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Adding an Internet-delivered Treatment to an Efficacious Treatment Package for Opioid Dependence

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Abstract

Objective—To examine the benefit of adding an internet-delivered behavior therapy to a buprenorphine medication program and voucher-based motivational incentives.

Method—A block-randomized, unblinded, parallel, 12-week treatment trial was conducted with 170 opioid-dependent adult patients (mean age 34.3 years; 54.1% male; 95.3% white). Participants received an internet-based community reinforcement approach intervention plus contingency management (CRA+) and buprenorphine, or contingency management alone (CM-alone) plus buprenorphine. The primary outcomes, measured over the course of treatment, were longest continuous abstinence, total abstinence, and days retained in treatment.

Results—Compared to those receiving CM-alone, CRA+ recipients exhibited on average 9.7 total days more of abstinence, 95% CI: (2.3, 17.2), and had a reduced hazard of dropping out of treatment, Hazard Ratio (HR)=0.47; 95% CI: (0.26, 0.85). Prior treatment for opioid dependence significantly moderated the additional improvement of CRA+ for longest continuous days of abstinence.

Conclusions—These results provide further evidence that an internet-based CRA+ treatment is efficacious and adds clinical benefits to a contingency management/medication based program for opioid dependence.

Keywords

Internet-based; community reinforcement approach; contingency management; buprenorphine; opioid dependence

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The authors have worked extensively with their respective institutions to monitor the relationship between these organizations, oversee all aspects of collaborative projects between the organizations, and ensure that no conflict exists between the authors' roles in each organization.

INTRODUCTION

Recently, mental health and substance abuse treatments have been increasingly implemented using computer-based and internet-delivered approaches (Bickel, Marsch, Buchhalter, & Badger, 2008; Brooks, Ryder, Carise, & Kirby, 2010). These technologically-focused methods (Bickel, Christensen, & Marsch, 2011) have advantages over traditional therapist-delivered approaches as they are more cost-effective (McCrone et al., 2004) and require significantly less therapist time (Bickel, et al., 2008; Wright et al., 2005). These delivery systems are particularly suited to behavioral treatments where participants learn skills that can be trained to a level of mastery using programmable methods (Bickel, et al., 2008). Behavioral treatments that show efficacy in the treatment of substance abuse are the Community Reinforcement Approach (CRA: Hunt & Azrin, 1973) and CRA plus Contingency Management (CM: Higgins et al., 1993). The CRA plus CM treatment package has been extensively researched and shown to be a demonstrably efficacious treatment for cocaine dependence (Higgins, Bickel, & Hughes, 1994; Higgins et al., 2003; Van Horn & Frank, 1998). This treatment package was derived from research examining drug self-administration and behavioral analyses of drug dependence. Evidence from these literatures suggest that drugs of abuse are partly so potent due to their over-powering and more immediately reinforcing effects than more pro-social behaviors (Higgins, et al., 1994). The CRA plus CM program uses two important components (1) increasing non-drug reinforcement by teaching skills and encouraging behaviors that help improve employment status, family/social relations and increased recreational activities via the CRA treatment (Hunt & Azrin, 1973), and (2) providing immediate positive reinforcement for non-drug use via motivational incentives for abstinence (CM) (Anker & Crowley, 1982; Stitzer & Higgins, 1995). The increased non-drug sources of reinforcement and the immediately available incentives for abstinence are then expected to successfully compete with the powerful and immediately reinforcing effects of drug use as the preferred behavior.

In a recent variation of this approach, Brooks et al. (2010) examined whether an internet-based CRA program had an impact on cocaine-user's knowledge of the skills taught in the CRA program (as measured by participant's cognitive and behavioural responses, communication skills, and coping skills to quizzes and tests, and measures of drug use). Participants were randomized to either an 8-week CRA program (48 modules) with CM payments for completing CRA modules (rather than abstinence) or a yoked condition where participants did not participate in the CRA program but received payments tied to the performance of a CRA condition participant. Brooks et al. (2010) found participants in the CRA condition demonstrated statistically significant improvements in CRA knowledge and were significantly more likely to select CRA-style coping responses, relative to the yoked group.

