12-1-2015

Intrathecal pain pumps for the treatment of neuropathic pain: A retrospective review of the electronic medical record

Kathleen L. Reyes

Kathleen Lopez Reyes

Candidate

Biomedical Research Education Programs

Department

This thesis is approved, and it is acceptable in quality and form for publication:

Approved by the Thesis Committee:

Erin Milligan, PhD, Chairperson

Shiraz Mishra, MBBS, PhD

Eugene Koshkin, MD

INTRATHECAL PAIN PUMPS
FOR THE TREATMENT OF NEUROPATHIC PAIN:
A RETROSPECTIVE REVIEW OF THE
ELECTRONIC MEDICAL RECORD

by

KATHLEEN LOPEZ REYES

B.A., DARTMOUTH COLLEGE
M.D., UNIVERSITY OF NEW MEXICO

THESIS

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Master of Science
Biomedical Sciences

The University of New Mexico
Albuquerque, New Mexico

December, 2015

INTRATHECAL PAIN PUMPS
FOR THE TREATMENT OF NEUROPATHIC PAIN:
A RETROSPECTIVE REVIEW OF THE
ELECTRONIC MEDICAL RECORD

by

KATHLEEN LOPEZ REYES

B.A., DARTMOUTH COLLEGE. 2004
M.D., UNIVERSITY OF NEW MEXICO. 2009
M.S., BIOMEDICAL SCIENCES, UNIVERISTY OF NEW MEXICO, 2015

ABSTRACT

Most patients suffering from neuropathic pain will not obtain sufficient pain relief from current recommended therapy. The present study sought to compare patients with neuropathic pain treated with intrathecal drug delivery systems (IDDS) to those with oral opioid treatment alone via a retrospective analysis of electronic medical records. Pain scores and number and amount of adverse events were the primary endpoints of analysis. The most important finding of our study was that significantly fewer adverse events were found among patients treated with IDDS compared to patients treated with traditional oral medications. We examined the differences in recorded pain scores over time, but did not have statistically significant findings due to too many missing data points in the warehouse database. Future research will target pain outcomes utilizing a national database to enhance sample size.

TABLE OF CONTENTS

Chapter 1

Introduction

Existing therapies for chronic neuropathic pain, which affects 10% of the United States population (1), leave much to be desired. Most patients suffering from this condition do not obtain sufficient pain relief from current recommended pharmacological therapy (2, 3). Current treatment approaches typically rely heavily upon oral opioids, which lead to problems with drug tolerance as well as hyperalgesia and contribute to drug abuse risk and potentially death from overdose. An alternative treatment to oral opioids is the use of IDDS, which provides centrally administered medication with automated control decreasing the potential for unintended side effects. Multiple types of medications may be infused simultaneously through IDDS to optimize the therapeutic benefit.

Normal pain, the typical pain response produced by tissue injury (nociceptive pain), is a protective mechanism that serves as a warning signal for the body and induces behavioral changes that facilitate healing. A painful stimulus such as tissue damage first activates peripheral afferent (Aδ and C) neurons, sending an electrical signal down the nerve's axon towards the dorsal horn of the spinal cord. Second order neurons then relay the message to centers in the brainstem and thalamus, where synapses with third-order neurons then send signals to the cortex in the brain. As physiological nociceptive transmission occurs, the activity of these pain-projection neurons is also influenced by local inhibitory interneurons in the spinal cord and by input of descending neurons from

the brain (4).

The etiology of chronic neuropathic pain differs from that of normal pain. Any pathologic process that disrupts normal pain processing after an initial lesion to the nervous system can cause neuropathic pain. Non-neuronal cells of the central nervous system may contribute to neuropathic-pain processing by releasing classic immune cytokine signals. These signals induce pro-inflammatory responses with pathological effects such as spinal dorsal horn neuronal hyperexcitability (and therefore hyperalgesia), neurotoxicity, and chronic inflammation (5) resulting in neuropathic pain. Short-term perineural inflammatory activity is likely to be an adaptive response to acute nerve injury. When persistent, it unfortunately may become maladaptive and paradoxically result in severe, "burning"-type pain that persists even in the absence of any overt lesion. Neuropathic pain is clinically described as a burning sensation, a sensory deficit, pain caused by light touch (allodynia), or increased sensitivity to pain (hyperalgesia). Despite expanding knowledge of the distinct and complex mechanisms underlying chronic neuropathic pain over several decades (5), all current first-line drugs for neuropathic pain target neurons.

