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Ameliorative Response to Detoxification, Psychotherapy, and Medical Management in Patients Maintained on Opioids for Pain

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Background and Objectives: The prevalence of opioid-induced hyperalgesia (OIH) among patients maintained on opioids for chronic non-malignant pain has not been estimated.[1] As a contribution toward establishing its prevalence, we report a case series of opioid maintained patients whose pain tolerance was measured by the cold pressor test at baseline.
Methods: A case series of 117 patients who had undergone detoxification was reviewed retrospectively. Most patients ($n = 108$) and selected non-addicted support persons who accompanied them (controls; $n = 37$) had cold pressor time (CPT) assessments at baseline. Twenty patients had a repeat CPT after 1 month.
Results: When 61 patients completed one month abstinent reported pain was improved (51%), unchanged (46%), or worse (3%). Baseline CPT was 48 sec for patients and 102 sec for controls, suggesting that opioid maintained patients were more pain sensitive than opioid naïve controls. CPT increased for 90% of 1-month completers, suggesting improved pain tolerance. Ameliorative response to detoxification, psychotherapy, and medical management, as defined as the absence of worsening pain with removal of opioids, was 97% in this population.
Conclusion: The difference in CPT between opioid maintained patients and controls, and the response to detoxification, psychotherapy and medical management suggest the possibility that the prevalence of OIH may be high.
Scientific Significance: This study adds to the growing evidence that chronic opioid treatment contributes little to the management of chronic pain and in fact appears to frequently make it worse. (Am J Addict 2017;XX:1–6)

INTRODUCTION

In the mid-1990s, pain became a new focus of healthcare. Concerned that pain was being undertreated, the American Pain Society[2] argued that pain be evaluated as a "fifth vital sign."[3] Adequate treatment of pain was considered to be a patient right, and providers were urged to assess pain often and to treat it aggressively. Following this cultural shift, there was a dramatic increase in the number of opioid prescriptions: a 198% increase for hydrocodone, 588% for oxycodone, and 933% for methadone over a 20-year period.[3] Treatment of chronic non-malignant pain with maintenance opioid medications has become ubiquitous. In 2012, physicians wrote 259 million opioid prescriptions, a figure equal to the U.S. adult population.[4]

Not surprisingly, opioid misuse has escalated as well. Opioid addiction has increased, as evidenced by the shift in admission patterns to substance abuse treatment centers. Patients with a primary opioid addiction increased from 2% of admissions in 2000 to 9% in 2010.[5] Between 1999 and 2009, deaths related to overdoses of prescription opioids quadrupled from a rate of 1.54 per 100,000 to 6.05 per 100,000.[6]

While many patients do not progress to opioid misuse or addiction, there are other complications associated with the use of opioids for pain. Prescribing opioids for pain may actually increase pain sensitivity. This phenomenon is known as opioid-induced hyperalgesia (OIH). OIH is defined as nociceptive sensitization caused by opioid exposure.[1] It is a paradoxical phenomenon, as patients being treated with opioids for pain actually develop increased pain. It presents clinically in opioid-using patients several ways: increased pain intensity that cannot be attributed to disease progression, little analgesic effect following dose escalation, improved pain control following dose reduction, or a change in pain quality and/or location from the preexisting condition.[7]

Both patients and physicians may respond to OIH-induced pain intensification with opioid medication dose escalations, temporarily improving pain before again making the pain worse. This is the seductive nature of opioids. OIH may also cause a shift from opioid pill use to higher morphine equivalent dosing diacetylmorphine (heroin) use, as patients

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perceive dose escalations as a necessary treatment for worsening pain that is being caused by the opioid exposure itself. These processes may contribute to the risk of accidental overdose, as each dose escalation feels helpful in the moment, but actually produces OIH over time.

