychiatry*. 1998; 55:683–690. [PubMed: 9707377]
- Heinala P, Alho H, Kiianmaa K, Lonnqvist J, Kuoppalalmi K, Sinclair JD. Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double blind, placebo controlled trial. *J Consult Clin Psychol*. 2001; 21:287–292.
- Henggeler SW, Melton GB, Brondino MJ, Scherer DG, Hanley JH. Multisystemic therapy with violent and chronic juvenile offenders and their families: the role of treatment fidelity. *J Consult Clin Psychol*. 1997; 65:821–833. [PubMed: 9337501]
- Higgins ST, Badger GJ, Budney AJ. Initial abstinence and success in achieving longer term cocaine abstinence. *Exp Clin Psychopharmacol*. 2000a; 8:377–386. [PubMed: 10975629]
- Higgins ST, Budney AJ, Bickel WK, Foerg FE, Donham R, Badger GJ. Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. *Arch Gen Psychiatry*. 1994; 51:568–576. [PubMed: 8031230]
- Higgins ST, Budney AJ, Bickel WK, Hughes JR. Achieving cocaine abstinence with a behavioral approach. *Am J Psychiatry*. 1993; 150:763–769. [PubMed: 8480823]
- Higgins ST, Delany DD, Budney AJ, Bickel WK, Hughes JR, Foerg F, Fenwick JW. A behavioral approach to achieving initial cocaine abstinence. *Am J Psychiatry*. 1991; 148:1218–1224. [PubMed: 1883001]
- Higgins ST, Wong CJ, Badger GJ, Haug-Ogden DE, Dantona RL. Contingent reinforcement increases cocaine abstinence during outpatient treatment and one year follow-up. *J Consult Clin Psychol*. 2000b; 68:64–72. [PubMed: 10710841]

- Huey SJ, Hennegler SW, Brondino MJ, Pickrel SG. Mechanisms of change in multisystemic therapy: reducing delinquent behavior through therapist adherence and improved family and peer functioning. *J Consult Clin Psychol*. 2000; 68:451–467. [PubMed: 10883562]
- Irvin JE, Bowers CA, Dunn ME, Wong MC. Efficacy of relapse prevention: a meta-analytic review. *J Consult Clin Psychol*. 1999; 67:563–570. [PubMed: 10450627]
- Kadden, R.; Carroll, KM.; Donovan, D.; Cooney, JL.; Monti, P.; Abrams, D.; Litt, M.; Hester, RK. Cognitive-behavioral Coping Skills Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals with Alcohol Abuse and Dependence Project MATCH Monograph Series. Vol. 3. NIAAA; Rockville, MD: 1992.
- Kampman KM, Alterman AI, Volpicelli JR, Maany I, Muller ES, Luce DL, Mulholland EM, Jawad AF, Parikh GA, Mulvaney FD, Weinrieb RM, O'Brien CP. Cocaine withdrawal symptoms and initial urine toxicology results predict treatment attrition in outpatient dependence treatment. *Psychol Addict Behav*. 2001; 15:52–59. [PubMed: 11255939]
- Kosten TR, Biegel D. Therapeutic vaccines for substance dependence. *Expert Rev Vaccines*. 2002a; 1:363–371. [PubMed: 12901575]
- Kosten TR, Oliveto A, Feingold A, Poling J, Sevarino K, McCance-Katz E, Stine S, Gonzalez G, Gonsai K. Desipramine and contingency management for cocaine and opiate dependence in buprenorphine maintained patients. *Drug Alcohol Depend*. 2004; 70:315–328. [PubMed: 12757969]
- Kosten TR, Rosen MI, Bond I, Settles M, Roberts JS, Shields J, Jack L, Fox B. Human therapeutic cocaine vaccine: Safety and immunogenicity. *Vaccine*. 2002b; 20:1196–1204. [PubMed: 11803082]
- Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA. for the Naltrexone Cooperative Study 425 Group. Naltrexone in the treatment of alcohol dependence. *N Engl J Med*. 2001; 345:1734–1739. [PubMed: 11742047]
- Lavori PW. Clinical trials in psychiatry: should protocol deviation censor patient data. *Neuropsychopharmacology*. 1992; 6:39–48. [PubMed: 1571068]
- Leshner AI. Science-based views of drug addiction and its treatment. *JAMA*. 1999; 282:1314–1316. [PubMed: 10527162]
- Levine RJ. The use of placebos in randomized clinical trials. *IRB: Rev Hum Subj Res*. 1985; 7:1–4.