Opioids are one such class of drugs that target neurons and are commonly used to treat neuropathic pain. Opioids can be quite effective at treating nociceptive (normal) pain. They are traditionally known to bind mu opioid receptors in the substantia gelatinosa in the dorsal horn of the spinal cord. Recently it has been discovered that opioids also directly activate supporting neuronal cells (glia), which in turn induce the release of neuroexcitatory pro-inflammatory cytokines (as noted above) that oppose the

analgesic effects of opioids (5). This action causes opioids to counter their own benefits. This exacerbation or facilitation of the underlying mechanisms of chronic pain ultimately makes opioids a particularly poor choice to treat a condition already known to have a strong immune signaling component. However, because the management of patients with neuropathic pain is challenging (2, 6, 7), opioids are frequently used in combination with alternative pharmacological treatment. Treatment guidelines recommend their use in addition to other first line therapies such as tricyclic antidepressants, serotonin-norepineprhine reuptake inhibitors, pregabalin/gabapentin, and topical lidocaine (8, 9).

We have seen a nearly four-fold increase in the use of prescribed opioids (10) for the treatment of pain. This increase coincides with the increase in opioid overdose deaths (11) since the late 1990's when the Model Guidelines for the Use of Controlled Substances for the Treatment of Pain (12) were adopted by the Federation of State Medical Boards. While these guidelines were initiated by a justified concern that pain was being undertreated, overdose deaths due to prescription opioids now far outweigh those due to illicit drugs (13). Even when prescribed oral opioids are taken as recommended, side effects such as constipation, sedation, dizziness, nausea and vomiting are common (14). Long-term use can be associated with hypogonadism and opioid-induced hyperalgesia, which diminishes their benefit in chronic, nonmalignant pain (6).

Adverse events associated with use of IDDS must be weighed when considering these as a treatment option. These can be divided into opioid-related and device-related. Opioid-related adverse events (15) include nausea/vomiting (33%), urinary

retention (24%), pruritus (26%), pituitary dysfunction (16), and hypogonadism (17). Device-related complications include wound infection (12%), meningitis (2%), pump malposition (17%), catheter migration/dislodgement (12%), catheter obstruction/occlusion (19%), and mechanical failure (5%) (15). Case reports have demonstrated additional associated problems such as pump malfunction leading to overinfusion of contained medications (18), inadvertent injection of medication outside the pump with subsequent opioid overdose (19), a fractured intrathecal catheter migrating intracranially and causing a subarachnoid hemorrhage (20), radiographic evidence of spinal deformity (21) with IDDS implantation, and the self-administration of intramuscular morphine after a patient accessed the pump reservoir (22). Animal studies support that intrathecal granulomas arise from opioids degranulating meningeal mast cells (23, 24) and opioid concentration might correlate with granuloma formation was confirmed for the first time (25). Pump replacements are often performed prior to year 6 (26) for various reasons.

Despite the device-related complications and frequent maintenance, IDDS is thought to have the potential to be a life-long pain management solution in appropriately selected patients (27). Typically, a combination of medications can be simultaneously infused and generally consists of: 1) a local anesthetic/numbing medication such as bupivacaine, 2) an opioid analgesic such as morphine or hydromorphone, 3) sometimes the addition of the muscle relaxant, baclofen, and 4) occasionally an α-2 receptor agonist, clonidine. Advantages of treatment with IDDS are customizability under clinician supervision, reversibility, programmability, low risk

profile, and potential for improved pain relief and quality of life and reduced demand for health-care resources (28). They are considered to be accurate drug delivery systems that provide effective and a safe means for intrathecal administration of opioids for the treatment of chronic intractable pain (29). IDDS are thought to be beneficial for refractory cancer pain (30, 31) are considered for patients with chronic non-cancer pain when more conservative options fail (32), and are thought to provide sustained significant improvement in pain and functioning (33, 34) among this group of patients.

