

Anesthesia-Assisted vs Buprenorphine- or Clonidine-Assisted Heroin Detoxification and Naltrexone Induction

A Randomized Trial

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HEROIN DEPENDENCE REMAINS a significant public health problem in the United States. Most of the approximately 1 million¹ heroin-dependent individuals in the United States are not in treatment. Their main initial contact with the treatment system is often detoxification,² partially because the prevailing societal view favors drug-free approaches and because restricted access to and inconvenience (eg, daily clinic visits) of methadone maintenance programs may outweigh their better outcomes.³⁻⁵

Throughout the 20th century, many methods of opioid detoxification, including insulin-induced seizures,⁶ artificial hibernation,⁷ and electroconvulsive therapy,⁸ have been proposed. These approaches at times produced greater morbidity and mortality than untreated withdrawal.^{9,10} However, despite improvements in recent decades, medically supervised heroin withdrawal remains plagued by patient discomfort and high dropout rates.¹¹ Many patients fear the physical discomfort of withdrawal and either avoid treatment or leave it prematurely. Even those who complete the detoxification process

Context Rapid opioid detoxification with opioid antagonist induction using general anesthesia has emerged as an expensive, potentially dangerous, unproven approach to treat opioid dependence.

Objective To determine how anesthesia-assisted detoxification with rapid antagonist induction for heroin dependence compared with 2 alternative detoxification and antagonist induction methods.

Design, Setting, and Patients A total of 106 treatment-seeking heroin-dependent patients, aged 21 through 50 years, were randomly assigned to 1 of 3 inpatient withdrawal treatments over 72 hours followed by 12 weeks of outpatient naltrexone maintenance with relapse prevention psychotherapy. This randomized trial was conducted between 2000 and 2003 at Columbia University Medical Center's Clinical Research Center. Outpatient treatment occurred at the Columbia University research service for substance use disorders. Patients were included if they had an American Society of Anesthesiologists physical status of I or II, were without major comorbid psychiatric illness, and were not dependent on other drugs or alcohol.

Interventions Anesthesia-assisted rapid opioid detoxification with naltrexone induction, buprenorphine-assisted rapid opioid detoxification with naltrexone induction, and clonidine-assisted opioid detoxification with delayed naltrexone induction.

Main Outcome Measures Withdrawal severity scores on objective and subjective scales; proportions of patients receiving naltrexone, completing inpatient detoxification, and retained in treatment; proportion of opioid-positive urine specimens.

Results Mean withdrawal severities were comparable across the 3 treatments. Compared with clonidine-assisted detoxification, the anesthesia- and buprenorphine-assisted detoxification interventions had significantly greater rates of naltrexone induction (94% anesthesia, 97% buprenorphine, and 21% clonidine), but the groups did not differ in rates of completion of inpatient detoxification. Treatment retention over 12 weeks was not significantly different among groups with 7 of 35 (20%) retained in the anesthesia-assisted group, 9 of 37 (24%) in the buprenorphine-assisted group, and 3 of 34 (9%) in the clonidine-assisted group. Induction with 50 mg of naltrexone significantly reduced the risk of dropping out (odds ratio, 0.28; 95% confidence interval, 0.15-0.51). There were no significant group differences in proportions of opioid-positive urine specimens. The anesthesia procedure was associated with 3 potentially life-threatening adverse events.

Conclusion These data do not support the use of general anesthesia for heroin detoxification and rapid opioid antagonist induction.

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have high relapse rates,¹¹ partly due to the absence of continuing treatment, such as antagonist maintenance. These problems have given rise, in the past 15 years, to ultra-rapid, or anesthesia-assisted opioid withdrawal and antagonist induction procedures, which have been publicized as a fast, painless way to withdraw from opioids. However, these treatments are expensive (up to \$7500 in 1997,¹² and as much as \$15 000 in 2005), are not covered by insurance, and lack good evidence to support efficacy.¹³ There are also significant concerns about risk, including marked increases in plasma corticotropin,¹⁴ cortisol,¹⁴ respiration,^{15,16} sympathetic activity,¹⁶ and catecholamines^{17,18}; suppression of thyroid hormones¹⁹; pulmonary distress^{14,20}; pulmonary edema¹⁹; acute renal failure¹⁹; ventricular bigeminy²¹; psychosis^{21,22}; delirium^{23,24}; suicide attempts^{21,25}; and deaths associated with the procedure.²⁶⁻²⁹ In addition, several reports describe persistent, marked withdrawal symptoms following the procedure.^{14,25,30,31} The eagerness with which both patients and the public have accepted claims of success highlights the desperation many patients and families feel about treating opioid dependence. Their vulnerability to unproven promises of success, combined with the expanding problem of prescription opioid dependence, increased the need for well-controlled research to test anesthesia-assisted withdrawal.³² Physicians in general practice need such evidence to advise patients seeking treatment for opioid dependence.

Virtually all published reports on anesthesia-assisted opioid withdrawal come from nonrandomized, uncontrolled series or trials.* An early double-blind study⁴² described methohexitone anesthesia in 18 individuals randomly assigned to receive naloxone or placebo. But the study only compared withdrawal induced by naloxone vs placebo and included only a week of follow-up. A single prior randomized controlled study⁴³ compared outpatient anesthe-

sia with an inpatient alternative, but only 54% of the anesthesia group received naltrexone induction under anesthesia, making the procedure unrepresentative, and there were no systematic withdrawal severity measures, precluding comparison of the course and severity of withdrawal symptoms. All other reports on anesthesia have been weakened by selection bias or lack of randomized control groups, increasing the need for a comprehensive randomized trial of the procedure.^{12,32,44,45}

General anesthesia has been offered as a mechanism for rapid induction of an opioid antagonist at higher dosages than opioid-dependent patients can usually tolerate. Opioid antagonists (eg, naltrexone, nalmeferone) block opioid effects without themselves producing tolerance, dependence, or psychic effects. Although maintenance on opioid antagonists typically yields low treatment retention in unselected samples,⁴⁶ it fares better in selected populations.⁴⁷ A fair study of the general anesthesia procedure required that comparison treatments use naltrexone induction procedures. Given the anticipated advent of depot naltrexone formulations, which could improve the typically poor compliance with oral naltrexone, procedures for opioid antagonist induction should take on greater importance.

