Should Cocaine-Abusing, Buprenorphine-Maintained Patients Receive Auricular Acupuncture? Findings from an Acute Effects Study

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ABSTRACT

Objective: Buprenorphine is a synthetic opioid with \( \mu \)-agonist properties currently pending Food and Drug Administration (FDA) approval as a maintenance agent for treating heroin-addicted individuals. Unlike methadone, a widely used opioid maintenance agent, buprenorphine is a \( \kappa \)-receptor antagonist. Research linking the effects of acupuncture to the release of dynorphin, the endogenous ligand for the \( \kappa \)-receptor, raised the possibility that buprenorphine may block acupuncture's effects. In this study, we sought to gather preliminary data on this issue in order to guide the clinical care of cocaine-abusing, buprenorphine-maintained patients.

Design: Between-group analysis comparing buprenorphine- and methadone-maintained patients on ratings of acute effects after a single session of auricular acupuncture.

Subjects: Thirty-four (34) cocaine-abusing, opioid-dependent patients, eighteen (18) maintained on buprenorphine, and sixteen (16) maintained on methadone.

Intervention: A single, 40-minute session of auricular acupuncture; four needles were inserted in each auricle.

Outcome measures: Acute effect ratings in four domains: pain, \( de \ qi \) sensations, relaxation effects, subjective experiences.

Results: There were no significant differences in acute-effects ratings between the two groups. Patients in both groups reported positive effects.

Conclusions: These preliminary findings are consistent with the interpretation that buprenorphine does not block auricular acupuncture, supporting the provisional recommendation that cocaine-abusing patients maintained on buprenorphine should not be excluded from receiving auricular acupuncture or from participating in clinical studies of this treatment modality. Further, controlled research on this issue, with clinical outcomes, is needed.

INTRODUCTION

Methadone maintenance has been shown in numerous studies to be a generally effective treatment for illicit opioid abuse, with multiple benefits on health and psychosocial functioning (cf. Ball and Ross, 1991). These benefits, however, may be undermined by continued cocaine use among methadone-maintained patients (Condelli et al., 1992; Kolar et al., 1990).
Conventional treatment options for cocaine addiction are limited; to date, no pharmacologic agent has been found to be effective for the treatment of this disorder. Due, in part, to the lack of effective pharmacologic treatments, auricular acupuncture is currently used in numerous methadone programs to treat cocaine-abusing patients (Smith et al., 1997).

Although the ultimate efficacy of auricular acupuncture for the treatment of cocaine addiction is still undecided, several preliminary studies have suggested that methadone-maintained patients may derive benefit from this treatment (Avants et al., 1995; Margolin et al., 1993a; Wells et al., 1995). However, the advent of newer opioid agonist maintenance agents raises the issue of the interaction of acupuncture and agents whose pharmacologic profiles differ from methadone. One agent that has been the subject of intense research as an alternative to methadone is buprenorphine, a synthetic opioid that may possess some advantages relative to methadone as a maintenance agent, including a longer acting duration of action, obviating the need for daily dosing, and a less severe withdrawal profile (Lewis, 1985; Margolin and Kosten, 1991). Animal and clinical laboratory studies have suggested that buprenorphine may also decrease cocaine use (Mello and Mendelson, 1995); however, this has not been borne out in subsequent randomized clinical trials (Compton et al., 1995; Schottenfeld et al., 1997). A New Drug Application in support of buprenorphine’s use as an opioid maintenance agent has been submitted to the Food and Drug Administration (FDA). Approval of this application will raise the issue of whether cocaine-abusing, buprenorphine-maintained patients should be treated with auricular acupuncture. Currently, the literature offers little guidance on this potentially important question.

