Comparison of Pharmacological Treatments for Opioid-Dependent Adolescents

A Randomized Controlled Trial

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Context: The prevalence of heroin and other opioid use has markedly increased among adolescents in the last decade; however, virtually no research has been conducted to identify effective treatments for this population.

Objective: To evaluate the relative efficacy of 2 pharmacotherapies, the partial opioid agonist buprenorphine hydrochloride and the centrally active \( \alpha_2 \)-adrenergic blocker clonidine hydrochloride, in the detoxification of opioid-dependent adolescents.

Design, Setting, and Patients: A double-blind, double-dummy, parallel-groups randomized controlled trial conducted in a university-based research clinic from October 2001 to December 2003. Patients were a volunteer sample of 36 adolescents who met DSM-IV criteria for opioid dependence (ages 13-18 years eligible).

Interventions: Participants were randomly assigned to a 28-day, outpatient, medication-assisted withdrawal treatment with either buprenorphine or clonidine. Both medications were provided along with thrice weekly behavioral counseling and incentives contingent on opiate abstinence. Postdetoxification, all participants were offered the opportunity for continued treatment with the opiate antagonist, naltrexone hydrochloride.

Main Outcome Measures: Treatment retention, opiate abstinence, and human immunodeficiency virus risk behavior, along with measures of withdrawal and medication effects.

Results: A significantly greater percentage of adolescents who received buprenorphine were retained in treatment (72%) relative to those who received clonidine (39%) (\( P < .05 \)). For those in the buprenorphine group, a significantly higher percentage of scheduled urine test results were opiate negative (64% vs 32%; \( P = .01 \)). Participants in both groups reported relief of withdrawal symptoms and drug-related human immunodeficiency virus risk behavior. Those in the buprenorphine condition generally reported more positive effects of the medication. No evidence of opioid intoxication or psychomotor impairment was observed. Sixty-one percent of participants in the buprenorphine condition and 5% of those in the clonidine group initiated treatment with naltrexone.

Conclusion: Combining buprenorphine with behavioral interventions is significantly more efficacious in the treatment of opioid-dependent adolescents relative to combining clonidine and behavioral interventions.

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The prevalence of use of heroin and other opioids among adolescents has markedly increased in the last decade, reaching levels not observed since the 1960s. According to the national, school-based Monitoring the Future Survey, the percentage of eighth, 10th, and 12th graders who have used heroin more than doubled from between 0.4% and 0.6% in the early 1990s to 1.0% to 1.6% in recent years.² This dramatic increase in the number of young heroin users has been largely attributed to the markedly decreased price and increased purity of heroin in the last decade.² Many adolescents initiate use of such pure heroin by snorting it³; however, some then progress to injection of heroin.⁴ Indeed, heroin-using adolescents have the highest rate of injection drug use when compared with youth using other substances,⁴ increasing their risk of contracting and spreading hepatitis, human immunodeficiency virus (HIV), and other diseases.⁵,⁶,⁷,⁸,⁹

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Youth are also reporting high rates of nonmedical use of other opioids. Importantly, opioids are the second most commonly abused class of illicit drugs among adolescents, second only to marijuana. A total of 1.7%, 3.6%, and 4.5% of eighth, 10th, and 12th graders, respectively, re-
ported having recreationally used OxyContin (controlled-release oxycodone) in 2003. Additionally, 2.8% of eighth graders, 7.2% of 10th graders, and 10.5% of 12th graders reported recreational use of Vicodin (hydrocodone bitartrate and acetaminophen) in 2003.1

These trends and their potential consequences underscore the importance of identifying effective treatments for this growing cohort of opioid-dependent adolescents. Despite this need, virtually no research has been conducted to systematically characterize or evaluate treatment interventions for adolescent heroin and opioid abusers. Indeed, only a few articles have been published in the last 25 years reporting on some general characteristics of this growing population.5,9,14-16 Additionally, although a few small-scale treatment studies were conducted in the 1960s and 1970s with opioid-dependent youth,5 these studies typically did not include control groups or random assignment to treatments. Also, many of these studies did not focus on youth younger than 18 years. Importantly, no studies have been published examining treatments for opioid-dependent adolescents in the past 25 years.