We conducted a randomized controlled trial to evaluate the safety, tolerability, and efficacy of anesthesia-assisted rapid opioid detoxification compared with 2 inpatient withdrawal and naltrexone induction procedures: a positive control of rapid naltrexone induction, using a bridging dose of the partial μ opioid agonist, buprenorphine⁴⁸⁻⁵⁰; and a control treatment using clonidine^{49,51,52} with delayed naltrexone induction. The choice of the positive control, buprenorphine-assisted rapid opioid detoxification, was based on successes with bridging doses of buprenorphine for naltrexone induction.⁴⁸⁻⁵⁰ Buprenorphine has a longer duration of action and decreased withdrawal symptoms compared with heroin. The buprenorphine-assisted rapid opioid detoxification procedure included a single

facilitating dose of buprenorphine to minimize the time required for naltrexone induction and to make it nearly as rapid as the anesthesia procedure. The other control procedure, clonidine-assisted opioid detoxification, used the α_2 -adrenergic agonist, clonidine, which had previously shown efficacy in outpatient naltrexone induction⁴⁹ and which has been a standard of care in treating opioid withdrawal symptoms.^{51,52} Clonidine ameliorates symptoms of opioid withdrawal by acting on the locus coeruleus to decrease norepinephrine secretion.

METHODS

Protocol

Individuals seeking heroin detoxification were enrolled between April 2000 and July 2003. To achieve a power of 0.80, the study aimed to enroll 53 patients in each of the 3 groups to observe a predicted 25% absolute difference (45% vs 20%) in the 12-week treatment retention between anesthesia-assisted antagonist induction and clonidine-assisted antagonist induction. The data and safety monitoring board suggested that enrollment stop in July 2003 with a total of 106 participants because actual differences in withdrawal severity scores and treatment retention were smaller than anticipated, leading to an impractically large recalculated sample size ($N > 400$) needed to show significant withdrawal severity or treatment retention differences.

The institutional review boards of the Columbia University Medical Center and the New York State Psychiatric Institute approved this protocol. All participants provided voluntary oral and written informed consent. They provided baseline demographic information, including open-ended, self-identified race or ethnicity to allow comparison with results of prior studies. Participants were reimbursed \$3 at each screening visit to defray travel costs and \$15 at subsequent clinic visits to encourage attendance.

During screening, psychological and psychiatric assessments, a medical history, physical examination, and anes-

*References 14-19, 21, 23-25, 27, 30, 33-41.

thetia preprocedure assessment were performed. Screening tests for all patients included complete blood cell count, chemistries, liver profile, thyroid functions, urinalysis, urine culture, coagulation profile, chest x-ray, electrocardiogram, and echocardiogram. Patients were administered or completed the following baseline assessment instruments: Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, Addiction Severity Index,⁵³ Beck Depression Inventory II,⁵⁴ and Hamilton Depression Scale.⁵⁵ In addition, opioid dependence was confirmed in all patients by use of a naloxone challenge test.⁵⁶ The inclusion and exclusion criteria are shown in the BOX.

Participant Flow

FIGURE 1 shows the patient flow for the 169 individuals assessed for eligibility for the study. One hundred six participants were randomly assigned. Of those, 2 individuals (1 in the anesthesia-assisted and 1 in the clonidine-assisted groups) were treated but developed a mixed manic mood syndrome during detoxification and subsequently revealed a previously concealed history of bipolar disorder. Those patients were removed from the study. One patient in the anesthesia-assisted group refused the procedure immediately after learning of the randomization assignment, and another patient in the anesthesia-assisted group left the hospital several hours after admission and after receiving clonidine the night before planned anesthesia. A patient in the buprenorphine-assisted group left the hospital approximately 28 hours after admission and before naltrexone induction. Another patient in the anesthesia-assisted group developed pulmonary edema following anesthesia and was removed from the study.

Randomization to the 3 inpatient procedure groups was accomplished in blocks of 12, using random, computer-generated assignments, with stratification by sex. All staff remained unaware of the randomization sequence

Box. Study Inclusion and Exclusion Criteria

Inclusion Criteria

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for opioid dependence of at least 6 months' duration and seeking treatment for opioid dependence*†‡

In general good health§||¶

21 to 50 years of age||

Able to give informed consent and comply with study procedures*

American Society of Anesthesiologists physical classification status I or II ("otherwise healthy, no other medical problems" for class I, or "a chronic medical condition that is well-controlled," eg, hypertension, diabetes, asthma, for class II)*§¶

Exclusion Criteria

DSM-IV criteria for dependence on alcohol or drugs other than opiates, nicotine, and/or caffeine*†

Pregnancy or lactation or failure to use adequate means of birth control§||

History of significant violent behavior*

Diagnosis of schizophrenia and/or major mood disorder*

Significant suicide risk*

Current use of prescribed psychotropic medication (except for benzodiazepines, which may be prescribed for sleep; must not be taking other psychotropic medications for a minimum of 2 weeks)*||

Use of monoamine oxidase inhibitor medication within 2 weeks of study start*||

History of food or drug allergy, adverse reaction or sensitivity to any study medication (including malignant hyperthermia, history of egg allergy)*

Active medical illness, including coronary artery disease, acute hepatitis, renal failure, insulin-dependent or unstable diabetes, AIDS dementia or active human immunodeficiency virus or related infection, tuberculosis, severe thyroid abnormalities†||¶

Currently taking protease inhibitors||

Positive urine toxicology result for cocaine on the day of admission to the hospital†

Body mass index of 40 or higher¶

Inability to provide urine samples free of methadone during screening†

Blood glucose concentration greater than 160 mg/dL (8.8 mmol/L)§

Either multiple prior pneumonias or history of a complicated pneumonia (eg, pneumonia requiring intubation or pneumonia with empyema)*||

*Clinical interview.

†Urine toxicology.

‡Naloxone challenge test.

§Laboratory tests (urinalysis, thyroid function tests, coagulation profile, 12-lead electrocardiogram, serum and or urine β -human chorionic gonadotropin).

||Self-report.