- Little KY, Zhang L, Desmond T, Frey KA, Dalack GW, Cassin BJ. Striatal dopaminergic abnormalities in human cocaine users. *Am J Psychiatry*. 1999; 156:238–245. [PubMed: 9989560]
- Malison RT, Best SE, van Dyck CH, McCance-Katz EF, Wallace EA, Laruelle M, Baldwin RM, Seibyl JP, Price LH, Kosten TR, Innis RB. Elevated striatal dopamine transporters during acute cocaine abstinence as measured by [¹²³I]-CIT SPECT. *Am J Psychiatry*. 1998; 155:832–834. [PubMed: 9619159]
- Margolin A, Avants SK, Malison RT, Kosten TR. High- and low-dose mazindol for cocaine dependence in methadone-maintained patients: a preliminary evaluation. *Subst Abus*. 1997; 18:125–131.
- Marlatt, GA.; Gordon, JR. Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors. Guilford Press; New York: 1985.
- Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB. A double-blind, placebo controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry*. 1999; 56:719–724. [PubMed: 10435606]
- McDowell DM, Levin FR, Seracini AM, Nunes EV. Venlafaxine treatment of cocaine abusers with depressive disorders. *Am J Drug Alcohol Abuse*. 2000; 26:25–31. [PubMed: 10718161]
- McLellan AT, Arndt IO, Metzger D, Woody GE, O'Brien CP. The effects of psychosocial services in substance abuse treatment. *JAMA*. 1993; 269:1953–1959. [PubMed: 8385230]
- Mercer, DE.; Woody, GE. An Individual Drug Counseling Approach to Treat Cocaine Addiction: The Collaborative Cocaine Treatment Study Model. NIDA; Rockville, MD: 1999.
- Miller FG. Placebo controlled trials in psychiatric research: An ethical perspective. *Biol Psychiatry*. 2000a; 47:707–716. [PubMed: 10773177]
- Miller FG, Brody H. What makes placebo controlled trials unethical. *Am J Bioeth*. 2002a; 2:3–9. [PubMed: 12189059]

- Miller WR. Rediscovering fire: Small interventions, large effects. *Psychol Addict Behav.* 2000b; 14:6–18. [PubMed: 10822741]
- Miller WR, Mount KA. A small study of training in motivational interviewing: Does one workshop change clinician and client behavior. *Behav Cogn Psychother.* 2001; 29:457–471.
- Miller, WR.; Rollnick, S. *Motivational Interviewing: Preparing People for Change.* 2. Guilford Press; New York: 2002b.
- Miller WR, Wilbourne PL. Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction.* 2002c; 97:265–277. [PubMed: 11964100]
- Modesto-Lowe V, Van Kirk J. Clinical uses of naltrexone: a review of the evidence. *Exp Clin Psychopharmacol.* 2002; 10:213–227. [PubMed: 12233982]
- Monti, PM.; Rohsenow, DJ.; Abrams, DB.; Zwick, WR.; Binkoff, JA.; Munroe, SM.; Fingeret, AL.; Nirenberg, TD.; Liepman, MR.; Pedrasa, M.; Kadden, RM.; Cooney, JL. *Treating Alcohol Dependence: A Coping Skills Training Guide in the Treatment of Alcoholism.* Guilford Press; New York: 1989.
