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# Behavioral naltrexone therapy: an integrated treatment for opiate dependence

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**Abstract**

Treatment of opiate dependence with naltrexone has been limited by poor compliance. Behavioral Naltrexone Therapy (BNT) was developed to promote adherence to naltrexone and lifestyle changes supportive of abstinence, by incorporating components from empirically validated treatments, including Network Therapy with a significant other to monitor medication compliance, the Community Reinforcement Approach, and voucher incentives. An overview is presented of the BNT treatment manual. In an uncontrolled Stage I trial ($N = 47$), 19% completed the 6-month course of treatment. Retention was especially poor in the subsample of patients who were using methadone at baseline ($N = 18$; 39% completed 1 month, none completed 6 months), and more encouraging among heroin-dependent patients ($N = 29$; 65% completed 1 month, 31% completed 6 months). Thus, attrition continues to be a serious problem for naltrexone maintenance, although further efforts to develop interventions such as BNT are warranted. 

*Keywords:* Heroin; Behavior therapy; Naltrexone; Treatment

## 1. Introduction

Opiate dependence has been a significant public health problem since the turn of the century, with substantial morbidity, mortality, and social costs, including its role in recent decades in the spread of HIV and hepatitis B and C. Its prevalence may be increasing in the wake of greater international production, abundance, and purity of heroin (Hamid et al., 1997; NIDA 1995). Thus, improvement in the ability to attract opiate-dependent individuals into treatment and improvement of treatment effectiveness remain critical goals.

Methadone maintenance is a highly effective treatment, which has allowed many heroin addicts to reduce illicit drug use and improve their occupational and social functioning (Ball, Corty, Bond, Myers, & Tommasello, 1988). However, the success of methadone treatment is limited (Rounsaville & Kleber, 1985; Shaffer & LaSalvia, 1992). Many patients continue to abuse illicit drugs or alcohol. Further, methadone treatment availability is limited in many communities, and opiate addicts often avoid or refuse this option. New agonist maintenance agents, LAAM (leva-alpha-acetylmethadol), and buprenorphine, may have advantages over methadone in certain respects, such as reduced frequency of dosing and of mandatory clinic visits. However, there is no clear data that these will be more efficacious or acceptable to patients than methadone. Thus, alternatives to agonist maintenance are needed to help attract a wider range of heroin addicts into effective treatment.

Antagonist maintenance with naltrexone is one such alternative, but it has not, to date, lived up to its potential (Callahan et al., 1980; Kosten and Kleber, 1984). An ideal pharmacotherapy in many respects, naltrexone blocks the

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intoxicating and reinforcing effects of heroin and other opiates, but itself has no opiate-like effects. When taken regularly, it helps to extinguish opiate-seeking and opiate-taking behavior. However, in practice, treatment outcome with naltrexone has been poor, as most patients drop out and resume opiate use. Despite the problems, there are compelling reasons to pursue improvements in naltrexone maintenance. Since naltrexone is neither an opiate agonist, nor a controlled substance, it has no abuse potential and offers increased flexibility both for patients and for treatment settings.

Early studies assessing psychosocial interventions for promoting adherence to naltrexone (Callahan, Rawson, Glazer, McCleave, & Arias, 1976; Callahan et al., 1980; Grabowski, O'Brien, Greenstein, & Ternes, 1979; Resnick, Washton, & Stone-Washton, 1981; Stone-Washton, Resnick, & Washton, 1982) showed promise. In the past two decades, there has been an expansion of well-controlled research on psychotherapy and behavior therapy for drug-dependent patients. Rounsaville (1995) recently called for a renewed effort to bolster the efficacy of naltrexone by applying advances in behavioral therapy, and such efforts have begun to appear (Carroll et al., 2001; Preston et al., 1999). This is consistent with the recent call from the Institute of Medicine (1998) for increased efforts to translate research advances into the clinical practice of addiction treatment.

Here, we report the development of Behavioral Naltrexone Therapy (BNT), an integrative behavioral therapy intended to improve the outcome of naltrexone maintenance for opiate addiction. BNT seeks to embed naltrexone maintenance in a strong psychotherapeutic context, based on Network Therapy (Galanter, 1993) and the Community Reinforcement Approach (CRA; Hunt & Azrin, 1973; Meyers & Smith, 1995) while addressing three specific problem areas impeding naltrexone maintenance: (a) difficulty transitioning to naltrexone; (b) poor compliance; and (c) possible dysphoric effects.