Moreover, evidence has very recently emerged that suggests that web-based CRA may independently improve clinical outcomes. Marsch et al. (2013) randomly assigned 160 opioid dependent patients to either standard treatment (including therapist time and methadone maintenance) or a reduced standard treatment and an internet-based CRA component. Marsch et al. (2013) found that participants assigned to the CRA condition reported statistically significantly higher rates of overall study and tested weeks of opioid

abstinence over 12 months than the standard treatment group. CRA participants also had a statistically significant greater percentage of tested weeks of continuous abstinence (but not overall study weeks of continuous abstinence) from opioids compared to the standard treatment group. However, although Marsch et al. (2013) reported no differences in drop-out between groups, they did report high attrition rates across both groups. The high drop-out rate in both groups might suggest that only the most motivated participants continued with the program, where those who left the program in either group may have continued to be opioid dependent, possibly compromising the between group differences. Nonetheless, Marsch et al. (2013) suggested these results were the first evidence of the effectiveness of computerized CRA in the absence of CM incentives.

Although participants in studies examining CRA interventions are typically evenly assigned to treatment and non-treatment groups (Brooks et al., 2010; Bickel et al., 2008), no study has examined the effect of previous CRA treatments on clinical outcomes. This appears to be an anomaly as CRA gains some of its therapeutic power from building on the skills, knowledge, and outcomes from previous therapeutic experiences (Budney & Higgins, 1998). Further, as substance dependence is typically characterized as a chronic relapsing condition (McLellan, McLellan, Lewis, O'Brien, & Kleber, 2000), treatment approaches need to be considered across 'treatment careers' and that treatment practices need to be coordinated across treatment episodes (McLellan, 2002). Therefore, this study will also examine the effects of previous treatment on clinical outcomes.

Further, no study to our knowledge has yet to trial the combination of CRA and CM for drug *abstinence* using web-based approaches. Typically, when CM is added to a treatment suite contingent on substance use abstinence participants report improved clinical outcomes including higher rates of abstinence and program retention (Higgins, et al., 2003). Then again, as the Marsch et al. (2013) study has demonstrated, web-based CRA-alone may independently improve clinical outcomes above standard substance dependence treatment. Therefore, this study examines whether web-based CRA approaches improve treatment outcomes over and above the combined influence of CM for abstinence and a standard pharmacological treatment for opioid dependence (in this case, buprenorphine maintenance).

In the present study, we randomly assigned opioid-dependent outpatients to either CM-alone: a treatment suite of contingency management (vouchers for submitting negative urine specimens), buprenorphine, and minimal therapist counseling; or CRA+: the same suite of treatments and an internet-based CRA intervention. Our hypothesis was that the addition of an internet-based CRA treatment component would increase participant abstinence rates from opioid and cocaine use but not participant retention. Further, we hypothesize that previous treatment histories will impact on primary outcomes.

METHOD

Participants

We recruited participants using radio and newspaper advertisements, flyers, and received referrals from existing participants and local clinics. The study was conducted at the Center for Addiction Research, University of Arkansas for Medical Sciences (UAMS), Little Rock,

Arkansas. After complete description of the study to the subjects, written informed consent was obtained. The study was conducted in compliance with UAMS Institutional Review Board approval evaluated for study eligibility. Those who were eligible met the DSM-IV criteria for opioid dependence and met the FDA qualification criteria for buprenorphine treatment. Additionally, participants could not be pregnant or incarcerated nor have shown evidence of an active (non-substance dependence) psychiatric disorder or significant medical illness. After consent we excluded six participants with very high drug concentrations for their own safety and referred them to specialist detoxification clinics. We also excluded three consented participants whom the study physician deemed were inappropriate for study participation (i.e., they reported high heart rate, syncope and seizures, severe buprenorphine side effects; nausea, vomiting and sweating). Six other consented participants were excluded for other reasons (see Figure 1).

Of the 206 consented, 170 participants aged 20 to 63 were randomly assigned to one of two conditions for 12 weeks of treatment. All consented participants experienced our intake procedures (i.e., the Addiction Severity Index, buprenorphine induction, and an interview with a therapist) before randomization. A sample size of $N=170$ was estimated to provide 0.80 power to detect a 3.0 week difference between treatment conditions in mean weeks of continuous abstinence using a .05 significance level on a two-sided t -test, while assuming a within-group standard deviation of 7.0 weeks based on reports from previous trials using CRA+.