To our knowledge, this article reports on the first randomized controlled study to systematically evaluate the efficacy of 2 pharmacotherapies as detoxification agents in the treatment of opioid-dependent adolescents. In this double-blind, double-dummy trial, opioid-dependent adolescents were randomly assigned to receive a 28-day, outpatient, medication-assisted withdrawal treatment with either the partial μ-agonist buprenorphine hydrochloride or the centrally active α2-adrenergic blocker clonidine hydrochloride. Both medications were provided along with intensive behavioral interventions. All participants were then offered the opportunity for continued treatment with the μ-opiate antagonist, naltrexone hydrochloride, along with continued behavioral counseling.

We chose to examine the efficacy of buprenorphine because it has a unique profile of effects that are of clinical utility and may make it an appealing medication to provide to opioid-dependent youth.17 As a partial agonist, buprenorphine has a ceiling effect on its agonist activity,18,19 which greatly increases its safety profile and limits its abuse liability as well as the possibility of overdose relative to full-agonist medications such as methadone hydrochloride.20 Buprenorphine can also dose-dependently block the subjective and physiological effects of exogenously administered opioids.18,21,22 Because of buprenorphine’s slow dissociation from the μ-opioid receptor, discontinuation of buprenorphine treatment results in reduced withdrawal symptoms relative to discontinuation of full agonists.22-24 Numerous controlled trials have demonstrated that buprenorphine is safe and efficacious in alleviating opiate withdrawal symptoms, reducing illicit opiate use, and promoting treatment retention among opioid-dependent adults in detoxification.25,26-28 Buprenorphine’s safety and efficacy as a pain medication have also been established in children and adolescents as well as adults.29-32

We chose to examine the efficacy of clonidine because it is a nonnarcotic medication with limited abuse potential33 and it has been widely studied as a detoxification agent that decreases sympathetic nervous hyperactivity and suppresses the acute dysphoric state during the opioid withdrawal period among adults.25,34-37 Although clonidine has been used with adolescents in the treatment of psychiatric disorders,38,39 to our knowledge, no controlled studies have explored its efficacy in the opiate detoxification of adolescents who may have a shorter history of opioid abuse and a lower degree of opioid dependence relative to opioid-dependent adults. Thus, although prior research has shown that buprenorphine is generally a more efficacious detoxification agent compared with clonidine among opioid-dependent adults,25,40 one of the relative efficacy of these medications in the detoxification of opioid-dependent adolescents is unknown, as is their relative efficacy when combined with intensive behavioral interventions that may improve outcomes.

### METHODS

**PARTICIPANTS**

Participants were self-referred adolescents (ages 13-18 years eligible) who met DSM-IV criteria for opioid dependence. Participants received a medical evaluation prior to enrollment. If a female were pregnant at intake or at any time during the study (via weekly urine tests), she would have been excluded. Evidence of an active, significant psychiatric disorder (eg, psychosis) or significant medical illness (eg, cardiovascular disease) was also exclusionary. To increase generalizability, codependence/abuse of alcohol, cocaine, or marijuana were not exclusion criteria. All medications participants were consuming at intake or during the study were tracked to ensure that they were not contraindicated with study medications. Individuals who sought treatment but did not meet inclusionary criteria were referred to a local treatment center.

Each participant’s parent/guardian provided informed consent for the adolescent (if <18 years), and the adolescent provided informed assent to participate. A total of 38 individuals enrolled in this trial. Two individuals left the study before being randomized to a study condition. Thus, the final sample size was 36 (18 per condition). This study was conducted at an outpatient research clinic at the University of Vermont (Burlington) and approved by the university’s institutional review board.

