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Study Results from the Clinical Trials Network's First Ten Years: Where Do They Lead?

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Abstract

The National Drug Abuse Treatment Clinical Trials Network (CTN) began in 2000 with the goal of "improv[ing] the quality of drug abuse treatment throughout the country using science as the vehicle." Since then, 24 discrete clinical trials were launched, 20 are completed, and 15 have published main outcome papers. Of the latter, four tested pharmacological treatment, eight, psychosocial/behavioral treatment, one, a combination of medication and counseling, and two targeted HIV/HCV risk behavior. We review main study findings for these trials, including treatment retention, substance use or risk behavior outcomes, and secondary outcomes when analyzed. The purpose of this review is to identify the incremental progress toward improving drug treatment made by these trials and to propose next steps for the CTN and for the field arising from these studies. The CTN provides a unique opportunity to systematically design trials that incorporate treatment improvements from previous trials and to direct efforts toward innovations most likely to be incorporated into practice.

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1. Introduction

The 1998 the Institute of Medicine (IOM) report, "*Bridging the Gap between Practice and Research"* (Lamb, Greenlick & McCarty, 1998), called attention to and proposed solutions for the divergent directions of research and practice in the addictions field. NIDA's response to that report, The National Drug Abuse Treatment Clinical Trials Network (CTN) (Rotrosen et al., 2002) began in 1999 with the goal of "improv[ing] the quality of drug abuse treatment throughout the country using science as the vehicle." The establishment of the CTN responded not only to the IOM report but also to the convergence of developments in both research and policy related to addiction treatment.

The 1980's and 1990's saw a great deal of progress by addiction researchers toward development and testing of both pharmacological and behavioral treatments for drug and alcohol abuse/dependence (NIDA, 1999) as well as interventions to reduce HIV risk behavior (Des Jarlais & Semaan, 2008). Buprenorphine had been developed and tested and was ready for approval as a treatment for opioid dependence. NIDA's Behavioral and Integrative Treatment Development Program (Rounsaville, Carroll, & Onken, 2001) had defined the necessary stages involved in developing and testing potential treatments and had spawned a number of new therapies, some of which showed evidence of efficacy in controlled trials (Carroll & Onken, 2005). As pointed out in the 1998 IOM report, most of this work was not incorporated into current practice, both because the necessary effectiveness trials had not been carried out, and because the practice and research communities were not in sync regarding needs and priorities for the field (Lamb et al., 1998).

At the same time, state governing bodies and regulatory agencies were putting increased emphasis on use of empirically-based practices (Miller, Zweben & Johnson, 2005). Growing awareness that there was a developing evidence-base and that treatment outcomes did not meet funders' expectations was fueling demands for greater accountability and for practitioners to certify that they were using practices with known efficacy in order for their services to be reimbursed.

Outlined to a certain extent in the first CTN Request for Applications (RFA), but later refined as a guiding principle by the first CTN National Steering Committee, was the notion that efficacious treatments would be moved into practice through behavioral and pharmacological Stage III (effectiveness) studies conducted in the CTN. This would accomplish the two goals of testing these treatments in real world settings and exposing community treatment programs to the interventions. Efficacy and effectiveness trial designs lie along a continuum defined by the degree to which emphasis in trial design is placed on internal versus external validity. Whereas efficacy trials may be conducted with expert clinicians, a narrowly defined patient population and with a high degree of control over potentially confounding factors, effectiveness trials assess intervention outcomes in a more real-world setting. Treweek and Zwarenstein (2009) distinguish between "pragmatic" and "explanatory" trials, calling for greater emphasis on the former as studies that will better inform clinical decision making. Glasgow (2008) refers to "practical" trials, a concept that shares many features of Carroll and Rounsaville's (2003) "hybrid model" of clinical trial design. In the hybrid model, pragmatic aspects include: use of community clinicians to deliver interventions; broader inclusion of representative patients; comparison conditions that represent treatment as usual; cost-effectiveness evaluation; and assessment of patient and clinician satisfaction. Design aspects that support internal validity, such as random assignment, use of treatment manuals, monitoring of treatment fidelity, and use of objective outcome measures are retained.

While the CTN sought to conduct more pragmatic or practical trials, it also became clear that there needed to be a balance between completely pragmatic and completely explanatory trials if the endeavor was going to inform both practice and science. Thus, in general, the "hybrid model" has been adopted with CTN trials varying along the pragmatic – explanatory continuum. For example, all trials have taken place in a variety of community treatment programs (CTPs); however, the protocols vary in the extent to which they employ central versus local training, supervision, and fidelity monitoring. With two exceptions, the CTN studies reviewed here followed the principle of conducting research on treatments with known efficacy. The first of exception (CTN 0010) was a trial of buprenorphine, a medication with known efficacy, but conducted with a novel population, adolescents. In this case, the CTN's expanded adolescent treatment capacity allowed for a study that would have been difficult to complete at one site. The second (CTN 0011), a test of a telephone procedure to increase engagement in continuing care following inpatient treatment, was designed in the spirit of bi-directionality between providers and researchers as a pilot test of an intervention first developed at a treatment site.

The stage and hybrid models inform the field and the CTN about how to design and conduct studies, but they provide little guidance about how the CTN should envision its overall program of research. That is, what interventions should be studied; what information should trials provide about each intervention, and how should current CTN trials inform future trials. The tradition of investigator-initiated research at NIH, while guided by priorities set by institutes, can sometimes result in a lack of continuous progress toward the ultimate research goal, i.e., more effective treatment. For the trials reviewed here, the CTN used a collaborative and democratic process to generate and select research concepts. Members wrote research concepts that were voted on by the Steering Committee, composed of the Principal Investigator (PI) and community treatment program (CTP) from each of the regional CTN nodes. After concept selection, protocols were designed by a team, also composed of both research and provider members. Designs were finalized based on input from both an independent Protocol Review Committee and a Data Safety and Monitoring Board.

This node-initiated concept submission process, combined with the available array of interventions that are currently considered evidence-based practices (Miller et al., 2005) can lead to a more discrete (one stand-alone trial at a time) rather than incremental approach to determining the program of research. A question that can be asked is the degree to which CTN trials can and do build on each other. Are outcomes of completed CTN studies able to be used in selecting new studies, so as to make incremental progress. While most trials address one type of intervention, e.g., motivational interviewing, buprenorphine detoxification, or motivational incentives, a program of research designed to improve treatment might reasonably be expected to combine interventions, when appropriate.

As of August, 2009, 24 discrete clinical trials had been launched in the CTN, 20 were completed, and 15 had published their main outcome papers. Of the latter, four tested pharmacological treatment, eight, psychosocial/behavioral treatment, one, a combination of medication and counseling, and two targeted HIV/HCV risk behavior. We review main study findings for these 15 trials, including treatment retention, substance use or risk behavior outcomes, and secondary outcomes when analyzed. The purpose of this review is to identify the incremental progress toward improving drug treatment made by these trials and to propose next steps for the CTN and for the field arising from these studies by addressing the following questions:.

1. Overall, what have we learned and how should the CTN proceed?
2. How do CTN-completed trials inform practice?

3. What do CTN-completed trials suggest about next steps for each CTN-studied intervention? For example, what additional knowledge is needed about CTN-studied interventions to be able to use them to improve community practice?
4. How can the outcomes of completed CTN trials be used to improve the designs and outcomes of future trials?

Our focus is on next steps, considering how progress thus far in the CTN can help us define its future program of research. The degree to which prior trial designs have included pragmatic vs. explanatory elements is important to the implications of these trials and so will be addressed as it is relevant.

Method

2.1 Selection of reports

Space does not allow a complete listing of the CTN protocols. The 27 studies that have completed enrollment are described at http://www.nida.nih.gov/CTN/Research.html, and a comprehensive listing of all 48 CTN protocols with links to associated publications can be found at http://ctndisseminationlibrary.org/protocols.htm. We chose to examine only the primary outcome paper for those clinical trials that have such a paper published or in press at this writing. This strategy, while potentially missing important information about the trials, assures that comparable information is being evaluated across studies. Studies that are still in progress or that have not yet published results were excluded. In addition, this review limits itself to those studies concerned with providing an intervention to individual patients and examining individual patient outcomes. Thus, completed studies of treatment program characteristics, practices, or policies (Brown et al., 2007; McCarty et al., 2008), or evaluating an intervention directed at providers and measured at the level of caseload outcomes (Forman et al., 2007) are not included. There were 15 clinical trials meeting these criteria. Their outcomes, reported in 14 manuscripts (see Table 1), are the subject of this review.