Firstly, naltrexone precipitates withdrawal in opiate-dependent patients, so it normally cannot be given until 7 to 10 days after detoxification, by which time most patients, unless continuously hospitalized, will relapse. Protracted withdrawal symptoms and immediate relapse to opiates contribute to high dropout from naltrexone treatment (Callahan et al., 1980). Therefore, BNT begins by rapidly transitioning patients onto naltrexone in the hospital, using an established regimen of buprenorphine, clonidine, and other ancillary medications found to reduce withdrawal discomfort (Collins and Kleber, 2000; Stine and Kosten, 1992). Motivational interviewing techniques and procedures to promote continuity of care between inpatient and outpatient treatment are also applied.

Secondly, naltrexone maintenance has been plagued by poor long-term medication compliance. Patients can easily stop their naltrexone for a few days, after which opiate blockade wears off and patients rapidly become re-dependent. Once re-dependent, they must be detoxified again to resume naltrexone. Therefore, BNT requires involvement of a significant other to monitor medication ingestion and positively reinforce compliance (Azrin, Sisson, Meyers, & Godley, 1982), and further, provides voucher incentives contingent on adherence to naltrexone (Bickel, Amass, Higgins, Badger, & Esch, 1997; Grabowski et al., 1979; Higgins, Budney, Bickel, & Badger, 1994; Silverman et al., 1998; Silverman, Chutuape, Bigelow, & Stitzer, 1999).

Lastly, some reports suggest opiate antagonists may produce dysphoria, even in long-abstinent opiate addicts (Crowley et al., 1985) and depression has been found to be common in opiate addicts, and to be associated with poor outcome (Kosten, Rounsaville, & Kleber, 1986; LaPorte, McLellan, O'Brien, & Marshall, 1981; Magura, Siddiqi, Freeman, & Lipton, 1991; Rounsaville, Weissman, Crits-Christoph, Wilber, & Kleber, 1982; Rounsaville, Kosten, Weissman, & Kleber, 1986) and craving (Childress et al., 1994). Therefore, BNT incorporates cognitive techniques to address management of dysphoric moods and guidelines for use of antidepressant medication based on experience treating depressed methadone patients (Hamilton, Nunes, & Klimchak, 1998; Nunes, Quitkin, Brady, & Stewart, 1991; Nunes, Quitkin, Brady, & Koenig, 1994; Nunes, Quitkin, Donovan, & Deliyannides, 1998).

In what follows, we present an overview of the BNT treatment manual with therapist training and adherence procedures and results of an uncontrolled trial to assess the feasibility and efficacy of BNT for outpatient opiate addicts.

## 2. Materials and method

### 2.1. Overview of BNT

Behavioral Naltrexone Therapy is delivered over a six-month period in weekly individual and network therapy sessions. The major therapeutic components included in BNT are Relapse Prevention, Community Reinforcement Approach and Network Therapy (NT). The goals of BNT are for patients to take naltrexone continuously and to abstain from opiates. These goals are reinforced by vouchers and the support of significant others who monitor medication ingestion and attend network therapy sessions. Individual treatment sessions continuously assess and challenge motivation for treatment and abstinence and integrate cognitive-behavioral techniques to facilitate all of these goals.

Behavioral Naltrexone Therapy is divided into three phases, Induction, Stabilization, and Maintenance, based on suggestions of Kosten and Kleber (1984) for establishing an effective treatment for opiate dependence with naltrexone. These phases serve as a conceptual guideline for BNT therapists; all areas of focus are cumulative and can be reviewed as often as deemed clinically important. The components of the three phases are listed in Table 1 and guidelines for conducting each phase are summarized below.

Table 1
Treatment components emphasized in the three phases of Behavioral Naltrexone Therapy (BNT)

| Treatment components | Behavioral Naltrexone Therapy phases | | |
|---|---|---|---|
| | Induction | Stabilization | Maintenance |
| Education and support | X | X | X |
| Motivational techniques | X | X | X |
| Involvement of significant others | X | X | X |
| Integrated pharmacotherapy (naltrexone) | X | X | X |
| Behavioral analysis | | X | X |
| Coping with triggers, cravings | | X | X |
| Coping with dysphoria | | X[a] | X |
| Contingent rewards, positive incentives | | X | X |
| Social skills | | | X |
| Social, other non-drug rewards | | | X |
| Relationship change | | | X |

[a] Antidepressant medication is offered for patients with a depressive syndrome persistent during stabilization phase.