**DESIGN**

Participants were randomly assigned to either: (1) detoxification with buprenorphine or (2) detoxification with clonidine. In this process, participants were stratified by (1) sex and (2) past-month route of opiate use (injection vs intranasal). This study used a parallel groups, double-blind, double-dummy design. Participants were required to attend the clinic daily during all 28 days of the detoxification. Behavioral treatment with contingency management procedures was offered during the entire detoxification. Failure to consume scheduled medication 5 times in a row or provide 3 scheduled urine samples in a row resulted in discharge from the study and referral to a local treatment program.

**MEDICATION ADMINISTRATION**

**Buprenorphine Detoxification**

Participants in the buprenorphine condition received sublingual buprenorphine tablets (Subutex; Reckitt Benckiser Pharmaceuticals, Inc, Hull, England) daily under observation via a
flexible dosing procedure based on weight and self-reported opiate use at intake. If participants were less than 70 kg and/or their self-reported opiate use at intake was 1 to 3 bags of heroin or the equivalent in other opiates, they were given a starting dose of 6 mg of buprenorphine hydrochloride. If participants were 70 kg or more and/or their self-reported use was more than 3 bags of heroin or the equivalent in other opiates, they were given a starting dose of 8 mg of buprenorphine hydrochloride. Buprenorphine doses then decreased for participants in this condition by 2 mg every 7 days. Because the maximum dose given in the study was 8 mg and each tablet contained 2 mg of buprenorphine hydrochloride, all participants were given a total of 4 tablets daily composed of either active or placebo buprenorphine hydrochloride. Also, participants in the clonidine group received placebo buprenorphine tablets throughout the study, which paralleled the timeline of administration of active buprenorphine doses to those in the buprenorphine group. Participants were instructed to hold the tablets under the tongue for a period of 5 minutes without speaking. To prevent precipitating withdrawal, participants were required to not have used any opiates for 24 hours prior to intake and to exhibit observable, mild opioid withdrawal symptoms on their intake day before medication administration (as measured via pupil dilation and the Clinical Investigation Narcotic Assessment scale). These buprenorphine doses are in the low to moderate range of doses that have been used with youth and opioid-dependent adults.17,63-66

Clonidine Detoxification

Participants in the clonidine group received transdermal clonidine patches (Catapres TTS; Boehringer Ingelheim, Ingelheim Germany). Patches (as opposed to other clonidine formulations) were selected to provide steady-state levels of clonidine. On intake day and day 1, participants wore a single patch of 0.1 mg of clonidine hydrochloride. A second patch of 0.1 mg was added on day 2 and worn for days 2 to 6 (resulting in a 0.2-mg dose on these days). An optional third patch (depending on the severity of withdrawal symptoms) may have been added on day 4 and worn through day 6 (for a total of 0.3 mg on these days). All patches were removed on day 7 and replaced with a 0.2-mg dose. On day 14, all patches were again removed and replaced with a 0.1-mg dose. On day 21, all patches were removed and replaced with a 0-mg dose (placebo patch, which looked identical to the active clonidine patch but did not contain any active medication). Participants in the buprenorphine group received placebo clonidine patches throughout the study, which paralleled the timeline of administration of active clonidine patches to those in the clonidine group. These doses and dosing schedule with clonidine are similar to and in the low to moderate range of doses that have been used in opioid detoxification studies with adults17,48 and in studies that have used clonidine in treating psychiatric disorders in adolescents.18,30 All participants were also provided with the opportunity to consume adjunctive, over-the-counter medications, such as ibuprofen and sleep aids, as needed to help manage symptoms during detoxification.

Observations of Medication Effects

On intake day, all participants were required to remain at the clinic for a minimum of 3 hours after receiving their first medication dose. This observation period allowed for any opiate withdrawal symptoms and agonist effects to be systematically monitored. Specifically, participants were initially required to pass breathalyzer and field sobriety tests and provide a urine sample. A variety of baseline (time 0) measures were obtained (including heart rate, blood pressure, pupil radius, self-reported opioid agonist effects, withdrawal symptoms, and other medication effects, as described later).

