Published in final edited form as:
J Subst Abuse Treat. 2010 June ; 38(Suppl 1): S53–S60. doi:10.1016/j.jsat.2010.01.009.

From Research to the Real World: Buprenorphine in the Decade of the Clinical Trials Network

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Abstract

The National Institute on Drug Abuse (NIDA) established the National Drug Abuse Treatment Clinical Trials Network (CTN) in 1999 to bring researchers and treatment providers together to develop a clinically relevant research agenda. Initial CTN efforts addressed the use of buprenorphine, a mu-opioid partial agonist, as treatment for opioid dependence. Strong evidence of buprenorphine's therapeutic efficacy was demonstrated in clinical trials involving several thousand opioid-dependent participants, and in 2002, the FDA approved buprenorphine for the treatment of opioid dependence. With the advent of a sublingual tablet containing both buprenorphine and naloxone to mitigate abuse and diversion (Suboxone®), buprenorphine appeared poised to be the first-line treatment for opioid addiction. Notwithstanding its many attributes, certain implementation barriers remained to be addressed in CTN studies, and these efforts have brought a body of knowledge on buprenorphine to front-line clinicians. The purpose of this article is to review CTN-based buprenorphine research and related efforts to overcome challenges to the implementation of buprenorphine therapy in mainstream practice. Furthermore, this paper explores current issues and future challenges that may require additional CTN efforts.

Buprenorphine was as much a proof-of-concept vehicle for the National Drug Abuse Treatment Clinical Trials Network (CTN) as the CTN was a platform for demonstrating the clinical utility and practicability of buprenorphine. That is, buprenorphine gave the CTN its first line of inquiry, providing the newly established entity with substantial credibility. Buprenorphine is a mu-opioid partial agonist approved by the FDA in 2002 for the treatment of opioid dependence, and it appears to have less potential for psychological and/or physical dependence

than traditional full-agonist opioids like methadone (Jasinski et al., 1978). Although buprenorphine, as an opioid partial agonist at the mu-opioid receptor, produces typical opioid-associated subjective and physiological effects, these effects are less than those produced by full agonists such as morphine, and is effective in preventing the onset of the opioid-abstinence syndrome in opioid-dependent individuals (McCance-Katz, 2004). Notably, its use in the office-based treatment setting provides the patient the opportunity to avoid the "stigma" sometimes attached to traditional opioid maintenance treatment programs (Torrington et al. 2007). Buprenorphine treatment allows patients to receive medication by prescription for self-administration at home for days, weeks or even months, rather than daily attendance at a traditional opioid treatment program. This allows opioid-dependent individuals to return to a more "normal" life routine more quickly.

Anticipating FDA approval of the medication, the CTN recognized that best-practices research was needed to facilitate implementation of this new opioid pharmacotherapy. The CTN was emerging as a nationwide community-based participatory clinical research enterprise that was well positioned to deliver the evidence needed to launch buprenorphine's use into private practice settings. The CTN's early buprenorphine research portfolio included many implementation aspects of buprenorphine treatment:

- effectiveness in different treatment settings and with different populations
- medication delivery methods,
- tapering from the medication
- safety (e.g., liver health, etc), and
- effectiveness in heroin versus prescription opioid medication dependence.

The CTN Approach Strikes a Balance

Adoption of buprenorphine has been slower than anticipated (Ducharme, Knudsen, Roman, & Johnson J.A, 2007; Knudsen, Ducharme, & Roman, 2006; Knudsen, Ducharme, & Roman, 2007; Knudsen, Abraham, & Roman, 2009). The combination product of buprenorphine and naloxone, Suboxone®, was developed to reduce the potential for abuse (Strain et al., 1997) and increase acceptance by the treatment community. Combining buprenorphine with naloxone increases safety in that it cannot then be readily diverted to injection drug use, which has been found responsible for most buprenorphine-related deaths in other countries (e.g Pirnay et al., 2004). The combination product has been used in CTN research, and this article refers to both buprenorphine/naloxone (BUP/NX) in CTN studies, and the general use of buprenorphine.