Procedure

All participants received regular buprenorphine dosing and therapist counseling. Allocation to treatment groups was based on the “minimum likelihood allocation” method (Aickin, 1982), which balances treatment groups on patient characteristics likely to influence treatment outcomes. We stratified the randomization on four characteristics: (1) buprenorphine stabilization dose (6 to 18 mg of the buprenorphine sublingual tablet, where 12 mg was categorized as low and >12mg as high; see Buprenorphine section below), (2) distance from the clinic in minutes (i.e., near < 30 min, medium =30 to 60 min, and far > 60 min), (3) receipt of previous treatment for opioid dependence (yes, no), and (4) cocaine use in the past month (yes, no). For statistics with multiple levels, group membership was randomized for each level; half of the participants in each level (e.g., ‘near’) were assigned to the CRA+ group while the other half were assigned to the CM-alone condition. Because the dose of buprenorphine is adjusted during the first week, this allocation occurred at the end of the induction period. Allocation to treatment groups was randomly assigned (un-blinded) by 1:1 allotment to either the CRA+ or CM-alone treatment conditions. No additional compensation was available other than vouchers earned from the CM treatment. The study consisted of 12 weeks of treatment, during which participants visited the clinic on Monday, Wednesday and Friday of each week. At each visit participants had to provide a urine specimen that was tested using the Siemens V-Twin® drug testing diagnostic system with Syva® EMIT reagents for methadone, opioids, propoxyphene, cocaine, and once a week for benzodiazepines. Oxycontin was tested using a single-panel Andwin Scientific clia-waved Oxycontin dipstick. If a participant’s urine specimen showed a benzodiazepine

level >1000 parts per million, their buprenorphine dose was temporarily halved under supervision of the study physician to reduce the risk of respiratory depression.

Buprenorphine—A sublingual buprenorphine mono tablet was used for induction (Subutex®: Reckitt Benckiser) and the buprenorphine/naloxone combination tablet (Suboxone®: Reckitt Benckiser) was used for the treatment and dose taper phases (Bickel & Amass, 1995). Participants were stabilized on a daily buprenorphine dose of between 8 – 16 milligrams (based on dependence). During treatment, participants received double the daily dose on Monday and Wednesday, and triple the daily dose on Friday. This approach for managing buprenorphine dosing has been safely used in similar interventions (Marsch, Bickel, Badger, & Jacobs, 2005) and found to be effective due to its long half-life (Bickel, Amass, Crean, & Badger, 1999). At the end of treatment participants were either referred to another treatment provider or detoxified under supervision by the study physician (MJM).

Contingency Management—This procedure was designed to reinforce abstinence as indicated by urinalysis results. Participants submitted a urine specimen at each clinic visit where staff informed participants of the urinalysis results immediately after testing. Specimens that were negative for opioids (i.e., opiates, propoxyphene, oxycontin and methadone) and cocaine earned points that were recorded on vouchers that could be subsequently redeemed for either gift cards at a variety of local businesses or for checks when participants had un-spent study credit over \$100. The first negative specimen earned 10 points worth \$0.25 each. The value of subsequent consecutive negative specimens increased by 5 points and an additional \$10.00 was available for each set of three consecutive negative samples. To receive a voucher the most recent urine specimen had to be opioid and cocaine negative. Submission of an opioid and/or cocaine positive urine specimen or failure to submit a scheduled specimen resulted in no points earned and the resetting of a negative specimen to 10 points. Submission of three consecutive opioid- and cocaine-negative specimens resulted in the return of vouchers to the level before the reset. Participants who presented urine specimens positive to benzodiazepines only would earn points but would not be allowed to redeem vouchers on that day. The maximum possible amount that could be earned over the 12-week program was \$997.50.