The lead investigator and protocol team for each CTN trial develops a publication plan that is reviewed by the CTN Publication Committee. The numbers and types of planned and completed manuscripts varies across protocols, depending upon the goals of the research, the types of data collected, and the interests of members of the protocol team. For each protocol, however, there is one primary outcome paper that must be completed, and this is generally the first paper to be written after “data lock.” The primary outcome paper always includes analysis of the study’s primary hypotheses and may include analysis of secondary hypotheses and other issues, such as site effects. Following publication of this paper, the data are made available to the public, leading potentially to analyses not included in the original publication plan.

2.2 Examination of reports

We conducted a qualitative review, examining the population, design (including pragmatic and explanatory elements), treatment, treatment exposure, follow-up completion, primary and secondary outcomes, and retention in treatment program (primary outcome for some studies). The focus of the review is not primarily on methodology, since this is fairly consistent across studies, but on what can be learned from the studies about the interventions and how this information may benefit practice and future research. Although the CTN has undergone a number of administrative changes during its first ten years (e.g., changes in committee structure), the process for selection, implementation, and monitoring of trials did not diverge widely for the 15 protocols reported here. A historical analysis of the effect of any CTN structural changes on study outcomes is beyond the scope of this review.

Results

Table 1 gives the CTN study number, citation, dates of data collection, design, population, treatments, and results (primary, secondary, and treatment retention) for the 15 CTN trials. Below we discuss these results by type of trial: medication and medication/behavioral combination, behavioral trials targeting treatment retention and substance use; and behavioral trials targeting HIV/STI (Human Immunodeficiency Virus/Sexually Transmitted Infection) risk behavior. Because next steps following from each study are usually specific to the intervention(s) being discussed, we include these recommendations following each results summary. Broader recommendations concerning implications for the CTN's future activity are reserved for the Conclusions section.

2.3 Medication and combination (medication and behavioral treatment) trials

2.3.1 Buprenorphine/naloxone (bup-nx) studies

2.3.1.1 Bup-nx study designs: Buprenorphine, a high-affinity, partial μ-opioid agonist, was approved as a pharmacotherapy for opioid dependence in 2002. It is usually combined with naloxone to reduce abuse potential (referred to as bup-nx or Suboxone®). Designs and results for the bup-nx protocols are summarized in Table 1. Among the first group of studies pursued by the CTN Steering Committee were trials comparing bup-nx to clonidine as medications for short-term (13 day) inpatient (CTN 0001) and outpatient (CTN 0002) detoxification (Ling et al, 2005). These were initiated prior to FDA approval of buprenorphine, and, as such, were intended to give community treatment programs (CTPs) experience with a medication that had not been previously available. A third study (CTN 0003) examined the effectiveness of longer (28 day) versus shorter (7 day) tapers from Suboxone®. The fourth buprenorphine trial (CTN 0010), sought to extend bup-nx treatment to a population not usually treated with maintenance medications, young people, age 15-21 who were opioid-dependent. Twelve weeks of bup-nx treatment were compared to detoxification. The latter protocol was one of the early CTN exceptions to studying treatments for which efficacy data were already available.

All 4 studies examined treatment retention and opioid-free urines as primary outcomes along with craving and withdrawal as secondary outcomes. In addition, they shared certain aspects of practical trials, i.e., lack of placebo control or blinding of research staff, intervention delivery by CTP staff, and control conditions reflecting standard practice, while retaining random assignment, a well-specified medication protocol, and objective outcome measures.

2.3.1.2 Inpatient and outpatient detoxification results and recommendations: Consistent with expectation, the two detoxification studies (Ling et al., 2005) showed that bup-nx was superior to clonidine in bringing about a positive outcome (treatment retention and opioid negative urine at 13 days) and, for the most part, in reducing withdrawal symptoms and craving. Notably, the outcome of bup-nx *outpatient* detoxification, although superior to the clonidine condition, was poor; only 29% were both retained and provided an opioid-free urine at the last day of detoxification. In contrast, 77% of bup-nx *inpatients* were able to meet this criterion. Neither of these studies followed participants past the detoxification period.

Short-term detoxification for opioid addiction has a history of being unsuccessful, and the results, particularly of the outpatient study, are consistent with this history. If one accepts, however, that there are reasons to continue to offer outpatient detoxification as a service, the current findings offer several directions. Buprenorphine-based outpatient detoxification may benefit from studies examining methods of better retaining patients and supporting motivation to remain abstinent as medication is reduced. Concomitant behavioral treatments

that increase motivation and retention should be examined. Regarding outpatient detoxification, bup-nx is clearly a better medication than clonidine, and research should continue to focus on monitoring current practice (Knudsen, Ducharme & Roman, 2006). In addition, research is needed on best practices for dissemination and adoption of medications in the addiction field (Saxon & McCarty, 2005).

Although inpatient bup-nx detoxification was highly successful in the short term (Ling et al., 2005), it is not known how the successful patients fared long-term. Future studies should provide longer follow-up for bup-nx inpatient detoxification to determine the long term success and test interventions (during or following the inpatient stay) designed to prolong success and assist people to transition into some form of treatment. This could include strategies studied in other CTN trials, including Motivational Interviewing, the use of motivational incentives to reinforce retention and engagement in treatment beyond detoxification, strategies targeting therapeutic alliance (Campbell et al., 2009), or engagement in 12 Step programs. It could also include long term pharmacotherapy with naltrexone. For both outpatient and inpatient detoxification, research that provides clinicians with predictors of successful detoxification would be helpful in treatment planning.

2.3.1.3 Suboxone taper results and recommendations: Unlike the prior two studies, CTN 0003, a comparison of Suboxone® tapering lengths, included 1- and 3-month follow-ups. There was no difference at these time points between short- and longer-term tapers (Ling et al., 2009). In addition, by three months, only 12-13 percent of patients provided opioid-free urines. This confirms the commonly held understanding that detoxification is not the best option for many opioid-dependent individuals, if the goal is to achieve opioid abstinence. For purposes of establishing buprenorphine-maintained patients, with whom to compare taper length, this study employed a one-month Suboxone® stabilization period. As discussed by the investigators (Ling et al., 2009), one month of stabilization does not necessarily achieve clinical stability, so there is some question whether this study reflects the real world situation in which a patient who has been maintained on Suboxone® wants to be tapered after “treatment.” The extent to which length of treatment affects response to taper and optimal length of taper is not known from this study. A naturalistic study following individuals tapering off of some minimum length of Suboxone® treatment would be a useful next step as would an additional controlled comparison of taper length following a longer period of Suboxone® maintenance. Again, as in the previous recommendations, methods to engage and retain individuals in some form of ongoing continuing psychosocial treatment once detoxified would be important.

2.3.1.4 Adolescent buprenorphine results and recommendations: The adolescent buprenorphine study (Woody et al., 2008), comparing two versus 12 weeks of bup-nx detoxification, also followed patients long-term (6, 9 and 12 months) and found that a 12 week bup-nx detoxification was superior to 2 weeks detoxification over this time period. However, there were high rates of relapse in both conditions, as patients were tapered off the medication. As a first study involving use of this medication with youth and young adults, CTN 0010 established the feasibility of doing so. There is more to be learned about tapering in adolescents and young adults; we don’t have many, if any, data on how long individuals with a brief history of opioid dependence need to be maintained on medication. From this study, we see that 14 days is not enough, and results from 12 weeks of bup-nx can be improved upon. Is someone who has a 1 or 2 year (or less) history just as likely to relapse after a taper as someone with a 10-20 year history? Longer term (greater than 12 weeks) bup-nx maintenance should be examined for younger (less than age 21) opioid-dependent individuals; however, knowing which patients will require longer maintenance is even more important in this age group than for adults. There is less willingness among providers and regulatory agencies to entertain the idea of maintaining a young person on an opioid agonist.