¶Physical examination.

throughout the study. In addition, the Berger-Exner test⁵⁷ was used to confirm that no selection bias in enrollment occurred. Patients were not blinded to treatment. Blinding would have required sham anesthesia and raised practical concerns about the adequacy of blinding a sham procedure

and safety issues related to potential opioid overdose for individuals who might challenge expected opioid blockade (initially absent in clonidine arm) with high doses of heroin. All patients were admitted to a National Institutes of Health–funded general clinical research center at Columbia University

Medical Center, with single rooms and medical-surgical nursing care, on Monday (day 0) and discharged on Thursday (day 3), with a few exceptions: some patients seemed unable to ambulate or care adequately for themselves due to fatigue or sedation; the team needed to rule out adverse cardiac consequences (none occurred); the patient asked to stay an extra night in the hospital.

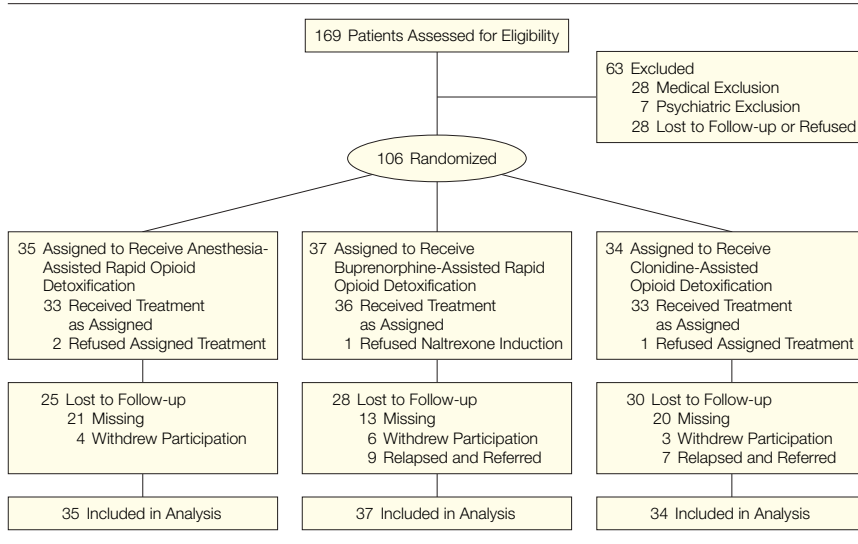
FIGURE 2 provides a schematic timeline for the screening, inpatient, and outpatient phases of the study. During the inpatient phase, withdrawal severity was assessed 4 times daily, at 8:30

AM and 12:30, 4:30, and 10 PM. Withdrawal assessment time point 1 occurred on day 0 at 4:30 PM, with subsequent assessment time points numbered sequentially. The withdrawal measures used were the Subjective Opiate Withdrawal Scale,⁵⁸ Objective Opiate Withdrawal Scale,⁵⁸ and Clinical Institute Narcotic Assessment.⁵⁹

All patients were administered clonidine, as needed, up to 0.2 mg every 4 hours (maximum 1.2 mg/d); clonidine was withheld if heart rate and blood pressure did not remain in the normal range (heart rate >55/min, systolic blood pressure >90 mm Hg, dia-

stolic blood pressure >55 mm Hg). Clonazepam was also administered, up to 2 mg every 8 hours, with additional dosing available for severe persistent withdrawal. Other adjuvant medications were administered as needed: ketorolac, 30 mg intramuscularly every 6 hours for myalgias, bone pain, cramping; ondansetron, 8 mg orally every 8 hours or prochlorperazine, 10 mg orally or intramuscularly every 8 hours for nausea and vomiting; octreotide, 100 µg every 8 hours subcutaneously for diarrhea; and acetaminophen, magnesium hydroxide, and aluminum hydroxide/magnesium hydroxide/simethicone for dyspepsia.

Figure 1. Participant Flow Chart

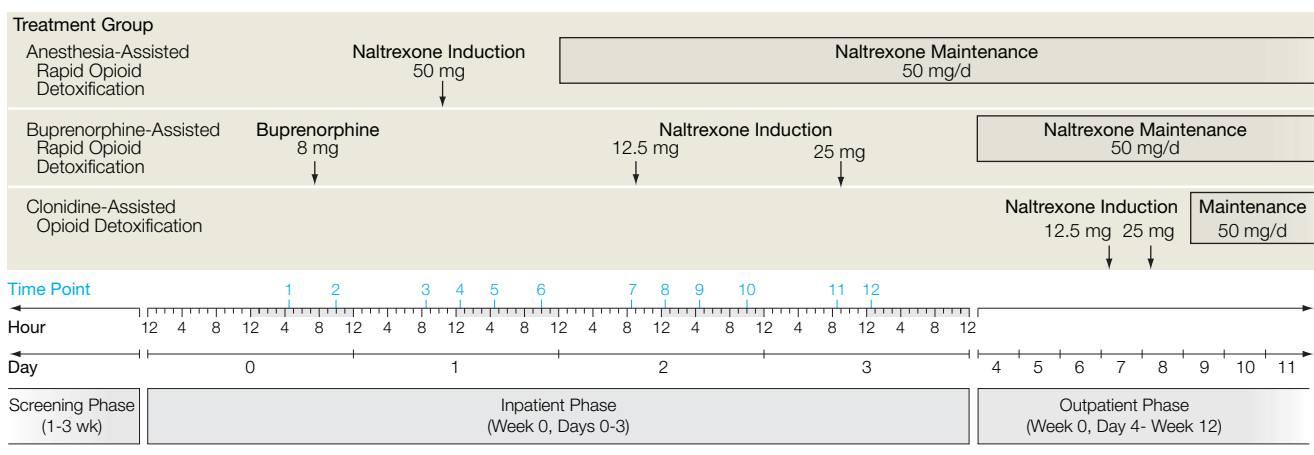


Anesthesia Protocol

A board-certified anesthesiologist (R.A.W.), assisted by a certified registered nurse anesthetist, performed anesthesia. Patients received nothing orally after midnight before the procedure, which always occurred on Tuesday (day 1) at approximately 8:30 AM. Medications, interventions, and monitors used before and during anesthesia are shown in TABLE 1. Anesthesia was maintained for 4 to 6 hours, followed by approximately 2 hours in the postanesthesia care unit.