However, IDDS are only used inconsistently for neuropathic pain conditions. Perhaps because of this, their role in the treatment of chronic neuropathic pain is poorly studied. The few existing studies on IDDS for treatment of chronic non-cancer pain suggest that patients experience significant pain reduction and some improvement in physical functioning (15, 35-40). In patients treated with IDDS delivering opioids with or without adjuvant medications, the proportion of patients reporting a 50% or more pain reduction ranged from 30-56% (35, 36, 39) at 6 months in 3 studies, and 44% after a mean follow-up of 29 months (1 study) (36). While patients with neuropathic pain could potentially benefit from IDDS, there is evidence that annual increases in daily opioid dosage were higher among patients with neuropathic pain than among patients with other modalities (41). IDDS might be especially useful for patients with neuropathic pain of cancer origin where the pain is refractory to the highest tolerable doses of oral morphine and neuromodulator drugs (42, 43).

Therefore, the current study sought to examine the relative analgesic efficacy of IDDS compared to oral opioid treatment alone via a retrospective analysis of electronic

medical records. We hypothesized that pain pumps are linked to better pain relief and fewer side effects. Pain scores in neuropathic pain patients were the primary endpoint of analysis. As a secondary outcome, we also analyzed whether side effects occur significantly less frequently in neuropathic pain patients treated with combination therapy via intrathecal pumps compared to those treated with oral opioid medications.

Chapter 2

Methods

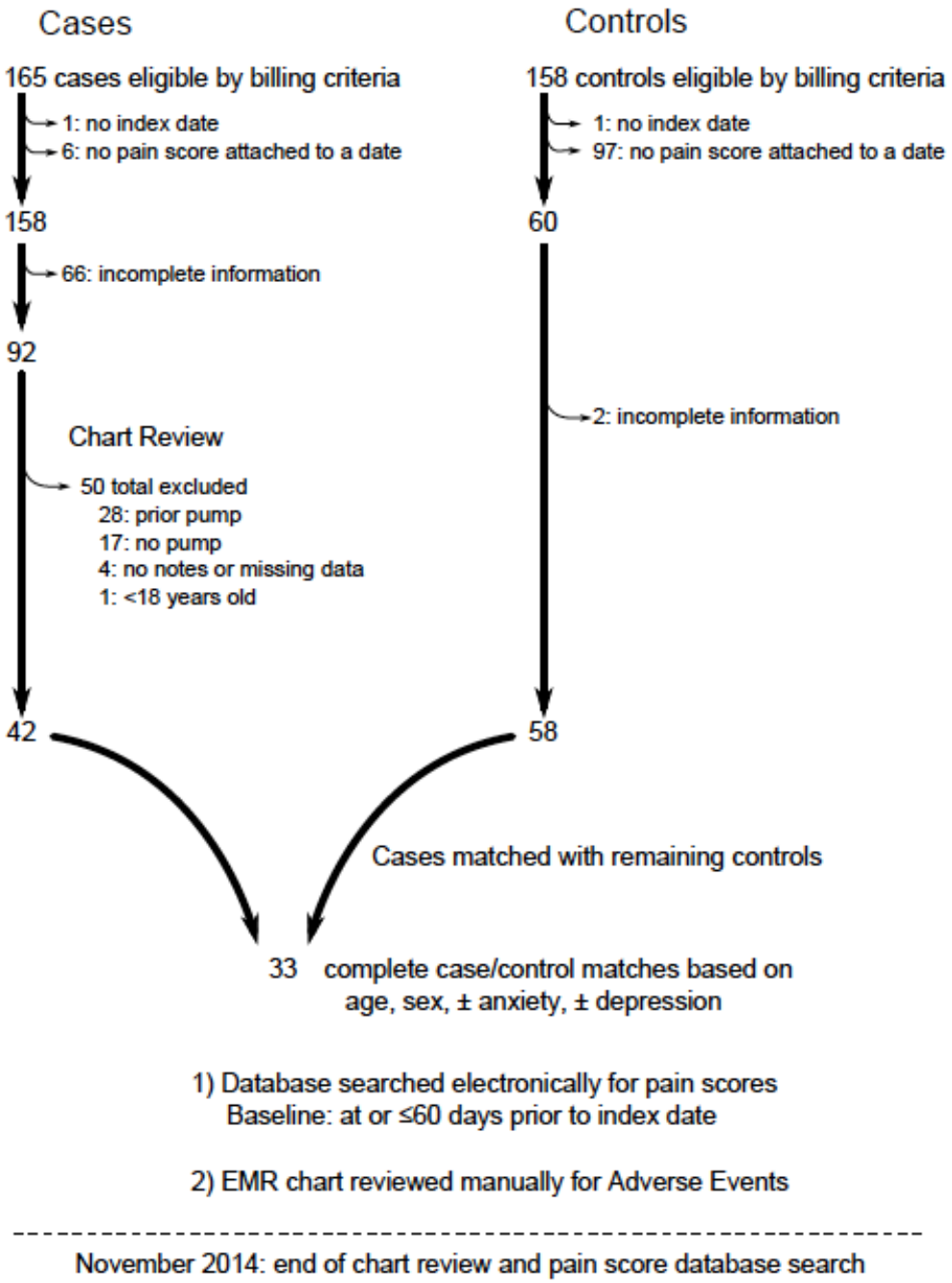
An outcomes-based retrospective analysis was performed as part of a two-part study using the electronic medical records of patients with neuropathic pain who received care at the University of New Mexico (UNM) from January 2000 through May 2014. Part one of the study consisted of comparing the difference in pain scores recorded electronically over time for patients treated with IDDS versus patients treated with traditional oral medications. Part two consisted of manual chart review of provider notes to identify and compare pertinent side effects from treatments.