Community Reinforcement Approach—Participants in this treatment completed a set of 69 computerized topics (e.g., Self-Management Planning, Drug-Refusal Training, etc.) grounded in CRA (Budney & Higgins, 1998). Participants completed web-based topics each clinic visit (three times a week) for approximately 30 minutes per visit. These modules were presented on the clinic computers where the therapeutic content was held on secure password protected servers located on the internet. The supervising therapists determined the sequence of these modules based on a functional analysis of the participant's drug dependence. Participants could re-visit any completed module but were required to complete the sequence of modules in the order prescribed by the therapist. In addition, several video simulations of different scenarios were presented where participants could explore different responses and receive feedback from various role-playing situations. Given that we wished to examine the efficacy of this program alone and not have these results confounded with issues of compliance, treatments were only accessible from the clinic site. Participants were

provided with free access to the treatment content. The program required participants to develop a predetermined level of accuracy and speed on each topic to ensure content mastery. Presentation and response times were progressively shortened if the participant answered successfully, or increased if answered incorrectly. Three consecutively correct answers were required to progress to the next question. The questioning was interspersed within each module and then reinforced at the completion of a module with personalized worksheets (for a more detailed explanation see Bickel, et al., 2008).

Therapist Counseling—Participants from both treatment conditions were also required to meet with a therapist every two weeks for 30 minutes to review their progress and treatment plan. The therapists were informed of the urinalysis results and discussed with the participants their results and any issue the participants requested. There was no manual for this component. The two therapists were a masters-level counselor and a certified substance abuse counselor.

Measures

Retention was the number of days from the start of the 12-week intervention until the participant either left the trial, or completed the trial (a maximum of 81 days). Participants were allowed to leave the trial at will; or if a patient failed to attend 3 clinic visits in a row, he or she was removed from the trial. Abstinence from drug taking was measured as the number of documented urine specimens negative for opiates and cocaine. The two primary measures were longest continuous abstinence (LCA) and total abstinence (TA) measured by the number of negative specimens during the 12-week intervention: both LCA and TA had a maximum of 36 visits. Missed visits were interpreted as positive results. The number of abstinent visits was multiplied by 2.25 days (81 days / 36 visits) to represent the amount of time the subjects were abstinent.

The Addiction Severity Index (ASI; McLellan et al., 1992) was used as a measure of addiction-related severity across several life domains (medical, employment, alcohol/drug, legal, family/social, and psychological). Composite scores were calculated from the individual responses in each domain separated in the following areas: medical status, employment status, alcohol use, drug use, legal status, family/social status, psychiatric status, cocaine use, and opioid use. The ASI was administered at intake, week 6 (mid-trial), and week 12 (trial-end). Psychometric assessments have shown the ASI as an internally consistent and valid instrument for measuring addiction severity (Butler et al., 2001; Leonhard, Mulvey, Gastfriend, & Shwartz, 2000).

Statistical Methods

For baseline measures, the two groups were compared using χ^2 tests for categorical measures, two-sided *t*-tests for continuous measures having (approximate) normal distributions, and Wilcoxon-Mann-Whitney tests for ordinal or non-normal measures. If any baseline measure was found to differ between the two groups, the impact of that measure on group comparisons was assessed by entering it into the analysis as a covariate. The significance cut-off was set at *p* .05. All analyses were conducted in SAS® v9.2, with

mixed models being fitted in the MIXED procedure. There were no missing abstinence data from attended clinic visits.

Retention and Drug Abstinence—Days in treatment, the primary measure of retention, was analyzed with Cox proportional hazards regression. We also compared the proportions of those completing treatment within a logistic regression framework. The regression models allowed us to include potential confounders.

We compared the two treatments' means of longest continuous abstinence (LCA) and total abstinence (TA) with Welch's *t*-tests (which allow for variances to differ between the two groups). We evaluated potential confounders in an analysis of variance and accounted for an established confounder with stratified analyses. We report η^2 effect sizes, and bootstrapped confidence intervals for these.

Addiction Severity Index (ASI)—Changes in ASI composite scores from baseline values were analyzed using repeated-measures ANOVA where group, period (mid-trial, trial-end) and their interaction, were included in the model. These analyses were run individually for each of the nine composite scores. Evidence of prior treatment for opioid use was categorized as either yes or no.

RESULTS

The Journal Article Reporting Standards (JARS) Flowchart, indicating the flow of participants through experimental stages, is provided in Figure 1.

Table 1 contains comparisons between the two groups on demographics and key baseline measures. The CRA+ group had a lower median monthly income than those in the CM-alone group: \$1,000 vs. \$1,808 (Wilcoxon-Mann-Whitney $z=2.09$, $p=.037$). We thus included income in analyses of treatment outcomes, but in all instances, income had no statistical effect; hence, we omit these results.