Merely being an efficacious medication and a viable alternative to existing therapy did not ensure buprenorphine's acceptance among clinicians, patients, agencies, and payers. Several factors influence the adoption of innovative medications. The characteristics of the individual medication are critical. Naltrexone, for example, is effective for opioid addiction but is objectionable to patients so that few seek it or remain on it (Digiusto et al., 2004). Another factor arises from societal attitudes. Methadone is not condoned in many circles because its full agonist properties are seen as too similar to the effects of the very drug that is being counteracted—rather than an effective treatment for the disease state. What is needed in most cases is a compromise, whereby the treatment for addiction is effective but not negatively perceived by society. In that regard, buprenorphine is a balanced medication, with agonist and antagonist characteristics that yield minimal reinforcing effects and negligible noxious side effects. It meets the needs of both patients and society, striking a successful therapeutic balance.

In a similar fashion, the CTN's efforts to examine and improve buprenorphine implementation have been balanced. By neither emphasizing nor downplaying the pros and cons of

buprenorphine, the research efforts and associated findings are more instructive for real-world clinicians struggling to address a difficult addiction problem within sometimes confusing regulatory boundaries. The CTN focused on discovering and developing practical applications of effective therapeutic procedures. Whereas the overall CTN portfolio balances behavioral and pharmacotherapy initiatives, in the case of the CTN buprenorphine research, a pairing of the two was selected from the outset to ensure buy-in from all stakeholders. Acknowledging the importance and need for psychosocial treatment reassured those who may have been reluctant to endorse pharmacotherapy.

The CTN research on buprenorphine provided impetus for many hesitant clinicians, program directors, and regulators by demonstrating the effectiveness and safety of Suboxone. A good example of this is evident in the shift away from treatment clinic practices that did not use medication toward an acceptance of Suboxone for opioid-addicted patients (Brigham, Amass, Winhusen, Harrer J.M., & Pelt, 2007; Collins, Horton, Reinke, Amass, & Nunes, 2007; Kovas, McFarland, Boverman, McCarty, & Thayer, 2007). Ultimately, clinic staff and leadership acknowledged the repeated failure of most of their opioid-addicted patients to attain abstinence and the failure of *any* patients to remain opioid-free for any duration when only provided with behavioral therapy. Those failures were in contrast to the successful recovery demonstrated among most buprenorphine-maintained opioid addicts. Given the evidence, pragmatism and true concern for the well-being of patients overrode any philosophical position against opioid replacement therapy; and clinicians accepted the use of buprenorphine.

The First CTN Protocols

The first three CTN protocols involved the study of buprenorphine. After documenting the effectiveness of the medication with adults, the CTN also tested buprenorphine for treating opioid dependent adolescents and young adults.

CTN 0001 and CTN 0002: Suboxone versus Clonidine for Opiate Detoxification

The first two CTN studies compared the combination buprenorphine/naloxone product (BUP/NX) to clonidine for opiate detoxification (Amass et al., 2004; Ling et al., 2005). The protocols were identical except for setting: inpatients in CTN 0001 and outpatients in CTN 0002. The investigations compared the relative clinical utility of BUP/NX to clonidine in short-term opiate detoxification. It was hypothesized that BUP/NX-assisted detoxification, compared to detoxification with clonidine, would be associated with a better treatment response. A treatment responder was defined as a participant who completed the 13-day detoxification and whose last urine specimen collected on day 13/14 was negative for illicit opiates. Secondary objectives assessed abstinence from opiates and other drugs of abuse throughout the detoxification period and during follow-up (at 1, 3, and 6 months post-detoxification), withdrawal symptoms, treatment retention, safety, patient satisfaction, and the use of ancillary medications. Multiple Community Treatment Providers participated in the studies. Counseling procedures already being used—in other words, treatment as usual—at each CTP were used throughout the study. For the inpatient study, 77 (77%) participants assigned to the Suboxone condition achieved the treatment success criterion compared to only 8 of the 36 (22%) assigned to clonidine. Forty-six of the 157 (29%) outpatients assigned to Suboxone achieved the treatment success criterion, compared to only 4 of the 74 (5%) assigned to clonidine (Ling et al., 2005).

