Use of conventional, complementary, and alternative treatments for pain among individuals seeking primary care treatment with buprenorphine-naloxone

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Abstract

Previous studies have not examined patterns of pain treatment use among patients seeking office-based buprenorphine-naloxone treatment (BNT) for opioid dependence.

Objectives—To examine, among individuals with pain seeking BNT for opioid dependence, the use of pain treatment modalities, perceived efficacy of prior pain treatment, and interest in pursuing pain treatment while in BNT.

Methods—244 patients seeking office-based BNT for opioid dependence completed measures of demographics, pain status (i.e. “chronic pain (CP)” [pain lasting at least 3 months] vs. “some pain (SP)” [pain in the past week not meeting the duration criteria for chronic pain]), pain treatment use, perceived efficacy of prior pain treatment, and interest in receiving pain treatment while in BNT.

Results—In comparison to the SP group (N = 87), the CP group (N = 88) was more likely to report past-week medical use of opioid medication (AOR 3.2, 95% CI 1.2–8.4), lifetime medical use of non-opioid prescribed medication (AOR 2.2, 95% CI 1.1–4.7), and lifetime use of prayer (AOR 2.8, 95% CI 1.2–6.5), and was less likely to report lifetime use of yoga (AOR 0.2, 95% CI 0.1–0.7) to treat pain. While the two pain groups did not differ on levels of perceived efficacy of prior lifetime pain treatments, in comparison to the SP group, the CP group was more likely to report interest in receiving pain treatment while in BNT (P < 0.001).

Conclusions—Individuals with pain seeking BNT for opioid dependence report a wide range of conventional, complementary, and alternative pain-related treatments and are interested (especially those with CP) in receiving pain management services along with BNT.

Keywords
Pain; Opioid Dependence; Complementary Therapies; Buprenorphine/Naloxone

Office-based buprenorphine-naloxone treatment (BNT) is a relatively new treatment modality that has greatly expanded access to treatment for opioid dependence\textsuperscript{1} (Sullivan et
al., 2005). It is estimated that approximately 250,000 to 300,000 individuals receive this treatment at any one time, many from primary care physicians (Fiellin, 2011). One clinical challenge to providing opioid agonist treatment for opioid dependence is the high prevalence of chronic pain, defined here as non-cancer physical pain lasting at least three months, as a comorbid condition along with addiction, among treatment seekers (Barry et al., 2009c; Barry et al., in press). Providers report clinical management difficulties treating patients with co-occurring chronic pain and opioid dependence—in part because of the high rates of psychiatric comorbidity (Rosenblum et al., 2003; Barry et al., 2008; Barry et al., 2009b; Berg et al., 2009; Barry et al., 2010b).

While the use of pain treatments among opioid dependent patients seeking methadone maintenance treatment (MMT)—a mainstay opioid agonist treatment for opioid dependence in the U.S.—have been examined (Barry et al., 2010a), to our knowledge, no published studies have investigated such patterns among opioid dependent patients seeking office-based BNT. Given that office-based BNT attracts opioid dependent patients with no prior experience of MMT (Sullivan et al., 2005), it is important that researchers and clinicians not assume that pain treatment use patterns among opioid dependent patients in MMT extend to those seeking BNT. Office-based BNT providers who wish to address pain management issues among opioid dependent patients may benefit from an increased understanding of pain treatment utilization patterns and patient interest in pursuing pain-related interventions via their BNT provider.

Research findings point to the importance of assessing recent pain (i.e., pain experienced in the past week) in addition to chronic pain among opioid dependent patients since both types of pain may be associated with adverse treatment outcomes (Sheu et al., 2008; Barry et al., 2009b). Providers should consider assessing complementary and alternative medicine (CAM) treatments in addition to conventional or allopathic treatments among patients with chronic medical conditions since CAM interventions are prevalent and may affect the safety and efficacy profile of conventional treatments (Barry and Beitel, 2008). Complementary medicine comprises non-conventional medical treatment that is used in conjunction with standard medical interventions, whereas alternative medicine refers to treatment interventions that are used in place of standard medical care (Kim et al., 2002). Pain relief is a common motivator for CAM use. For example, data from the 2002 National Health Interview Survey (NHIS) indicate that approximately 6% of the U.S. population used CAMs for back pain relief in the previous 12 months, the majority of whom (60%) reported a “great deal” of benefit from these interventions (Kanodia et al., 2010). However, data regarding the efficacy and safety of different CAM treatments for pain are mixed (Cherkin et al., 2003; Furlan et al., 2010).