#### 2.1.1. Induction phase: assessment and engagement

The goals of the Induction phase are to recruit, educate, motivate, and support the patient through the screening process and hospitalization for rapid transition to naltrexone. Opiate-dependent patients seeking treatment in BNT are initially evaluated by a Master's or doctoral level clinician and a psychiatrist to determine psychiatric and medical eligibility. Because a central feature of BNT is the involvement of at least one significant other who will monitor naltrexone compliance and support continued adherence, potential network members are evaluated and are excluded if they abuse substances or are involved in a physically abusive relationship with the patient. A patient's network may contain one or more members. One member is chosen to be the medication monitor.

Eligible patients undergo a 7–10 day hospitalization for detoxification and transition to naltrexone which is modeled after the clonidine-naltrexone technique (Charney, Heninger, & Kleber, 1986). Buprenorphine is utilized initially to reduce the severity of withdrawal symptoms; thereafter naltrexone is administered in ascending doses until a 50-mg dose is tolerated (Collins and Kleber, 2000; Stine and Kosten, 1992). Hospital staff is instructed in techniques for dealing with fluctuating motivation and supporting patients through the considerable physical discomfort of withdrawal.

To smooth the transition to outpatient treatment, the BNT therapist meets with the patient and significant others at the end of the hospital stay to once again orient them again to the goals and parameters of BNT and the importance of adherence to naltrexone. Managing protracted withdrawal symptoms and addressing ambivalence toward abstinence and treatment are reviewed in the first outpatient network session that is scheduled on the day of discharge. Arrangements are made for a network member to escort the patient from the hospital to the first outpatient session and then safely home to reduce the risk of immediate relapse. Because we have found that some withdrawal discomfort, mainly anxiety and insomnia, may continue into the first week of outpatient treatment, upon discharge patients are offered a 5–7 day schedule of certain pain medications that they have been receiving in hospital (mainly clonidine for residual withdrawal symptoms and trazodone or zolpidem for insomnia).

#### 2.1.2. Stabilization phase (first month of outpatient treatment)

The first month of naltrexone maintenance is marked by a high risk of dropout. Thus, the primary focus of the Stabilization Phase is to keep the patient in treatment, on naltrexone, and abstinent from opiates. This phase is additionally devoted to developing a strong therapeutic relationship, encouraging the support of the network, and identifying goals for lifestyle change. Relapse prevention techniques and rewards contingent on compliance with naltrexone and abstinence are introduced. Also, skills for coping with dysphoria are emphasized and patients with persistent depressive syndromes are offered antidepressant medication. The Stabilization Phase is planned to last one month, but it may be lengthened for patients who continue to struggle with ambivalence around naltrexone adherence and heroin abstinence.

In the initial two weeks of treatment, patients with their significant other attend three sessions per week (typically on Monday, Wednesday, and Friday) and ingest naltrexone under direct staff observation (e.g. 100 mg Monday, 100 mg Wednesday, 150 mg Friday). The therapist trains the patient and his/her significant other to monitor naltrexone ingestion during network sessions. Urine is collected under staff observation at each visit and tested on site for opioids with the Accutest® (Roche Diagnostics; Indianapolis, IN) method, providing immediate feedback to patients and clinical staff.

After the first two weeks, naltrexone is dispensed and ingested at home daily (50 mg of naltrexone with 50 mg of riboflavin), under observation of the monitor. In BNT, patients continue to attend one individual and one network therapy session per week, during which motivational techniques and relapse-prevention skills are fostered and rehearsed.

#### 2.1.3. Voucher reinforcement program

Behavioral Naltrexone Therapy provides vouchers contingent on abstinence from heroin and adherence to naltrexone. Each day of abstinence and each pill taken are rewarded with one voucher point ($2), totaling a maximum of 14 points or $28 per week, or $672 total if all vouchers are earned over six months. Naltrexone compliance is confirmed by both recording sheets completed by the monitor and by the presence of riboflavin marker in urine samples. Network

members are also reinforced with vouchers, specifically, $1 for each pill recorded as monitored; a maximum of $168 may be rewarded for consistent monitoring.

Voucher points are exchangeable for goods and services chosen by the patient, approved by the therapist and purchased for the patient by a program staff member or by the significant other, as in the system developed by Higgins and colleagues for treating outpatient cocaine dependence (Higgins et al. 1991, 1993, 1994). Goods and services are chosen to further the goal of developing social and recreational outlets to compete with drug use.