These two studies documented the superiority of BUP/NX as compared with the clonidine-assisted method of detoxification, and confirmed the feasibility of conducting rigorous clinical research in community-based treatment programs. At the time, clonidine was the usual choice for medication-assisted detoxification from opioids. The use of a partial agonist, buprenorphine, was a break from that tradition, requiring a different approach and an adjustment to clinical practice and philosophy. The two studies framed the initial test of the

CTN process: could the research effort be conducted with fidelity in CTPs where opioid agonists were unavailable or that had long been opposed to opioid agonist medication (i.e., methadone)? The issues and potential problems in such trials became apparent to the CTN stakeholders during discussions regarding protocol development, which included representatives of CTPs that were potential sites for the studies. Bi-directional communication was an important feature of the protocol development process, in which the concerns and interests of CTP personnel were taken into account, and CTPs were encouraged to become invested in the successful implementation of the study protocol. Regular protocol conference calls, invitations to the CTP staff to participate in the analyses and publications, and meetings to bring together all the CTP staff and other CTN personnel were designed to facilitate the open communication considered vital for the success of the CTN projects.

The “starting point” in protocol development was noteworthy in that one of the treatment arms was anchored in the familiar routine of daily practice—whereas the clinics and the clinicians were clearly involved in research, they were still treating some of the research participants with a behavioral component just as they had been doing all along. This comfort level lessened resistance and allowed the research to progress. Furthermore, these studies sought to compare the two treatment approaches on familiar treatment outcomes: whether patients complete treatment and whether they are free of illicit drugs at the end—without arguing about the merits of detoxification.

CTN 0003: Suboxone Taper: A Comparison of Two Schedules

This study compared the relative advantage of two taper schedules (7 days vs. 28 days) of BUP/NX following four-weeks of medication stabilization for detoxification in outpatient settings. Data were collected in a randomized, open-label, parallel-group design study. A total of 516 participants seeking detoxification for opiate dependence were inducted onto BUP/NX over a period of 3 days, followed by three weeks of medication adjustment based on the clinical judgment of the treating physician. During the fourth and final week of buprenorphine delivery, participants received a stable daily dose of buprenorphine (8, 16, or 24 mg). Participants were then randomized to one of the two taper schedules, 7- and 28-days, and followed for three months post-taper. The duration of study participation for each participant was a maximum of approximately 5 months, including screening, stabilization, tapering, and post-tapering follow-up, and data were collected at 17 time points for each group. Findings indicated no advantage in prolonging the duration of the taper. At the end of the taper, 44% of the 7-day taper group ($n = 255$) provided opioid-free urine specimens compared to 30% of the 28-day taper group ($n = 261$; $P = 0.0007$). There were no differences in opioid-free urine specimens at the 1-month and 3-month follow-up assessments (7-day = 18% and 12%; 28-day = 18% and 13%, 1 month and 3 months, respectively) (Ling et al., 2009).

Similarly to the previous studies, the CTN 0003 project added crucial information to the evidence-based practice of buprenorphine pharmacotherapy. Questions remained in the treatment community regarding the optimum length of taper, and the results of a previous study assessing buprenorphine taper (Amass et al., 1994) led to a widely held belief that a longer taper period would result in better outcomes. The CTN study was not aimed to advance short tapering over longer tapering, but merely to determine whether a rapid taper would be acceptable to patients and clinicians. CTN 0003 also reconfirmed the logistic workings of CTN-initiated projects, demonstrating the network's capacity to conduct multi-site trials with complex data sets. The study met recruitment targets early (480 within 2 years across 11 sites), and the Nodes' data management facilities handled more than 54,000 forms for data processing. Perhaps most indicative of the continued feasibility of “blending” research into clinical practice settings, a survey of participants found that more than 90% were satisfied with the study and were agreeable to participating in another such research project.

It is worth noting that the investigators again aimed to generate valid and reliable data, not to advocate a certain treatment philosophy. The protocol included 5 months of participation not based on any theoretical consideration of its merit, but on the pragmatic ground that this trial would provide clinicians with additional tools to work with patients who volunteered for the study.