While OIH and tolerance may present in a similar way, decreasing response to opioid medications, the two processes are distinct. OIH is a change in pain sensitivity while tolerance is a diminished analgesic response to the medication. Increasing opioid dose will alleviate pain in a patient with tolerance but will exacerbate pain in a patient with OIH.[8]

OIH has been observed in patients with both chronic and acute opioid exposure. In a 2006 retrospective study, Baron and McDonald found that 21 of 23 patients maintained on high-dose opioids for chronic pain reported a significant improvement in pain after detoxification.[9] Miller, Swiney, and Barkin[10] reported faces pain scores falling almost in half over a week of detoxification from opioid pain medications. Harden et al.[11] reported no change or decreased pain in 70% of patients whose opioid dose was slowly tapered. In a meta-analysis of 27 studies, Fletcher and Martinez[12] found that patients treated acutely with high opioid doses intra-operatively reported increased post-operative pain compared to reference groups.

The clinical prevalence of OIH is unknown.[1] No adequate laboratory method has been developed that would meet a definitive standard for measurement of hyperalgesia.[13] It would be helpful to know the clinical prevalence of OIH, as it appears to be an important complication of chronic opioid treatment of pain.

The biological mechanism by which opioids enhance pain sensitivity is generally understood as a progression from homeostatic regulation of drivers of distress such as pain, anxiety, and depression into an allostatic state of increasing distress by overshooting of countervailing neuroregulators; glucocorticoids, corticotropin releasing factor, dynorphin, tachykinin, and neurotensin,[14,15] Apparently, the brain requires an ability to sense pain as an affect that enhances survival. Attempts at long-term suppression of pain cause a resultant overcompensation/overshoot of pain drivers.[14,15]

High doses of exogenous opioid were understood to downregulate opioid receptors, resulting in protracted withdrawal. According to Brown and Panksepp[16]: "LDN increased opioid receptors and elevated circulating beta endorphin (BE) and met-enkephalin (ME) after a 4–6 h-period of receptor blockade. This "rebound phase" may release the increased density of mu and delta opioid receptors for endogenous opioid stimulation. This is the explanation asked for by and the increasing availability of BE and ME. The general principle operative here may be that the increased concentrations of BE and ME that gain access to increased density of mu opioid receptor and delta opioid receptors may "functionally supersensitize" endogenous opioid systems." With this hypothetical mechanism in mind, LDN has been used to ameliorate protracted withdrawal. This approach has been reported in a case series,[17] but a randomized double blind placebo controlled study has not yet been undertaken Table 1.

A multidisciplinary Pain Service is embedded within Addiction Medicine (AM) at SUNY Upstate so as to evaluate pain complaints and identify the subset of pain patients who are opioid addicted.[17] We often observe low pain tolerance despite high opioid doses as well as improved pain after opioid cessation. We have hypothesized that daily brief blockade of opioid receptors with low-dose naltrexone (LDN) improves receptor function and normalizes opioid tone after it has been disrupted by opioid maintenance.[17] We have shown significant improvement in pain tolerance as measured by cold pressor time (CPT − see below) in detoxified patients treated with LDN.[18] We sought to quantify our observations.

METHODS

Subjects

We retrospectively reviewed all patients who presented to AM between September 2014 and June 2015. New patients are required to bring a non-addicted support person (SP) to the evaluation. The SP is present for the entire evaluation, including the recommendations for treatment. Pain Service meets 1 day per week. As pain complaints are common among patients who present with opioid addiction on other days of the week, Cold Pressor Times were available for a subset of these patients when they underwent the CPT within a week of admission. An initial cold pressor time was therefore not done on 100% of new patients since it was only available one day per week. Faces pain scale scores are routinely done on all admissions.

The SUNY Upstate Medical University institutional review board approved the study protocol, including establishing normal control values for the cold pressor test using SP volunteers with no recent opioid exposure and no tobacco or

TABLE 1. Results

Subjects	Number	Treatment	Successful (%)	Not successful (%)
Pain patients	117	Opioid detoxification	77 (66)	40 (34)
Detoxified patients	77	1-month opioid free	61 (79)	16 (21)
Detoxified patients	77	Compliant with LDN	53 (69)	24 (31)
LDN compliant	53	1-month opioid free	43 (81)	10 (19)
LDN non-compliant	24	1-month opioid free	18 (75)	6 (25)

cannabis use. The control group included 37 SP volunteers. Although there were no repeat CPT for this group, test-retest times have been shown to be stable 2 weeks after initial testing for normal controls.[19] The case series included 117 patients maintained on opioids for pain. Exclusion criteria included pregnancy and opioid use that was not related to pain complaints.

