DISCOVERY MEDICINE®
www.discoverymedicine.com
ISSN: 1539-6509; eISSN: 1944-7930

Clinical Utility of the Cold Pressor Test: Evaluation of Pain Patients, Treatment of Opioid-induced Hyperalgesia and Fibromyalgia with Low Dose Naltrexone

Zachary Oaks, Anola Stage, Bradley Middleton, Stephen Faraone, and Brian Johnson

Abstract: *Background*. The cold pressor test (CPT) has been used in experimental paradigms to measure pain tolerance. It is used clinically to evaluate for opioid-induced hyperalgesia (OIH), as part of the clinical evaluation of fibromyalgia, to document reversal of OIH by low dose naltrexone (LDN), and to document the clinical response of fibromyalgia to LDN. *Methods*. We reviewed charts of 254 outpatients admitted to addiction medicine with chronic opioid treatment for pain, opioid addiction, or fibromyalgia. Controls were 46 non-addicted support persons. We invented the term "morphine years," a year at 60 mg/day, to estimate opioid exposure. *Results*. The mean age of patients was 41.4 years and controls 51.5. Age was not significantly correlated with CPT within each group. Female patients' mean CPT score (in seconds) was 35.0, male patients' 56.1, female controls' 110.8, male controls' 114.3. More morphine years correlated with younger age, more depression, higher prevalence of borderline personality disorder and attention deficit hyperactivity disorder, and low CPT. LDN increased CPT and reduced pain symptoms for both opioid users and fibromyalgia patients, with the increase being significantly higher for opioid users. *Conclusions*. CPT is an objective complement to the subjective FACES pain scale. It gives an objective measure of changes in pain sensitivity accompanying administration of LDN. Limitations of a case series report are noted. *Significance*. CPT is shown to be an objective test of pain tolerance with clinical applications: evaluation of OIH, evaluation of fibromyalgia, reversal of OIH, protracted withdrawal with LDN, and amelioration of fibromyalgia with LDN. [*Discovery Medicine* 26(144):197-206, November 2018]

***Zachary Oaks**, M.D., Ph.D., **Anola Stage**, M.D., **Bradley Middleton**, M.D., **Stephen Faraone**, Ph.D., and **Brian Johnson**, M.D., **
Department of Psychiatry, State University of New York (SUNY) Upstate Medical University, Syracuse, NY 13210, USA.

** Corresponding Author: Brian Johnson, M.D. (johnsonb@upstate.edu)*

Introduction

Pain Medicine suffers from the lack of an objective measure of pain. There are limited tools to quantify pain clinically. Currently, self-report scales are the "gold standard" (Jensen, 2016). The most commonly used test, the FACES Pain Scale, is inherently subjective and lacks pain sensitivity information. Using the FACES Pain Scale puts the physician addressing chronic pain in a difficult position. When pain patients are maintained on opioids, dose is typically proportional to the estimate of pain. Many patients want opioid pills because of addiction or because of anxiety about pain that they experience as intolerable. They know that if they report higher scores on the FACES Pain Scale, it is more likely that their physician will grant their wish for more opioid pain medication. If the patient claims 10/10 pain, on what grounds might a treating health professional disagree? The main objective of the present work is to solve this problem. It would be useful to have an objective test of pain sensitivity, a kind of "blood pressure" equivalent to the pain system. One would never guess blood pressure by speaking with a patient. Similarly, we

cannot know pain tolerance without an objective measure. Our answer is the cold pressor test (CPT). By combining subjective pain complaints with an objective measure of pain tolerance, Pain Medicine services have a way to assess pain complaints with precision.

The cold pressor test (CPT) has a long history as an experimental paradigm for cold pain tolerance (Treister *et al*., 2015). A normal forearm is immersed in an ice water bath at 1 degree Celsius. This experience is made more painful by the presence of a circulating pump that prevents the buildup of a warmer layer of water around the forearm. Pain tolerance is the elapsed time before the subject finds the pain intolerable and withdraws the arm from the ice water. The test-retest reliability of the CPT is high. In a study of healthy undergraduate students, there were no significant differences in pain tolerance (65 seconds to 63 seconds two weeks later, p=0.53) with two weeks in between the initial and repeat CPT (Koenig *et al*., 2014). In another study testing the reliability of blood pressure changes with the CPT, the test's original function, repeat measurements were taken four years after the initial tests. The correlation coefficient of 0.42 (95% confidence interval: 0.35-0.49) indicated the blood pressure response to the CPT is a long-term reproducible and stable characteristic (Zhao *et al*., 2012).