CTN 0010: Suboxone-Facilitated Rehabilitation for Adolescents/Young Adults

This study in 152 opioid-addicted adolescents and young adults aged 15 to 21 years old (Woody et al., 2008) compared outcomes after 3 months of psychosocial treatment (individual and/or group drug counseling) with brief detoxification using BUP/NX versus 3 months of BUP/NX stabilization with the same psychosocial treatment. Results of the study showed that continuing BUP/NX for 3 months improved outcomes in terms of less opioid use ($p < 0.001$), better retention (70% vs. 21%; $p < 0.0001$), less injection use ($p = 0.01$), and less use of cocaine ($p < 0.001$) and marijuana ($p < 0.001$). BUP/NX treatment for 3 months appeared to be safe in this sample of opioid-addicted adolescents and young adults.

The CTN 0010 study was constrained by a limited number of subjects age 18 or younger to definitively analyze results in that cohort, but the effort to recruit and enroll the younger addict population was important to the field. Rates of opioid addiction among this age group have been increasing, especially with the rapid rise of prescription opioid abuse, and services for youths have been limited. Longer-term pharmacotherapy with BUP/NX would appear to be feasible and effective, based on the CTN 0010 data. This study was expanded into other areas via two substudies that delved into topics that are of vital interest to clinicians: CTN 0010a: Cost-Effectiveness Analysis (CEA) in the CTN: Buprenorphine/Naloxone Treatment for Opioid Addicted Youth and CTN 0010b: Comorbid Conditions in Adolescents with Opioid versus Alcohol/Marijuana Use Disorders.

Ongoing CTN Buprenorphine Research

CTN 0027: Starting Treatment with Agonist Replacement Therapies (START)

START is a randomized, open-label, outpatient-based study assessing changes in liver enzymes related to treatment with buprenorphine/naloxone compared to the changes in liver enzymes related to treatment with methadone. The project is also examining potential risk factors at baseline and during treatment that could be associated with buprenorphine-related or methadone-related liver dysfunction. The FDA requested the study as part of post-marketing surveillance to assess the safety of buprenorphine. This study is a collaboration between NIDA and the producer of the medication; the CTN undertook the work to achieve rapid and broadly generalizable results and to help meet the FDA requirements.

START has spawned two related projects, each of which is distinct from the original study, providing unique opportunities to gather crucial information to advance the scientific understanding of buprenorphine and enhance the implementation of buprenorphine in opioid treatment programs (OTPs) that traditionally provided methadone treatment. In CTN 0027-A-1: START Pharmacogenetics, there are two exploratory genetic aims implemented within the framework of START. For the first aim, investigators are exploring the frequency of gene variants that have primarily been associated with addiction, whereas in the second aim, researchers are examining the relationship between drug plasma concentrations and gene variants associated with drug disposition and transport.

The second project is CTN 0027-A-2: Retention of Suboxone® Patients in START: Perspectives of Providers and Patients. The aim of the study is to identify and describe the barriers to retention among START participants randomized to buprenorphine relative to methadone and strategies to overcome them.

The ability to add such projects to a major trial exemplifies the flexibility and responsiveness of the CTN, in which emerging research questions and practice issues are accommodated readily by the CTN's approach of welcoming concept proposals followed by careful and timely consideration by the Steering Committee, and pursued as appropriate by coordinated and inclusive protocol development efforts.

CTN 0030: Prescription Opiate Abuse Treatment Study (POATS)

The growing concerns with prescription opioid abuse motivated the CTN to rapidly develop and implement a study to examine treatments for that population. POATS is a randomized, open-label study set in outpatient CTPs, seeking to identify optimally effective treatment approaches for using BUP/NX in patients dependent on prescription opioids. Conducted in 10 sites, POATS will first determine whether adding counseling to BUP/NX plus medical management improves outcomes during an initial 4-week period, followed by a subsequent 12-week stabilization treatment for those who relapsed during or soon after the first phase. Thus, subjects with poor outcomes in Phase 1 enter Phase 2, at which time they are randomized to a new condition. This approach reflects real-world clinical practice (i.e., instituting one treatment, then trying a different approach if the first treatment fails) while still maintaining scientific rigor. That BUP/NX provides the pharmaceutical “platform” for this exploration reflects the consistent and predictable outcomes from the medication for opiate-dependent patients. The study closed recruitment in November 2008 after enrolling 653 participants into Phase 1 and 360 participants into Phase 2. A publication describing this study (Weiss et al., in press), will appear soon.