Retention

Figure 2 illustrates the percentage of participants retained in treatment across the days in the trial for the two groups. Figure 2 shows that participants in the CRA+ group are retained in treatment at a greater rate than the CM-alone condition (80% CRA+ vs. 64% CM-alone).

This difference was borne out in the statistical comparisons of retention. The hazard of dropping out of treatment for CM-alone participants was 2.12 times that for the CRA+ participants ($\chi^2[1]=6.14$; $p=.013$; see Table 2). The odds ratio for completing the 12-week treatment was 2.30 favoring CRA+ ($\chi^2[1]=5.57$, $p=.018$; see Table 2). We also compared missing urine specimen rates between the two treatments. Because some participants did not complete the trial, we weighted each participant's rate with the proportional amount of time he or she was in the trial, thus accounting for differences in retention between the groups. The two groups did not statistically differ on missed urine specimens: 3.4% for CM-alone vs. 2.8% for CRA+, $t[167]=0.54$, $p=.590$.

We evaluated whether prior treatment status affected retention by adding it, as well as its interaction with treatment, into the regression models. The Cox proportional hazards regression of retention found prior treatment interacted with group ($\chi^2_{[1]} = 5.46, p=.020$); thus when we stratified prior treatment the hazard of dropping out for CM-alone participants was 6.57 times ($\chi^2_{[1]} = 9.01, p=.003$) that for CRA+ participants. For treatment-naïve participants, the hazard for CM-alone participants was 1.15 times ($\chi^2_{[1]} = 0.13, p=.718$) that for CRA+ participants. The logistic regression of treatment completion found a significant interaction of group and prior treatment ($\chi^2_{[1]} = 5.63, p=.018$). The odds of not completing treatment for CM-alone participants who had received prior treatment was 8.03 times ($\chi^2_{[1]} = 9.37, p=.002$) that for their counterparts receiving CRA+; whereas the odds for treatment-naïve CM-alone participants was attenuated to 1.13 times ($\chi^2_{[1]} = 0.07, p=.798$) that for their CRA+ counterparts. See Table 2 for confidence intervals.

Abstinence

On average, the longest continuous abstinence (LCA) for CRA+ participants was 55.0 days compared to CM-alone participants mean of 49.5 days ($t[152.4] = 1.25, p=.214$). The mean total abstinence (TA) was 67.1 days for the CRA+ group and 57.3 days for the CM-alone group ($t[133.4] = 2.59, p=.011$). Entering prior treatment status and its interaction with group into an ANOVA revealed significant interactions for each outcome (LCA: $F[1, 166]=4.03, p=.046$; TA: $F[1, 166]=3.97, p=.048$); we thus stratified our treatment comparison on prior treatment status. For CRA+ participants having previously undergone treatment for opioids, their mean LCA and TA were 61.1 and 72.6 days, respectively, compared to their CM-alone counterparts' means of 46.0 and 54.8 days, respectively (LCA: $t[74.6]=2.52, p=.014$; TA: $t[53.8]=3.70, p=.001$). For treatment-naïve participants, the two treatment groups did not differ statistically on abstinence: the CRA+ participants had LCA and TA means of 51.0 and 63.4, respectively, and the CM-alone participants had LCA and TA means of 53.5 and 60.1, respectively (LCA: $t[69.6]=0.39, p=.700$; TA: $t[66.4]=0.59, p=.558$). See Table 2 for confidence intervals and effect sizes.

ASI Composite Scores¹

At both mid- and end-trial, participants tended to show improvement from baseline levels of the ASI subscales for opioids, drugs, alcohol, psychological issues, employment, and family issues (mid-trial: all six $p<.03$; trial-end: all six $p<.01$). None of these changes over time statistically differed between the two groups (all six time interactions, $p>.24$). For the cocaine subscale, participants showed decreases from baseline levels at mid-trial ($t[165]=2.03, p=.04$), but did not maintain a statistical difference at trial-end ($t[189]=0.33, p=.74$). The subscales for legal issues and medications did not show a change from baseline values at either time point (mid-trial: both $p>.05$; end-trial both $p>.16$). However, the CRA+ group had more improvement in their medication ASI scores than the CM-alone group ($t[127]=2.11, p=.04$).

¹These analyses and also the treatment counseling hours and vouchers earned do not include 18 participants for whom the data were lost.