While we previously reported on the pain characteristics (intensity, frequency, duration, interference, location, and genesis) and pain-associated substance use (e.g., heroin, non-medical use of prescription opioids, and alcohol) among the study sample (Barry et al., in press), we did not report on their utilization of conventional or CAM interventions for pain relief. Consequently, the aim of this needs assessment study was to examine among adults seeking BNT for opioid dependence: (a) prior pain treatment utilization with a particular focus on CAM treatments, (b) perceived efficacy of pain treatment received, and (c) interest in receiving pain treatment in addition to BNT for opioid dependence. These data might be useful for BNT resource and treatment planning.

\[1\] In this manuscript, the terms “opioid dependence” and “opioid dependent” are used in accordance with the Diagnostic and statistical manual of mental disorders (4th edition, text revision) DSM-IV-TR (APA, 2000).
METHODS

As previously reported (Barry et al., in press), participants were 244 adults who were consecutively evaluated for enrollment in a primary care office-based BNT research program for opioid dependence (and not for pain management) between January 2008 and October 2010. All those who presented for enrollment (100% compliance) completed the study questionnaire as part of the screening process for determining study eligibility. This study received appropriate institutional review board approval at Yale University School of Medicine.

Data Collection

As described elsewhere (Barry et al., 2010a), the needs assessment survey was deliberately designed to be brief (< 10 minutes), self-administered, and easy to understand to help increase respondent compliance and reduce burden. Survey questions covered multiple domains, including: (a) the prevalence of pain types (i.e., recent pain, chronic pain), (b) the use of conventional, complementary, and alternative medical pain treatments (past-week and lifetime), (c) perceived efficacy of lifetime pain treatment received, (d) interest in receiving pain treatment along with BNT, and (e) demographics (age, gender, and race).

Recent pain and chronic pain were assessed by asking participants whether they had experienced ongoing physical pain in the last week (yes/no) and whether they were currently experiencing an episode of physical pain lasting at least three months (yes/no).

Use of conventional, complementary, and alternative pain treatments was assessed by providing participants with a list of interventions and asking them, “Which of the following treatments for ongoing physical pain have you used in the last 7 days [recent] and ever in your life [lifetime]?” The list included: (a) “Opiate medication as prescribed by a doctor (e.g., Demerol, Fentanyl, Morphine, OxyContin, Percocet, Percodan, Tylenol with Codeine),” (b) “Non-opiate medication as prescribed by a doctor (e.g., Celebrex, Celexa, Clonidine, Depakote, Elavil, Fiorinal, Ketalar, Ketaset, Neurontin, Prozac, Soma, Tegretol, Topamax),” (c) “Benzodiazepine as prescribed by a doctor (e.g., Ativan, Halcion, Klonopin, Valium, Xanax),” (d) “Over the counter pain reliever (e.g., Advil, Aleve, Aspirin, Ibuprofen, Motrin, Orudis KT, Prilosec, Tylenol),” (e) “Acupuncture,” (f) “Prayer,” (g) “Counseling/Psychotherapy,” (h) “Meditation,” (i) “Self-help support group,” (j) “Yoga,” (k) “Hypnosis,” (l) “Herbs/Herbal medicine (e.g., Aloe vera, Ephedra, Ginkgo biloba),” (m) “Stretching,” (n) “Physical exercise,” (o) “Heat therapy,” (p) “Massage,” (q) “Physical therapy,” (r) “Ice therapy,” and (s) “Chiropractor.” As described elsewhere (Barry et al., 2010a), this list of interventions was generated by the authors based on their experience treating patients receiving opioid agonist treatment and was revised based on the feedback of patients, intake staff, and research assistants.