But using this simple test immediately brings up the question: "Why would some patients have normal times, others short times?" The answer is the concept of brain-mediated pain. Pain signals from peripheral body parts such as the forearm are interpreted by the brain. The endogenous morphine receptor system is an important contributor to pain damping. We have suggested that endogenous opioids are hormones that circulate through the blood with receptors on diverse tissues including gut, synovium, keratinocytes, monocytes, T and B lymphocytes, mast cells, peripheral nerve fibers, dorsal root ganglia, substantia gelatinosa of the spinal cord and midbrain, periaqueductal grey, medial thalamus, locus ceruleus, striatum, and hippocampus (Johnson *et al*., 2014). Our answer is that opioid-induced hyperalgesia is a disorder of low receptor tone provoked by exogenous hormone administration. Pud *et al*. (2006) showed that opioid-addicted patients had CPT times roughly half of non-addicted controls, suggesting that opioids had sensitized the pain system (OIH). CPT times did not change over a month of abstinence (Pud *et al*., 2006). The OIH was enduring.

This brings up another related question. If exogenous opioid administration degrades the opioid receptor system, does more exposure to exogenous hormone cause more harm? To answer this question, we combined our careful histories of opioid use in our patients with a novel concept, "morphine years." We defined one morphine year as one year at a reasonable dose for pain control of 60 morphine milligram equivalents (MME) per day. Since we have the information, we could also look at who uses large amounts of opioids. What psychopathology drives receptor system degradation?

Fibromyalgia is conceptualized as an autoimmune disease that strikes the opioid receptor system (Ramanathan *et al*., 2012; Johnson *et al*., 2014). It has the 3:1 female/male ratio typical of autoimmune disease. There are decreased central mu opioid receptors (Harris *et al*., 2007). Central nervous system opioids increased (Baruniak *et al*., 2004), as if trying to get a degraded opioid receptor system to respond. Opioids are prescribed for most patients with fibromyalgia (Berger *et al*., 2010). If there were already a degraded receptor system caused by an autoimmune process, exogenous opioid administration would be likely to degrade the opioid receptor system further.

We have hypothesized that low dose naltrexone (LDN) blockade can improve pain tolerance by increasing the efficacy of opioid receptors by opposing receptor downregulation provoked by chronic opioid treatment and partially reversing the autoimmune process of fibromyalgia (Johnson *et al*., 2014). According to Brown and Panksepp (2009), "LDN increased opioid receptors and elevated circulating beta-endorphin (BE) and met-enkephalin (ME) after a 4-6 hour period of receptor blockade. This 'rebound phase' may release the increased density of mu and delta opioid receptors for endogenous opioid stimulation and the increasing availability of BE and ME. Our overarching hypothesis is that increased concentrations of BE and ME gain access to an increased density of mu opioid and delta opioid receptors to 'functionally supersensitize' endogenous opioid systems." Using our concept about what fibromyalgia is, we would expect a more robust response to LDN in patients who had potentially restorable opioid receptor system to fibromyalgia patients where we could only oppose the autoimmune disease that has caused damage to the receptors.

Use of the CPT for evaluation and for follow-up of opioid-maintained chronic pain, opioid-addicted, and fibromyalgia patients may provide an objective measure of improvement, either with discontinuation of opioids, use of LDN, or both. We report the clinical utility of using the CPT as a routine measure of pain tolerance,

including showing the amelioration of subjective pain with LDN and a corresponding increase in CPT for both OIH and fibromyalgia.

Patients and Methods

Participants

We reviewed all patients who presented to the Addiction Medicine (AM) Service at State University of New York Upstate Medical University (SUNY Upstate) between June 2015 and July 2016. AM sees patients with a variety of addictions including alcohol, cannabis, gambling, etc. CPT is done once a week for opioid dependent and fibromyalgia patients. A total of 429 unique patients were seen over those 14 months. Of those patients, 254 met our inclusion criterion, which required at least one CPT recorded.

Controls

New patients are required to bring a non-addicted support person (SP) to their initial evaluation. 46 SPs who reported no recent use of opioids, cannabis, or tobacco (all three may change pain tolerance: Hill *et al*., 2017) served as normal controls. We believed that SPs would be an ideal comparison group because they were chosen by our patients, were most commonly first degree relatives, and were similar in ethnicity and socioeconomic background. Many of our patients bring their parents, which made this group slightly older than the patient participants.

The SUNY Upstate Institutional Review Board (IRB) approved the study protocol. All subjects over 18 provided written informed consent prospectively which allowed us to use their de-identified information. Those under 18 had the informed consent cosigned by a parent. SPs signed an IRB approved control group informed consent form. Information on patients was obtained by retrospective record review.

Evaluation

Baseline measures were: chief complaint, history of present illness, psychiatric, medical, family and social histories, a comprehensive grid of all drug use including onset of use, amount used, last date used, the Structured Clinical Interview for DSM5 (SCID2) checklist for borderline personality disorder, the Adult ADHD Self Report Scale (ASRS) for attention deficit hyperactivity disorder (ADHD) followed up by a DSM5 interview if ADHD was suspected, a Hamilton Rating Scale for Depression, a Modified Mini-Mental Status Examination for cognitive impairment, CPT, FACES Pain Scale, and physical examination looking for pain drivers. Cases were discussed in a conference style that included senior author, trainees, patient, and support person. Diagnoses were made by consensus using the above measures.