One hour after completing baseline assessments (time 1), participants in the buprenorphine condition received their scheduled buprenorphine dose (or placebo if assigned to the clonidine condition). To further ensure safety, at time 0, participants were given a dose of 0.1 mg of oral clonidine hydrochloride in the clonidine condition and an oral placebo dose (that looked identical to an active oral clonidine dose) in the buprenorphine condition and the effect of this dose on blood pressure 1 hour later (time 1) was assessed. If a participant who received active oral clonidine experienced a blood pressure of less than 90/50 or more than 160/100 or pulse of less than 30 or more than 100, the participant was placed in the buprenorphine condition and received their first dose of buprenorphine at time 1 (in a blind manner) instead of continuing in the clonidine condition. No participant had to be switched to the buprenorphine condition for this reason, and participants in the clonidine condition instead received their appropriate transdermal clonidine patches at time 1 (while those in the buprenorphine condition received placebo patches). Provision of the 0.1-mg dose of oral clonidine hydrochloride at time 0 was also important to provide on intake day because steady-state levels of transdermal clonidine are not reached for about 24 to 48 hours after application of the patch.34

Dependent measures were then collected at hourly intervals for the next 2 hours. If a participant were to exhibit signs of opioid intoxication at any time, no further medication would have been provided. (This was not necessary for any participant.) All participants were required to pass a field sobriety test prior to discharge. On the remaining 28 days of detoxification, dosing procedures were identical to those on intake day, except that dependent measures were only collected at baseline (premedication) and 1 hour postdosing.

URINALYSIS

Urine specimens were collected at intake and every Monday, Wednesday, and Friday for the duration of the study under the observation of a research staff member. Samples were immediately screened prior to behavioral therapy sessions using semiquantitative urinalysis procedures (Cobas MIRA; Roche Diagnostic Systems, Branchburg, NJ) for methadone, opiates, propoxyphene, cocaine, benzodiazepines (once weekly), and marijuana (once weekly). If a participant failed to provide a scheduled urine sample, the sample was counted as opiate positive. Blood alcohol levels were also analyzed via a breathalyzer every time urine samples were collected and had to be less than or equal to 0.03 g/mL for participants to receive medication.

BEHAVIOR THERAPY

Behavioral therapy based on the Community Reinforcement Approach for adolescents31-33 was provided during 3 one-hour, individual sessions per week. Participants were provided with counseling on (1) stimulus control training to eliminate situations that are precursors to drug use and increase activities incompatible with or unrelated to drug use, (2) urge control training to help participants recognize and control thoughts/plans to use drugs, and (3) social control/contracting to encourage participants’ parent/family member (via family counseling sessions for those willing to participate) to provide reinforcement outside of the clinic setting for drug abstinence. Therapy sessions also addressed other needs of adolescents (eg, educational, vocational, HIV prevention, and skills training needs). Masters-level therapists were trained in these manual-guided therapy procedures and provided with weekly clinical supervision.
All participants were offered incentives to reinforce opiate abstinence. Specifically, participants could earn vouchers contingent on the provision of opioid-negative urine samples. Specimens negative for opioids earned points (each worth $0.25) recorded on vouchers. The first opioid-negative specimen was worth 10 points at $0.25 each or $2.50. Each subsequent consecutive opioid-negative specimen increased the voucher value by 3 points. A $10.00 bonus was provided to participants for each set of 3 consecutive negative samples. Submission of an opioid-positive sample or failing to submit a scheduled sample reset the value of the next earned voucher to the initial $2.50 level. Continuous abstinence resulted in vouchers earnings equivalent to $152.50. The cash equivalent of the points earned was used by staff to buy material reinforcers requested by participants (eg, ski passes, CDs, gym passes, clothing). As part of their therapy, participants were encouraged to develop new recreational activities and social networks that did not involve drug use. The activities in which patients engaged using the vouchers they earned were used to support these lifestyle changes.