Hypotheses concerning potential differences in clinical response to auricular acupuncture between patients maintained on methadone or buprenorphine may be formulated based on dissimilarities in the pharmacologic profiles of these two agents. Unlike methadone, a “pure” μ-receptor agonist with little or no activity at the κ-receptor, research suggests that buprenorphine is a partial μ-agonist—as evidenced by a U-shaped dose–response curve—and a κ-antagonist (Dykstra and Negus, 1995; Leander, 1987). This may be relevant to auricular acupuncture because acupuncture effects have been hypothesized to be mediated by release of endogenous opioids, including both β-endorphin, the endogenous ligand for the μ-receptor, and dynorphin, the endogenous ligand for the κ receptor (Liao, 1994; Pomeranz, 1987). This raises the possibility that if auricular acupuncture is primarily or partially dynorphin-mediated, buprenorphine-maintained patients receiving acupuncture treatments may experience less intense acute effects relative to methadone-maintained patients, because of buprenorphine’s κ-receptor blockade. This is of particular interest in view of recent findings that the dynorphin system is dysregulated in long-term cocaine abusers, leading to suggestions that dynorphin agonists may be fruitful to explore as treatments for cocaine addiction (Kreek, 1996). Before resources are expended attempting to treat cocaine-abusing buprenorphine-maintained patients with auricular acupuncture clinically or in long-term research studies, we sought to gather preliminary evidence concerning the response of buprenorphine-maintained patients to this form of treatment. In addition, we also explored the effect of other commonly used psychoactive substances, such as caffeine and alcohol, on response to auricular acupuncture. We investigated these issues in an acute-effects study, using rating scales that we have used previously in investigations of auricular acupuncture in cocaine-abusing methadone-maintained patients (Avants et al., 1995; Margolin et al., 1993b, 1995, 1996; Margolin and Avants, 1997).

METHODS

Participants

Participants were 34 opioid-dependent patients (23 male, 11 female; 18 white, 10 African American, 6 Hispanic) receiving opioid maintenance treatment (16 were maintained on methadone, 18 were maintained on buprenor-
phine). Prior to entering treatment, they had been using heroin for an average of 15.9 (±9.8) years. All patients had reached a stable daily maintenance dose of their respective agonists (methadone mean: 83.7 [±20.0] mg; buprenorphine mean: 23.6 [±9.3] mg) and had been maintained on this dose for at least 4 weeks.

All patients self-reported cocaine use, and had been using cocaine for an average of 13.1 years (±8.9); 11 (32%) used by intravenous route of administration, 20 freebased (59%), and 3 (9%) used intranasally. The majority of patients (62%) were regular users, using an average of 2.3 (±4.0) days per week and an average of 4.0 (±2.8) "dime bags" per week in the month prior to the acupuncture session. Four participants reported using cocaine within 24 hours of the acupuncture session (range 7-24 hours); 2 were maintained on methadone; 2 on buprenorphine.

Other drug use reported included alcohol (38%); marijuana (9%); benzodiazepines (18%); other opiates (9%); and caffeine (94%). The majority of participants (over 70%) reported taking no other prescribed or over-the-counter medications. With the exception of caffeine and the opiate maintenance agent (methadone or buprenorphine), there was no reported use of any drug within 7 hours of receipt of acupuncture; 15 of 34 (44%) had ingested caffeine within 3 hours of the session.

Procedure

Patients reported to the research unit after receipt of their dose of buprenorphine or methadone. Patients were treated individually, seated in a reclining chair in a quiet room.

Presession assessments. Prior to receiving the acupuncture treatment, participants completed a brief assessment battery that included the following: a sociodemographic questionnaire; drug use history, including length of time since last use of illicit and prescribed drugs; and ratings of severity of current pain. In order to assess the potential influence of participants' perceptions of acupuncture as a credible treatment and their level of presession anxiety on the acute effects of acupuncture, the Treatment Credibility Scale (TCS; Vincent, 1990), and the State-Trait Anxiety Inventory (STAI-state version, Spielberger et al., 1970) were also completed prior to needle insertion.

Auricular acupuncture treatment. Acupuncture treatments were provided by an acupuncturist licensed to practice acupuncture in the State of Connecticut with many years experience treating drug-addicted individuals. The auricular protocol used in this study was originally developed and used to assess the efficacy of the National Acupuncture Detoxification Association (NADA) protocol for the treatment of cocaine-dependent patients (Margolin et al., 1996). Four needles were inserted bilaterally in the auricles at the following locations: "sympathetic," located in the deltoid fossa at the junction of the infra-antihelix crus and the medial border of the helix; "lung," located in the center of the cavum concha; "liver," located in the posterior to upper portion of the helix crus; and "shen men," located in the inferior corner of the bifurcating point of the antihelix. Acupuncture needles (0.20 X 15 mm) were inserted into the cartilage at each point such that they were perpendicular to the surface of the ear. Needles remained in place for 40 minutes, at which time they were removed and disposed of by the acupuncturist.