- Morgenstern J, Longabaugh R. Cognitive-behavioral treatment for alcohol dependence: A review of the evidence for its hypothesized mechanisms of action. *Addiction.* 2000; 95:1475–1490. [PubMed: 11070524]
- Morgenstern J, Morgan TJ, McCrady BS, Keller DS, Carroll KM. Manual-guided cognitive behavioral therapy training: A promising method for disseminating empirically supported substance abuse treatments to the practice community. *Psychol Addict Behav.* 2001; 15:83–88. [PubMed: 11419234]
- Mulvaney FD, Alterman AI, Boardman CR, Kampman KM. Severity of cocaine use and prediction of treatment attrition. *J Subst Abus Treat.* 1999; 16:129–135.
- National Institute on Drug Abuse. *Principles of Drug Abuse Treatment: A Research-Based Guide.* NIDA; Bethesda, Maryland: 2000.
- Nowinski, J.; Baker, S.; Carroll, KM. *Project MATCH Monograph Series. Vol. 1. NIAAA; Rockville, MD: 1992. Twelve-Step Facilitation Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals with Alcohol Abuse and Dependence.*
- Nunes EV, Quitkin FM, Donovan SJ, Deliyannides D, Ocepek-Welikson K, Koenig T, Brady R, McGrath PJ, Woody GE. Imipramine treatment of opiate dependent patients with depressive disorders: A placebo-controlled trial. *Arch Gen Psychiatry.* 1998; 55:153–160. [PubMed: 9477929]
- O'Brien CP. A range of research-based pharmacotherapies for addiction. *Science.* 1997; 278:66–70. [PubMed: 9311929]
- O'Farrell TJ, Cutter HS, Choquette KA, Floyd FJ. Behavioral marital therapy for male alcoholics: Marital and drinking adjustment during two years after treatment. *Behav Ther.* 1992a; 23:529–549.
- O'Farrell TJ, Litten RZ. Techniques to enhance compliance with disulfiram. *Alcohol Clin Exp Res.* 1992b; 16:1035–1041. [PubMed: 1471757]
- O'Malley SS, Jaffe AJ, Chang G, Rode S, Schottenfeld R, Meyer RE, Rounsaville BJ. Six month follow-up of naltrexone and psychotherapy for alcohol dependence. *Arch Gen Psychiatry.* 1996; 53:217–224. [PubMed: 8611058]
- O'Malley SS, Jaffe AJ, Chang G, Schottenfeld R, Meyer RE, Rounsaville BJ. Naltrexone and coping skills therapy for alcohol dependence: A controlled study. *Arch Gen Psychiatry.* 1992; 49:881–887. [PubMed: 1444726]
- O'Malley SS, Rounsaville BJ, Farren C, Namkoong K, Wu R, Robinson J, O'Connor PG. Initial and maintenance naltrexone treatment for alcohol dependence using primary care vs. specialty care: a nested sequence of three randomized trials. *Arch Int Med.* 2003; 163:1695–1704. [PubMed: 12885685]
- Owens SM. Antibodies as pharmacokinetic and metabolic modifiers of neurotoxicity. *NIDA Res Monogr Ser.* 1997; 173:259–272.
- Patten CA, Martin JE, Myers MG, Calfas KJ, Williams CD. Effectiveness of cognitive-behavioral therapy for smokers with histories of alcohol dependence and depression. *J Stud Alcohol.* 1998; 59:327–335. [PubMed: 9598714]

- Petrakis I, Carroll KM, Gordon LT, Nich C, Kosten TR, Rounsaville BJ. Fluoxetine treatment of depressive disorders in methadone maintained opioid addicts. *Drug Alcohol Depend.* 1998; 50:221–226. [PubMed: 9649975]
- Petry NM. A comprehensive guide to the application of contingency management procedures in clinical settings. *Drug Alcohol Depend.* 2000; 58:9–25. [PubMed: 10669051]
- Petry NM, Martin B. Low-cost contingency management for treating cocaine- and opioid abusing methadone patients. *J Consult Clin Psychol.* 2002; 70:398–405. [PubMed: 11952198]
- Petry NM, Martin B, Cooney JL, Kranzler HR. Give them prizes and they will come: Contingency management treatment of alcohol dependence. *J Consult Clin Psychol.* 2000; 68:250–257. [PubMed: 10780125]
- Petry NM, Petrakis I, Trevisan L, Wiredu L, Boutros N, Martin B, Kosten TR. Contingency management interventions: From research to practice. *Am J Psychiatry.* 2001; 20:33–44.