Medications

Some patients arrived while on opioids, others came a few hours after their last opioid dose because they wanted to begin detoxification at the initial visit. We have not found that being on opioids or recently discontinuing them has much effect on CPT scores because long-term opioid administration makes the CPT already dramatically lower. Similarly, Doverty *et al*. (2001) found there was little difference between CPT at peak and trough methadone doses.

Cold pressor test and opioid-induced hyperalgesia

The CPT was performed on new patients during an initial evaluation and some follow-up visits. For high pain tolerant patients, the test was terminated after 180 seconds for safety. The CPT was repeated to evaluate changes in pain sensitivity and to reassess treatment plans, especially how long to continue LDN. LDN was discontinued when CPT maximized at 180 seconds.

Patients were also asked to gauge their pain during the initial evaluation on the FACES pain scale from 0-10. Pain was reassessed at follow-up visits and categorized as better, worse, or no change. OIH was defined as a short CPT, less than 35 seconds (the bottom 10% of a previous series of non-addicted controls), or by a history of escalating opioid dose past the limit of high dose prescribing, 200 morphine equivalents/day, without any improvement in pain.

Treatment

Treatment has been described at length in a previous publication (Johnson and Faraone, 2013). If physically dependent on opioids, patients were detoxified using a single dose of buprenorphine, adjunctive medications, and transference-focused psychotherapy with a previously reported completion rate of 92%. At the time of this case series, low-dose naltrexone was begun one week after administration of buprenorphine and given daily starting at 0.1 mg/day and building up gradually to 4.5 mg/day. More recently we administered it immediately after buprenorphine and gave it twice a day. For fibromyalgia patients not physically dependent on opioids, naltrexone was immediately begun at 0.1 mg

twice a day. Patients came daily for the first week, then twice a week until stable and dischargeable.

Morphine years

Patients were asked about onset, duration, and dose of opioid medications or illicit opioids on admission. Morphine years is a new concept. Using the principle from tobacco use research of "pack years," we chose a moderate dose of morphine, 60 mg/day, administered over a year as our definition of one "morphine year" to see if opioid exposure would correlate with CPT. The academic estimate of the amount of diacetylmorphine in one "bag of heroin" is 81 mg (Reichle *et al*., 1962). Diacetylmorphine is three times more potent per-milligram than morphine. An average "habit" is ten bags/day (i.e., injecting the estimated equivalent of 2,430 mg morphine). No physician would prescribe as much as a drug dealer would routinely sell to a client. Users of illicit diacetylmorphine were likely to show high morphine years.

Statistical analysis

Statistical analyses were performed using GraphPad Prism software. Results are expressed as the mean± SEM of individual experiments. For patients with multiple visits, we performed listwise deletion to analyze only those with 2 or more CPT times. CPT times were log transformed for some analyses to account for positive data skewing because we set a maximum time of 180 seconds. Pairwise repeated-measures analyses of variance (ANOVA) and Student's t-tests were used for analyses of the results. Patients served as their own control in time-course and 2-way ANOVA analyses of response to LDN and change in CPT. Interaction of multiple variables on CPT was calculated by brute-force analysis with GraphPad Prism. P values less than 0.05 were considered significant.

Results

Participant patients

Of the 254 new patient consults, 252 reported past opioid use. Two of 37 fibromyalgia patients did not have a history of opioid use. 183 of the 252 patients reported initial opioid use for pain management. The other participants (27%) reported emotional/addictive initial use of opioids.

The age range of the 254 subjects was 14 to 89 years, with a mean age of 41.4±1.1 years. There were 152 females and 102 males. The average age of female patients was 42.5±1.4 years, while male patients were 39.7±1.5 years old (p=0.20).

Participant controls

The age range of the 46 controls was 19 to 94, with a mean age of 51.5±2.3 years. There were 23 females and 23 males. The average female control age was 48.8±3.3 years while male age was 54.1±3.1 years old (p=0.24).

Initial cold pressor time

At their first visit, the cold pressor time (CPT) of patients was 43.5±4.4 seconds, whereas control CPT time was 112.5±9.7 seconds ($p=2.72\times10^{-11}$). Overlaying the frequency distribution data shows the majority of patients had times less than 100 seconds, while the vast majority of controls had times greater than 100 seconds (Figure 1).