Treatment Counseling Hours and Vouchers Earned

Participants received on average 29 and 30 counseling minutes per session in the CRA+ and CM-alone groups, respectively. Over the course of the study, CRA+ participants earned a median (25th percentile, 75th percentile) total voucher value of \$730.63 (\$345.00, \$997.50) while the CM-alone participants earned a median \$736.88 (\$128.75, \$997.50).

DISCUSSION

This study examined the benefit of adding an internet-delivered therapy to motivational incentives and buprenorphine as treatments for opioid dependence. CRA+ was found to have lower drop-out rates and higher rates of treatment completion than CM-alone suggesting that CRA provides value to opioid-dependent participants additional to motivational incentives and buprenorphine medication. Although improved retention is consistent with previous contingency management effects (Preston et al., 1999), we believe this is the first demonstration of improved retention in an internet delivered program of CRA+ for abstinence.

Although CRA+ had equivalent longest continuous abstinence weeks as CM-alone, CRA+ participants reported greater numbers of total days abstinent than CM-alone. Further, for participants who experienced prior treatment, those in the CRA+ condition had longer continuous abstinence and longer total abstinence weeks than the CM-alone group. These results support the hypothesis that computer-delivered CRA+ implemented over the internet during treatment improves clinical outcomes in the treatment of opioid dependence.

Computer-delivered approaches have now been found to be effective in treating a variety of substance use disorders (Bickel, et al., 2008; Carroll et al., 2009). Moreover, some researchers have suggested new technologies are perfectly positioned to improve substance-abuse treatment accessibility. Specifically, a growing literature suggests technology-based interventions are more reliable, provide greater program fidelity, are easier to develop, reach larger populations, are more cost-effective, and provide similar levels of client satisfaction than traditional face-to-face therapies (Craske et al., 2009; Griest, 2008; Munoz et al., 2009; Rotondi et al., 2010; Marsch et al., 2013). These results are important developments as previous studies have reported that training clinicians to deliver evidence-based counseling treatments is extremely time consuming and that trainee clinicians often have difficulty making accurate assessments about their interventions (Martino et al., 2011; Moyers et al., 2008; J. L. Smith et al., 2012). The practical implications of using an internet-based counseling program are likely to be less clinician training time and greater standardization of treatment resulting in significant financial savings and treatment improvements to time-poor and resource challenged counseling services. However, as opioid-dependent individuals typically report low incomes (Marsch, et al., 2005), and low income households are less likely to have access to the internet (US Census Bureau, 2005), technology-delivered treatment programs will need to be creative in their delivery to their target population. One possibility could be to provide programs designed for mobile phones: research indicates low-income households have greater access to mobile phones than personal computers (Smith, 2010). These and similar innovations in the mobile delivery of evidence-based tools

that target behavioral and mental health are likely to provide low-cost treatment solutions to both clinicians and clients (Hertel et al., 2014).

We note that among those having undergone opioid treatment in the past, CRA+ increased LCA over CM-alone, whereas for those naïve to opioid treatment, the effects of CRA+ were attenuated. As previously stated, a possible explanation for these results is that for those who had a prior treatment experience CRA+ was able to build on gains participants made in previous treatment episodes. This could be due to the interconnected and self-reinforcing nature of CRA+ as the individual CRA modules are designed to support the program as a whole and support individual skill acquisition in other modules (Meyers, 1999; Schottenfeld, Pantalon, Chawarski, & Pakes, 2000). Further, the skills taught in CRA+ appear to also be congruent with other interventions, even those experienced in the past, allowing it to build on those previous experiences. A practical outcome from the existence of such phenomena would be to evaluate the previous treatment histories of prospective clients and determine whether a proposed treatment fits with the client's previous treatment experience. Perhaps prior treatment somehow sensitizes the participant such that he/she is able to therapeutically respond to web or mobile delivered treatments.

The study has some limitations. The most important was the lack of a "usual care/standard treatment" or "best practice" arm, although we note both groups achieved high levels of abstinence. Another was the sample size which was designed to detect a difference in LCA of 3 weeks (9 visits) between the two groups, and might have been under-powered to pick up smaller differences. Our differences in LCA were in the right direction, but were approximately 1/3 of the difference we expected. In addition, another limitation is the lack of participant data post-treatment. Further, as this study was a controlled clinical trial with imposed constraints, further work using a more ecological implementation is required to affirm our results and the efficacy of this approach.