For data analytic purposes, we classified CAM use according to the taxonomy employed by the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health: (1) Alternative medical systems, some of which were developed in Eastern cultures (e.g., ayurveda), and others in Western cultures (e.g., naturopathic medicine), are based on complete systems of theory and practice and often predate conventional medicine used in the U.S.; (2) Mind-body interventions, which are comprised of different techniques that attempt to magnify the mind’s capacity to control bodily functions and symptoms (e.g., meditation); (3) Biologically-based therapies, which encompass treatments that use biological agents found in nature such as herbs, foods, and vitamins; and (4) Manipulative and body-based methods, which include interventions that systematically manipulate or alter movement in one or more body parts (e.g., chiropractic) (National Center for Complementary and Alternative Medicine, 2010). We did not assess
energy therapies—biofield therapies and bioelectromagnetic-based therapies—the fifth NCAAM CAM classification (e.g., Reiki, Qi Gong), because of their infrequent use among individuals in our previous studies (see above). We adopted a conservative approach to the designation of interventions as either conventional or CAM: Interventions with demonstrated efficacy and safety that are generally available during BNT treatment were designated as conventional; otherwise, they were classified as CAM (Barry et al., 2009a; Barry et al., 2010a).

Perceived efficacy of pain treatment received was assessed by an item that asked respondents to rate the degree to which medical treatment received for ongoing pain was helpful (on an ordinal scale between 1 [did not help] to 5 [helped completely]). Medical treatment was defined as treatment provided by a trained medical professional. Interest in pain treatment was assessed by an item that asked participants whether they were interested in receiving pain treatment in addition to addiction treatment with buprenorphine-naloxone (yes/no).

Pain Groups

Participants’ answers to pain-related items were used to classify them into one of two groups: “chronic pain” (i.e., pain lasting at least three months) and “some pain” (i.e., pain reported in the past week but not meeting the duration threshold for chronic pain).

Data Analysis

Pain group (i.e., chronic pain [CP], some pain [SP]) and recent pain (yes/no) differences on demographic variables were examined using Pearson chi-square tests for categorical data and t-tests for continuous data. Since the CP and SP groups differed significantly on age, we performed an analysis of covariance (ANCOVA) to control for age on the comparison involving pain-related continuous data (i.e., perceived efficacy of pain treatment received).

We examined differences between CP and SP groups on past-week and lifetime pain treatment utilization by conducting two series of binary regression models (adjusting and not adjusting for age) with conventional medicine, CAM subgroup classifications, and interest in receiving pain management along with BNT as the predictor variables of interest and the 2-level pain group (i.e., CP, SP) as the dependent variable. Since a similar pattern of findings emerged in both series, in this paper we report only on regression model findings adjusting for age. Our analyses began by examining pain-related binary variables (i.e., “yes”/“no”) grouped into conventional and CAM subgroup categories, followed by further analysis of the individual category variables. The SP category was used as a reference level for calculating adjusted odds ratios: CP versus SP. We combined the alternative medical systems and biologically based therapies since each category contained only one item (i.e., acupuncture and herbal medicine). Statistical significance was set at \( P < 0.05 \). Statistical analyses were performed using SPSS Version 17.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Demographic Characteristics

As previously reported (Barry et al., in press), of the 244 respondents, 84% (N = 204) were white, 68% (N = 167) were male, 72% (N = 175) reported recent pain, and 36% (N = 88) reported chronic pain; individuals with chronic pain, in comparison to those with some pain, reported higher current pain intensity and past-week pain frequency, as well as higher typical pain duration, typical pain intensity, and typical pain interference (\( p < 0.001 \) for all comparisons). Among those reporting recent pain, the CP (N = 88) and SP (N = 87) groups...
did not differ on gender or race but did differ on age (t = −1.98, df = 173, P = 0.049): On average, the CP group was older than the SP group (36.3 years vs. 33.2 years).

**Use of Conventional Pain Treatments**

Table 1 summarizes past-week and lifetime conventional pain treatment use among CP and SP groups. Overall, 70% of the CP group and 46% of the SP group reported past week use of conventional pain treatments. Over-the-counter (OTC) pain medication was the most frequently reported conventional medicine for pain relief among CP (55% past-week and 83% lifetime) and SP (40% past-week and 69% lifetime) groups. In multivariable analyses, the CP group was more likely than the SP group to report past-week medical use of opioid medication (27% vs. 8%; AOR 3.2, 95% CI 1.2–8.4) and lifetime medical use of non-opioid medication (58% vs. 29%; AOR 2.2, 95% CI 1.1–4.7).