Demographic data, pain score data, and identification of eligible patients for chart review was facilitated by the Clinical Data Warehouse service provided by the UNM Clinical and Translational Science Center (CTSC). Approval was obtained from the Human Research Review Committee at the UNM Health Sciences Center prior to data collection. CTSC data warehouse procedures for hybrid research projects involving both de-identified information and chart review were followed. This required that all detailed demographic information for patients involved in the study be de-identified and linked to a study identification number. Medical Record numbers were provided for chart review only after all records were sorted and matched based on the detailed demographic information and billing criteria. The crosswalk file linking medical record numbers to study identification numbers was kept by a data warehouse specialist not involved in data analysis or chart review.

Study Design Overview

De-identified patient data obtained from the CTSC data warehouse were loaded into SAS 9.4 statistical software program to build a study database. Complete data sets were compiled by uploading data from multiple warehouse data outputs and incomplete datasets were not used (see Figure 1). Eligibility criteria (see *inclusion* and *exclusion criteria*) that identified all patients with a primary complaint of selected neuropathic pain conditions at a hospital or clinic encounter identified 165 cases (patients treated with IDDS) and 158 controls (patients treated with traditional oral medications). Absence of a recorded date attached to first visit or to any pain scores in the database resulted in 158 cases and 60 controls remaining. Incomplete information across databases in the CTSC data warehouse (such as age, gender, or comorbidities) resulted in 92 cases and 58 controls remaining. At this point, a list of medical records was requested from the CTSC data concierge and a chart review was performed. After chart review, 50 patients were found to be ineligible for the pump group, leaving 42 patients in the pump group. The 42 pump patients were matched with the 58 controls based on age, gender, and presence or absence of anxiety and depression. Based on these criteria for selection, 33 complete matches were found.

Fig. 1. Study Design Overview



Inclusion Criteria

We included all patients ages 18 through 90 with new or existing neuropathic pain conditions diagnosed from January 2000 through May 2014 that would potentially be treated with an IDDS at the UNM Pain Consultation and Treatment Center (PCTC). Diagnoses were identified by the billing sheet used at the PCTC and these were verified using the Ninth Revision of International Classification of Diseases (ICD-9) Codes (44). Diagnoses included post-herpetic neuralgia, herpes zoster, diabetic neuropathy, spastic torticollis, meralgia paresthetica, ilioinguinal neuropathy, entrapment neuropathy, spinal stenosis with radiculopathy and reflex sympathetic dystrophies. Data collection included new diagnoses only through May 2014 in order to permit at least three months of data collection for each relevant patient. Data were collected using the data warehouse up to December 15, 2014 to account for typical lag time with billing information entered into the database and provider notes dated through November 2014 were reviewed. The cases (IDDS group) contained patients meeting initial diagnostic criteria that were also assigned one of four Current Procedure Terminology (CPT) codes representing implantation or revision of an intrathecal pain pump. Controls (patients treated with traditional oral medications) had to have three or more clinic appointments that contained at least one included neuropathic pain diagnosis as the reason for visit.