An innovative outcome related to 0030 was a practice improvement effort conducted by a research group from one of the nodes participating in the study. The Oregon group devised a ‘standardized patient’ to represent a type of prospective participant coming in for a research study screening, presenting with certain symptoms (Fussell et al., 2008). A ‘walk through’ exercise was developed to test the screening process to be undertaken. The exercise revealed weaknesses in the procedures and helped guide training for CTP personnel who were to be involved in the 0030 project, improving screening and recruitment to enhance study implementation.

POATS has led to two other studies. The first involves the collection of economic data that will provide information necessary to conduct cost effectiveness, cost-benefit and cost-utility analyses of the treatment models being evaluated in the POATS clinical trial. The second assesses neural changes that may occur in chronic prescription drug users by comparing the anatomical magnetic resonance scans to those of age/gender matched healthy controls. Again, the objectives of the substudies are quite distinct from the basic 0030 project, but the projects will provide useful information of interest to scientists, treatment providers and policymakers. This multi-pronged approach to the issues that surround any form of treatment is a hallmark of the CTN, and results will serve to provide the basis for a cogent strategy regarding implementation of optimum buprenorphine-based treatments for opioid addiction.

Training and Dissemination Efforts

The Blending Initiative: CTN and Buprenorphine at the Forefront

In 2001, NIDA and SAMHSA/CSAT Addiction Technology Transfer Centers (ATTCs) launched the Blending Initiative to disseminate research findings into the treatment community, emphasizing CTN findings. Six Blending Initiative Training Packages have been completed and are being disseminated across the country (training materials are available at several sites: http://www.nattc.org/aboutUs/blendingInitiative/products2.htm, http://bupdetox.nattc.org, http://www.aaap.org/buprenorphine/buprenorphine.htm, and

http://www.buprenorphinecme.com/). Three of these products focus specifically on buprenorphine research, primarily derived from CTN protocols. *Buprenorphine Treatment: Training for Multidisciplinary Addiction Professionals*, is designed to enhance awareness among multi-disciplinary addiction professionals about buprenorphine treatment and dispel common myths associated with medication-assisted treatment. The program educates providers about how buprenorphine works and offers strategies for creating collaborative relationships between physicians, counselors, nurses, recovery support workers, and patients and other stakeholders to ensure that the patient receives effective, comprehensive care.

Short-Term Opioid Withdrawal Using Buprenorphine details the results of the first two CTN clinical trials, which evaluated buprenorphine-naloxone versus clonidine for short-term opiate detoxification. The training package provides basic information about buprenorphine and clonidine and then details the specific results of the protocols. Providers are guided through the information to ensure that that they understand the results and then participate in discussion about the implications of these results in real-world settings. Additional information about how the protocols were conducted (e.g., inclusion and exclusion criteria, ancillary medications used, etc.) is offered so that providers can fully understand the results, compare the study procedures to their current practices, and replicate the methodology used in the study if they choose to do so within the context of their program or agency.

Buprenorphine Treatment for Young Adults: Findings and Strategies from a CTN Study, is currently in development. This package details the results of CTN research regarding extended (12-week) versus short-term (14-day) buprenorphine-naloxone for treatment of opioid-addicted young adults. Again, an overview of the medication is provided followed by a detailed discussion of the results and implications of the findings as they may be applied in diverse clinical settings.

To further enhance dissemination of CTN materials, Drs. Freese, Storti, and Brigham have also developed and conducted a “training of trainers” (TOT) program in six cities across the country to develop expert trainers who can conduct the training in their local areas. The TOT is designed to ensure that the trainers have adequate content knowledge to accurately and effectively deliver the information. These trainings ensure an ever-broadening base of providers and others with a working familiarity with evidence-based practices, particularly regarding buprenorphine treatment.