All subjects over age 18 provided written informed consent prospectively. In other words, patients were asked to allow us to use their de-identified information before the result of treatment was known. For the one patient under age 18, her guardian provided written informed consent. The results were then examined retrospectively.

Treatment/Detoxification Procedure

Detoxification included a single dose of buprenorphine and symptomatic treatment of withdrawal. Patients arrived in opioid withdrawal, and withdrawal symptoms were used to gauge the dose of buprenorphine. A medical student or resident in training on AM sat with the patient for the entire procedure, which lasted about 15 min. Average doses were 24 mg for maintenance at below 180 morphine equivalents per day and 32 mg for higher maintenance. We have found[16,18] that when patients leave this first meeting feeling well because of ingesting a dose of buprenorphine that matches the amount of opioid they had been taking before entering withdrawal, it makes for a strong therapeutic alliance and a high rate of completion of outpatient detoxification. Patients on methadone treatment were switched to a short-acting opioid, usually oxycodone, 2 weeks prior to beginning the detoxification process. A more detailed explanation of our approach is available.[16]

Acute withdrawal symptoms were treated with the following medications as needed: clonidine for anxiety and agitation; trazodone for insomnia; dicyclomine for gut cramps and diarrhea; loperamide for diarrhea; NSAID for pain; and chlorpromazine for nausea, vomiting, and anxiety.

All patients were recommended to start LDN 1 week after buprenorphine administration. Use of LDN at the one week point was an effort to improve our outcomes. The dose was started at 0.1 mg per day and titrated to a maximum of 4.5 mg per day. Since this case series was completed, we have begun the first dose of LDN immediately after the single dose of buprenorphine. Patient feedback has been that it seems more efficacious when started immediately.

Cost was often cited as the reason for non-compliance with LDN (24/77 did not fill their LDN prescription). Most insurers did not cover the prescription, and patients often stated that they could not afford a medication that cost $33 for the first month, and somewhat more for the 4.5 mg continuation dose.

During the first week of detoxification, patients were seen daily for medical assessment and transference focused psychotherapy. Patients received a handout of treatments for chronic pain that included physical activity and physical therapy as the most efficacious approach. Therapists would ask, "Most people who get better go to physical therapy or exercise at least 1 h per day. You are not doing that. Tell me your thoughts." After the initial week, patients were seen twice weekly. The number of weekly sessions was then tailored to each patient's needs. 100% of scheduled visits equated to 11 sessions in the first month of treatment.

All patients were given the cell phone number of the senior author and told to "call day or night if there is a problem." This helped prevent patients from returning to opioid use for pain management, as all pain complaints between treatment hours were immediately addressed. Patients were told that their pain was expected to improve with detoxification. They were given a hand out that included a menu of non-opioid alternatives for treatment of pain, an explanation of OIH, and a table from Miller, Swiney, and Barkin[9] showing reduction in pain scores during detoxification from oxycodone and hydrocodone. We cannot be sure why there was not 100% completion given the comprehensiveness of treatment and the complete availability of help. However, a common experience is that those who return to opioid use before one month used the "pain exception" justification that is part of the denial of addiction—that their pain is unique and requires opioids for immediate relief.

Measurement of Pain Sensitivity

Patients underwent an initial evaluation, during which pain was assessed with a visual analog scale that ranged from zero to ten. Pain was re-assessed at each follow-up visit and categorized as worse, no change, or improved.

Pain sensitivity was estimated using the cold pressor time (CPT). This test consists of a stirred ice-water bath at 1°C. Each subject is asked to submerge their forearm into the bath and remove it when the pain was no longer tolerable. If withdrawal from the bath was not necessary, the test was terminated after 180 sec. Duration of submersion was used as a measure of pain tolerance.[18] Repeat CPT was performed for a subset of patients. We ideally would have liked repeat CPT for all patients. However, there were several factors that prevented repeat tests in many cases, including unavailability of the patient when the CPT ice bath was set up, patient refusal to undergo a repeat test because of the pain involved, and shifting trainees at a busy academic practice. Length of time between initial and repeat CPT ranged from 2 weeks to 2 years, but was usually repeated at 1 month. Repeat CPT was performed to measure treatment response.