Postsession assessments. Immediately after the acupuncture session, the following assessment battery was completed, with ratings of items on a 5-point-scale (0, not at all to 4, extremely). (1) Pain: pain in ears on needle insertion; pain at needle sites during session. (2) De qi sensations relative to pretreatment levels: warmth in ears; activity in ears; radiating sensations from ears to face, neck, or shoulders. (3) Relaxation effects relative to pretreatment levels: muscles looser; body feeling heavier; body feeling warmer; feeling sleepier; feeling more relaxed. (5) Subjective experiences: session enjoyment; stress reduction; feelings of happiness and peacefulness; confidence in acupuncture as a treatment for cocaine problems. As an additional measure of treatment desirability, participants were asked how much they would be willing to pay for such a treatment session in the future ($0, $5, $10, $15, $20).
RESULTS

Presession differences

Table 1 presents sociodemographic information, cocaine use and acupuncture treatment history, confidence in acupuncture as a credible treatment, and presession anxiety by type of opioid maintenance agent. As shown in Table 1, patients maintained on buprenorphine were significantly more likely to be male and to perceive acupuncture as less credible than were patients maintained on methadone. Perceived treatment credibility did not differ by prior experience with acupuncture treatment. That is, “acupuncture naive” patients did not perceive acupuncture as less or more credible than “acupuncture experienced” patients. Subsequent analyses of differences between methadone- and buprenorphine-maintained patients therefore included gender as an independent variable and treatment credibility scores as covariates.

Postsession acute effects

In order to reduce the likelihood of Type I error caused by a large number of multiple comparisons, four composite scores were calculated based on the acute effects data: mean pain, mean de qi sensations, mean relaxation effects, and mean subjective experiences. These four composite scores were entered into 2 (Maintenance Agent) X 2 (Gender) analyses of covariance (ANCOVAs) with TCS scores as the covariate. These analyses showed no main effects for Maintenance Agent or Gender, and no significant Agent X Gender interactions. Mean responses were very similar in the two groups: (1) pain—methadone 0.68 (± .15), buprenorphine 0.42 (± .14); (2) de qi sensations—methadone 0.81 (± 0.15), buprenorphine 0.74 (± 0.14); (3) relaxation effects—methadone 1.41 (± 0.20), buprenorphine 1.63 (± 0.19); (4) subjective effects—methadone 2.28 (± 0.25), buprenorphine 2.11 (± 0.23).

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>39.4 (±9.6)</td>
<td>37.3 (9.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (50%)</td>
<td>15 (83%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8 (50%)</td>
<td>3 (17%)</td>
<td></td>
</tr>
<tr>
<td>Race:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6 (37%)</td>
<td>12 (67%)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>6 (37%)</td>
<td>4 (22%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (26%)</td>
<td>2 (11%)</td>
<td></td>
</tr>
<tr>
<td>Graduated high school</td>
<td>7 (44%)</td>
<td>14 (78%)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>1 (6%)</td>
<td>7 (39%)</td>
<td></td>
</tr>
<tr>
<td>Drug use history:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years using heroin</td>
<td>13.6 (±9.6)</td>
<td>18.0 (±9.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Years using cocaine</td>
<td>13.4 (±8.5)</td>
<td>12.8 (±9.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Used cocaine in past month</td>
<td>11 (69%)</td>
<td>10 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Bags cocaine per week</td>
<td>3.7 (3.2)</td>
<td>4.3 (2.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Days cocaine per week</td>
<td>2.0 (1.8)</td>
<td>2.7 (1.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Used cocaine within 24 hrs</td>
<td>2 (12.5%)</td>
<td>2 (11.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Route of cocaine use:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous (inject)</td>
<td>2 (12.5%)</td>
<td>9 (50%)</td>
<td></td>
</tr>
<tr>
<td>Freebase (smoke)</td>
<td>12 (75%)</td>
<td>8 (44%)</td>
<td></td>
</tr>
<tr>
<td>Intranasal (snort)</td>
<td>2 (12.5%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Acupuncture history:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% acupuncture naive</td>
<td>5 (31%)</td>
<td>10 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment credibility (1–6)</td>
<td>4.74 (±1.14)</td>
<td>3.55 (±1.19)</td>
<td>t(32) = 3.01, p &lt; .005</td>
</tr>
<tr>
<td>Presession anxiety (STAI)</td>
<td>41.2 (±2.4)</td>
<td>38.4 (±12.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant.
Session desirability