**Use of CAM Pain Treatments**

Table 1 also summarizes past-week and lifetime CAM pain treatment use among CP and SP groups. Overall, 64% of the CP group and 44% of the SP group reported past week use of CAM pain treatments (P = 0.08). The most frequently reported past-week and lifetime conventional medicine for pain relief among both groups were stretching and physical exercise. While significant differences did not emerge in multivariable analyses between the CP and SP groups on acupuncture or herbs, in comparison to the SP group, the CP group was more likely to report lifetime use of prayer (AOR 2.8, 95% CI 1.2–6.5) and was less likely to report lifetime use of yoga (AOR 0.2, 95% CI 0.1–0.7). In multivariable analyses, no differences emerged between CP and SP groups on individual manipulative and body-based method interventions.

**Perceived Efficacy of Prior Pain Treatments and Interest in Receiving Pain Treatment**

After controlling for age, the CP group (mean = 2.5, SD = 1.2) and SP group (mean = 2.5, SD = 1.3) did not differ on perceived efficacy of prior lifetime medical treatments for pain, F (1, 99) = 0.009, P = 0.92; however, in comparison to the SP group, the CP group was more likely to report interest in receiving pain treatment in addition to addiction treatment with the BNT (89% vs. 56%) (AOR 6.1, 95% CI 2.6–14.1, P < 0.001).

**DISCUSSION**

This study is among the first to examine the use of conventional, complementary, and alternative medicine (CAM) treatments for pain relief among individuals with pain seeking primary care office-based buprenorphine-naloxone treatment (BNT) for opioid dependence. Overall, 72% reported recent pain, one half of whom were experiencing chronic pain. Those with recent pain reported a wide array of pain-related treatments and an interest in pursuing pain management while in BNT.

Over-the-counter (OTC) medication was the most frequently reported conventional medicine for pain relief; approximately one-half of the CP group reported using OTC analgesics in the prior week (55%). While patients with co-occurring chronic pain and opioid dependence often encounter obstacles accessing opioid-based medical treatments for pain relief (Simopoulos, 2008) and debate persists about the efficacy and safety of these medications for treating chronic pain (Noble et al., 2010), it is noteworthy that approximately one-quarter (27%) of those with chronic pain reported past-week medical use and the majority (75%) reported lifetime medical use of prescription opioid medications for pain relief. In multivariable analyses, CP patients were more likely than the SP patients to report past-week use of prescription opioid medications and lifetime medical use of prescription non-opioid medications. These findings suggest that office-based providers...
should specifically inquire about opioid and non-opioid medications for pain relief among those seeking BNT with recent pain. Furthermore, given the relatively high proportions of SP and CP patients reporting lifetime medical use of benzodiazepines coupled with the potentially harmful effects of combining opioid and benzodiazepine medications (e.g., respiratory depression) (Stitzer and Chutuape, 1999), our findings suggest that providers might benefit from routinely assessing and addressing the use of benzodiazepine medications among those with recent pain seeking BNT for opioid dependence, irrespective of their chronic pain status. These recommendations may be particularly warranted given that a prior investigation of these patients found that CP and SP groups reported comparably high rates of past week use substance use to alleviate pain, including heroin use (39% and 33%, respectively), taking someone else’s prescription opioid medication (61% and 45%, respectively) and alcohol use (24% and 25%, respectively) (Barry et al., in press).

Prayer, counseling, and self-help support groups were the most frequently used lifetime mind-body interventions among CP and SP patients. While certain types of counseling, such as cognitive-behavioral therapy, have demonstrated efficacy in addressing chronic pain and substance use disorders (Irvin et al., 1999; Keefe et al., 2004), the efficacy of prayer in treating pain has not been systematically examined. Self-help groups for substance use disorders such as Narcotics Anonymous are widely available in the U.S. Since some patients seek these out, future research might focus on the feasibility and efficacy of adapting this approach to address both chronic pain and opioid dependence. If such groups were shown to be efficacious, they would likely represent a cost-effective intervention that might also be of use as a referral source for BNT providers.