Vouchers were also used to reinforce clinic attendance and completion of weekly assessments because consistent clinic attendance and willingness to complete assessments are challenges that are commonly encountered in adolescent substance abuse treatment. Participants received $2.50 each time they attended the clinic (for maximum attendance earnings of $70). For completing all scheduled weekly assessments, participants received $5 at the end of each week (for maximum earnings of $20).

NALTREXONE PHASE

At the end of the study, participants were offered the opportunity to take the opioid antagonist, naltrexone, to help prevent them from relapsing to opiate use postdetoxification. To be eligible to initiate naltrexone treatment at the end of the 28-day detoxification, all 3 urine samples that participants provided during the last week of detoxification had to be opiate negative. If they were not, participants had up to a month to provide 3 consecutive samples negative for opiates to initiate naltrexone treatment. Participants in aftercare also received continued counseling and urinalysis. Participants could continue in aftercare at the clinic for up to 2 months or until they were referred to a community-based facility for continuing care.

OUTCOME MEASURES

Primary Measures

Treatment retention was examined as (1) the percentage of participants who completed the entire detoxification treatment and (2) time retained in treatment. Opiate abstinence was examined as the percentage of scheduled urine samples documented to be opiate negative during detoxification. Drug-related HIV risk behavior was measured via the drug scale composite score from the HIV Risk Behavior Scale (HRBS) administered once weekly.

Secondary Measures

Pupil constriction, a physiologic indicator of μ-opiate effects, was determined from photographs taken with a Polaroid camera at magnification ×2 at 1 foot-candle of ambient illumination (pupil radius measured in millimeters).

Adjective Rating Scale

Self-reports of drug effects were rated on a modified computerized version of an adjective rating scale, a standardized measure listing 32 items describing opioid drug effects and withdrawal effects (with scores ranging from 0-9, anchored at each end by “not at all” and “severe”). For example, opioid effects included nodding, rush, high, coasting, and itchy skin, and withdrawal effects included irritability, chills/gooseflesh, runny nose, and yawning.

Visual Analog Scale

On this computerized measure, participants rated the extent to which they experienced 6 effects (drug effect, drug liking, good effect, bad effect, drug-related high, and sick). The scales were anchored by “not at all” and “severe” (with corresponding scores from 0-100).

Digit Symbol Substitution Test

The Digit Symbol Substitution Test was used to measure psychomotor performance. On this task, the digits 1 to 9 were displayed continuously at the top of a computer screen, each associated with a 3-step symbol code. One of the 9 digits was randomly displayed on the screen. The participant was to reproduce the correct 3-step symbol code using the numeric keypad. The percentage of items correctly matched by participants within 90 seconds was calculated.

Other Drug Use

We tracked the percentage of urinalysis results documented to be negative for cocaine, benzodiazepines, and marijuana.

Initiation of Naltrexone Treatment

We tracked the percentage of participants in each medication condition who successfully initiated naltrexone treatment postdetoxification.

STATISTICAL ANALYSES

Comparisons between groups on baseline characteristics were performed using t tests for continuous measures and χ² tests for categorical variables. The primary analyses included all participants randomized to treatment groups independent of early dropout/noncompliance, consistent with an intent-to-treat approach to clinical trials. The t tests were used to compare groups on the average percentage of scheduled urine samples documented to be opiate negative. A χ² test was used to compare groups on the percentage of participants retained through the entire detoxification, and time-to-event analysis, using a log-rank test, was used to compare groups on retention time.