A preponderance of patients (88%) reported that they would have been willing to pay for the treatment had it not been provided free of charge ($0 = 12%; $5 = 20%; $10 = 29%; $15 = 15%; $20 = 24%); 69% of methadone-maintained patients and 67% of buprenorphine-maintained participants reported that they would be willing to pay $10 or more for the session (Chi-square not significant).

Pain reduction

Seven participants (20%) reported experiencing pain immediately prior to the session (mean severity rating on a scale from 1-4 = 2.29 ± 1.11). No participant reported increased pain after the acupuncture treatment, and decreases in pain did not differ by type of opioid maintenance agent.

Exploratory analyses: influence of presession factors on acute effects of acupuncture

Pearson correlational coefficients were computed between the four acute effects composite scores and the following variables: methadone/buprenorphine dose; presession anxiety; perceived credibility of acupuncture; time since last use of cocaine, caffeine, and alcohol. Substance use correlations were computed on data provided only by those participants who reported any use of each substance; thus, sample sizes tended to be relatively small and results should be interpreted with caution.

Presession dose of opioid maintenance agent, anxiety, and treatment credibility. There were no significant relations among pretreatment dose, STAI, or TCS scores and any measured acute effect of acupuncture.

Presession substance use. No significant relation was found between acupuncture effects and length of time since last cocaine or alcohol use. Time since last caffeine use (hours) was significantly and positively related to de qi sensations [r(23) = 68, p < .001]. That is, caffeine intake proximal to the acupuncture session was related to less intense acupuncture effects.

Further exploration of the effects of caffeine on response to acupuncture

With the exception of methadone or buprenorphine, the only reported substance used within 3 hours of the treatment session was caffeine. Forty-four percent (44%) of patients reported caffeine intake within 3 hours of the treatment session. ANCOVAs as described earlier were therefore repeated to include caffeine intake status (did/did not ingest caffeine within 3 hours of session). There were no significant interactions with Gender or Maintenance Agent. However, there were main effects for caffeine intake status. Participants who had ingested caffeine reported less acupuncture needle-related pain [ingested: 0.26 ± 0.13); not ingested: 0.77 ± 0.12]; F(1,31) = 8.23, p < .007, less de qi sensations [ingested: 0.40 ± 0.12); not ingested: 1.07 + 0.11]; F(1,31) = 17, p < .001], less relaxation effects [ingested: 1.23 ± 0.18); not ingested: 1.76 ± 0.16]; F(1,31) = 4.78, p < .04], and marginally less subjective experience [ingested: 1.89 ± 0.23); 2.42 (± 0.20); F(1,31) = 2.91, p < .098]. In order to investigate the potential influence of anxiety on the caffeine effects, a t test was conducted comparing the STAI scores of patients who had/had not ingested caffeine within 3 hours of the session. There was no significant difference [ingested caffeine = 38.3 (± 12.9); no caffeine within 3 hours = 40.8 (± 12.3); t(32) = 0.58, p = .57].

DISCUSSION

This study comparing acute effect ratings after a single session of auricular acupuncture found no significant differences between the ratings of cocaine-abusing patients maintained on buprenorphine or methadone. Patients in both groups had positive responses in the moderate range. This level of response is commensurate with that found in previous acute-effect studies of auricular acupuncture studies in methadone-maintained patients (Margolin et al., 1993b, 1995), and is consistent with the interpretation that buprenorphine does not block auricular acupuncture's effects.