#### *2.1.4. Maintenance phase (second through sixth months of BNT)*

Once abstinence and naltrexone adherence are successfully established, the focus of BNT expands to address broader life-style changes and goals. Network members continue to monitor medication and attend weekly network sessions. Patients continue to attend one individual and one network therapy visit per week. In keeping with the CRA model, individual and network therapy sessions are devoted to establishing competing/ alternative reinforcers to drug use. These reinforcers could include improved marital satisfaction, a better vocational situation, improved social relationships and involvement in enjoyable recreational activities.

During the Maintenance Phase, CORE modules to be reviewed include: (a) Orientation to the Program, Rapport Building; (b) Functional Analysis of Opiate and Other Drug Use; (c) Coping with Cravings; (d) Monitoring Thoughts about Drug Use; (e) Problem-Solving Skills; (f) Drug-Refusal Skills; (g) Planning for Emergencies; (h) Seemingly Irrelevant Decisions (i) Building a Supportive Network; (j) Assessment and Support of Medical Monitoring; and (k) Termination. There is no set order of presentation; however, all information from these modules should be addressed. It is important to note that Managing Negative Moods and Depression is a core module for all patients who have elevated depression scores at baseline or who present with significant depressive symptoms or thinking. For non-depressed patients, this module is an elective.

The BNT therapist will also choose elective modules that complement the core material and reflect the patient's strengths, limitations, and individual goals of treatment. These modules include: (a) Social Skills and Relationship Enhancement Training; (b) Management of Mood and Emotions, which incorporates treatment modules for Awareness of Anger, Anger Management, Awareness of Negative Thinking, Managing Negative Thinking, and Managing Negative Moods and Depression; (c) Increasing Pleasant Activities; (d) Enhancing Social Support Networks; and (e) Job-Seeking Skills.

#### *2.1.5. Handling of lapses and relapses*

Although taking naltrexone provides a safety net for patients while they are in BNT, patients may slip, relapse, or discontinue the medication. Because we have encountered a variety of complex situations that demand difficult decision-making, the BNT manual provides clinical guidelines to troubleshoot problems that arise. Such situations may include use of, or relapse to, opiates during treatment, non-compliance with naltrexone or attendance, use of other drugs, breakdown of the network, unmasked psychopathology once detoxified, and need for additional medication.

With regard to naltrexone maintenance and potential relapse to opiate use, supervised urine samples are collected at all visits and tested for opiates on site with an Accuttest providing immediate feedback. Naltrexone 50-mg pills are packaged in gelatin capsules with riboflavin, which is excreted in urine and fluoresces under ultraviolet light, providing a check on medication compliance. Naltrexone may also be safely resumed if the specimen tests opiate-negative but does not fluoresce, indicating a lapse in medication compliance but continued abstinence. However, when non-fluorescent urine samples are positive for opiates, the patient is offered a naloxone challenge (0.8 mg), which must be negative (i.e. produce no withdrawal symptoms) for naltrexone to be safely resumed. If the challenge is failed or re-dependence on heroin is presumed on clinical grounds, the patient is unable to restart naltrexone. Clinical efforts are made to promote abstinence with relapse-prevention and motivational enhancement techniques and then a challenge is re-attempted. If a second challenge is failed, then the patient has relapsed and is removed from BNT and referred for inpatient detoxification or methadone maintenance.

### *2.2. Therapist training procedures*

Similar to manualized approaches upon which BNT is based, the following criteria for prospective therapists are preferred: (a) a master's degree or equivalent in psychology, counseling, social work, or a closely related field; (b) at least 3 years of experience working with a substance-abusing population; and (c) some familiarity with and commitment to cognitive-behavioral theory and approach. All therapists-in-training must complete a didactic seminar introducing an overview of cognitive-behavioral theory and the therapy approaches inherent to BNT. This forum includes role-plays and discussions of clinical vignettes and is supplemented with review of training tapes and reading materials.

In order to be certified as a BNT therapist, candidates in training are assigned cases that are closely monitored by the supervising psychologist. Further, an independent team of clinicians trained in BNT must review an audiotaped therapy session and complete the BNT Therapist Skillfulness Form, an original assessment tool which monitors therapist adherence, effectiveness, ability to establish treatment boundaries, and overall clinical skill. Once the supervising BNT psychologist has certified a new clinician, the taped sessions are continually monitored in weekly individual and group supervision to ensure the therapist's fidelity to the treatment delivered and to minimize technique drift.