CP patients were less likely than SP patients to report lifetime utilization of yoga. The proportion of CP respondents reporting lifetime use of yoga (6%) is similar to the proportion of 2007 NHIS respondents who reported past-year use of yoga (6.1%) (Barnes et al., 2008). Research evidence suggests that yoga has salutary effects on a variety of mental (anxiety, depression, sleep disorder) and physical (pain, cardiovascular, autoimmune, immune, pregnancy-related distress, and weight loss) conditions (see (Field, 2011) for a review). The American College of Physicians and American Pain Society list one form of yoga (Viniyoga) as having fair evidence for moderate benefit in the treatment of chronic lower back pain (Chou et al., 2007). While no published studies, to our knowledge, have investigated yoga as an adjunctive pain treatment in opioid dependent patients, a number of studies have demonstrated the benefits of yoga for physical pain conditions that are common in opioid-dependent patients, including low back pain (Sherman et al., 2005; Saper et al., 2009) and migraine (John et al., 2007). While yoga is practiced less among ethnic/racial minorities (as opposed to whites) and low as compared to high socioeconomic status individuals (Saper et al., 2004), a recent pilot randomized controlled trial involving patients with chronic low back pain demonstrated the feasibility and efficacy of yoga in attenuating pain and reducing the use of pain medications among ethnic/racial minority patients of low socioeconomic status (Saper et al., 2009).

The lifetime rates of acupuncture use among the CP (21%) and SP (9%) groups were noticeably higher than the past-year rate reported by the 2007 NHIS respondents (1.4%) (Barnes et al., 2008). Although the efficacy of acupuncture in treating chronic pain is unclear, in part because of the paucity of well-designed randomized clinical trials, the American College of Physicians and American Pain Society in 2007 included acupuncture as a weak recommendation in their list of suggested interventions for treating chronic pain. Acupuncture was categorized as a potentially efficacious treatment based on evidence of moderate quality (Chou et al., 2007). Given the relatively high rate of lifetime use of herbs/herbal medicine for pain relief in the CP group (22%), coupled with concerns about their safety, side effects, and the possible harmful interactions of herbs with prescribed
medications (Izzo and Ernst, 2001; De Smet, 2004; Gagnier et al., 2006), providers might benefit from assessing and addressing (e.g., via education about possible safety risks) their use among opioid dependent patients with pain enrolling in BNT.

Lifetime use rates of manipulative and body-based methods were generally high among respondents reporting recent pain, especially among the CP group. The majority of CP patients reported lifetime use of interventions that are frequently employed by physical and occupational therapists in the promotion of tissue recovery and rehabilitation, including stretching, physical exercise, heat therapy, and physical therapy (Stanos and Rader, 2008). Randomized clinical trials that have examined the long-term efficacy of manipulative and body-based methods in pain management have demonstrated mixed treatment outcomes (Ernst, 1999; Furlan et al., 2008; Walker et al., 2010)—in part due to variability in diagnostic and treatment methods (van de Veen et al., 2005). The examination of the efficacy of manipulative and body-based methods in pain management for BNT patients with pain warrants further research investigation, especially since many of these interventions could either be prescribed directly by the BNT provider (e.g., stretching, physical exercise, heat therapy) or are likely to be available as a referral (e.g., physical therapy). While there is a paucity of national data on insurance companies’ coverage of manipulative and body-based or other CAM interventions for pain management, one national survey found that full or partial insurance coverage was independently associated with frequent CAM treatment use (i.e., 8 or more visits per year to a CAM provider); however, it has been estimated that the majority of individuals who avail of CAM providers pay out-of-pocket (Wolsko et al., 2002; National Center for Complementary and Alternative Medicine National Institutes of Health, 2008).

The CP and SP groups did not differ on their ratings of perceived efficacy of prior lifetime pain treatment. Both groups, on average, rated their prior pain treatment between “helped a little” and “helped somewhat.” Despite the relatively low rating of perceived efficacy of prior pain treatments, the majority of the CP group (89%) reported interest in receiving pain management along with BNT for opioid dependence. These results complement recent findings indicating that office-based physicians are frustrated by the absence of treatments addressing chronic pain and opioid dependence (Barry et al., 2010b).

Several potential limitations are worth noting. Participants were seeking office-based BNT as part of a research study; thus, our findings may not generalize to non-research-based BNT settings. The survey was cross-sectional and thus limits statements regarding causation between study variables, and it relied upon patient self-report; no independent assessment of prior treatment use was made. Data regarding the medical and psychiatric status and drug treatment history were not assessed in the study survey. Given the absence of published pain-related needs assessment measures for BNT, we used an instrument that had been developed for patients seeking entry into methadone treatment; although face-valid, this measure has not yet been formally validated (Barry et al., 2009c). The report of illicit drug use for pain relief by these patients is reported elsewhere (Barry et al., in press).