This study also presented the opportunity to
explore possible mechanisms of action of auricular acupuncture. Although the effects of body acupuncture have been linked to release of endogenous opioids (Pomeranz, 1987), virtually nothing is known concerning the mechanism of action of auricular acupuncture. In view of the putative \( \kappa \)-antagonist properties of buprenorphine, and a lack of differences between the acute-effect ratings of the two treatment groups, our findings do not support the hypothesis that the dynorphin system mediates the effects of auricular acupuncture. As noted above, both methadone and buprenorphine possess \( \mu \)-receptor agonist properties, and both maintenance agents appear to normalize beta-endorphin levels disregulated by chronic heroin abuse (Kreek et al., 1983; Kosten et al., 1992). However, buprenorphine possesses a significantly greater affinity for the \( \mu \)-receptor compared to methadone (Cowan, 1995) and thus may also block \( \beta \)-endorphin, the endogenous ligand, at this site, particularly at higher doses. It is interesting to speculate that the finding of no differences may therefore also fail to support a \( \beta \)-endorphin, \( \mu \)-receptor mediation hypothesis. Other hypotheses, such as mediation by the \( \delta \)-receptor, enkephalin system, or through vagal stimulation (Ulett, 1992), may also be worthwhile to explore.

Exploratory analysis of ratings across groups in relation to recent ingestion of other psychoactive substances suggested that acupuncture's effects may be diminished by caffeine. Across groups, patients who had ingested caffeine within 3 hours prior to the acupuncture session reported significantly less de qi sensations and relaxation effects compared to patients who did not recently ingest caffeine. Pre-session anxiety did not account for differences by caffeine intake. Caffeine is an adenosine receptor antagonist (Fredholm, 1995; Marangos and Boulenger, 1985), and has been found to decrease the analgesic effects of transelectrical nerve stimulation (TENS) and electroacupuncture (Liu et al., 1994; Marchand et al., 1995), as well as opioid activity (Kuribara and Uchihashi, 1994). Whether adenosine has a role in mediating the therapeutic effects of auricular acupuncture, or whether apparently diminished patient response was primarily due to the stimulatory effect of caffeine increasing wakefulness, may be a worthwhile subject for further investigation. Our findings, albeit preliminary, suggest that response to acupuncture may be enhanced if patients refrain from ingesting caffeine within a time period of at least 3 hours prior to treatment.

We note that this study had several limitations that should be considered in the interpretation of our findings. First, this study was undertaken in a clinical context, based on patient self-report, and with patients who abuse cocaine. Cocaine-abusing patients constitute a relevant target subpopulation that is likely to be offered auricular acupuncture; however, unreported cocaine use in our sample could possibly have been a confounding factor. Pharmacologic implications of our findings should therefore be interpreted with caution. Future studies of the mechanism of auricular acupuncture could be investigated using assays for specific neuropeptides, with objective measure of cocaine use or nonuse. Second, in the absence of a nonneedle insertion control group, the systemic effects cannot be definitively ascribed to acupuncture, they may have been due to patients relaxing in a quiet room. Acupuncture-and nonacupuncture-induced relaxation responses may have physiologic processes in common, and ways of teasing these apart should be further investigated. Third, our study's sample size was relatively small, raising the issue of whether we had sufficient power to detect statistically significant differences between the two groups. However, regardless of sample size, the differences between the methadone and buprenorphine patients on mean effect ratings—a few tenths of a point—are probably not clinically significant. Furthermore, these small differences did not consistently favor one group over the other. Lastly, we note that our findings do not shed light on the effectiveness of auricular acupuncture for the treatment of cocaine addiction in either methadone- or buprenorphine-maintained patients—our acute effects study was not designed to address this issue. Treatment comparison studies with clinical outcomes are needed to determine possible differential effectiveness of auricular acupuncture with respect to patients maintained on either methadone or buprenorphine.
In summary, in this preliminary, acute effects study, we found the response of buprenorphine- and methadone-maintained patients to auricular acupuncture to be virtually equivalent. These findings support the hypothesis that buprenorphine does not block the effects of auricular acupuncture. Thus, we provisionally recommend that buprenorphine-maintained patients who abuse cocaine not be excluded from receiving auricular acupuncture or from participating in clinical research involving this treatment modality.

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