*2.2.1. Measure of therapist adherence*

In order to reliably monitor adherence to BNT, a 33-item BNT Session Checklist has been established that integrates core elements of Network Therapy, CRA, Motivational Enhancement, RPT, and contingency management. These checklists are completed after each therapy session by the therapist and provide a clinical tool to assess adherence to BNT as they are reviewed in weekly supervision meetings. The BNT Checklist requires that the therapist endorse whether an event or a particular topic was covered in that session (e.g., yes, no) or how extensively he/she reviewed the selected manualized material (1 = not at all; 5 = very extensively). In general, measures of adherence to, and competence with BNT as well as training procedures have been developed according to the guidelines set forth by Carroll, Nich, and Rounsaville (1998).

*2.3. Pilot trial*

*2.3.1. Design and methods*

Prospective participants were evaluated with a psychiatric history, a modified SCID interview which delineates substance use and onset of psychiatric symptoms (Nunes et al., 1996), and physical and laboratory evaluations and were eligible if they met DSM-IV criteria for current opiate dependence, were voluntarily seeking treatment, and had a significant other who could commit to participating in treatment. Unstable medical or psychiatric disorders, which might make participation hazardous, were exclusionary. After providing informed consent, consents that were in accord with the standards of our institution, patients were hospitalized for detoxification and transition to naltrexone. Those able to tolerate two daily doses of the full dose (50 mg) of naltrexone at the end of a 7–10 day hospitalization were discharged to outpatient treatment with BNT. Doctoral level psychologists conducted BNT according to the working treatment manual. Selection, training, and ongoing monitoring and supervision of therapists were conducted as described above over the subsequent 24 weeks. Patients were monitored weekly for drug use by self-report and urine toxicology, naltrexone compliance, psychiatric symptoms, and adverse events.

## 3. Results

*3.1. Participants*

More than 150 potential subjects were initially evaluated, with approximately 70% (105/150) returning for second visits. Of these individuals, 78% (82/105) were eligible for treatment; the remaining applicants were found to be ineligible secondary to either medical (e.g. significantly elevated liver enzymes) or psychiatric exclusion criteria, or failing to have an available or appropriate monitor. Of those who were deemed eligible, 47 subjects completed the detoxification and transition to naltrexone and entered outpatient treatment with BNT. The 35/82 participants who were eligible but did not enter treatment either failed to enter due to ambivalence or accepted referrals to alternative treatment settings when the delay to enter was experienced as too long. Enrolled participants averaged 33.6 ± 9.3 years of age (range: 20–54) and included 36 (77%) males, 11 (23%) females, 30 (64%) Caucasians, 12 (25%) Hispanic-Americans and 5 (11%) African-Americans. 17 (36%) were currently married and 32 (68%) were employed. 18 (39%) met criteria for a Depressive Disorder, 16 (35%) for an Anxiety Disorder, and 7 (15%) for Antisocial Personality Disorder. Concurrent drug use in addition to opiates was common (13 (27%) abusing Cocaine, 14 (30%) Marijuana, 7 (15%) Alcohol, and 25 (51%) Nicotine. Seventeen (37%) used heroin intravenously, and 29 (63%) used heroin intranasally, and one patient used exclusively methadone. On average, participants in this sample were using 5.42 (*SD* = 5.89) number of bags of heroin per day and using opiates regularly 8.62 years (*SD* = 8.14). Seventeen (36%) were using illicit methadone regularly, and one was in methadone maintenance. Five (11%) patients attended adjunct treatment opportunities such as AA or NA while participating in BNT.

*3.2. Reliability of BNT session checklist*

In order to assess the reliability of this 33-item instrument, inter-rater reliability coefficients were computed. Thirty audio-taped therapy sessions were rated by both the therapist who conducted the session and by a master's level clinician who was introduced to the manual and trained on the session checklist and rating task. The thirty tapes, all from different patients, were randomly selected from early sessions (i.e., sessions 2, 3, or 4) to reduce bias and other complications including early dropout from treatment. Kappa coefficients were computed for nominal items (e.g., yes, no) and intraclass correlations were computed for continuous items. The majority of Kappa and ICC estimates fell within the good (0.60–0.75, 27% (9 of items) or excellent (>.75, 52% (17) of items) range and reflected core clinical ingredients of BNT. The seven remaining items which demonstrated weaker reliability are being modified and re-evaluated.

*3.3. Treatment outcome*

On average, 7.8 (*SD* = 10.3) individual sessions and 4.9 (*SD* = 6.7) network sessions were attended. The session checklists reflect that in 45-min sessions, on average, 29.5 (*SD* = 9.6) minutes were devoted to BNT skill building elements.

The principal outcome measure was retention in treatment. Participants were removed from the trial and counted as dropouts if they ceased naltrexone and resumed opiate use with physiological dependence as indicated by failure to

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