Exclusion Criteria

We excluded patients with ICD-9 codes representing diagnoses that would interfere with pain score reporting including dementia, psychosis, schizophrenia and bipolar disorder. These criteria were selected based on consensus from providers at the UNM Pain Consultation and Treatment Center who felt that 1) patients with these diagnoses would be less likely to be offered an IDDS and 2) these psychiatric diagnoses would interfere with reliable pain score reporting. We excluded patients with CPT codes indicating refill or maintenance of their pump without an initial implantation code, as these patients would not have a baseline pain score in our database.

Additional Patient Information

A CTSC biomedical informatics specialist accessed data in the electronic medical record. The database was searched for demographic features including age, sex, weight, height, BMI, race/ethnicity, medical diagnoses, smoking history and prescribed medication classes. All comorbidities were examined based on lifetime diagnosis, or any record of the diagnosis within the data collection period. Financial class was represented by type of health insurance. Patients were sorted by presence or absence of insurance that would typically qualify a patient for IDDS implantation. Insurance qualifying patients for IDDS implantation with a prior authorization included Medicare, Medicaid, HMO/PPO, Workman's Compensation, Champus, and other private or government payors. Self-pay, UNM Care Plan (healthcare assistance program for qualified Bernalillo County residents, out-of-county financial assistance, pending

Medicaid, and referral billing) would not typically pay for IDDS implantation, according to our billing coordinator.

Medical diagnoses were searched by ICD-9 codes including neuropathic pain and other pain conditions, obesity, obstructive sleep apnea, diabetes, hepatitis, depression, anxiety, substance abuse, smoking, and alcohol abuse. Hemoglobin A1C prior to index date was used as a marker for glucose control in diabetic patients. When BMI was not directly available, it was calculated based on the most current height and weight from date of baseline pain scores. Dosing regimens for oral opioids and medications contained in pumps were obtained by chart review when needed.

Pain Score Measures

Pain score outcome data were obtained by searching the database for electronically recorded 11-point pain scales, referred to as "Numeric Pain Scale" and "Pain Severity Score reported by patient." These pain scores are routinely entered with the vital signs by healthcare staff when patients check in for a clinic visit. The dates of patient pain score responses were arranged so that baseline pain scores corresponded to the initial pain score just prior to pump implantation date for the cases and at first consultation for neuropathic pain in the controls. Patients were excluded if there was no pain score within 60 days prior to pump implant date for the pump group or within 60 days prior to first visit for the control group. Pain scores at additional visits were acquired by using the dates of sequential clinic visits that were linked to at least one neuropathic pain diagnosis.

Adverse Events Measures

Adverse event outcome data were obtained by chart review of clinic notes at each relevant visit and graded using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (45). Provider notes were searched for keywords that included nausea, vomiting, constipation, sedation, dizziness, overdose, tiredness, hypogonadism, pump site infection, granuloma, and hyperalgesia. Review of all pertinent notes during the treatment period was performed. Relevant outpatient clinic notes included the services of internal medicine, family practice, pain management, neurology, neurosurgery, orthopedic, emergency room, and complementary and alternative medicine. Inpatient notes reviewed included history and physicals, operative reports, interim summaries and discharge summaries. The subjective portion of each note was reviewed along with the review of systems and the assessment and plan. The admission date for the relevant diagnoses was used as a starting point for chart review; however, if the neuropathic pain was noted in prior notes, the earliest note where the patient received an evaluation for neuropathic pain was used as there starting point for the referenced time period. The last note where the symptoms were no longer being treated or through the study end date of November 2014, whichever came first determined the end date of chart review. The total number of clinic notes reviewed was tallied. Adverse events were recorded using the CTCAE scale. Adverse events were weighted by multiplying each adverse event for a patient by the CTCAE score. The summed total of all weighted events was used for analysis.

Data Analysis

Descriptive statistics that included frequencies and cross-tabulations were used to characterize demographic information, pain scores, and mean and median adverse event weighted scores. Demographics of cases and controls were compared with chi-square analyses enough cells in each table had five or greater expected counts.