Analyses on the HRBS and all secondary outcome measures were confined to data from the time of treatment intake to the end of the first week of the detoxification when retention was still high in both conditions. This procedure allowed for a more direct comparison of outcomes to be obtained before markedly different retention rates across groups were observed. Repeated-measures analyses of variance were used in analyzing predosing to postdosing data during the first week of treatment. Statistical analyses were performed using SAS software (SAS Institute, Cary, NC). Statistical significance was determined at P≤.05.
Table. Participant Characteristics by Medication Condition at Treatment Intake*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Buprenorphine Condition (n = 18)</th>
<th>Clonidine Condition (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>17.3 (0.7)</td>
<td>17.4 (0.7)</td>
</tr>
<tr>
<td>Age of first opiate use, mean (SD)</td>
<td>15.0 (1.6)</td>
<td>14.7 (1.7)</td>
</tr>
<tr>
<td>Male</td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>White</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>Injection route of opiate use</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>Heroin primary opiate used</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>No. of days used opiates in last 30 d, mean (SD)</td>
<td>27.7 (3.0)</td>
<td>27.7 (4.8)</td>
</tr>
<tr>
<td>No. of prior outpatient substance abuse treatments, mean (SD)</td>
<td>0.9 (1.05)</td>
<td>1.1 (1.13)</td>
</tr>
<tr>
<td>No. of prior inpatient substance abuse treatments, mean (SD)</td>
<td>0.8 (1.06)</td>
<td>0.4 (0.85)</td>
</tr>
<tr>
<td>Other drug dependence (currently dependent at intake)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>17</td>
<td>18</td>
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<tr>
<td>Cannabis</td>
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<tr>
<td>Nicotine</td>
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<td>29</td>
</tr>
<tr>
<td>Cocaine</td>
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<td>3</td>
</tr>
<tr>
<td>Amphetamine</td>
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<td>6</td>
</tr>
<tr>
<td>DSM-IV/psychiatric diagnoses (meeting criteria at intake)</td>
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</tr>
<tr>
<td>Attention-deficit/hyperactivity disorder</td>
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<tr>
<td>Oppositional defiant disorder</td>
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<tr>
<td>Major depressive disorder</td>
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<td>18</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

*Values are expressed as percentages unless otherwise indicated. No significant differences between groups were detected on any participant characteristic (P > .05 for all characteristics). Buprenorphine was given as buprenorphine hydrochloride; clonidine was given as clonidine hydrochloride.
†Of the participants randomly assigned to the buprenorphine condition, 7 participants began their buprenorphine hydrochloride taper at a starting dose of 8 mg and 11 participants began their taper at a starting dose of 6 mg.

RESULTS

PARTICIPANT CHARACTERISTICS

Participant characteristics are provided in the Table.

RETENTION

Seventy-two percent of those receiving buprenorphine were retained for the duration of the detoxification compared with 39% of those receiving clonidine ($\chi^2=4.05; P = .04$). The time-to-event distributions associated with retention, as shown in Figure 1, were also statistically significant across groups (log-rank test $\chi^2=4.02; P = .04$).

OPIATE ABSTINENCE

As shown in Figure 2, participants in the buprenorphine and clonidine groups provided a mean of 64% and 32% opiate-negative urine samples, respectively, during the entire detoxification ($t_{54}=2.62; P = .01$). When considering results from those retained in treatment only, independent of the larger attrition among those in the clonidine group, 78% and 81% of urine samples were opiate negative in the buprenorphine and clonidine groups, respectively.

HIV RISK BEHAVIOR SCALE

Drug-related HIV risk behavior significantly decreased from treatment intake to the end of the first week (time effect, $F_{1,26}=9.51; P = .005$), but there was no evidence of differential reduction across groups (interaction test, $F_{1,26}=0.03; P = .86$). Drug-related risk composite scores decreased from mean (SEM) 4.93 (1.22) to 1.10 (1.26) among those in the buprenorphine condition and from 3.99 (1.27) to 0.58 (1.56) among those in the clonidine condition during the first week.