Concomitant behavioral therapies should also be examined. Given that those receiving 12-weeks of treatment showed less use over time, what other psychosocial treatments could be used to boost effects by increasing motivation and supporting abstinence?

2.3.2 Smoking cessation using counseling and nicotine patch

2.3.2.1 Smoking cessation study design: CTN 0009 compared a nine-session mood management smoking cessation group counseling intervention adapted for substance abusers from Hall, Munoz and Reus (1994) plus nicotine replacement therapy (SC) to treatment as usual (TAU) among smokers in methadone or psychosocial outpatient treatment (Reid et al., 2008). Assessments occurred both during treatment and at 3 and 6 months post-treatment.

This trial leaned towards the pragmatic side of the effectiveness-efficacy continuum. For example, nicotine replacement therapy (NRT) was chosen by the CTN as the medication for this protocol, due to the fact that many community-based treatment programs do not have the medical management resources available to prescribe and monitor other potentially more effective medications. Counseling fidelity to the mood management intervention was monitored by site supervisors as opposed to centralized monitors.

2.3.2.2 Smoking cessation study results and recommendations: Despite the high prevalence of smoking behavior among substance abusers, smokers were difficult to recruit for this study and were retained at only moderate rates in the intervention. Although during-treatment abstinence rates were significantly higher in the SC than the TAU condition, there were few participants who were not smoking (10-11%). Follow-up at 3 and 6 months revealed no differences between treated and control groups. Results were modest compared to treatment success in the general population but in line with other studies involving substance abusing populations.

The poor rate of recruitment, poor retention and overall lack of treatment efficacy for SC suggest that substance users need different treatment elements to motivate and assist them in quitting smoking. These results could perhaps have been anticipated based on prior literature, but the design of this trial appears to have been a compromise between the smoking cessation literature and the existing situation in community-based treatment programs.

Regarding next steps, medications such as bupropion or varenicline (Hays & Ebbert, 2008; Jorenby et al., 1999), combination therapies, such as nicotine patch and short acting nicotine replacement (Fiore et al., 2008), or such as bupropion plus nicotine replacement therapy (NRT), are worthy of study with this population. As will be seen later in this review, either motivational incentives or motivational interviewing can be used to motivate and achieve better levels of treatment attendance. A new CTN protocol, (CTN 0046) will examine the use of bupropion and provide prize-based incentives for smoking abstinence, both of which are expected to enhance outcomes. In this regard the new protocol builds on the prior and provides both motivation and support, yet it abandons CTN 0009's mood management behavioral treatment platform in favor of brief weekly counseling. Since there is some evidence of dose response with behavioral treatments (Fiore et al., 2008), more intensive behavioral treatments need to be studied. Given the extent of treatment resistance of smoking in substance abuse treatment patients, a longer term approach that supports repeated quit attempts, treating smoking as a chronic relapsing versus acute condition requiring a single treatment episode, may be required.

CTN 0009's group-based treatment was not feasible in many outpatient psychosocial clinics due to slow recruitment. This resulted in psychosocial outpatient clinics that had signed up for the trial dropping out, because recruitment was not feasible. Only 2 of this type of clinic

and 5 methadone clinics participated. To avoid this problem in the future, it would be useful to examine individually-oriented treatment models or smoking cessation that is fully integrated with "required" aspects of substance abuse treatment. In addition, barriers to motivation to quit smoking in substance abuse treatment samples should be examined and addressed.

2.4 Psychosocial/behavioral treatment trials

Eight psychosocial/behavioral treatment protocols were reviewed, including 2 motivational incentive studies (CTN 0006/0007), 4 studies of motivational interviewing/motivational enhancement (CTN 0004/0005/0013/0021), 1 pilot study of a telephone procedure to increase engagement in continuing care (CTN 0011), and 1 study of an integrated cognitive behavioral treatment for comorbid PTSD and substance use (CTN 0015).

2.4.1 Prize-based incentives among stimulant users

2.4.1.1 Incentive study designs: CTN 0006 (Petry et al., 2005) and CTN 0007 (Peirce et al., 2006) employed similar designs in outpatient psychosocial and methadone maintenance treatment (MMT) programs, respectively, to study prize-based abstinence incentives compared to TAU among cocaine and methamphetamine users. The outpatient psychosocial and MMT incentive protocols were quite similar in design, except that the MMT study was successful in completing 1- and 6- month follow-ups in addition to following patients during a 12-week treatment period.

Regarding pragmatism of the trials, prize-based, as opposed to voucher, incentives were selected as a lower-cost alternative that might have greater transferability to real world clinics than does the voucher incentive approach (Petry et al., 2005). Although these two protocols took a practical approach to the method of reinforcement, they retained twice per week urine sampling as the basis for reinforcement and used research staff, as opposed to existing clinic staff, to manage and deliver incentives, both of which may limit the real-world practicality. However, at the time these studies were designed, motivational incentives were rarely used in community-based treatment, and the protocols sought to maximize acceptability to the clinics (by minimizing counselor burden) while mimicking prior efficacy trials (i.e., frequent urines) to obtain positive results.

2.4.1.2 Incentive study results and recommendations: Results of the two protocols were quite different in ways that would be expected with the two treatment modalities and patient populations. In outpatient psychosocial treatment, incentives improved treatment attendance and retention, and effects on substance use measured by urine tests were inconsistent, depending upon the measure employed (positive urines versus longest duration of abstinence, and missing urines counted as negative, positive or missing). Conversely, in MMT, incentives produced robust effects on stimulant-negative urines and consecutive abstinence during the treatment phase but had no impact on counseling attendance or treatment retention. Differences in substance use, however, were lost by 6-month follow-up.

Whatever the target of reinforcement, studies that combine prize-based incentives with other behavioral or pharmacological interventions would potentially extend the reach of incentives. CTN 0006 was not successful in conducting long term follow-up assessments, and CTN 0007 found that incentive effects were not maintained. There are several possible explanations for this finding. Either being abstinent is not sufficiently reinforcing in itself, or these studies did not provide a sufficient length of time for participants to experience the reinforcing effects of abstinence. Alternatively, it has been suggested that intrinsic motivation is undermined by providing external rewards (Schwartz, 1990). Regarding this latter explanation, it has been shown that contingent reward, as was provided in these trials,

does not reduce intrinsic interest in continuing a task (Eisenberger & Cameron, 1996). To address the lack of sustained effects, combining incentives with therapies that are known to have longer term effects, such as Cognitive Behavioral Therapy (CBT), (Carroll & Onken, 2005) has strong appeal. In any event, given the chronic-relapsing nature of addiction problems (McLellan et al., 2000), future studies should take a longer view regarding both treatment and assessment.

As previously mentioned, the incentive protocols based reinforcement on twice weekly urines. In addition, the incentive program was managed and delivered by staff added to the CTPs by the research protocol. Aside from the cost of reinforcers themselves, these two elements (frequent urine collection and management of reinforcers) are often cited by community providers as barriers to implementing incentive programs. Can incentives be delivered by existing staff under existing funding mechanisms and continue to enhance retention or abstinence outcomes? A useful next step in the CTN's study of incentives would be a true effectiveness study that examines whether CTP staff can faithfully follow contingency management principles (e.g., as outlined by Petry, 2000), the degree to which programs can manage the treatment, and whether such efforts result in increased abstinence or retention. An observer unfamiliar with the addiction specialty care system might question why such a study would be necessary. However, the IOM report (Greenlick et al., 1998) that resulted in establishment of the CTN identifies multiple reasons why such a study might be useful in identifying and eliminating barriers to utilization of this research-based practice.

As an alternative to tangible reinforcers, social incentives have been efficacious in increasing engagement in continuing care (e.g., Lash et al., 2007) and, as a highly transferable incentive approach, are ready for a practical multi-site trial. Finally, assessing current clinical practice outside the CTN with regard to incentive-based treatments would be useful in identifying directions for further dissemination/implementation research (Ducharme, Knudsen, Roman & Johnson, 2007)..