Given reports of sudden death²⁷ following rapid opioid detoxification, patients were monitored with telemetry and continuous pulse oximetry throughout the inpatient hospitalization. To rule

Figure 2. Timeline of Study Procedures



out occult myocardial ischemia during anesthesia, troponin and serial cardiograms were performed. Serum chemistries, including calcium and magnesium, were also checked on day 2.

Buprenorphine Protocol

Unlike the usual use of buprenorphine for maintenance or detoxification, this procedure used a single facilitating buprenorphine dose to enable more rapid and comfortable naltrexone induction. The buprenorphine group received 8 mg of sublingual buprenorphine in the evening of day 0. Naltrexone induction occurred on day 2, with an initial dose of 12.5 mg. Patients received 25 mg of naltrexone on day 3, and the dosage was increased to 50 mg/d on subsequent days. Clonidine, clonazepam, and ancillary medications were administered as described above.

Clonidine Protocol

In this group, patients received no anesthetic agents, no buprenorphine, and no naltrexone during the inpatient phase. Clonidine, clonazepam, ketorolac, ondansetron, octreotide, prochlorperazine, and over-the-counter medications were given as needed as described above. Naltrexone induction was scheduled a week following hospital admission. Patients with opioid-negative urine, reporting little or no opioid use and demonstrating minimal opioid withdrawal on a naloxone challenge test,⁵⁶ received naltrexone on day 7 with an initial dose of 12.5 mg, followed by 25 mg the next day and 50 mg on subsequent days.

Standardized Outpatient Phase

Following hospital discharge, all patients were treated for 12 weeks with 50 mg of naltrexone daily and twice weekly manual-guided relapse prevention psychotherapy⁶¹ provided by master's- and doctoral-level psychotherapists. Patients met with the study psychiatrist weekly during the first month and monthly thereafter. In the first 2 weeks after discharge from the hospital, patients with residual withdrawal symptoms received up to 0.1 mg

of clonidine 3 times a day and 10 mg of zolpidem tartrate and/or 50 mg of trazodone taken orally every night as needed for sleep. At all outpatient visits, which were scheduled twice weekly, patients met with their therapist, nursing staff, and the research assistant, and urine was collected for toxicology. Naltrexone maintenance was strongly en-

couraged but not required. Patients still receiving naltrexone at study end were continued on it, if desired, and referred for additional aftercare. Individuals who relapsed during outpatient treatment were referred for alternative treatment. For the evaluation of treatment retention, *dropout* was defined as relapse to opioid depen-

Table 1. Anesthesia Medications and Interventions

Medications	Interventions and Monitoring
Preanesthesia	
Sodium citrate, 30 mL, orally	Inflatable compression stockings*
Ranitidine, 150 mg, orally	Electrocardiogram, pulse oximeter, noninvasive blood pressure monitor
Clonidine, 0.3 mg, orally	
Heparin sodium 5000 U, subcutaneously*	
Anesthesia induction	
100% Oxygen via inhalation (preoxygenation)	Endotracheal intubation and mechanical ventilation
Midazolam 1-3 mg, intravenously	
Propofol 2-3 mg/kg, intravenously	Capnometer†
Lidocaine 1 mg/kg, intravenously	Anesthetic gas analyzer‡
d-Tubocurarine 3 mg, intravenously	
Succinylcholine 1.5 mg/kg, intravenously	
Anesthesia maintenance	
Propofol 25-150 µg/kg per min	Peripheral nerve stimulator§
Isoflurane 0.5%-1.0% in a 70% nitrous oxide/30% oxygen mixture via inhalation	Bispectral Index Monitor
Midazolam 1-2 mg, intravenously, as needed every 1-2 h*	Arterial line placement and monitoring¶
Vecuronium as needed*§	
Opioid antagonist induction	
Octreotide acetate 100-150 µg intravenously over 30 min (prior to nalmeferne administration)	
Nalmeferne hydrochloride 4 mg intravenously over 30 min	
Naltrexone 50 mg via nasogastric tube	
Esmolol, labetalol, or nitroglycerin as needed¶	
Procedure termination/emergence from anesthesia	
Ketorolac 30 mg intravenously 1 h before end of procedure	
Ondansetron hydrochloride 4 mg intravenously 30 min before end of procedure	
Neostigmine 3.5 mg and glycopyrrolate 0.6 mg, as needed—reversal of neuromuscular blockade	
	Emergence and tracheal extubation
	Transport to postanesthesia care unit (with cardiac transport monitor)
	Chemistry monitoring Arterial blood samples (1-2 mL), acid-base status, arterial PaO ₂ , and PCO ₂ , serum electrolytes, and serum glucose

*Lower risk of deep venous thromboembolism. Monitoring occurred continuously throughout the procedure.
 †Monitor end-tidal carbon dioxide concentration (target between 25 and 35 mm Hg).
 ‡Monitor nitrous oxide and isoflurane concentration.
 §Maintain muscle relaxation.
 ¶Monitor patient awareness (Bispectral Index score target: 40-60).^{66,60}
 ¶Heart rate and blood pressure control.

dence requiring referral to alternative treatment (another detoxification or agonist maintenance therapy) or missing outpatient visits for 2 consecutive weeks. Patients who dropped out of treatment were counted as retained in treatment through the end of the week of their last outpatient visit.

Outcome Measures

The primary outcome measures for this study were (1) opioid withdrawal severity (assessed using the Subjective Opiate Withdrawal Scale, Objective Opiate Withdrawal Scale, and Clinical Institute Narcotic Assessment) during the 4-day inpatient phase of the trial, (2) the proportion of patients completing inpatient detoxification, (3) the proportion of patients receiving naltrexone induction (at any dose and at 50 mg), and (4) the number of weeks completed in treatment. Drug use over the course of the 12-week outpatient treatment was assessed by examining the proportions of urine specimens that tested positive for opiates and any drug, defined as positive if any of marijuana, phencyclidine, benzodiazepine, methadone, cocaine, barbiturate, or amphetamine were present.