Because OIH can manifest clinically as improved pain following a reduction in opioid dose,[7] we measured subjective pain scales and CPTs before and after opioid cessation. Improvement in these measures after detoxification, or removal of opioids without any worsening of pain, was considered to suggest the resolution of OIH. As this was a clinical case series, assessments were not blinded.

Measurement of Outcomes

Urine Drug Screens (UDS) are not done in our drug-free treatment approach. The nature of transference focused

psychotherapy requires that we trust patients to be honest. There is no penalty for relapse. Relapses are taken as a sign that something is wrong in the relationship with treaters that needs to be addressed as a part of examining the therapeutic alliance and transference, a routine aspect of treatment. In a funded case series being prepared for submission, where we were able to have a research assistant perform UDS that were not reported to treaters until the end of a 6 month observation period, reported use and UDS matched completely.

Statistical Analysis

Cold Pressor test data was not distributed normally due to the 180 sec cutoff (mode = 180) and the inherent subjectivity of the test. Therefore all CPT statistics utilized non-parametric tests. All other criteria were treated as normally distributed. Statistics were calculated using IBM SPSS Statistics Version 22.

RESULTS

Subjects

Of 225 consecutive new evaluations in the 10-month period, 118 presented with pain. One patient was excluded from the study because she was pregnant. Of the remaining 117, 112 were using conventional opioids only, and five were using diacetylmorphine (heroin) alone or in combination with conventional opioids. The age range of the 117 subjects was 14–79 years, with a mean age of 47.2 years (SD = 12.8). There were 48 males and 69 females.

The age range of the 37 controls was 19–94 years, with a mean age of 52.4 years (SD = 14.1). There were 20 males and 17 females.

There was no significant difference in gender distribution between the control and the experimental groups ($t(152) = 1.39$, $p = .166$). There was a significant difference in the age distribution between the two groups ($t(152) = 2.09$, $p = .039$). However, there was no significant correlation between CPT and age in either group (control: $r = -.026$, $p = .879$; subjects: $r = -.029$, $p = .763$).

As an attempt to show who these patients were, we give the payer mix on AM in 2015: 51% Medicare or Medicaid, 35% commercial insurance, 9% self-pay, and 5% workers compensation. Patients were more commonly poor and unemployed than employed and commercially insured. The payer mix for the study sample is unavailable.

Completion of 1 Month of Abstinence From Opioids

Of the 117 subjects using daily opioids for pain, 61 (52%; 95%CI [43, 61]) completed at least one month abstinent from opioids after detoxification.

Subjective Pain

Of 61 patients who reported 1 month of opioid and other drug abstinence (excluding nicotine and non-addictive alcohol use), two reported a worsening of pain (3%, 95% CI [−1, 8]), 28 reported no change in pain (46%, 95%CI [33, 59]) and 31 reported an improvement in pain (51%, 95%CI [38, 64]).

Initial Cold Pressor Test

Cold pressor times for the controls ($n = 37$, mean = 102 sec, median = 94, SD = 66, Skewness = 0.33, Kurtosis = 1.7), and daily opioid users for pain ($n = 108$, mean = 48, SD = 54, Skewness = 1.4, Kurtosis = 0.65) were not normally distributed. The distributions were determined to be statistically different with $p < .001$ using Independent Sample Mann–Whitney U Test ($U = 3070$, $z = 4.85$, $p < .001$, $r = 0.402$).

Repeat Cold Pressor Test

Of 61 patients who completed 1 month of abstinence, 20 underwent a repeat CPT. 18 (90%) saw an improvement in CPT. Six subjects had several repeat CPTs performed. The change in CPT was calculated by subtracting the initial CPT from the most recent repeat CPT. Change in CPT was found to be statistically significant using the Related-Samples Wilcoxon Signed Rank Test ($T = 189$, $p = .002$, $r = .50$).