2.4.2 Motivational Interviewing (MI) and Motivational Enhancement (MET) Trials

2.4.2.1 MI/MET study designs: The CTN completed four studies employing Motivational Interviewing (MI) techniques and strategies. CTN 0004 (Ball et al., 2007) and CTN 0005 (Carroll et al., 2006) exemplified practical trials with a number of pragmatic elements. For example, originally planned as one trial, the two were split to accommodate differences in CTP standard treatment. CTN 0005 compared a Motivational-Interviewing-integrated intake session to a standard intake session in programs that offered group, and not individual treatment. CTN 0004 tested a 3-session Motivational Enhancement Therapy (MET) protocol in programs for which three individual sessions could be offered as the standard care control condition. Additional pragmatic elements included broad inclusion criteria and local training and supervision with the support of centralized fidelity monitoring. The studies retained explanatory elements of random assignment, use of manuals, fidelity monitoring, and standard objective outcome measures. CTN 0013 (Winhusen et al., 2008), and CTN 0021 (Carroll et al., in press) extended MET to two special populations, pregnant women and Spanish-speaking substance users, respectively. While the Spanish MET protocol followed CTN 0004 very closely (translated into Spanish), MET for pregnant substance users (MET-PS) re-designed MET sessions to include an emphasis on the woman's pregnancy and adopted a centralized training and supervision protocol. All four studies included follow-ups to 3 to 4 months post-randomization.

2.4.2.2 MI/MET results and recommendations: Increased retention or attendance at the CTP was a primary hypothesis for all of the MI/MET studies. Contrary to expectation, MET compared with standard individual counseling had no across-clinic effect on amount of

outpatient treatment received or retention at the CTP (Ball et al., 2007; Carroll et al., in press; Winhusen et al., 2008). In contrast, integrating MI into a single intake session in programs primarily offering group treatment, enhanced retention and session attendance (Carroll et al., 2006), and these effects were more long-lasting among primary alcohol users. Regarding substance use, the main MET study (CTN 0004) and the Spanish MET (CTN 0021) study had parallel results. For primary alcohol users only, days per week of alcohol use increased more during follow-up in the standard care condition than in MET. Primary drug users did not experience this effect. Both the main MET study and the study of pregnant women (CTN 0013) produced site effects in which differences between MET and standard care varied from site to site. Differences that were found among sites in patient and treatment characteristics as well as MI-adherence could account for the interaction of site and treatment condition. However, there were an insufficient number of sites to test hypotheses about the reasons for site effects. A single MI-integrated intake session (CTN 0005) produced no effect on substance use outcome.

Taken together, these outcomes indicate there is little value in continuing to study 3-session Motivational Enhancement Therapy for primary drug users in community treatment. They also suggest caution in dissemination efforts around Motivational Interviewing, since the type of MI intervention seems to matter. The main MET study, and to some extent, MET-pregnant women, highlight site and therapist as potential moderators and as having potential direct effects on outcomes (Martino, Ball, Nich, Frankforter & Carroll, 2009). The CTN has allowed the opportunity to examine the influence of the therapeutic alliance as a mediator of effective treatments. It also is a system large enough in scope and sample size to examine the mechanisms of action of MI and MET to attempt to improve their effectiveness with primary drug abusers. Superior effects of MI and MET with primary alcohol users suggest the importance of patient characteristics as moderators. The opportunity for this kind of analysis in the CTN is discussed below at greater length as is the issue of site effects.

Carroll and colleagues (2006) found that an intake session that includes MI improves retention in treatment. MI should be included as a component of intake in future trials in which optimal treatment exposure is desired. Although MI itself had no impact on substance use, it would be useful to combine MI-enhanced intake and other treatment elements (e.g., CBT, motivational incentives or pharmacotherapy).

The protocols dealing with pregnant women and Spanish speaking patients were launched based on pre-CTN MET efficacy data and prior to outcomes being known for CTN 0004. Recommendations for strong efficacy data as a criterion for intervention selection are discussed below. These studies demonstrated the feasibility of carrying out CTN trials targeting specific subpopulations that may be difficult to recruit in single-site trials. Pregnant substance users could be a continued focus of the CTN, as they pose specific problems in recruitment and retention in treatment and were apparently not well served with MET. The fact that CTN 0021 could be carried out in Spanish, with appropriate procedures for translation and back-translation in Spanish and with Spanish-speaking clinicians, trainers, and supervisors indicates the possibility of continuing to do such trials in the CTN.

2.4.3 Telephone Enhancement Procedure (TELE)

2.4.3.1 TELE study design: The transition from short term inpatient or residential treatment to outpatient care is a road often paved with good intentions. The TELE protocol (CTN 0011) (Hubbard et al., 2007) was a pilot study of an intervention developed at one of the CTN CTPs, Betty Ford Center, to improve engagement and follow-through with outpatient treatment plans. For this trial, the CTN purposefully stepped outside its principle of selecting interventions based on efficacy data from controlled trials. It was selected by the Steering Committee to address the CTN's goal of bridging research-practice gaps. One source of

such gaps was the lack of attention by researchers to problems and interventions identified in current practice. In a small number of CTPs (4) telephone follow-up calls were compared with standard care. Arising as it did from one of the CTPs, the protocol intervention had a good deal of practical applicability. Once telephone counselors completed centralized training, they were supervised locally without the use of the centrally managed fidelity rating. The trial used a manualized intervention, random assignment, and objective outcome measures, including documentation through clinic records.

2.4.3.2 TELE results and recommendations: Based on *self reports* at baseline and 13-17 weeks neither substance use nor treatment attendance was improved by the telephone calls. However, based on *clinic records*, patients receiving the telephone calls had more documented attendance at outpatient treatment.

This was a pilot study not powered to detect effects, because the intervention was not viewed as having sufficient evidence for a powered multi-site study. Small pilot studies have been used quite fruitfully outside the CTN, e.g., in NIDA's integrated and behavioral therapy development program. However, it is likely that such pilots would be less costly if conducted outside the CTN in single sites. The trial demonstrated feasibility, although treatment adherence could have been better, and some aspects of the protocol were not consistently followed (e.g., recording calls, obtaining treatment records) at all sites. While not impacting substance use, the intervention does appear to show some promise as shown in documented aftercare compliance. A logical next step, to be conducted outside the CTN, would be an additional pilot study improving upon the telephone protocol, for example, incorporating aspects of "Contracting, Prompting, and Reinforcing," an efficacious continuing care engagement strategy (Lash et al., 2007)

2.4.4 Integrated treatment for PTSD and SUD among women

2.4.4.1 "Women and Trauma" study design: The "Women and Trauma" project (CTN 0015) (Hien et al., 2009) compared a 12-session group version of Seeking Safety (SS) (Najavits 2002) to a time-and-attention-matched control, Women's Health Education (WHE), among women with co-occurring PTSD and substance abuse/dependence in outpatient treatment. Follow-ups occurred at 1 week and 3-6- and 12-months posttreatment. Pragmatic aspects of the protocol included use of rolling admission to group treatment, use of broad inclusion criteria that extended to women with sub-threshold PTSD, and training of local supervisors in the intervention. Explanatory elements included assessors blind to condition, use of a credible "active" control condition, and multiple longitudinal assessment points.

2.4.4.2 Women and Trauma results and recommendations: Although women in both conditions reduced their PTSD symptoms markedly during treatment, the two treatments did not differ from each other in reducing either PTSD symptoms or substance use. The groups also did not differ at 12 month follow-up. The two-group design does not allow us to determine whether PTSD reductions were due to the Seeking Safety and Women's Health interventions or to simultaneous attendance at standard outpatient treatment. Prior trials suggest integrated trauma treatment would be superior to TAU (Hien, Cohen, Miele, Litt & Capstick, 2004), but this could not be determined from this design.

For future studies, the impact of treatment on substance use might be enhanced by extending the treatment (e.g., increased number of sessions over a longer period of time), using motivational interviewing or motivational incentives to increase treatment exposure, or combining medications and therapy. This is the first CTN trial treating a co-occurring mental health and substance use disorder and the only one that could be reported here. Outcomes of two others involving methylphenidate treatment for co-occurring Attention

Deficit Disorder and substance use are anticipated. The importance of this kind of research is highlighted below.