In summary, our study demonstrated increased overall abstinence and retention efficacy in an internet-delivered computerized CRA+ group over motivational incentives and buprenorphine, and increased continuous abstinence for those CRA+ individuals who engaged in prior treatment. It indicates that CRA appears to build on previous treatment episodes despite research that suggests people who previously entered substance abuse treatment have greater drug problems, higher psychiatric co-morbidities, and suffer more life challenges than those without previous treatment experience (Claus, Mannen, & Schicht, 1999). An illustrative report on a study participant's substance abuse and previous treatment histories is attached (see case vignette). Of course, future research will need to examine whether the effect of previous treatment seen here can be replicated and whether an internet-based program would be effective outside the clinic, i.e., is attendance at a clinic a necessary component for encouraging clients to complete CRA modules. Perhaps when the results of NIDA's Clinical Trial Network study examining a similar computerized study are reported these questions may be answered (Campbell et al., 2012). If that or other studies are positive there would be a body of scientific support for the notion that efficacious CRA can be provided via modalities other than face-to-face visits, and in principle permits the consideration of other technologically-based ways to deliver and manage treatments.

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APPENDIX

Case Vignette

Upon arriving at the research clinic, SM provided informed consent, had a thorough physical examination (including a urine drug test positive for opiates and Oxycontin) and completed a structured substance abuse interview. SM was a 22-year old single female with a 6-year history of opioid addiction. As a teenager, SM was treated for cocaine, Adderall, and alcohol use at an inpatient unit following an overdose. At study onset, she reported daily oral use of hydrocodone, Percocet, and/or Oxycontin. SM also reported being prescribed Xanax as needed for anxiety. SM expressed a desire to become abstinent so that she could “establish better relationships in order to stay clean” and indicated that she wanted to further her education. After the study physician determined she was eligible to enroll in the combined buprenorphine and computerized behavioral therapy clinical trial, SM was assigned to the computerized behavior therapy plus contingency management (i.e., vouchers) group.

On the first day of buprenorphine induction, SM’s urine screen was negative for opiates and remained negative throughout her participation, including at the 3- and 6-month follow-ups. This resulted in SM experiencing an 11-month abstinence period. During the trial, SM attended hour-long sessions at the clinic 3 times per week for 12 weeks. During these sessions, she provided urine and breath samples, completed computerized therapy modules, and received a 12 mg dose of buprenorphine. Upon logging into the computerized therapy program, SM received visual feedback regarding the results of her urine screens, as well as her cumulative voucher earnings. Each session, the computerized therapy modules presented a novel interactive environment wherein (1) the module’s content was presented, (2) a comprehension of the material was assessed through a brief quiz, and (3) relayed feedback regarding comprehension of the material. Every other week, she met with a study therapist for about 30 minutes to check in about her treatment goals and progress on the computer modules. SM earned a total voucher amount of \$997.50, as a result of attending every treatment session and providing only negative urine specimens. Upon trial completion, SM was given the option of (a) gradually reducing her dose of buprenorphine or (b) referral to another opioid replacement provider. She chose to participate in the 5-week gradual

reduction of her buprenorphine dose. By the 3-month follow-up visit, SM reported, via the Addiction Severity Index, being in school and not having any serious family or social problems.

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Figure 1.
JARS Flow of Participants

Figure 2.
Participant retention in the two study groups.

Table 1

Demographic and Participant Baseline Characteristics of the Two Study Groups.