The p-value for comparing CPT between patients and controls was 1.1×10^{-11}. The p-value comparing CPT between male and female patients was 0.00039. The p-value of control CPT between male and female patients

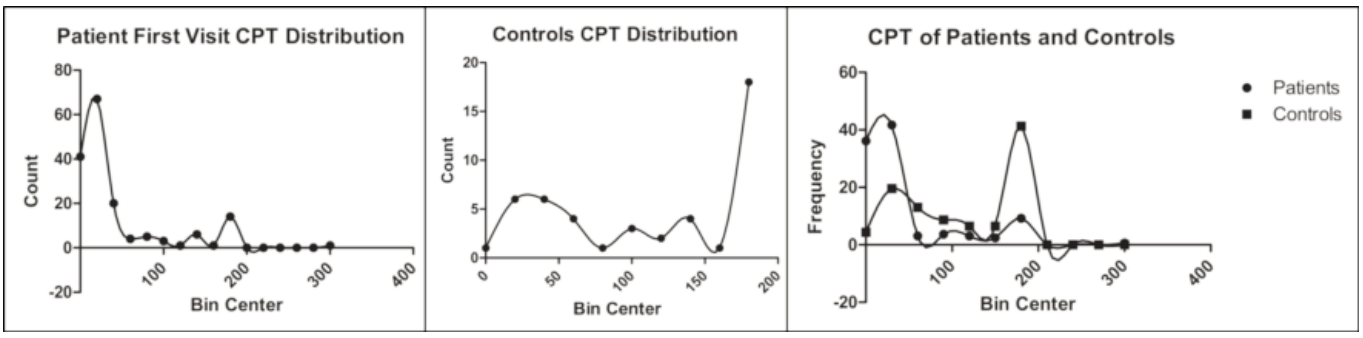

Figure 1. Mean initial CPT of patients is 44 seconds, controls 113 seconds.

was 0.45.

In summary, the mean first CPT for opioid-maintained patients was 39% (much more pain sensitive) of the mean first CPT for normal controls. This difference was statistically significant.

Age and initial CPT

The median age of the patient population (39 years) was used as a cut-off to compare younger (≤39 years of age) and older (>39 years of age) patients. There was no significant correlation between age and CPT in either patients (r^2=0.0017, p=0.60) or controls (r^2=0.0093, p=0.52). Younger patients (39.2±5.8 seconds) had significantly reduced CPT compared to controls (119.1±26.2 seconds) within the same age group ($p=9.9\times10^{-5}$). Older patients (47.1±6.6 seconds) had significantly reduced CPT compared to controls (111.2±10.5 seconds) within the same age group ($p=2.6\times10^{-7}$). In summary, within each group, there was no significant correlation between age and CPT and the calculated interaction between these two groups was not significant (p=0.37).

Gender and initial CPT

There were gender differences in CPT time for patients. Female patients had an average time of 35.0±5.3 seconds while males had an average time of 56.1±7.4 seconds (p=0.02). Controls, on the other hand, did not show gender differences. Female controls had an average CPT of 110.8±14.8 seconds while males had an average time of 114.3±12.8 seconds (p=0.85). The gender difference was limited to women who had been maintained on opioids. Interaction was not significant between gender and opioid use when participants were grouped by gender (p=0.20) or by patients vs. controls (p=0.12).

Response to treatment

Pain tolerance improved with treatment. The mean time interval between the first CPT and second CPT was 14.4±3.8 weeks. The mean time interval between the first and third CPT was 26.1±6.3 weeks. The mean time interval between the first and fourth CPT was 30.9±8.0 weeks.

Across all patients on our service, CPT times improved at subsequent follow-up visits with patients having a baseline mean of 25.1±4.3 seconds with significantly increased CPT at visits 2 (46.6±6.7 seconds, p=0.008), 3 (45.6±9.4 seconds, p=0.03), and 4 (50.3±13.4 seconds, p=0.03) relative to baseline (Figure 2).

Comparison of high and low morphine year cohorts

More morphine years were correlated with younger age, more depression, higher prevalence of borderline

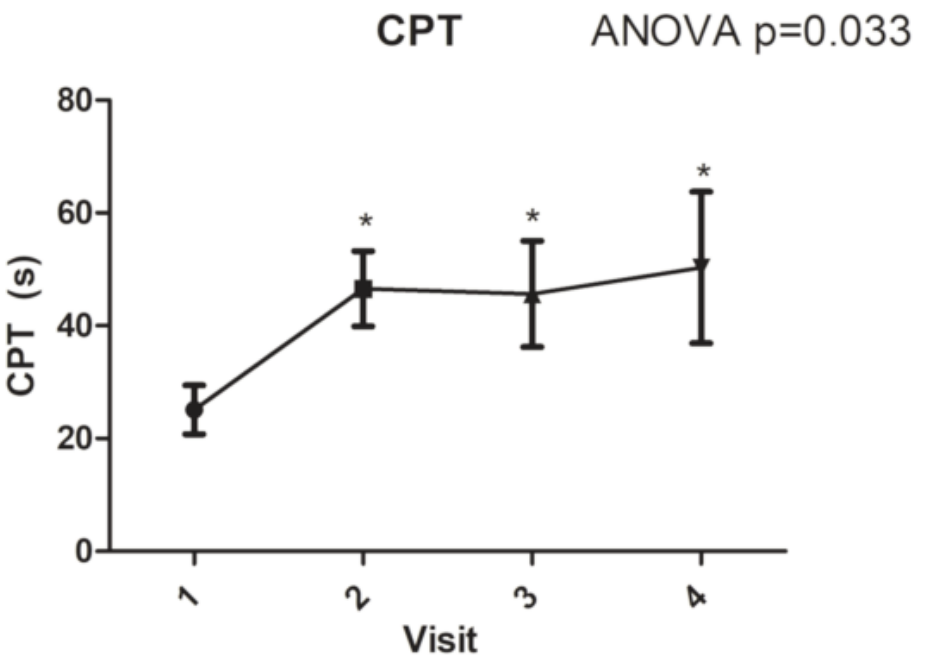

Figure 2. CPT rose over time.