2.5 Psychosocial/behavioral trials targeting HIV/STI risk behavior

2.5.1 HIV/STI study designs—We reviewed primary outcomes for two gender-specific HIV/STI prevention trials targeting sexual risk behavior (CTN 0018/CTN 0019). The two trials were designed and operated in parallel, although the interventions were distinct, and measures were specifically selected for each trial. Some CTPs were included in both the men's and women's studies and some participated in only one. Both MMT and outpatient psychosocial programs participated. Both studies compared a 5-session group sexual risk reduction intervention to a 1-session sexual risk reduction session designed to reflect the standard of care and follow-ups at 3 and 6 months. Pragmatic elements included a comparison condition reflecting TAU (and, therefore, not matched for time and attention), broad participant inclusion, and clinicians drawn from performance sites. Explanatory elements were random assignment, a well-defined patient population, use of manualized treatments, and monitoring adherence and competence.

2.5.2 HIV/STI results and recommendations—In the men's study, "Real Men are Safe" (REMAS) participants reported fewer unprotected sexual occasions at 3 and 6 months than those in 1-session HIV education, with an even larger effect for intervention "completers" (3 or more sessions for experimental intervention, 1 session for control) (Calsyn et al., 2009). "Safer Sex Skills Building" (SSB) for women had even more pronounced effects on unprotected sex, with those in the HIV education control increasing unprotected sex at 6 month follow-up while those in the 5-session intervention continued to decrease (Tross et al., 2008). "Completer" analysis again showed more pronounced effects.

The 1-session control condition used in these protocols reflects what is commonly offered in community treatment for HIV prevention. Although the 5-session treatment was clearly superior, it may be difficult to implement due to the cost, and the substantial change in practice that it reflects. In the trial, few participants actually received 5-sessions; 41 percent in CTN 0018 and 43 percent in CTN 0019 attended 3 or more sessions. For maximum applicability to community treatment, dismantling studies are needed that investigate how many, and which, sessions are sufficient to achieve reduction in unprotected sex. The strongest effect for both men and women was for treatment "completers" a finding that has at least 2 plausible interpretations, neither of which can be discerned from the current design. Either increased treatment exposure leads to reduced risk, or a third factor, e.g., patient motivation, leads to both treatment exposure and reduced risk (Walker, 2009). These alternatives could also be investigated by manipulating, independent of patient motivation, the number of sessions to which participants are exposed. To increase intervention exposure, if desired, studies could integrate sexual risk reduction in TAU so that additional session attendance is not required or use incentives for attendance. CTN 0018 and CTN 0019 offered gender-specific intervention but cannot answer the question whether the gender-specificity is responsible for outcomes. For this, non-specific comparison groups would be needed. Similarly, because of the difference in number of sessions between experimental and control groups in these protocols, it is not known whether structure and content are responsible or amount and attention. CTN 0018 focused on men in treatment without regard to sexual orientation or whether their partners were women, men, or both. Men who have sex with women are a neglected group when it comes to research on sexual risk reduction and need for gender-specific interventions. There should be a continued focus on this population as an STI/HIV vector. CTN 0019 is one of three women's specific CTN trials we reviewed (also CTN 0013 and CTN 0015). Women have been identified as having unique

treatment needs (Greenfield et al., 2007); the CTN has responded to this need by pursuing studies of women's treatment, a direction that should continue.

Conclusion

2.6 What have we learned from CTN trials?

The CTN has accomplished an impressively large number of studies, including clinical trials, only a portion of which have been reviewed here. These 15 trials represent 5,328 individuals in community-based substance abuse treatment who have been randomized to treatment or control conditions and had their outcomes evaluated. The trials have, for the most part, followed the hybrid model (Carroll & Rounsaville, 2003), integrating effectiveness and efficacy elements into their designs. A wide variety of interventions has been studied.

The following treatments have demonstrated superiority over control conditions at retaining patients in detoxification or treatment: 1) bup-nx in outpatient detoxification and bup-nx in inpatient detoxification (Ling et al., 2005); 2) 12 weeks of bup-nx treatment vs. 2 week detoxification with adolescents (Woody et al., 2008); 3) motivational incentives in outpatient psychosocial treatment (Petry et al., 2005); and 4) motivational interviewing integrated into program intake (Carroll et al., 2006). In addition, a telephone engagement strategy showed, on clinic documentation, but not self report, a greater proportion of patients initiating outpatient treatment (Hubbard et al., 2007). Although expected to improve retention, 3-session Motivational Enhancement Therapy was unsuccessful in three separate studies (Ball et al., 2007; Carroll et al., 2006; Winhusen et al., 2008). Treatment drop-out is a chronic concern in the addiction field, and CTN trials have not been immune from the problem. Trials of interventions comprised of multiple sessions have had difficulty retaining patients through all sessions (e.g., CTN 0014, CTN 0018, and CTN 0019). The ability of abstinence-based incentives and motivational interviewing added to intake to increase retention and attendance in outpatient psychosocial treatment have important implications for future studies.

During-treatment substance use was reduced by the following treatments compared to control: 1) bup-nx in both outpatient and inpatient detoxification (Ling et al., 2005); 2) 12- versus 2-week detoxification in adolescents (Woody et al, 2008); 3) smoking cessation mood management counseling plus NRT (Reid et al., 2008); and 4) prize-based motivational incentives in both psychosocial outpatient and methadone treatment (Peirce et al., 2006: Petry et al., 2005). Interventions that produced differences from control in substance use in the weeks or months following treatment included: 1) 12 weeks of bup-nx treatment for adolescents (Woody et al., 2008); and 2) 3-session Motivational Enhancement Therapy among primary alcohol users (both English and Spanish versions) (Ball et al., 2007; Carroll et al., in press). In general, CTN interventions have done better at reducing substance use than at maintaining reductions, the exception to this being MET among primary alcohol users; this intervention was not superior to standard treatment at reducing use but was better at maintaining reductions. Keeping in mind that substance use was not the primary or secondary outcome for two of the 15 protocols (Calsyn et al., 2009; Tross et al., 2008), and that some trials did not follow patients after treatment (Ling et al., 2005; Petry et al., 2005) the pooled impact on substance use, especially on maintenance of reduction or abstinence, of all the trials is disappointing. What should we conclude about the CTN and how well it has met its goal?

We might be tempted to conclude that we have chosen the wrong interventions; in this case we would try to identify other interventions to test that would have greater impact. However, most of the CTN treatments were selected based on prior efficacy data. If they have been

less successful than expected, how well will other treatments fare? There is an ongoing debate in the field of psychotherapy research about the degree to which specific treatment methods account for variance in outcome and about the utility of focusing research on treatment method comparisons (Norcross, Beutler & Levant, 2006). Some argue that treatment method accounts for very little variance (Wampold, 2006), while others argue that there are superior treatment methods and that method is as important as other elements of therapy in understanding outcome (Chambless & Crits-Christoph, 2006; Ollendick & King, 2006). It is beyond the scope of this review to resolve this debate, but the argument suggests care should be taken in simply continuing to test one treatment after another in designs similar to those that have been employed.

Regarding elements of treatment other than method, interactions of site and condition were reported in several of the primary outcome papers (Ball et al., 2007; Carroll et al., in press). Differences by site cannot be addressed in this review across all CTN trials, because not all site analyses have been completed or reported in primary outcome papers. We do know that the treatment programs in the CTN differ from one another in the characteristics of patients that are seen (Ball et al., 2007), in provider characteristics, and in what kinds of treatment are offered (McCarty et al., 2008). Differences in outcome by site could arise because of the relative effectiveness of the standard treatment to which a treatment of interest is being compared, differences in substance use severity or other aspects of case mix, or differences in how well providers are able to adhere to a given manualized protocol. With its large and diverse set of CTPs, the CTN is fertile ground for studies that examine these issues in greater detail. If we are truly to improve drug abuse treatment in the nation, we must better understand what is going on in specific types of programs and how the introduction of new treatment methods interacts with patient, provider and program characteristics. Consistently assessing the effects of therapeutic alliance on outcome in future CTN trials might help to elucidate the extent to which specific treatment methods as opposed to more inchoate elements of treatment affect outcomes (Norcross & Lambert, 2006).