Future research investigations might benefit from a more detailed assessment of pain-related conventional medicine, including medication types or formulations (e.g., tramadol-based formulations, gabapentin), dosing and duration, and CAM interventions (e.g., electrical stimulation, aquatic therapy) among opioid dependent patients seeking BNT. The extent to which each of the individual interventions surveyed was beneficial was not assessed. Future research on pain treatment use patterns among opioid dependent patients might benefit from a more detailed examination of the perceived efficacy of discrete pain management interventions prior to and after initiating BNT, including for example, the perceived efficacy of other opioid or non-opioid medications prescribed for pain relief.
Despite these limitations, this study represents an important initial investigation of pain-related treatment utilization among opioid dependent individuals seeking BNT. Overall, respondents reported a wide range of conventional and CAM pain treatment interventions. Respondents with chronic pain, in comparison to those with some pain, were more likely to report past-week medical use of prescribed opioid medications, lifetime medical use of non-opioid prescribed analgesics, and lifetime use of prayer, and they were less likely to report lifetime use of yoga, for pain relief. These findings may have implications for resource and treatment planning in BNT programs. Specifically, BNT providers might consider assessing and addressing recent pain in addition to chronic pain and conventional in addition to CAM pain treatment utilization among those seeking BNT. The very high rate of interest in receiving pain management along with BNT for opioid dependence among respondents with chronic pain suggests that if BNT providers were to offer pain management strategies onsite or via referral, opioid dependent patients with chronic pain would be interested in participating.

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References


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Table 1

Comparison of CP and SP Groups on Conventional, Complementary, and Alternative Medical Treatment Use in the Last 7 Days and Lifetime †

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<td>CP %</td>
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<td>AOR (95% CI)</td>
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<td>OTC Pain Medication</td>
<td>55</td>
<td>40</td>
<td>1.8 (0.9–3.3)</td>
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<td>83</td>
<td>69</td>
<td>1.2 (0.5–2.8)</td>
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<td>48</td>
<td>1.7 (0.8–3.8)</td>
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<td>Non-Opioid Medication ‡</td>
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<td>58</td>
<td>29</td>
<td>2.2 (1.1–4.7) *</td>
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<td>1.4 (0.4–4.6)</td>
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<td>36</td>
<td>21</td>
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<td>0.8 (0.05–14.1)</td>
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<td>1.7 (0.7–4.1)</td>
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<td>0.7 (0.3–2.3)</td>
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<td>2</td>
<td>0.3 (0.02–4.4)</td>
<td></td>
<td>6</td>
<td>14</td>
<td>0.2 (0.1–0.7) *</td>
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<td></td>
<td></td>
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<td>3</td>
<td>0.9 (0.1–7.7)</td>
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<td>&lt;0.001</td>
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<td>Stretching</td>
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<td>33</td>
<td>1.1 (0.5–2.7)</td>
<td></td>
<td>73</td>
<td>48</td>
<td>1.2 (0.4–3.2)</td>
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<tr>
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<td>23</td>
<td>1.6 (0.7–3.9)</td>
<td></td>
<td>73</td>
<td>49</td>
<td>0.9 (0.4–2.5)</td>
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<td>4.2 (0.8–20.9)</td>
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<td>58</td>
<td>25</td>
<td>2.5 (0.9–7.0)</td>
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<tr>
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<td>33</td>
<td>0.9 (0.4–2.0)</td>
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<tr>
<td>Physical Therapy</td>
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<td>7</td>
<td>0.03 (0.01–0.5)</td>
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<td>66</td>
<td>33</td>
<td>1.7 (0.7–3.8)</td>
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<td>18</td>
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<tr>
<td>Chiropractor</td>
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<td>24</td>
<td>2.0 (0.9–4.8)</td>
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</table>

† Respondents were 175 patients reporting pain in the past week.
Examples of non-opioid medications provided to participants included “Celebrex, Celexa, Clonidine, Depakote, Elavil, Fiorinal, Ketalar, Ketaset, Neurontin, Prozac, Soma, Tegretol, Topamax.”

CP = Chronic pain, SP = Some pain, OTC = Over the counter.

*P < 0.05.