- Pettinati HM, Volpicelli JR, Pierce JD, O'Brien CP. Improving naltrexone response: An intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. *J Addict Dis.* 2000; 19:71–83. [PubMed: 10772604]
- Pettinati, HM.; Weiss, RD.; Miller, WR.; Donovan, D.; Rounsaville, BJ. Medical Management (MM) Treatment Manual: A Guide for Medically-Trained Clinicians Providing Pharmacotherapy as Part of the Treatment of Alcohol Dependence. NIAAA; Bethesda, MD: in press
- Preston KL, Silverman K, Umbricht A, DeJesus A, Montoya ID, Schuster CR. Improvement in naltrexone treatment compliance with contingency management. *Drug Alcohol Depend.* 1999; 54:127–135. [PubMed: 10217552]
- Project MATCH Research Group. Matching Alcohol Treatments to Client Heterogeneity: Project MATCH posttreatment drinking outcomes. *J Stud Alcohol.* 1997; 58:7–29. [PubMed: 8979210]
- Rawson RA, Huber A, McCann MJ, Shoptaw S, Farabee D, Reiber C, Ling W. A comparison of contingency management and cognitive-behavioral approaches during methadone maintenance for cocaine dependence. *Arch Gen Psychiatry.* 2002; 59:817–824. [PubMed: 12215081]
- Rawson RA, Shoptaw SJ, Obert JL, McCann MJ, Hasson AL, Marinelli Casey PJ, Brethen PR, Ling W. An intensive outpatient approach for cocaine abuse treatment: The Matrix model. *J Subst Abuse Treat.* 1995; 12:117–127.
- Rigsby MO, Rosen MI, Beauvais J, Cramer JA, Rainey PM, O'Malley SS, Dieckhaus KD, Rounsaville BJ. Cue dose training with monetary reinforcement: Pilot study of an antiretroviral adherence intervention. *J Gen Int Med.* 2000; 15:841–847.
- Rohsenow DJ, Colby SM, Monti PM, Swift RM, Martin RA, Mueller TI, Gordon A, Eaton CA. Predictors of compliance with naltrexone among alcoholics. *Alcohol Clin Exp Res.* 2000; 24:1542–1549. [PubMed: 11045863]
- Rounsaville, BJ. Can psychotherapy rescue naltrexone treatment of opioid addiction?. In: Onken, LS.; Blaine, JD., editors. *Potentiating the Efficacy of Medications: Integrating Psychosocial Therapies with Pharmacotherapies in the Treatment of Drug Dependence.* NIDA; Rockville, MD: 1995. p. 37-52.
- Rubel EC, Sobell LC, Miller WR. Do continuing workshops improve participants skills? Effects of a motivational interviewing workshop on substance-abuse counselors' skills and knowledge. *Behav Ther.* 2000; 23:73–77.
- Rychtarik RG, Connors GJ, Derman KH, Stasiewicz PR. Alcoholics Anonymous and the use of medications to prevent relapse: An anonymous survey of member attitudes. *J Stud Alcohol.* 2000; 61:134–138. [PubMed: 10627107]
- Schmitz JM, Averill P, Stotts AL, Moeller FG, Rhoades HM, Grabowski J. Fluoxetine treatment of cocaine-dependent patients with major depressive disorder. *Drug Alcohol Depend.* 2001a; 63:207–214. [PubMed: 11418225]
- Schmitz JM, Stotts AL, Rhoades HM, Grabowski J. Naltrexone and relapse prevention for cocaine-dependent patients. *Addict Behav.* 2001b; 26:167–180. [PubMed: 11316375]
- Seal KH, Kral AH, Lorvick J, McNeas A, Gee L, Edlin BR. A randomized controlled trial of monetary incentives vs. outreach to enhance adherence to the hepatitis B vaccine series among injection drug users. *Drug Alcohol Depend.* 2003; 71:127–131. [PubMed: 12927650]

- Sholomskas D, Syracuse G, Rounsaville BJ, Carroll KM. We don't train in vain: a randomized trial of three strategies for training clinicians in CBT. 2002 under review.