personality disorder, higher prevalence of attention deficit hyperactivity disorder (ADHD), and lower CPT - measured pain tolerance (Figure 3).

Effect of LDN on CPT

Tracking the result of LDN required that the patient completed detoxification (except for the two patients who came to our pain service without being on opioids), that the patient purchased a medication that was not covered by insurance (most of our patients are indigent and on Medicaid or Medicare), that they continued in treatment, and that they agreed to undergo a second CPT when they knew it would be a painful experience. The number of patients who complied in all these ways was 35 opioid dependent and non-fibromyalgia patients and 15 fibromyalgia patients. LDN compliance correlated with improved CPT, ANOVA p=0.037 (Figure 4).

Comparison of opioid users and fibromyalgia patients on LDN

While opioid users (n=35) and fibromyalgia patients (n=15) both improved with LDN, the improvement was significantly more marked for opioid users, ANOVA p=0.028; interaction between groups was not significant with p=0.78.

Effect of LDN compliance

Both opioid users and fibromyalgia patients, with or without a history of opioid use, who were compliant with LDN improved more than non-compliant patients. Here, we show significant differences between the two groups over time, p=0.015. For the fibromyalgia patients on naltrexone who were grouped independent of past opioid use, there were 15 patients, with a mean follow-up time (between visit 1 and 2) of 10.1±3.7 weeks. For the patients with no fibromyalgia, opioid users, and on naltrexone, there were 35 patients, with a mean follow-up time of 13.4±5.4 weeks. For fibromyalgia patients who were not on naltrexone, there were two patients with a mean follow-up time of 13.5±5.6 weeks. For patients with no fibromyalgia, opioid users, and who were not receiving naltrexone, there were nine patients with a mean follow-up time of 25.5±13.3 weeks. There were no significant differences between groups regarding mean follow-up time (Figure 5).

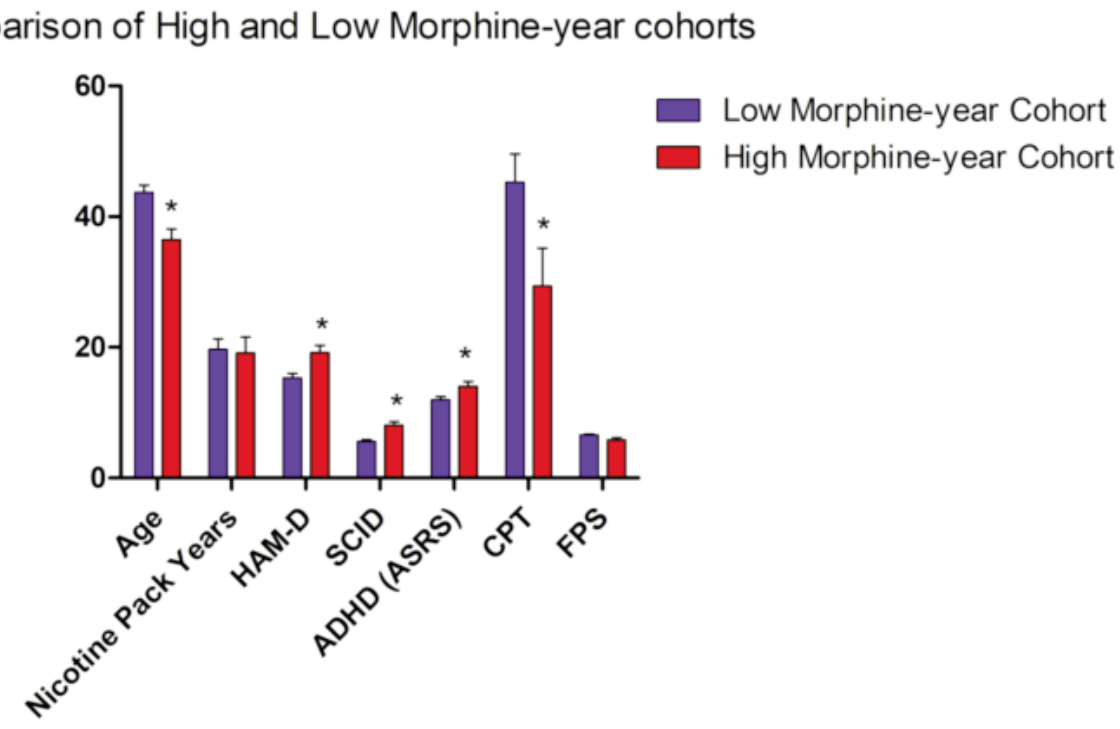

Figure 3. More morphine years was significantly associated with younger age, more depression, more borderline personality, more ADHD, and less CPT measured pain tolerance. * indicates a statistically significant difference.