Data Analysis

All analyses were carried out on the intent-to-treat population and all tests were 2-tailed with the α significance level set at .05. Baseline demographic variables and clinical characteristics were compared across groups using χ^2 tests for categorical variables and a 1-factor (treatment) analysis of variance for continuous variables. The Berger-Exner test was conducted on each outcome measure to test for selection bias in enrollment that might not have been captured by baseline comparisons of the sample.

Retention in treatment was compared using Kaplan-Meier curves and the log-rank statistic. Cox regression was used to examine the effect of naltrexone induction on retention. Aggregate measures of drug use during the outpatient phase (proportions of positive urine specimens) were compared

using Kruskal-Wallis 1-way analysis of variance by ranks.

To examine time trends during the inpatient phase, models were fitted on the (postnaltrexone induction) log-transformed withdrawal scores on days 2 and 3 using general estimating equations as implemented by PROC GENMOD (SAS Institute Inc; Cary, NC). The outcome was modeled as a function of time, treatment assignment, and time \times treatment interaction. Given significant baseline differences in current marijuana use, days using marijuana was explored as a covariate in the model but was found not to be a significant factor ($P > .20$) and therefore excluded from the model.

RESULTS

Patient Characteristics

Demographic and clinical characteristics of the 106 participants were comparable (TABLE 2). The Berger-Exner test for selection bias was performed on all response measures and was found to be nonsignificant for all outcomes ($P > .10$). Fifty-three percent of the participants were white and 72% were men, with a mean (SD) age of 36 (8) years (range, 21-50 years) and an average 14 (2) years of education. With respect to baseline drug use, the groups differed significantly only in marijuana use, with more use among those in the buprenorphine-assisted group, which used a mean (SD) of 8 (12) days in the month before screening vs 4 (7) days among those in the anesthesia-assisted and 2 (6) days among those in the clonidine-assisted groups ($F_{2,103} = 4.23, P = .02$). The groups did not differ on any of the Addiction Severity Index subscales.

Opioid Withdrawal Scores

Mean opioid withdrawal scores are presented in FIGURE 3. Withdrawal severity for the anesthesia group was greatest on day 1, immediately before receiving the anesthesia treatment, and differed significantly from withdrawal severity in the buprenorphine-assisted and clonidine-assisted groups ($P < .001$; withdrawal assessment time point, 3). This greater severity was at-

tributed to anticipatory anxiety about anesthesia and perhaps less use of the available clonazepam before receiving anesthesia. Following anesthesia treatment, withdrawal scores among those in the anesthesia-assisted group decreased, although not below pretreatment levels. For those receiving buprenorphine, withdrawal severity decreased on both the Clinical Institute Narcotic Assessment and the Objective Opiate Withdrawal Scale on the day after receiving buprenorphine, but severity increased (on all 3 withdrawal assessment instruments) following naltrexone induction on the morning of day 2. Subjective Opiate Withdrawal Scale mean scores were lower for all groups on measurements taken at night (10 PM). This pattern was not replicated on the Objective Opiate Withdrawal Scale or Clinical Institute Narcotic Assessment. Longitudinal analyses on log-transformed withdrawal scores on days 2 and 3 (withdrawal assessment time points 7 through 12) did not reveal significant differences in withdrawal severity.

Other Detoxification Outcomes

TABLE 3 shows the number of patients in each group completing various study milestones. During outpatient treatment, no group differences occurred in the proportions, mean (SDs), of urine samples positive for opiates (anesthesia, 0.54 [0.39]; buprenorphine, 0.62 [0.39]; clonidine, 0.73 [0.41]; $\chi^2_2 = 3.18, P = .20$) or for "any drug use" (anesthesia, 0.50 [0.41]; buprenorphine, 0.65 [0.35]; clonidine, 0.50 [0.42]; $\chi^2_2 = 2.36, P = .31$). Five patients (14%) in each of the anesthesia-assisted and buprenorphine-assisted groups and 2 (5.9%) in the clonidine-assisted group were retained 12 weeks and provided no more than 2 opiate-positive urine specimens during the outpatient phase ($\chi^2_2 = 1.49, P = .48$).

Naltrexone Induction

As shown in Table 3, rates of naltrexone induction, defined as taking any dose of naltrexone, differed significantly across groups, with 33 (94%) of

35 patients in the anesthesia-assisted group and 36 (97%) of 37 in the buprenorphine-assisted group achieving higher rates of naltrexone induction than the 7 (21%) of 34 in the clonidine-assisted group ($\chi^2_2=64.52, P<.001$). Thirty-three (94%) of 35 patients in the anesthesia-assisted, 27 (73%) of 37 in the buprenorphine-assisted, and 6 (18%) of 34 in the clonidine-assisted groups received the full 50-mg maintenance dose of naltrexone ($\chi^2_2=45.89, P<.001$). A significant relationship existed between naltrexone induction at the full 50-mg maintenance dose and

attrition, with those achieving full-dose induction at lower risk of dropping out (odds ratio, 0.28; 95% confidence interval, 0.15- 0.51).

Treatment Retention

Treatment retention (FIGURE 4) over the course of the study did not differ significantly across intervention groups (mean [SE] weeks in treatment, anesthesia 2.83 [0.47] weeks; buprenorphine, 3 [0.45]; and clonidine, 2.47 [0.58]; log-rank₂=3.57, P=.17). By week 3, more than 50% of the patients had dropped out of each treatment arm.

Although the differences were not significant overall, 7 (20%) of 35 in the anesthesia, 9 (24%) of 37 in the buprenorphine, and 3 (9%) of 34 in the clonidine groups remained in treatment for 12 weeks.