PUPIL RADIUS

During the first week, pupil radius significantly decreased from predosing to postdosing among those in the buprenorphine condition but not those in the clonidine condition (interaction test, $F_{1,32}=41.97; P < .001$). Specifically, pupil radius decreased from mean (SEM) 4.64 (0.36) to 0.87 (0.36) from predosing to postdosing in the buprenorphine condition ($F_{1,32}=64.43; P < .001$), while mean (SEM) pupil radius was 6.19 (0.26) predosing and 6.28 (0.25) postdosing in the clonidine condition ($F_{1,32}=0.87; P = .36$).
The sum of withdrawal scores on the adjective rating scale significantly decreased from predosing to postdosing among participants in both conditions during the first week (predosing-postdosing time effect, F1,29 = 15.80; P < .001). Specifically, the sum of withdrawal scores decreased from mean (SEM) 50.88 (8.84) predosing to 36.05 (7.45) postdosing among those in the buprenorphine condition and from 60.06 (9.55) predosing to 41.18 (7.99) postdosing among those in the clonidine condition. This effect was not treatment-group dependent (interaction test, F1,29 = 0.22; P = .64).

The sum of agonist scores on the adjective rating scale changed in opposite directions for those in the 2 conditions from predosing to postdosing during the first week (interaction test, F1,29 = 15.47; P < .001). The sum of agonist scores significantly increased from mean (SEM) 26.49 (3.48) predosing to 36.05 (7.45) postdosing among those in the buprenorphine condition and from 20.94 (2.47) to 19.45 (4.02) among those in the clonidine condition. This effect was not treatment-group dependent (interaction test, F1,29 = 0.22; P = .64).

Participants in both groups reported decreases on the measure-group dependent (interaction test, F1,29 = 0.22; P = .64). The sum of agonist scores on the adjective rating scale changed in opposite directions for those in the 2 conditions from predosing to postdosing during the first week (interaction test, F1,29 = 15.47; P < .001). The sum of agonist scores significantly increased from mean (SEM) 26.49 (3.48) predosing to 36.05 (7.45) postdosing among those in the buprenorphine condition and from 20.94 (2.47) to 19.45 (4.02) among those in the clonidine condition. This effect was not treatment-group dependent (interaction test, F1,29 = 0.22; P = .64).

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Visual Analog Scale

Participants in the buprenorphine condition reported significant increases on measures of drug-related high, drug effect, good effect, and drug liking (all P values < .01), while participants in the clonidine condition reported no significant changes on these measures from predosing to postdosing during the first week (P values on all interaction tests < .05). Participants in the clonidine condition reported significant increases on the measure of bad effect (F1,31 = 8.08; P = .008), while participants in the buprenorphine condition reported no change on this measure (F1,31 = 0.44; P = .51) from predosing to postdosing during the first week (interaction test, F1,31 = 6.16; P = .02). Participants in both groups reported decreases on the measure of sick from predosing to postdosing during the first week (predosing-postdosing time effect, F1,31 = 18.93; P < .001), and this effect was not shown to be medication-group dependent (interaction test, F1,31 = 3.65; P = .07).

Digit Symbol Substitution Test

Percentage correct on the Digit Symbol Substitution Test task did not differ across groups (treatment group effect, F1,31 = 3.55; P = .07) and did not change from predosing to postdosing during the first week for participants in either group (predosing-postdosing time effect, F1,31 = 0.91; P = .35).

Other Drug Use

Eighty-seven percent and 85% of urine samples were cocaine negative, 90% and 93% were benzodiazepine-negative, and 36% and 29% were marijuana negative among those in the buprenorphine and clonidine conditions, respectively. None of these results were significantly different across groups.

Initiation of Naltrexone Treatment

As shown in Figure 3, at the conclusion of the detoxification, 61% of participants who had been in the buprenorphine condition and 5% of participants who had been in the clonidine condition participated in the naltrexone phase of the study after meeting the appropriate criteria (provision of 3 opioid-negative urine samples within a week).