A "single-factor analyses" was used to represent the effect of pump status on specific pain outcomes (e.g. pain reduction at 30 days) when particular factors were controlled for one at a time, e.g. diabetes status. This permitted the evaluation of the importance of each of these factors before construction of the final model. The standard for inclusion of a given factor in the final model was $p < 0.10$. These "single-factor analyses" allowed determination of the odds ratio (OR) estimates and 95% confidence intervals (CIs) for the listed reduction in pain. The test statistic for this comparison followed a chi-square distribution, and the resulting p-value for the ORs were reported.

For the adverse events, we used the summed CTCAE scores for all of a given patient's adverse events as a proxy for overall severity of adverse events. A Wilcoxon rank-sum (equivalent to Mann-Whitney U) test was used to compare these summed scores between cases and controls, because the distributions were not normal. This analysis was repeated for adverse events excluding those directly attributable to pump implantation (infection, broken catheter, CSF leak, granuloma, pump malfunction, and pump elective removal).

SAS 9.4 was used for analysis of pain scores and baseline characteristics and JMP 9.0.0 software, made by SAS Institute Inc, 2010 was used for analysis of adverse events.

Power analysis

For the power analysis, a 30% or greater change in pain scores across multiple visits for a fixed time interval was applied. Logistic regression was performed using an alpha of .025 (.05/2) for a two-sided test. We assumed a pairwise correlation of 0.1 between covariates of interest. To attain 80% power, a sample size of 834 would be required to see an odds ratio effect size of 1.24, and a sample size of 86 would be required to see an odds ratio effect size of 2.00.

Chapter 3

Results

Patient Characteristics

Our cases and controls were matched based on age, gender, and presence or absence of anxiety and depression (Table 1). Of the 33 matched pairs, 14 (42%) had a diagnosis of depression, while 19 did not. Anxiety was present in 3 (9%) of the matches.

Among the unmatched pairs, there was a higher number of patients with diabetes in the controls (10) compared with the cases (4), but this was not statistically significant. There was only one patient with hepatitis, and this was in the control group. The proportion of patients with sleep apnea was not statistically significant between the cases and controls, with 6 (18%) in the cases and 5 (15%) in the controls. There was one patient (3%) in the cases that did not have insurance while 5 (15%) patients in the controls did not have insurance, but this difference was not statistically significant. There were 7 (21%) patients with Hispanic ethnicity in both the cases and controls. Ethnicity was missing or marked as "other" in 5 (15%) of the controls. The number of patients who self-identified as "smokers" was not statistically significant between cases and controls: 8 (24%) for the cases and 6 (18%) for the controls. The proportions of both overweight and obese patients were similar across cases and controls. The cases had 15 (45%) overweight and 5 (15%) obese patients and the controls had 17 (51%) overweight and 7 (21% obese patients), but these differences were not statistically significant.

Table 1: Baseline characteristics among cases and controls.

Characteristics		Cases (n = 33)	Controls (n = 33)	χ^2 p-value
Age	18-29	1	1	*
	30-39	1	1	
	40-49	6	6	
	50-59	13	13	
	60-69	5	5	
	70-79	6	6	
	80+	1	1	
Sex	Female	17	17	1.0
	Male	16	16	
Depression	No	19	19	1.0
	Yes	14	14	
Anxiety	No	30	30	*
	Yes	3	3	
Diabetes	No	29	23	0.0708
	Yes	4	10	
Hepatitis	No	33	32	*
	Yes	0	1	
Obstructive Sleep Apnea	No	27	28	0.7412
	Yes	6	5	
Insurance	No	1	5	*
	Yes	32	28	
Ethnicity	Hispanic	7	7	*
	Non-Hispanic White	26	21	
	Missing/Other	0	5	
Smokes	No	25	27	0.5470
	Yes	8	6	
BMI	Normal weight	13	9	0.5528
	Overweight	15	17	
	Obese	5	7	

*χ^2 analysis not valid; too many cells have expected counts <5

Pain Outcomes

The differences in pain scores from baseline were examined at fixed time intervals (Table 2) based on a clinically meaningful difference in pain score (≥ 30%). At 30 days, there were 3 cases and 3 controls missing pain scores in the data set to compare with their baseline pain scores. There were 7 cases and 6 controls that had a ≥ 30% difference in pain scores from baseline, but the statistical analysis was not valid due to too many missing data points. At 90 days, there were 8 cases and 5 controls that had a ≥ 30% difference in pain scores from baseline, but this difference was not statistically significant. At 180 days, there were 7 cases and 6 controls that had a ≥ 30% difference in pain scores from baseline, but this difference was also not statistically significant. When looking at pain scores obtained 365 days after baseline pain scores, there were 13 cases and 9 controls that did not have pain scores for comparison, resulting in in insufficient data points for analysis.