Low-Dose Naltrexone (LDN)

There was no measurable difference in outcomes. ($p = 0.5$)

DISCUSSION

OIH serves as a potential explanation for the loss of opioid efficacy in chronic pain patients. After opioid cessation, patients in this case series were treated with non-opioid pain medications, LDN (when medication compliant) and psychotherapy. Following opioid detoxification and a 1-month period of opioid abstinence, we did not detected a positive effect on pain provided by opioid maintenance in 97% of our case series. Opioids for chronic pain were not superior to non-opioid pain medications, LDN and psychotherapy and were actually inferior in one half of patients. It is possible that opioid maintenance was offset by improved mood, actively addressing pain complaints as a result of psychotherapy interventions, and NSAIDs. While we have not been able to obtain an answer to the prevalence of OIH in this case series, and despite the limitations of our data as described below, the finding of a significant difference between the CPT of patients, 48 sec, and controls who accompanied the patients to the initial assessment, 102 s, may mean that OIH is the rule rather than the exception when patients are maintained on opioids for chronic pain.

The positive effect of LDN on pain tolerance, as we have suggested in previous publications[16,18] was not found. LDN may be helpful in restoring endogenous opioid damping of pain signals when examined with a larger sample of subjects. A randomized, double blind study is needed to adjudicate this question. We also note the important work

of Pud and colleagues[20,21] showing that OIH was still present at 1 month but had disappeared by 5 months after detoxification from opioids. This is a marker of protracted withdrawal that we aim to address with LDN. It is possible that the emotional relatedness involved in transference focused psychotherapy, pharmacotherapy, and LDN are having a synergistic effect on recovery of endogenous opioid tone for some of our patients. This suggestion also requires further evaluation.

Many methodological problems limit the generalizability of our results. This was an observational study with numerous dropouts. The sample is heterogeneous except for the specific treatment protocol. Cold pressor times were not available for all new patients (108 obtained for 117 subjects), introducing the possibility that there was a selection bias regarding which patients made themselves available for this test, and of those, which practitioners recognized the need for a baseline value. One month follow-up is insufficient to determine the effectiveness of this treatment approach. We relied on our patients to be honest. It is possible that some of the patients who reported improved or unchanged pain off opioids were taking opioids without our knowledge. The goal of showing the payer mix on AM is to suggest that our patients were mostly poor and disadvantaged. It is possible that the group reported here were not representative of AM patients.

This is a report of a retrospectively examined clinical case series. There were no blind assessments of pain complaints. It is possible that there were misreports either by patients who wanted to please their treating therapists, or therapists who wanted to experience an improvement in pain as part of countertransference.

Another limitation of this study is the lack of blinded assessment when performing the CPT. However, CPT among daily opioid users was found to be significantly lower than the average CPT among the non-opioid using SPs, suggesting that OIH had occurred. The improvement in CPT after cessation of opioids may represent amelioration of OIH. It may also represent a seriously biased sample in that we were able to report only a limited subset of repeat CPT.

CONCLUSIONS

Although there are limitations to this case series, it undermines the common practice of maintaining patients with chronic non-malignant pain on opioid analgesics. We found that compared with our non-opioid treatment opioids were having no effect on pain or making it worse in 97% of patients. Although it may be that the other treatments were as efficacious as chronic opioid therapy, the possibility of as much as 97% prevalence of OIH in a population of opioid maintained patients with chronic pain is a central concern.

In addition to the risk of OIH, opioid maintenance incurs side effects and financial cost without appearing to benefit patients. It may be that physicians are good at inducing patients onto opioid maintenance but lack the technology to get them off. This case series illustrates an outpatient model of opioid detoxification plus non-opioid pain management that is effective in treating patients with chronic pain. CPT may be a valuable tool in assessing pain complaints and following pain tolerance as part of clinical care. LDN may be a helpful adjunctive treatment for detoxification from opioids and should undergo further testing.

Jordan Levy received federal work study payment for a summer of reviewing records.

Declaration of Interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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