- Silverman K, Wong CJ, Umbrecht-Schneider A, Montoya ID, Schuster CR, Preston KL. Broad beneficial effects of cocaine abstinence reinforcement among methadone patients. *J Consult Clin Psychol*. 1998; 66:811–824. [PubMed: 9803700]
- Sofuoglu M, Gonzalez G, Poling J, Kosten TR. Prediction of treatment outcome by baseline urine cocaine results and self-reported cocaine use for cocaine and opioid dependence. 2002 under review.
- Stanton MD, Shadish WR. Outcome, attrition, and family-couples treatment for drug abuse: a meta-analysis and review of the controlled, comparative studies. *Psychol Bull*. 1997; 122:170–191. [PubMed: 9283299]
- Stitzer ML, Bickel WK, Bigelow GE, Liebson IA. Effect of methadone dose contingencies on urinalysis test results of polydrug abusing methadone maintenance patients. *Drug Alcohol Depend*. 1986; 18:341–348. [PubMed: 3816530]
- Stitzer ML, Iguchi MY, Felch LJ. Contingent take-home incentives: effects on drug use of methadone maintenance patients. *J Consult Clin Psychol*. 1992; 60:927–934. [PubMed: 1460154]
- Street LL, Luoma JB. Control groups in psychosocial intervention research: Ethical and methodological issues. *Ethics Behav*. 2002; 12:1–30. [PubMed: 12171079]
- Swift RM, Duncan D, Nirenberg TD, Femino J. Alcoholic patients' experience and attitudes on pharmacotherapy for alcoholism. *J Addict Dis*. 1998; 17:35–47. [PubMed: 9789158]
- Szapocznik J, Perez-Vidal A, Brickman AL, Foote FH, Santisteban DA, Hervis O, Kurtines WM. Engaging adolescent drug abusers and their families in treatment: A strategic structural systems approach. *J Consult Clin Psychol*. 1988; 56:552–557. [PubMed: 3198813]
- Volkow ND, Fowler JS, Wolf AP, Schlyer D, Shiue CY, Alpert R, Dewey SL, Logan J, Bendriem B, Christman D. Effects of chronic cocaine abuse on postsynaptic dopamine receptors. *Am J Psychiatry*. 1990; 147:719–724. [PubMed: 2343913]
- Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry*. 1992; 49:876–880. [PubMed: 1345133]
- Volpicelli, JR.; Pettinati, HM.; McLellan, AT.; O'Brien, CP. Combining medication and psychosocial treatments for addictions: the BRENDA approach. Guilford Press; New York: 2001.
- Wilk AI, Jensen NM, Havighurst TC. Meta-analysis of randomized controlled trials addressing brief interventions in heavy alcohol drinkers. *J Gen Int Med*. 1997; 12:274–283.

Table 1

Potential strengths/targets and weaknesses of available behavioral platforms

	Low intensity medication management approaches					Family/couples approaches			
Strengths/targets		Manualized drug counseling	Cognitive behavioral therapies	Contingency management	Motivational interviewing				
Reduce bias, error variance	X		X	X	X			X	X
Enhance medication compliance	X		X	X					X
Reduce substance use	X	X	X	X	X				X
Target-specific medication weaknesses				X					X
Improve retention	X	X	X	X	X				X
Address co-morbid symptoms, problems			X	X					X
Relative weaknesses									
Higher cost			X	X					X
Training burden/complexity			X	X	X				X
Potential ceiling effects			X	X					X
Limited generalizability				X					X
May have limited compatibility with medications		X			X				