Adverse Events

Three patients in the anesthesia group experienced serious adverse events. One developed severe pulmonary edema and aspiration pneumonia approximately 14 hours after extubation, necessitating reintubation and admission to the intensive care unit for 5 days. The patient's

Table 2. Demographic and Clinical Characteristics of Randomized Sample

Baseline Variable	Anesthesia (n = 35)	Buprenorphine (n = 37)	Clonidine (n = 34)	χ^2 or F	df	P Value
Demographics						
Age, mean (SD), y	36 (8)	36 (8)	35 (8)	0.16	2, 103	.85
Male, No. (%)	24 (69)	26 (70)	26 (77)	5.90	2	.74
Race, No. (%)*				7.14	6	.31
Black	6 (17)	5 (13)	2 (6)			
Hispanic	12 (34)	7 (19)	12 (35)			
White	14 (40)	24 (65)	18 (53)			
Other	3 (9)	1 (3)	2 (6)			
Education, mean (SD), y	14 (2)	14 (2)	14 (2)	0.02	2, 103	.98
Currently married or cohabit, No. (%)	15 (43)	12 (32)	11 (32)	5.84	4	.21
Employment status, No. (%)				3.14	2	.21
Currently employed	20 (57)	24 (65)	15 (44)			
Income level†				0.02	4	>.99
Low (<\$25 000/y)	17 (53)	18 (53)	18 (53)			
Medium (\$25 000-\$50 000/y)	11 (34)	12 (35)	12 (35)			
High (>\$50 000/y)	4 (13)	4 (12)	4 (12)			
Current substance use in last 30 d, mean (SD), d						
Alcohol	4 (8)	6 (10)	2 (4)	1.83	2, 103	.17
Marijuana	4 (7)	8 (12)	2 (6)	4.23	2, 103	.02
Cocaine	1 (1)	1 (2)	1 (2)	0.86	2, 103	.43
Heroin	30 (1)	29 (3)	29 (3)	2.28	2, 103	.11
Lifetime substance use disorders, mean (SD), y						
Alcohol	5.5 (8.6)	6.0 (7.4)	2.3 (3.2)	3.00	2, 103	.05
Marijuana	6.5 (7.5)	8.2 (7.7)	4.5 (5.1)	2.56	2, 103	.08
Cocaine	2.6 (3.6)	2.6 (3.9)	1.9 (2.7)	0.40	2, 103	.67
Heroin	7.6 (7.8)	7.4 (5.7)	6.4 (6.1)	0.35	2, 103	.71
Route of consumption, No. (%)						
Inhale	23 (66)	16 (43)	19 (56)	5.54	6	.48
Smoke	1 (3)	4 (11)	1 (3)			
Subcutaneous	1 (3)	2 (5)	1 (3)			
Intravenous	10 (28)	15 (41)	13 (38)			
Treatment history, mean (SD), No. prior discrete treatments of given type						
Inpatient detoxification	1.74 (2.9)	1.59 (2.3)	1.21 (1.8)	0.47	2, 103	.62
Inpatient rehabilitation	0.57 (1.1)	0.54 (0.87)	0.56 (1.1)	0.01	2, 103	.99
Outpatient detoxification	0.17 (0.38)	0.11 (0.32)	0.29 (0.68)	1.37	2, 103	.26
Methadone maintenance treatment	0.66 (0.73)	0.57 (0.87)	0.53 (0.79)	0.24	2, 103	.79

*Race determined by open-ended self-identification.

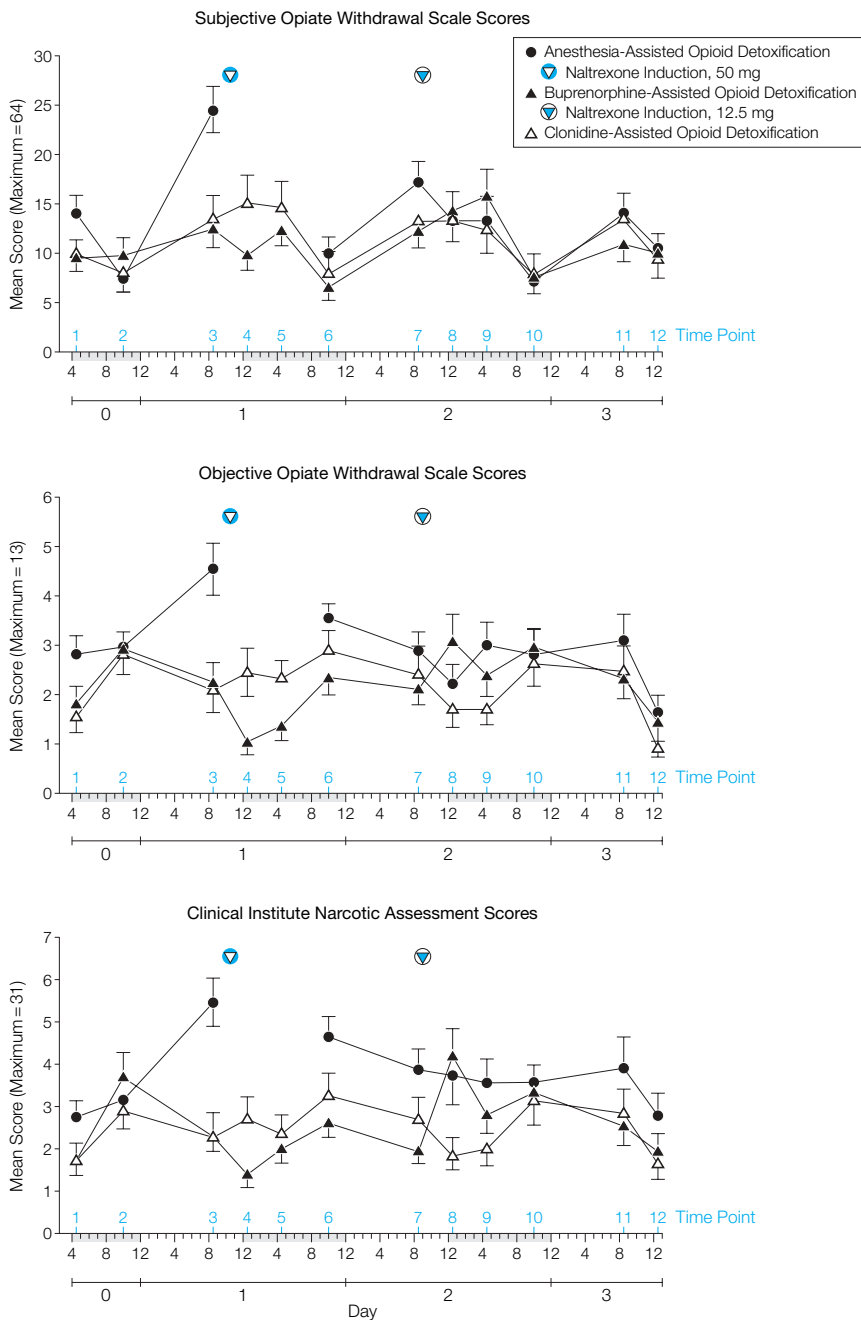
†Income data missing for 6 subjects (anesthesia-assisted intervention [n = 3], buprenorphine-assisted intervention [n = 3]).