Discussion

Clinical utility of the cold pressor test for diagnosis of opioid-induced hyperalgesia

Our results suggest that CPT is a helpful clinical test of the pain system. It avoids the subjectivity of the FACES scale. It balances the patient's concern about their pain symptoms with an objective measure. For example, the physician who evaluates a patient convinced that their chronic pain is best managed by daily opioid medications may use the CPT to introduce the concept of OIH. A patient managed with opioids who has a 3 minute CPT may receive a different approach than one with a 10 second CPT. In the latter case, the physician has objective evidence that opioid administration is causing central nervous system-mediated pain/hyperalgesia.

Clinical utility for treating opioid-addicted patients with pain complaints

In a previous case series we showed that, when patients complaining about pain were detoxified from opioids and given a combination of psychotherapy, low dose naltrexone, and non-opioid pain treatments, a month later 3% reported increased pain, 46% reported the pain was no different than when they had been maintained on opioids, and 51% reported that their pain was less than during opioid maintenance pain treatment (Belkin *et al*., 2017). A short CPT indicates that central sensitization is a driver of pain. For a patient maintained on opioids who must pull their normal forearm out of the ice water after a brief exposure, the physician can confidently predict that detoxification and alternative pain treatments, including LDN, will result in less pain. If the patient demands opioid maintenance, the reason for this cannot be to help their pain. Therefore the standard definition of addiction applies: "Urgent wish for the drug despite harm." This way of diagnosing opioid addiction is a new concept and a novel outcome of using the CPT on pain services.

Opioid exposure, prevalence, and severity of opioid-induced hyperalgesia

We have provided evidence that OIH may be a universal response to opioid maintenance, mediated by down-regulation of the opioid receptor system by exogenous hormone administration. Support persons were chosen as the control group for this case series because they come from the patients' cultural milieu, and most commonly are first-degree relatives. There is a striking difference in CPT time between patients and their support persons. This gives evidence that opioid maintenance treatment of chronic pain increases the chronic pain. If patient and physician are unaware of OIH, doses of opioids may be escalated for intensified pain. At an extreme, the patient may die from an unintentional opioid overdose. We have confirmed the hypothesis that more exogenous opioid exposure causes shorter cold pressor times/greater brain-medicated pain amplification.

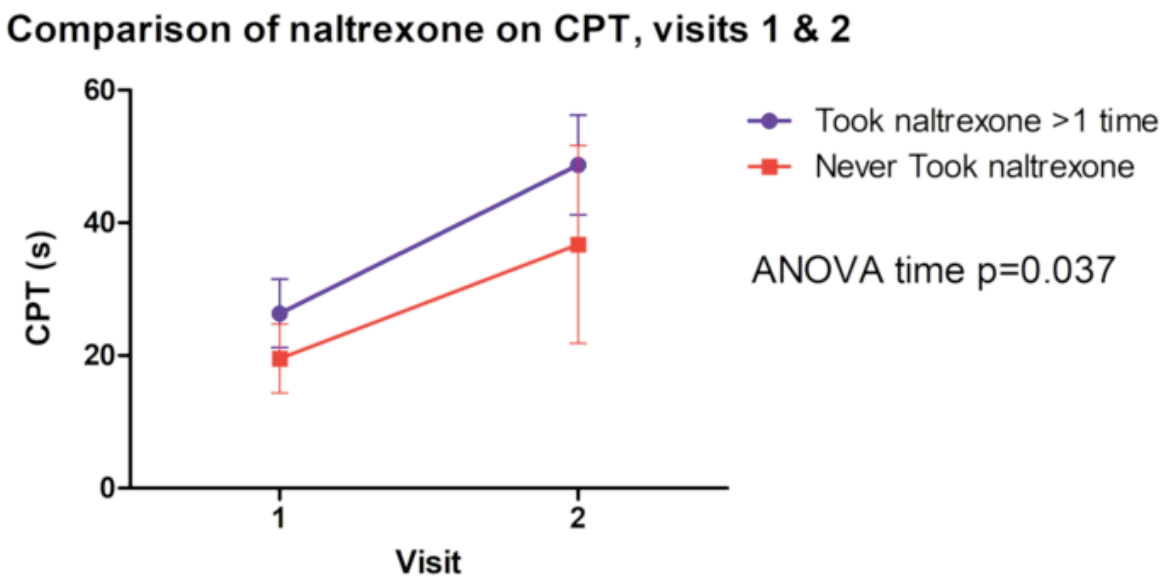

Figure 4. Low dose naltrexone compliance correlated with improved pain tolerance over time.