Characteristic (statistic)	CRA+ (n=92)	CM-alone (n=78)	p-value
Demographics			
White (%)	95	96	.63
Male (%)	48	62	.07
Never married ^d (%)	44	45	.90
Employed full time (%)	38	35	.64
Education in years [Md (Q1, Q3)]	12 (12-14)	12 (12-14)	.84
Age in years (M ± SD)	34.0 ± 10.2	34.8 ± 9.6	.58
Monthly income USD ^b [Md (Q1, Q3)]	1000 (0-2167)	1808 (550-2500)	.04
Opioid use			
Prior treatment (%)	40	53	.11
Regular use in years ^c [Md (Q1, Q3)]	5 (3-10)	6.5 (3.5-12.5)	.19
Previous month's spending on opioids USD ^c [Md (Q1, Q3)]	400 (180-750)	290 (11-900)	.15
Preferred route of administration ^c			
Injection (%)	13	15	.95
Intranasal (%)	8	9	
Oral (%)	79	76	
Other drug dependence			
Alcohol ^c (%)	13	13	.98
Cocaine ^c (%)	4	7	.30
Sedative ^c (%)	15	9	.22
Cannabis ^c (%)	27	32	.50
Regular use of cocaine in years ^c [Md (Q1, Q3)]	0 (0-1.5)	0 (0-2)	.32
ASI composite scales			
Medical [Md (Q1, Q3)]	0 (0, 0.67)	0 (0, 0.63)	.48
Employment [Md (Q1, Q3)]	0.50 (0.14, 0.50)	0.50 (0.12, 0.50)	.78

Characteristic (statistic)	CRA+ (n=92)	CM-alone (n=78)	p-value
Alcohol [Md (Q1, Q3)]	0.01 (0, 0.06)	0.01 (0, 0.09)	.30
Drug [Md (Q1, Q3)]	0.12 (0.08, 0.22)	0.11 (0.08, 0.23)	.72
Psychiatric [Md (Q1, Q3)]	0.10 (0, 0.42)	0.16 (0, 0.36)	.93
Legal [Md (Q1, Q3)]	0 (0, 0.03)	0 (0, 0.10)	.52
Family-Social [Md (Q1, Q3)]	0.10 (0, 0.46)	0.15 (0, 0.2)	.33
Cocaine ^d [Md (Q1, Q3)]	0 (0, 0)	0 (0, 0)	.19
Opioids [Md (Q1, Q3)]	0.64 (0.57, 0.69)	0.64 (0.54, 0.70)	.68

^a, ^b, ^c Number of participants failing to provide data: ^a 1 CRA+ participants; ^b 11 CRA+ participants and 18 CM-alone participants; ^c 8 CRA+ participants and 10 CM-alone participants.

^d 15 (19%) of the CM-alone participants had an cocaine ASI score above 0, compared to 11 (12%) of the CRA+ participants with scores above 0.

Table 2

Effects of treatment on clinical outcomes.

	Overall Effect of Treatment.			Effects of Treatment stratified by Prior Treatment Status					
				Treatment-naïve		Comparison	Prior Treatment		
	CRA+ (n=92)	CM-alone (n=78)	Comparison Estimate and 95% CI	CRA+ (n=55)	CM-alone (n=37)	Comparison	CRA+ (n=37)	CM-alone (n=41)	Comparison
Hazard of Drop-out ^a	--	--	HR = 2.12 (1.17, 3.83)	--	--	HR = 1.15 (0.53, 2.51)	--	--	HR = 6.57 (1.92, 22.45)
Treatment completion	80.4%	64.1%	OR = 2.30 (1.15, 4.60)	72.7%	70.3%	OR = 1.13 (0.45, 2.84)	91.9%	58.5%	OR = 8.03 (2.12, 30.47)
Longest Continuous Abstinence	55.0 SD=26.2	49.5 SD=30.6	5.5 (-3.2, 14.2) [η^2 =.010, (.000, .069)]	51.0 SD=27.5	53.5 SD=31.8	-2.5 (-15.3, 10.3) [η^2 =.002, (.000, .088)]	61.1 SD=23.1	46.0 SD=29.5	15.1 (3.2, 27.0) [η^2 =.079, (.002, .0245)]
Total Abstinence	67.1 SD=19.3	57.4 SD=28.0	9.7 (2.3, 17.2) [η^2 =.048, (.004, .147)]	63.4 SD=22.5	60.1 SD=27.7	3.2 (-7.7, 14.2) [η^2 =.005, (.000, .107)]	72.6 SD=11.4	54.8 SD=28.3	17.8 (8.2, 27.4) [η^2 =.203, (.052, .394)]

^a Since hazard of drop-out changes over time, a point estimate is not available for single groups. However, the hazard ratio (HR) of two groups remains constant over time; we report HR. We use effect size $\eta^2 = \frac{2}{t^2 + df}$, where t is the observed t -statistic (see text), and df is the degrees of freedom for the test. The confidence intervals for η^2 were computed with a nonparametric bootstrap.