condition was complicated by upper airway edema requiring aggressive glucocorticoid treatment. The patient was dis-

charged home in good condition a week after anesthesia treatment but quickly relapsed to heroin dependence. The inves-

tigators believed that this episode of pulmonary edema was postobstructive (negative pressure) pulmonary edema. The patient had concealed but subsequently admitted a history both of several prior complicated pneumonias and of possible obstructive sleep apnea. These conditions were subsequently exclusionary. The second patient, who had concealed a history of bipolar illness during the screening process, developed a mixed bipolar state about 5 days after anesthesia, with suicidal ideation requiring hospitalization. The third patient had reportedly stable insulin-dependent diabetes mellitus but concealed a prior episode of diabetic ketoacidosis. The patient's glucose level was difficult to manage following anesthesia, and the inpatient phase of the study was prolonged by a day. Two days after discharge, the patient developed diabetic ketoacidosis, resulting in a 3-day readmission to the hospital. Rapid relapse to heroin dependence followed discharge. Subsequently, patients with a glucose level greater than 160 mg/dL (8.8 mmol/L) or with insulin-dependent diabetes were excluded from the study.

Figure 3. Mean Opioid Withdrawal Scores



Error bars represent ±1 SEM. Some error bars omitted for clarity. Arrows indicate administration of naltrexone in the anesthesia-assisted intervention (after time point 3) and buprenorphine-assisted intervention (after time point 7). No withdrawal assessments were made in the anesthesia-assisted group during general anesthesia and the immediate postprocedure recovery phase (time points 4 and 5). Withdrawal assessment time points were numbered sequentially starting on Monday (day 0) at 4:30 PM, and so on, with assessments made daily at 8:30 AM, 12:30 PM, 4:30 PM, and 10 PM.

COMMENT

This is the first randomized controlled trial of anesthesia detoxification with a positive control group (buprenorphine-assisted detoxification) and systematic documentation of postdetoxification withdrawal symptoms. Anesthesia-assisted treatment was associated with a high rate of naltrexone induction but also with significant opioid withdrawal symptoms comparable with the alternative procedures. The buprenorphine-assisted procedure produced naltrexone induction comparable with the anesthesia-assisted intervention. The clonidine intervention produced a low rate of naltrexone induction (21% vs >90%, $P < .001$) and nonsignificantly lower rates of treatment retention (9% vs 20% for anesthesia-assisted group and 24% for buprenorphine-assisted group) over 3 months. Furthermore, 3 serious, potentially life-threatening adverse events occurred with the anesthesia procedure.

In the earlier Australian randomized trial,⁴³ anesthesia was also compared with inpatient clonidine detoxification. However, naltrexone induction was sometimes delayed for a few days following anesthesia, so that 40 (83%) of 48 participants actually received naltrexone (only 54% during anesthesia) compared with 14 (28%) of 50 in the clonidine group. Also, as a result of variable postprocedure levels of care, no systematic measures of withdrawal severity were made in the days following anesthesia, leaving unanswered the question⁶² of whether the procedure shortens and diminishes the withdrawal process. No adverse events were reported, and treatment retention appeared even lower than our own at 3 months, with 15% of the anesthesia group vs 2% of the clonidine group remaining in treatment. By 6 months, heroin use in each cohort was similar.

Uncontrolled reports on the experience with anesthesia for opioid withdrawal have shown somewhat mixed results. Many argue for the safety and efficacy of the procedure^{21,38,40,41,63,64} and report high rates of naltrexone induction and sustained opioid abstinence.^{21,35,38,65} Selection bias and the lack of controls, however, limit the validity and generalizability of these reports. Anesthesia advocates^{41,63,66-68} have claimed minimal withdrawal symptoms following anesthesia. Such reports lent weight to claims that the severe discomfort of opioid withdrawal could be avoided, contributing to the willingness of individuals or families to pay large sums for this unproven approach. However, other studies^{14,30,31} have reported significant, sometimes prolonged, withdrawal symptoms in patients detoxified under general anesthesia. In an open case series of 7 patients,¹⁴ persistent and clinically significant withdrawal was observed for nearly 3 weeks following the procedure, a result that was consistent with a laboratory study in which continuous naloxone infusion and anesthesia in rats lengthened and worsened opioid withdrawal signs.⁶⁹

Two nonrandomized comparison studies merit mention. The first com-

Table 3. Treatment Milestones Attained

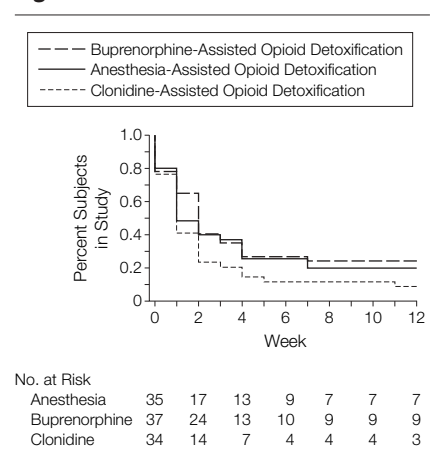
Treatment variables	No. (%)		
	Anesthesia	Buprenorphine	Clonidine
No. of patients randomized	35	37	34
Completed inpatient phase	32 (91)	34 (92)	31 (91)
Stayed extra night inpatient	6 (17)	3 (8.1)	4 (12)
Received naltrexone, ≥1 dose	33 (94)	36 (97)	7 (21)
Received naltrexone, 50-mg dose	33 (94)	27 (73)	6 (18)
Retained 12 wk	7 (20)	9 (24)	3 (8.8)
Retained 12 wk and provided ≤2 opiate-positive urine specimens	5 (14)	5 (14)	2 (5.9)

pared 15 patients detoxified under anesthesia with 15 patients receiving 1 to 2 weeks of inpatient methadone taper, with all offered supervised naltrexone maintenance.⁶⁵ Withdrawal symptoms were greater in the anesthesia group immediately following the procedure. Abstinence rates at 1 month (100%) and 2 months (93%) were extraordinarily high in the anesthesia group, compared with 40% and 33%, respectively, for the methadone taper, but statistical significance for treatment retention was lost after 3 months. The second study retrospectively compared 139 anesthesia patients with 87 inpatients detoxified with methadone over a month.⁷⁰ The methadone taper group reported nearly twice the rate of sustained opioid abstinence (42% vs 22%) in telephone follow-up after 12 to 18 months.