Psychopathology and opioid use

We have suggested that opioids are being used by persons who lack the ability to augment endogenous opioid tone via human interactions that involve emotional closeness (Johnson and Faraone, 2013). For persons with optimal opioid tone mediated by keeping others close and having warm, pleasant interactions, exogenous opioids are aversive. For persons who are frightened of emotional closeness and/or don't know how to conduct relationships effectively, opioid use promotes good feelings, a "person in a pill." The finding that more morphine years correlated with younger age, more depression, higher prevalence of borderline personality disorder, higher prevalence of attention deficit hyperactivity disorder (ADHD), and lower CPT, supports this hypothesis. The patients in our series with significant psychopathology started using opioids at a younger age and obtained the much larger doses available from drug dealers rather than physicians. This high exposure as shown by more morphine years appears to have degraded their pain tolerance more than other opioid-maintained patients.

Low dose naltrexone for treating opioid-induced hyperalgesia and fibromyalgia

We have previously noted the congruence of symptoms of opioid withdrawal and fibromyalgia. We hypothesized that the reason for this congruence was that both conditions downregulated the opioid receptor system (Johnson *et al*., 2014). Opioid receptor number and efficacy were hypothesized to decrease as a result of exogenous opioid administration as treatment of pain by physicians or administration of opioids received from drug dealers. In fibromyalgia, the decrease in opioid receptor efficacy was hypothesized to be the result of an autoimmune process (Ramanathan *et al*., 2012; Johnson *et al*., 2014). In this case series report, we have provided more preliminary evidence that LDN may be of value in treating OIH and fibromyalgia. If fibromyalgia is the result of autoimmune attack on the opioid receptor system, there would be less receptor to bring back than if the receptor system had merely been suppressed by exogenous opioid administration. This effect would account for the lesser response to LDN among fibromyalgia patients than the response of opioid-maintained patients. A randomized, double-blind study would be of value in further developing this use of naltrexone.

Limitations of a case series

The lack of blinding in all measures involved in this clinical case series compromises the validity of the reported results. We may have confirmed a bias that our treatment would be effective. Compliance with suggested treatment may have influenced patients to have an expectation of improvement. The results are also limited by the lack of compliance with LDN. Overall, the patient population treated on Addiction Medicine is poor. A common objection to taking LDN was that the patient's insurance would not pay for it and the patients stated that they could not afford to buy a medication

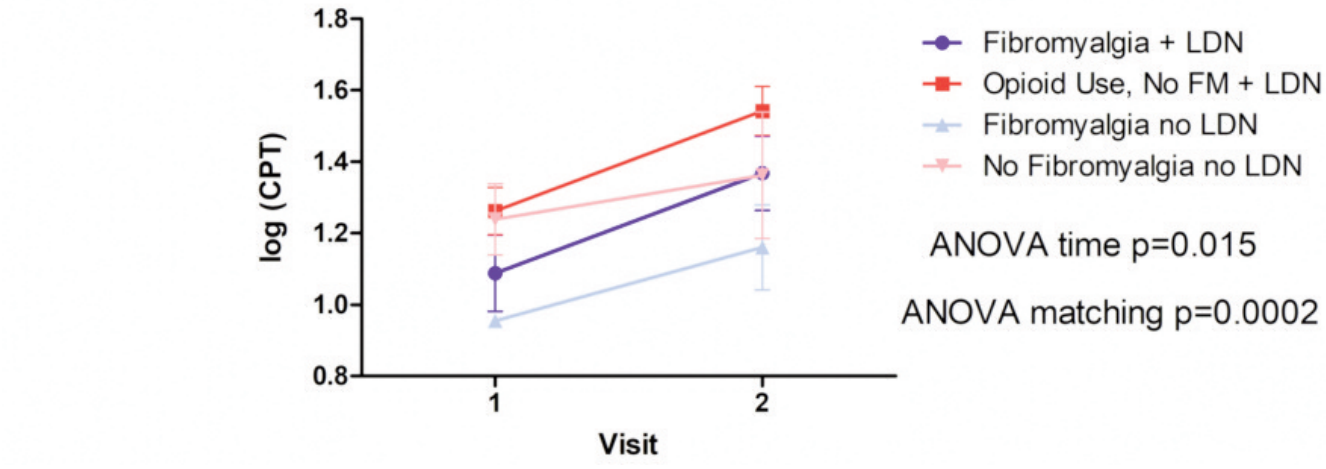

Figure 5. Comparison of opioids users vs. fibromyalgia patients on +/1 LDN, visits 1 and 2. LDN helps patients with fibromyalgia and with opioid use disorder.

that cost over $30. Sometimes this may have been true, other times it may be that emotional issues contributed to non-compliance.