Comment

This study, to our knowledge, was the first randomized controlled trial to evaluate combined behavioral and pharmacological treatments for adolescents dependent on opioids. Results clearly demonstrated that combining buprenorphine with behavioral interventions is significantly more efficacious in the treatment of opioid-dependent adolescents relative to combining clonidine and behavioral interventions. The marked differences observed across medication groups, despite a fairly small sample size and an intensive behavioral intervention common to both groups, underscore the robustness of these results. Adolescents who received buprenorphine were retained in treatment much longer and achieved markedly greater levels of abstinence from opioids relative to those who received clonidine. Although participants in both conditions reported reduced drug-related HIV risk behavior and relief of withdrawal symptoms, the profile of results from the various self-report measures indicated that those in the buprenorphine condition generally reported more positive symptoms during detoxification, likely owing to the reinforcing properties of the partial opioid agonist medication they received. This finding from self-report measures was supported by decreases in the physiologic measure of pupil radius from before to after buprenorphine dosing, indicating an opioid agonist effect of buprenorphine. Importantly, despite evidence of opioid agonist effects from buprenorphine administration, no evidence of opioid intoxication or psychomotor impairment was observed.

Importantly, almost two thirds of participants in the buprenorphine condition initiated treatment with naltrexone as part of the relapse-prevention phase of this study after meeting the necessary opioid abstinence criteria at the end of their detoxification, while only 3% of those in the clonidine condition initiated naltrexone treat-
ment. The opioid agonist-antagonist properties of buprenorphine and the better treatment outcomes participants who received buprenorphine experienced likely enabled this better transition to the opioid antagonist naltrexone, relative to clonidine. Prior research has shown that only 10% to 15% of opioid-dependent adults are willing to take naltrexone, although providing incentives to adult patients contingent on naltrexone consumption has been shown to improve compliance.60-62 The percentage of adolescents who were willing to consume naltrexone in this study is thus markedly higher than what is typically observed among their adult counterparts even in the absence of incentives contingent on naltrexone consumption. Given the efficacy of naltrexone in promoting continued abstinence postdetoxification from opioids, this finding further underscores the importance of and likelihood of success with early intervention among opioid-dependent adolescents.

Numerous medications have been successfully used in the treatment of adolescents with a broad array of psychiatric disorders.59,63-65 In contrast, medications have been infrequently used in treating substance abuse disorders among adolescents but have generally been shown to be a promising component of such interventions.64,66-71 Because of the nature and pharmacologic properties of opiate drugs, individuals who are physically dependent on opioids will experience a painful physical withdrawal syndrome if they abruptly discontinue their opiate use, presenting a major obstacle in the treatment of opioid dependence. The scientific literature examining effective treatments for opioid-dependent adults clearly indicates that pharmacotherapy is a necessary and acceptable component of effective opioid-detoxification regimens,72 although much of the current treatment offered in community-based settings to opioid-dependent adolescents is medication free. To our knowledge, the present study is the first to demonstrate via a randomized, controlled evaluation that combined pharmacotherapy and behavioral treatment can be safe and highly efficacious in the treatment of opioid-dependent adolescents.

All adolescents in this study were provided with intensive behavioral therapy and incentives contingent on opiate abstinence, attendance, and completion of assessments. Despite the differential retention rates observed across medication groups, the provision of these behavioral interventions likely helped to promote treatment retention among participants in both groups. To isolate the contribution of these behavioral interventions to treatment outcome and to identify how to further optimize outcomes from combined buprenorphine and behavioral treatment, we are now investigating the extent to which both the provision of incentives and varying durations of detoxification with buprenorphine impact treatment outcome. Additionally, this study largely focused on outcomes during treatment and not on outcomes posttreatment. This lack of follow-up data represents a limitation of the study and is an important component of our future research with this population. Finally, medication doses used in the study were in the low to moderate range relative to those used with adults. Future studies may systematically examine optimal doses and dosing regimens with this young population.

In sum, this research provides novel and clinically important empirical information regarding effective interven-

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