In our study, we took many precautions to screen individuals for preexisting conditions that increase anesthesia risk. Because pretreatment chest x-rays and echocardiograms significantly raise costs, they would potentially be omitted in clinical practice, further increasing risk. Despite these precautions, 1 individual in our study experienced pulmonary edema and aspiration pneumonia. Careful inpatient monitoring of pulmonary function, which enabled rapid tracheal intubation and transfer to intensive care, may have saved this patient's life. Indeed, in a study of 20 patients treated with anesthesia,²⁷ an unmonitored patient died in the hospital of unknown causes between 34 and 41 hours after anesthesia treatment.²⁸

The other 2 serious adverse events, an episode of diabetic ketoacidosis and a

Figure 4. Treatment Retention



bipolar mixed state requiring hospitalization (the patient in the clonidine-assisted group who had the mixed bipolar reaction did not require hospitalization), could have occurred with other opioid detoxification approaches, although the risk of each may have been greater as a result of increased physiological stress imposed by rapid antagonist exposure and precipitated withdrawal with anesthesia.¹⁷

Given the large doses of opioid antagonists typically used during anesthesia detoxification procedures, most practitioners have seen anesthesia as a means principally to achieve rapid antagonist induction. Some believe that rapid stripping of agonist from opioid receptors may itself be therapeutic,^{40,62,64} promoting long-term abstinence. Although the results from our study do not support this thesis, receptor agonist stripping can nevertheless occur with naltrexone induction following a single dose of buprenor-

phine. Some have pointed out that anesthesia could be offered electively to patients who desire it, because it will bring more individuals into treatment, especially those who intensely fear opioid withdrawal.⁷¹ Advocates compare this to offering anesthesia to individuals with dental phobia or for cosmetic surgery.²⁹ However, this argument relies on the usually false promise that anesthesia eliminates the severe discomfort of opioid withdrawal. This expectation probably contributed powerfully to patients' lying about their medical or psychiatric histories, as occurred with all 3 patients who experienced serious adverse events in our study.

Treatment retention and abstinence from illicit opioids are important goals of treatment, but specific detoxification methods, per se, do not appear to lead to either. Two previous studies^{43,65} showed that intermediate-term treatment outcomes at 3 months⁶⁵ and at 6 months⁴³ do not differ as a function of the detoxification approach used. Our results at 3 months, while demonstrating low rates of sustained abstinence and treatment retention, corroborate these earlier findings. Physicians must recognize that the method used to achieve opioid abstinence does not appear to affect the course of this chronic relapsing disease.

Although a formal cost-efficacy analysis is beyond the scope of this report, it appears that the cost per successful patient undergoing the anesthesia procedure is considerably greater than the cost per successful patient undergoing the buprenorphine procedure. Anesthesia entails major costs not associated with buprenorphine: obligatory preprocedure testing, physician anesthesiologist charges, anesthetic medications, operating rooms and possible intensive care unit beds, postprocedure monitoring, and the cost of treating adverse events that appear more likely with anesthesia. Considering the lower cost, greater safety, and equivalent withdrawal severity profile of the buprenorphine-assisted approach, a buprenorphine-mediated procedure appears preferable to anesthesia for initiation of opioid antagonist maintenance.

There are a number of limitations to this study. First, the total sample size of 106 patients for a 3-treatment trial made it difficult to show statistically significant differences in some important variables, including overall withdrawal severity and treatment retention. A larger sample might have shown anesthesia or buprenorphine superior to the other, but it appears this would have required a sample with more than 4 times the number of participants in the present study. Second, the sample size limited the ability to find patient subgroups that might selectively benefit from anesthesia. Third, follow-up data on the many individuals who dropped out of the study or were referred for additional treatment were not available, making it difficult to appreciate potential distal effects of the withdrawal methods used. Fourth, because prescription analgesic use was negligible and recent methadone use exclusionary, the inclusion only of patients dependent on heroin may limit generalizability of our findings to all opioid-dependent individuals. Earlier studies, however, have suggested that dependence on methadone made anesthesia-assisted withdrawal more difficult^{24,35} and produced lower subsequent treatment retention.²⁴ Methadone use also predicted poor retention in a series of heroin-dependent patients inducted onto naltrexone using a buprenorphine-mediated procedure similar to buprenorphine-assisted rapid opioid detoxification.⁷² These prior results suggest that naltrexone induction is complicated by methadone and that anesthesia would not likely fare comparatively better among methadone-maintained patients.

In summary, this randomized trial of general anesthesia for opioid withdrawal and naltrexone induction demonstrates no benefit of anesthesia over a safer, cheaper, and potentially outpatient alternative using buprenorphine as a bridge to naltrexone treatment. Taken together with the results of earlier studies,^{31,43,65,70} our findings suggest that general anesthesia for rapid antagonist induction does not currently have a meaningful role to play in the treatment of opioid dependence.

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Author Contributions: Dr Collins had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Collins, Kleber, Whittington, Heitler.

Acquisition of data: Collins, Kleber, Whittington, Heitler.

Analysis and interpretation of data: Collins, Kleber. **Drafting of the manuscript:** Collins, Kleber, Whittington, Heitler.

Critical revision of the manuscript for important intellectual content: Collins, Kleber, Whittington.

Obtained funding: Collins, Kleber.

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