The CPT may have inherent limitations. Other factors may influence the CPT. One limitation of the CPT may involve effort. Some patients appear to give their all to endure the pain of the CPT, while others do not. Effort may be correlated with treatment response. We have wondered about the significant gender difference in pain tolerance among patients that does not occur in controls. It may be that the pain of forearm immersion is startling and that our female patients have been more traumatized emotionally than our men, and that fear influences CPT.

Conclusions

Despite its limitations, this study supports the clinical utility of the CPT as an objective measure of pain sensitivity. Combining it with a FACES Pain Scale then gives objective and subjective measures of pain. A common combination, short CPT and high FACES Pain Scale, helps the patient understand that the use of opioids for pain has become counterproductive. Diagnosing OIH using the CPT leads to a treatment approach that requires discontinuation of opioid pain medications.

The CPT can be useful in assessing pain sensitivity as part of the initial evaluation of pain complaints. The CPT, if repeatedly used for the same patient over the course of treatment time, is helpful in following the progression of pain sensitivity. Efficacy of LDN to treat OIH, protracted withdrawal, and fibromyalgia, may be followed by combining subjective change in pain and withdrawal symptoms with pain tolerance as objectively measured by CPT.

Disclosure

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

References

Baron MJ, McDonald PW. Significant pain reduction in chronic pain patients after detoxification from high-dose opioids. *J Opioid Management* 2:277-282, 2006.

Baraniuk JN, Whalen G, Cunningham J, Clauw DJ. Cerebrospinal fluid levels of opioid peptides in fibromyalgia and chronic low back pain. *BMC Muscular Disord* 5:58, 2004.

Belkin M, Reinheimer S, Levy J, Johnson B. Ameliorative response to detoxification, psychotherapy, and medical management in patients maintained on opioids for pain. *Am J Addict* 26:738-743, 2017.

Berger A, Sadosky A, Dukes EM, Edelsberg J, Zlateva G, Oster G. Patterns of healthcare utilization and cost in patients with newly diagnosed fibromyalgia. *Am J Managed Care* 16:S126-S137, 2010.

Brown N, Panksepp J. Low-dose naltrexone for disease prevention and quality of life.*Med Hypotheses*72:333-337, 2009.

Doverty M, White JM, Somogyi AA, Bochner F, Ali R, Ling W. Hyperalgesic responses in methadone maintenance patients. *Pain* 90:91-96, 2001.

Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth* 112:991-1004, 2014.

Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central mu-opioid receptor availability in fibromyalgia. *J Neurosci* 12:10000-10006, 2007.

Hill KP, Palastro MD, Johnson B, Ditre JW. Cannabis and pain: a clinical review. *Cannabis Cannabinoid Res* 2(1):96-104, 2017.

Jensen B. Chronic pain assessment from bench to bedside: lessons along the translation continuum. *Transl Behav Med* 6:596-604, 2016.

Johnson B, Faraone SV. Outpatient detoxification completion and one month outcomes for opioid dependence: A preliminary open label study of a neuropsychoanalytic treatment in pain patients and addicted patients. *Neuropsychoanalysis* 15:145-160, 2013.

Johnson B, Ulberg S, Shivale S, Donalson J, Milczarski B, Faraone SV. Fibromyalgia, autism, and opioid addiction as natural and induced disorders of the endogenous opioid hormonal system. *Discov Med* 18:209-220, 2014.

Koenig J, Jarczok MN, Ellis RJ, Bach C, Thayer JF, Hillecke TK. Two-week test-retest stability of the cold pressor task procedure at two different temperatures as a measure of pain threshold and tolerance. *Pain Pract* 14:E126-E135, 2014.

Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 14:145-161, 2011.

Mao J. clinical implications of opioid-induced hyperalgesia. In: *Opioid-induced Hyperalgesia*. Mao J (ed.). pp174-180, Informa Healthcare USA, Inc., New York, NY, USA, 2010.

Pud D, Cohen D, Lawental E, Eisenberg E. Opioids and abnormal pain perception: New evidence from a study of chronic opioid addicts and healthy subjects.*Drug Alcohol Depend* 82:218-223, 2006.

Ramanathan S, Panksepp J, Johnson B. Is fibromyalgia an endocrine/endorphin deficit disorder? - Is low dose naltrexone a new treatment option? *Psychosomatics* 53:591-594, 2012.

Reichle CW, Smith GM, Gravenstein JS, Macris SG, Beecher HK. Comparative analgesic potency of heroin and morphine in postoperative patients. *J Pharmacol Exp Ther* 136:43-46, 1962.

Treister R, Nielsen CS, Stubhaug A, Rarrar JT, Pud D, Sawilowsky S, Oaklander AL. Experimental comparison of parametric versus nonparametric analyses of data from the cold pressor test. *J Pain* 16:537-548, 2015.

Zhao Q, Bazzano LA, Cao J, Li J, Chen J, Huang J, Chen J, Kelly TN, Chen CS, Hu D, Ma J, Rice TK, He J, Gu D. Reproducibility of blood pressure response to the cold pressor test. *Am J Epidemiol* 176(Suppl 7):S91-S98, 2012.