TIP #40, Blending Research into Practice Guidelines for Buprenorphine

The Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration issued in 2004 Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (TIP) #40 (CSAT, 2004). This set of guidelines became an important resource for clinicians, as it was based on the most current research by NIDA, particularly the CTN, and many of the CTN's senior researchers involved in buprenorphine research reviewed and/or contributed to it. The purpose of TIP #40 is to provide physicians with science-based clinical guidelines on the use of buprenorphine in the treatment of opioid addiction.

From the Trenches Back to the Benches and Onward

There are many instances of CTP personnel disseminating information from the CTN to their colleagues. The director of a Pacific Region CTP, for example, presented at the 2006 American Association for the Treatment of Opioid Dependence (AATOD) annual meeting (Cohen, 2006). His presentation distilled useful information gleaned from CTN research on buprenorphine, and discussed the concerns of community treatment providers—the long-standing history of methadone as the ‘gold standard’ of treatment for heroin addiction and

perceptions about buprenorphine among staff and clients. Issues of revenue and cost were also discussed. The presentation described a survey of patients in three CTN CTPs that revealed consumer preferences and concerns instructive to both researchers and clinicians: thrice-weekly dosing was a major benefit of buprenorphine, as was the ability to more easily withdraw from the medication under clinical management. Buprenorphine therapy, the presentation concluded, was “clinically flexible” and “easily integrated into diverse settings, with the potential for enhancing management of special populations.” By the same token, clinical directors of these CTPs who are involved in the START protocol have had to address differential drop-out rates in patients randomized to buprenorphine and methadone arms.

Another good example of the interaction among the elements of the CTN-involved treatment community is the development of an innovative physician mentoring network, the Physician Clinical Support System for Buprenorphine (PCSS-B), funded by SAMHSA and administered by the American Society of Addiction Medicine. Established in 2005, the goal of the PCSS-B is to promote implementation of buprenorphine by providing educational support to physicians interested in prescribing it for patients addicted to prescription opioids and heroin. The PCSS-B is directed by a Steering Committee composed of representatives from the leading addiction medicine societies, including a panel of five clinical experts. Three of these National Clinical Experts are also CTN investigators. The PCSS-B currently has 88 physician-mentors and 5 clinical experts located in 61 cities across 34 states and Puerto Rico. As of June 2009, 3,775 individuals have registered into the PCSS-B system representing all 50 states, Washington DC, and Puerto Rico. Between July 2005 and April 2009, 66 mentors and 4 clinical experts provided mentoring services to 606 participants in 48 states, Washington DC, and Puerto Rico.

Looking Inside the CTN from the Outside

In examining how the CTN functions and assessing its effects on the treatment community, a primary question regarding CTN efficacy was its own sustainability as well as the topic of whether the research conducted in CTPs actually drove any changes in practice. Reviews of CTN research confirmed that the CTN approach using a coordinated network of mutually contributing entities proved viable and productive, as reviewed in the assessment of the buprenorphine research conducted in the early years of the CTN. Again, buprenorphine's success in being proven and translated into real-world practice via the CTN is a marker for the efficacy of the CTN itself.

Knudsen, Abraham, Johnson, and Roman (2009), for example, examined the uptake of buprenorphine in mainstream practice as a result of the CTN research. They conducted interviews with administrators of 206 CTPs, finding that buprenorphine implementation doubled in the two-year period before the interviews. While CTPs with inpatient capability more readily used buprenorphine, as did for-profit CTPs, the most significant factor in promoting use of buprenorphine was prior involvement in a CTN buprenorphine study. In similar work, Ducharme and Roman (2009) explored the characteristics of opioid treatment programs within the CTN to determine factors that affected the adoption of buprenorphine and influenced its implementation.

McCarty and colleagues provided further evidence of the interactivity of CTN research and CTP practices (McCarty et al., 2007). Workforce surveys included 106 of 112 eligible CTN CTPs in order to document characteristics of the counselors, manager-supervisors, medical staff, and support staff as they might influence treatment-related behaviors. The survey found disparate attitudes among the groups, and noted “only modest levels of support” for the use of addiction medications, with less support for buprenorphine than for methadone (28% vs. 35%). The authors noted the need for greater training and promotion of evidence-based treatment practices to overcome resistance toward them found largely among non-degreed staff, which

is consistent with previous work on technology transfer (Rogers, 2003) that has shown the influence of higher levels of education, which predict greater receptivity to new practices. Among strong determinants of attitude and behaviors, the study found that staff who had been involved in buprenorphine protocols was more positive about the future and ongoing use of the medication for their patients.