Assuming the CTN were to discontinue consecutive 2-group trials of different treatment methods, what alternatives might be more productive? These first 15 trials, like most of those conducted in the addiction field, entail a single episode of time-limited therapy in which sometimes very brief experimental interventions are offered. In addition, few of the protocols include longer term follow-up to determine the degree to which lasting or emergent “sleeper” effects are present. While many of us have come to conceptualize addiction as a chronic relapsing condition (McLellan et al., 2000), the design of interventions and clinical trials has not caught up with that notion. While we are still searching for the “magic bullet,” the patient we are intending to “cure” has moved on to the next phase of her or his addiction or recovery, whether remission, relapse, or another treatment episode. Our current approach to trials does not provide sufficient data on the effect of the current treatment episode on that person’s trajectory, nor does it offer the opportunity to alter the course of treatment in response to different trajectories. One recently completed CTN study (CTN 0030) employed an adaptive treatment strategy or sequential multiple assignment randomized trial (SMART) design (Lavori & Dawson, 2008: Murphy, Lynch, Oslin, McKay, & TenHaye, 2007) in which the course of treatment could be altered based on patient response. Interventions of this type, and their corresponding trial designs, also hold promise for improving the utility of our work.

In addition to sequential approaches, more could me made of combining therapies. Single state agencies overseeing substance abuse treatment fund and monitor treatment programs, not specific interventions. From a policy perspective, it would be useful to know, not only how to sequentially step treatment up or down, but also what combinations of therapies can improve longer term outcome. In the CTN trials to date, the treatment being studied existed

alongside any number of other services that were provided to the patient before, during, or after their trial participation. These other services may enhance or diminish patient improvement, but their impact is largely unknown. Again, greater attention to combining therapies and to what is being provided is warranted.

Based on the sometimes disappointing results, should the CTN be abandoned? We would argue against doing so and for a reconsideration of the approach to selection and design of trials. The CTN has entailed mounting multiple field experiments within a diverse treatment system. Many of the potential challenges of such an endeavor have been successfully overcome, for example, most trials have had high levels of fidelity to treatment manuals and have collected usable outcome data on a high proportion of participants. Anticipated challenges have also led to compromises regarding study design that have perhaps led us to ask oversimplified questions. For example, a sequential design has been used in only one study, and long-term follow-up designs that measure a variety of factors in addition to the impact of a given therapy method have been avoided. If guided by its own findings to date, the system offers opportunity to examine questions that will continue to inform addiction treatment. We offer a limited set of recommendations as a starting point.

2.7 Recommendations

2.7.1 Follow an incremental model of protocol selection and design—The CTN trials to date raise a number of researchable questions that might either lead to more effective treatments or more transferable ones or both. While we have implemented more than one trial of a specific type of treatment these have either been designed simultaneous with one another or without benefit of the results from previous related studies.

2.7.2 Select treatment interventions with strong efficacy evidence for CTN study—As we can see, even when efficacious therapies are selected, their efficacy/effectiveness across multiple community sites may not hold up. However, given the expense and challenges of operating in the multi-site environment of the CTN, we recommend holding to the previous standard. Outcomes of therapies for which there is little prior information will be difficult to interpret when applied in the multi-site environment. Pilot and efficacy studies can be completed under other NIH mechanisms.

2.7.3 Utilize established methods to increase treatment exposure in CTN studies—Incentives should be consistently used, regardless of the nature of the active treatment being tested, to increase levels of attendance and obtain adequate treatment doses. Petry and colleagues (2005) propose directly reinforcing attendance and cite past research showing this is efficacious. MI should also be included as a component of intake in future trials in which optimal treatment exposure is desired. Although MI itself had no impact on substance use, it may be useful to combine MI-enhanced intake and other treatment elements (e.g., CBT, motivational incentives or pharmacotherapy).

2.7.4 Design trials based on current conceptions of addiction—There is not universal agreement that addiction is a chronic relapsing disorder, but to the extent that we can agree on this or any other conception of addiction, we should design our trials accordingly. Studies of short-term, single modality treatments, while addressing health care funding pressures for brief treatment, may fail or appear to fail, because the individual's trajectory has been ignored.

2.7.5 Include longer-term follow-up to address maintenance of treatment effects—Long term follow-up is costly but is the only way to determine maintenance of

treatment effects. As was seen in two of the MET studies, sometimes differences emerge only at follow-up as one group worsens while the other maintains gains.

2.7.6 Utilize the CTN's size and diversity to study moderators and mechanisms of treatment effects—There are a number of factors (patient, therapist, relationship, site, comparison condition) that affect outcome results besides treatment method, yet these factors are not currently systematically studied in CTN trials. The system could be used to greater advantage to examine these issues.

2.7.7 Study treatments that address prevalent conditions and emerging needs in the field—CTN studies have been selected to address emerging or especially challenging drug trends, such as methamphetamine or prescription opiate use. Relatively few studies to date have addressed co-occurring mental or physical conditions. There are potentially several good reasons to consider the CTN as a location for such trials. First, a large proportion of patients served by CTPs suffer from co-occurring disorders. Second, there is a need for pragmatic trials of interventions in this area. Future studies might focus again on trauma and PTSD or on depression or bipolar disorder, all of which have relatively high prevalence among substance abusers.

2.8 Limitations of the review

To simplify comparison, we chose to review only the primary outcome paper from CTN protocols that had such a paper published or in press. This limited us to 15 of the 24 completed protocols, but it also excluded many analyses published from the protocols that provide additional information. These include analyses of secondary outcomes, adverse events, patient, therapist, and program characteristics as predictors or moderators of outcome, and economic analyses. Had all the additional publications been considered they may have shed additional light on the points raised here. Further, while describing the basic elements of the design features in the trials reviewed, we did not evaluate the overall methodological rigor of the trials in any systematic fashion; however, we did point out limitations of a number of the trials based upon certain design features. The authors are affiliated with the CTN and have been involved in a number of the trials reviewed here. While we attempted to consider only what was presented in the primary outcome papers, our own experiences may bias the presentation.

While the NIDA Clinical Trials Network has accomplished a considerable amount in its first ten years of operation, it is clear that there is considerably more to accomplish to improve the quality of the research, as well as its dissemination, to fully realize the original goal of improving the quality of drug abuse treatment with science as the vehicle.

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Table 1

Summary of CTN trial outcomes

CTN#, Citation, Dates*	Sample	Design	Treatment	Primary Outcome	Secondary Outcome	Treatment Retention
Medication and combination (medication and behavioral treatment) trials						
CTN 0001 Ling et al., 2005; bup-nx detox inpatient 2/26/01 - 9/11/02	113 opioid-dependent, age 18+. 6 CTPs. 56% Caucasian, 19% African American, 16% Hispanic.	Open label 13-day detox - 2/1 randomization to bup-nx vs. Clonidine. Follow-up length: 13 days.	Bup-nx at 16mg-4 mg by day 3, reduced to 2 mg-.05 mg by day 12-13. Clonidine oral, replaced by patch, removed day 13.	59/77 (77%) bup-nx vs. 8/36 (22%) Clonidine retained for 13-days and provided opioid-free urine last day (***OR* =11.9**, $p < .0001$.)	Observed withdrawal: bup-nx < Clonidine, ns for Tx completers. Reported withdrawal: bup-nx < Clonidine. Craving: bup-nx < Clonidine, ns for Tx completers. Ancillary meds: ns.	bup-nx: M = 12.6 days (*SD* = 3.2). Clonidine: M = 6.7 days (*SD* = 4.8 ($p< 0.0001$, $\eta2 = 0.35$)
CTN 0002 Ling et al., 2005; bup-nx detox outpatient 1/5/01 -10/18/02	231 opioid-dependent, age 18+. 6 CTPS. 40% Caucasian, 37% African American, 20% Hispanic.	Same as above.	Same as above.	46/157 (29%) bup-nx vs. 4/74 (5%) Clonidine retained for 13-days and provided opioid-free urine last day (***OR* = 7.7**, $p < .0001$).	Observed withdrawal: bup-nx < Clonidine. Reported withdrawal: bup-nx < Clonidine. Craving: bup-nx < Clonidine. Ancillary meds: bup-nx < Clonidine - completers.	bup-nx: M = 11.3 days (SD = 4.2) Clonidine: M = 7.1 days (SD =5.3) ($p < 0.0001$, $\eta2 = 0.15$)
CTN 0003 Ling et al., 2009; bup-nx taper 6/30/03 - 11/5/05	516 opioid-dependent, age 15+. 11 CTPS. 76.2% Caucasian, 11.6% African American, 6.2% Hispanic.	Randomized to 7-day vs. 28 Suboxone taper. Follow-up: 1 & 3 months after taper.	3-day induction, 4 week stabilization (3 flexible dosing weeks, 1 stable dose week). Different taper regimens depending on dose at end of stabilization.	Opioid free urine at end of taper: 7 day - 44.31%; 28-day - 29.89% (**φ = .15**, p=.0007). Opioid free at 1-month: 7day −17.65%; 28-day - 17.62% (**φ = 0,** ns). Opioid free at 3-month: 7 day - 12.16%; 28-day −13.41% (**φ = .02**, ns).	Observed 1 month withdrawal: 7 day > 28 day. Reported withdrawal: ns. Craving: ns. Ancillary meds: ns. Tx satisfaction: 28 day > 7 day at 3 months.	End of taper retention: 7-day: 79%. 28-day: 66%
CTN#, Citation, Dates*	**Population**	**Design**	**Treatment**	**Primary Outcome**	**Secondary Outcome**	**Treatment Retention**
CTN 0010 Woody et al., 2008; bup-nx adolescent 7/17/03 -12/31/06	154 youth age 15-21, opioid-dependent with physiological features. 6 CTPs. 73.7% Caucasian, 2% African American, 25% Hispanic.	2/1 randomization to 12-weeks of bup-nx vs. 14-day bup-nx taper. Follow-up length: 12 months.	12-week: 9 weeks of up to 24 mg bup-nx and 3 week taper. 14-day: up to 14 mg tapered to day 14. Daily dosing on-site unless site not open 7 days. Psychosocial tx was 1 individual, 1 group per week using drug counseling manual.	Opioid positive urines at 4 weeks: detox - 61%; 12-week - 26% (***OR* = 7.05**, $p<.001$, at 8 weeks: detox - 54%; 12-week - 23%(***OR* = 5.07**, p=.001). at 12 weeks: detox - 51%; 12-week - 43% (***OR* = 1.84**, ns). Detox > 12-week across follow-ups (***OR* = 2.65**, $p = .01$).	During tx: Detox > 12-week on self-report opioid, marij, cocaine & injection. Detox fewer counseling sessions, more likely to enroll in other tx. Follow-up: Detox > 12-week on self report cocaine.	Retention at 12 weeks: detox: 20.5%; 12-week: 70% ($p<.001$).

CTN#, Citation, Dates*	Population	Design	Treatment	Primary Outcome	Secondary Outcome	Treatment Retention
CTN 0009 Reid et al., 2008; smoking cessation 4/9/03 -4/5/05	225 smokers in MMT or psychosocial outpatient tx. 7 CTPs. 39% Caucasian, 26% African American, 34% Hispanic	2/1 randomization by cohorts to 9 session smoking cessation + TAU (SC) vs. TAU alone. Follow-up length: 6 months.	SC: 7 weeks, 9 sessions mood management & CBT, quit date week 2, NRT - 21-mg/day weeks 1-6, 14-mg/day weeks 7 and 8, Could reduce to 14 mg if unable to tolerate 21 mg. Tau: no smoking cessation. Varied by CTP.	During-tx smoking abstinence: SC - 10-11%; TAU - 0. Smoking rates not different at 13 and 26 weeks. Smoking abstinence assoc with counseling attendance & NRT adherence.	SC < TAU on # cigarettes/day during tx & at follow-up. SC < TAU on withdrawal & craving during tx. No effect of condition on substance of abuse abstinence rates or craving for primary substance. Fewer cigarettes/day predicted lower craving for primary substance.	No difference in CTP tx attendance between two conditions, but in outpatient psychosocial tx, TAU better counseling attendance than SC.

CTN#, Citation, Dates*	Population	Design	Treatment	Primary Outcome	Secondary Outcome	Treatment Retention
Psychosocial/behavioral treatment trials						
CTN 0006 Petry et al., 2005; incentives outpatient psychosocial 4/26/01 -9/4/03	415 cocaine or methamphetamine users (79% dependence, 5% abuse) in outpatient psychosocial tx.. 8 CTPs. 36% African American, 12% Hispanic.	Randomized to TAU + abstinence-based incentives vs. TAU. Follow-up length: 12 weeks.	Incentive: 2 urines & breath tests/week. Stimulant-free urines &alcohol-free breath samples earn chip draws, increasing in # with each abstinent week & reset if positive. Bonus draws for marij & opioid free urines. More lower-value, fewer higher value chips in bowl. TAU: group & some individual counseling, 2 urines/week -congratulated neg & encouraged if pos.	If missing samples coded positive, incentive > TAU on % stimulant/alcohol-free samples (***OR* = 1.69**). Consecutive visits with confirmed abstinence: Incentive M = 8.6 (sd=9.2); TAU M = 5.2 (sd=6.9) (**Cohen's *d* = .42**, $p<001$). Incentive > TAU on # stim or alc neg urines submitted, but did not control for differences in # of specimens submitted.	Counseling sessions attended: Incentive *M* = 19.2 (*sd* = 16.8); TAU *M* = 15.7 (*sd* = 14.4) ($p<.02$). Proportion samples marij & opioid-free not different.	Incentive: 12-week retention -49%; TAU - 35% (**Unadjusted hazard ratio = 1.45**). Incentive more likely than TAU to submit urines.
CTN 0007 Peirce et al., 2006; incentives methadone 4/25/01 - 8/29/03	388 cocaine or methamphetamine users MMT. 6 CTPs. 75% cocaine abuse/dependence, 4% meth abuse/dep, 4% both. 26% Caucasian, 51% African American, 16.5% Hispanic.	Randomized to TAU + abstinence-based incentives vs. TAU. Follow-up length: 6 months.	Same incentive procedures as above. TAU included daily methadone dose.	Incentive > TAU on % samples neg for stimulants/alcohol (***OR* = 1.98**). Accounted for by stimulants, not alcohol. Consecutive abstinent visits: Incentive Mean (SD) = 5.5 (7.9); TAU Mean (SD) = 2.3 (3.8) (**Cohen's *d* = .51**, $p<.001$). No difference in samples neg for stimulants/ alcohol at 6 months.	Counseling sessions attended: Incentive: *M (SD)* = 8.6 (8.0) not different from TAU *M (SD)* = 10.3 (11.9).	Incentive 12-week retention - 67% not different from TAU - 65%. No difference in # urine samples submitted.

CTN#, Citation, Dates*	Population	Design	Treatment	Primary Outcome	Secondary Outcome	Treatment Retention
CTN 0004 Ball et al., 2007; MET 5/30/01 - 12/3/04	461 age 18+ substance abusers in outpatient psychosocial tx. 5 CTPS. 41.9% Caucasian, 42.1% African American, 10.6% Hispanic.	Randomized to Motivational Enhancement Therapy (MET) vs. Counseling as Usual (CAU). Follow-up length: 4 months.	MET: 3 individual sessions in 28-days, using MI microskills, structured handouts for personalized feedback and change plans. CAU: 3 sessions gathering info on substance use/ functioning, explaining tx program, discuss goals; case management & counseling; encourage 12-step, promote abstinence. MET: local training & supervision.	Self-reported days/week of primary substance: MET & CAU reduced use during tx (**Condition effect partial η^2 = .01**). For primary alcohol users, MET sustained reductions during next 12 weeks; CAU increased use. No condition effects for primary drug users. A number of site main effects and interactions.	NA	No difference between MET and CAU in # days in program (**partial η2 = .001**); % still enrolled at 16 weeks.
CTN 0005 Carroll et al., 2006; Motivational Interviewing 4/12/01 - 1/27/03	423 age 18+ substance users in outpatient psychosocial tx. 5 CTPs. 72% Caucasian, 10% African American, 3% Hispanic, 14% multi-ethnic.	Randomized to intake integrating motivational interviewing vs. standard intake. Counselors randomly assigned. Follow-up length: 3 months.	MI-integrated intake: 1 session standard information-gathering but using MI strategies and interviewing style. Standard intake: information-gathering session. Local MI expert provided training to clinicians and on-site supervisor.	# days use primary substance - not different between conditions during 28 or 84 days after randomization for full sample or primary alcohol users.	See Treatment Retention	Still enrolled at program at 28 days - MI: 84%; Standard: 75% (*p*=.05). MI attended sig more sessions in 28 days (*M* =5) than standard (*M*=4) (**Cohens *d* = .24**, *p*=.05). No difference in retention at 84 day. Primary alcohol-user sessions attended in 28 days: MI-integrated *M*=5.1; Standard *M*=3.3 (**Cohen's *d* = .56**, *p*=.01). Also sig difference at 84 days for primary alcohol users (p=.05).