Fitzgerald and McCarty (2009) provided additional documentation of the effects of CTN activities on community-based treatment practice. A secondary analysis of data from the CTN treatment unit and workforce surveys examined organizational and practitioner variables that affected utilization of medications. Staff attitudes varied greatly across the 247 clinical settings included in the survey. The variation correlated with clinical practice behaviors regarding use of medications (methadone, buprenorphine, and naltrexone). Several elements of the article's recommended steps to increase implementation of addiction medications are incorporated in ongoing CTN-based dissemination efforts, among them being creation of referral networks for prescribers; educating staff and clients about addiction medications, and enhanced training for all staff about addiction medications.

Echoing what others have noted, we wrote several years ago that “good science alone is no guarantee for successful adoption of a new treatment in the [addiction] field” (Ling, Cunningham, & Rawson, 2004; p 117). We believe this remains true in the case of buprenorphine. While much effort in medication development has been directed toward changing patients' attitudes and behaviors, the successful implementation of buprenorphine required (and still requires) that efforts be directed to help clinicians change their philosophies and practices (Ling & Compton, 2005). By bringing together research and practice and reducing the prevailing dichotomy, CTN work has been instrumental in opening minds and improving the treatment of opioid addiction.

Conclusion

The successful implementation of the first CTN protocols was exceedingly important to the CTN effort. As an outgrowth of the previous decade's medication development, CTN activities had to carry on the work in a way that included the community providers in a collaborative role. It was natural that the first protocols were brief examinations of the medication, conducted in trials whose intent was not to establish buprenorphine as a replacement for methadone nor to document a universally required component of existing opioid addiction treatment. Instead, the early trials were designed to be sensitive to the stance of many CTPs and regulators.

The most notable aspect of the CTN's buprenorphine research in the community setting is its demonstration that quality data can be generated without advocating any specific treatment philosophy. What the CTN did was to provide credible scientific evidence—valid and reliable data—and provide clinicians with the opportunity to incorporate the data into their own treatment philosophy.

The challenge facing CTN researchers was not simply to determine how to better implement buprenorphine/naloxone itself, but how to strengthen a buprenorphine-based response by determining which psychosocial treatment strategies will result in optimum outcomes for buprenorphine-maintained patients. That and other related goals remain to be fully attained by ongoing research (CTN 0030) and other research yet to be conducted. Clinical concerns include developing techniques to facilitate implementation of behavioral therapy procedures in office-based settings in which buprenorphine is provided to improve compliance with treatment, leading to better outcomes. Furthermore, new issues will arise regarding diversion and misuse of buprenorphine as it gains popularity. As they arise clinically, these and other matters will be tested in CTN research yet to be conceptualized.

Buprenorphine continues to inspire research both within the U.S. and internationally. Several of the CTN grantees host INVEST/CTN Fellows who are developing research on this medication both for dissemination in the U.S. and abroad. Research that will broaden our knowledge of the use of buprenorphine and buprenorphine/naloxone is also in the planning stages. Both are approved for treatment of opioid addiction, but this therapy may prove to have a beneficial effect as part of a treatment strategy for co-occurring cocaine addiction as well. This topic has been tentatively examined in other research (Gerra et al., 2006) but not in the definitive manner that could form the basis for any reliable practice guidelines. CTN researchers and CTPs are currently engaged in a consensus-building process to develop a clinical trial to assess the safety and utility of buprenorphine given concurrently with naltrexone for the treatment of opioid and cocaine addiction. The process involves many of the finest researchers and clinicians in practice in the CTN community. We are intrigued about the potential for buprenorphine to be part of the armamentarium for cocaine addiction and we believe the CTN is the optimal mechanism to test this promising medication.

Acknowledgments

Funding has been provided by the National Institute on Drug Abuse grants U10 DA15831, U10 DA 13045, and K24DA022288.

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