CTN#, Citation, Dates*	Population	Design	Treatment	Primary Outcome	Secondary Outcome	Treatment Retention
CTN 0013 Winhusen et al., 2008; MET pregnant women 10/15/03 - 9/6/06	200 age 18+ pregnant substance users in outpatient psychosocial tx. 4 CTPs. 40% Caucasian, 34.5% African American, 19.5% Hispanic.	Randomized to Motivational Enhancement Therapy for Pregnant Substance Users (MET-PS) or TAU. Clinicians randomized.	3 -session MET-PS: designed specifically for pregnant women, included feedback on health of pregnancy. TAU: intake plus 1st two individual sessions. Supervision centrally managed.	See Treatment Retention	No condition effects on self-report substance use. Urine positives: site effects in which condition effects reversed at different sites. URICA: - TAU readiness to change decreased from	% outpatient hours attended - no condition effect (**φ = .05**). # weeks at least 1 session attended - no condition effect. # days until tx dropout - site X

CTN#, Citation, Dates*	Population	Design	Treatment	Primary Outcome	Secondary Outcome	Treatment Retention
		Follow-up length: 4 months.			baseline to end of tx, MET-PS no change.	condition interaction in which one site had earlier dropout in MET-PS than TAU, other sites not different.
CTN 0021 Carroll et al., in press; Spanish MET 11/14/03-3/15/06	405 age 18+ Spanish speaking patients in outpatient psychosocial tx. 5 CTPS. All patients Hispanic from variety of birth places.	Design identical to CTN004 (above) except sites offered service in Spanish & had four fluent clinicians. Assessments in Spanish. Follow-up length: 3 months.	Same as CTN004 (above) except delivered in Spanish. Bilingual trainers & supervisors.	Self-reported days substance use reduced but no condition X time or site X time X condition interactions. % days abstinent primary substance - **during tx effect size = .16, follow-up effect size = .08**. Primary alcohol users only, sig interaction of weeks X phase X condition on Days Alcohol/week; both conditions reduced during tx phase & CAU increased days use during follow-up while MET maintained reductions.	NA	No effects on tx retention. 28-day MET retention = 93%, TAU = 91%. 84-day MET retention = 57%, TAU = 52%. Days enrolled in tx through week 16 - **effect size = .15**

CTN#, Citation, Dates*	Population	Design	Treatment	Primary Outcome	Secondary Outcome	Treatment Retention
CTN 0011 Hubbard et al., 2007; telephone engagement 1/7/03 - 5/8/04	339 age 18+ patients being discharged from short term inpatient/residential (STI/STR) tx. 4 CTPs. 34% African American, 2.5% Hispanic.	Randomized to Telephone Call Group (TCG) vs Standard Care Group (SCG). Follow-up length: 13-17 weeks.	TCG: 1. prepare & discuss discharge plan; 2. TELE counselor attempts calls weeks 1, 2, 4, 6, 8, 10, 12 after discharge; 3. gives positive feedback, encourages continuing care follow-through.	See Treatment Retention	No condition differences on substance use or other secondary outcomes.	Self-reported outpatient tx attendance not different between TCG & SCG. Documented outpatient attendance - 48% TGC vs. 37% SCG attended at least 1 session.
CTN 0015 Hien et al., 2009; women and trauma 1/20/04 - 2/22/07	353 women age 18-65 in outpatient psychosocial tx and met criteria for PTSD/ sub-threshold PTSD. 7 CTPs. 45.6% Caucasian, 34% African American, 6% Latina, 13%	Randomized to Seeking Safety (SS) or Women's Health Education (WHE). Counselors and supervisors randomized. Follow-up length: 12 months.	Rolling admission to group. SS - 12 groups + 1 individual session of integrated substance use/ PTSD tx. WHE - 12 groups + 1 individual session of didactic information about women-specific health issues.	PTSD symptoms reduced for both groups. No difference between SS and WHE. For Post-traumatic Stress Scale - Self Report, **post-tx effect size = .07, follow-up effect size = .15**. For Clinician Administered PTSD Scale, **post-tx**	No substance use differences between conditions.	No difference between SS and WHE on attendance at TAU.

CTN#, Citation, Dates*	Population	Design	Treatment	Primary Outcome	Secondary Outcome	Treatment Retention
	multi-racial.			**effect size = .04, follow-up effect size = .12.**		

CTN#, Citation, Dates*	Population	Design	Treatment	Primary Outcome	Secondary Outcome	Treatment Retention
Psychosocial/behavioral trials targeting HIV/STI risk behavior						
CTN 0018 Calsyn et al., 2009; safe sex men 4/19/04 - 4/19/06	590 men age 18+ in MMT or outpatient psychosocial tx who reported unprotected vaginal (UVI) or anal (UAI) intercourse in past 6 months. 14 CTPs. 56% Caucasian, 28% African American, 13% Hispanic., 2% American Indian., 1% Asian American.	Randomized by cohort to 5-session Real Men are Safe (REMAS) or 1-session HIV education. Follow-up length: 6 months.	REMAS: 5 90-minute sessions include HIV risk & prevention, sex without drug use, and communication with partners. HIV-Ed: single 60-min. session includes selected educational material from sessions 1 and 2 of REMAS.	Unprotected vaginal or anal sexual intercourse occasions (USO) over the past 90 days: REMAS reduced 90 day more than HIV-Ed at 3-month (M = 17.8 vs. 19.7) (***d* =.098**) and 6-month (M = 16.0 vs. 19.2) (***d*** = .167). Completer analysis showed greater effect in same direction(***d* = .213 at 3 months** and ***d* = .337 at 6 months**).	NA	TAU retention not an outcome.
CTN 0019 Tross et al., 2008; safe sex women 5/24/04 - 6/11/06	515 women age 18+ in MM or outpatient psychosocial tx who reported unprotected vaginal, anal intercourse with male partner past 6 months. 12 CTPs. 58% Caucasian, 24% African American, 9% Hispanic, 9% other minorities.	Randomized by cohort to 5-session Safer Sex Skills Building (SSB) or 1-session HIV/STI Education (HE). Follow-up length: 6 months.	SSB: Female specific, includes risk reduction skills, female-male control and negotiation of condom. Use of active problem-solving, modeling, rehearsal strategies. HE: Female-specific, information-only.	USO days change in SSB: 18.6 (BL) - 15.08 (3 mo) - 13.96 (6 mo); HE: 19.96 (BL) - 17.33 (3 mo) - 24.14 (6 mo) (time X condition interaction sig) (***d* = . 42 at 6 months**). SSB had 29% fewer USOs than HE at 6 month. SSB completers: predicted USO 13.37 (3 mo), 10.52 (6 mo); HE completers: predicted USO 16.07 (3 mo), 26.28 (6 mo). Completers -SSB 43% fewer USOs at 6 month than HE (***d* = .60 at 6 months**).	NA	TAU tx retention not an outcome.

Note: Effect size estimates, when available, appear in bold, in the column reporting primary outcomes or retention (if retention was the primary outcome).

*Dates refer to the time span from first patient randomization to study completion (end of data collection).