Table 2: Differences in scores from baseline at fixed time intervals

Time Period	Pain Difference	Cases (n = 33)	Controls (n = 33)	χ^2 p-value
30 days	Insufficient data	3	3	*
	< 30% decrease	23	24	
	≥ 30% decrease	7	6	
90 days	Insufficient data	6	4	0.4331
	< 30% decrease	19	24	
	≥ 30% decrease	8	5	
180 days	Insufficient data	9	5	0.3944
	< 30% decrease	17	22	
	≥ 30% decrease	7	6	
365 days	Insufficient data	13	9	*
	< 30% decrease	16	20	
	≥ 30% decrease	4	4	

*χ^2 analysis not valid; too many cells have expected counts <5.

To provide an overall view of the sample population, the odds of meeting the threshold of ≥ 30% difference in pains scores from baseline for cases versus controls was examined at fixed time intervals (Table 3). The odds of meeting this threshold (pain reduced by 30% or more) in cases were 1.049 times greater for cases than the corresponding odds in controls (95% CI: 0.326 – 3.377). The test statistic for this comparison followed a chi-square distribution, and the resulting p-value for the odds ratio was reported; in this case p = 0.9365. The 95% confidence interval spans 1, and the p-value is greater than 0.05, so this finding was not significant. The odds of meeting this threshold (pain reduced by 30% or more) in cases versus controls were not significant at any of the fixed time intervals.

Table 3. Odds of meeting 30% reduction threshold: cases vs. controls

	Odds ratio estimates			
Effect	Point Estimate	95% CI		χ^2 p-value
Pain 30 days	1.049	0.326	3.377	0.9365
Pain 90 days	1.794	0.454	7.093	0.4046
Pain 180 days	1.190	0.302	4.693	0.8041
Pain 360 days	0.737	0.065	8.322	0.8050

The odds of meeting the threshold of any (> 0%) difference in pains scores from baseline for cases versus controls was also examined at fixed time intervals (Table 4). The odds of meeting this threshold (pain reduced any amount) in cases versus controls were not significant at any of the fixed time intervals.

Table 4. Odds of meeting > 0% reduction threshold: cases vs. controls

	Odds ratio estimates			
Effect	Point Estimate	95% CI		χ^2 p-value
Pain 30 days	1.010	0.354	2.875	0.9858
Pain 90 days	0.967	0.325	2.874	0.9515
Pain 180 days	0.623	0.151	2.573	0.5134
Pain 360 days	0.370	0.086	1.590	0.1812

A single-factor analysis was performed to determine the odds of meeting the threshold of ≥ 30% difference in pain scores from baseline when each given factor was controlled for, in cases versus controls (Table 5). Here, each potential confounder was analyzed one at a time. When overweight/obese status was controlled for, the cases had 0.987 times the odds of controls for meeting the reduction threshold at 30 days after baseline pain scores, and this was not statistically significant (p= 0.9833). When insurance status was controlled for, cases had 2.161 times the odds of controls for meeting the reduction threshold at 90 days after baseline, and this approached significance for inclusion of this covariate in a multivariate model, but was not

significant ($p = 0.1509$). None of the variables showed statistically significant differences in odds ratios for meeting the threshold of ≥ 30% difference in pain scores from baseline between cases and controls when analyzed individually.

Table 5. Single-Factor Analyses: ≥ 30% decrease vs. < 30% decrease in pain scores

	Odds ratio estimates			
Effect	Point Estimate	95% CI		χ^2 p-value
Pain 30 days	0.987	0.296	3.289	0.9833
Overweight	0.893	0.300	2.659	0.8395
Obese	0.448	0.076	2.635	0.3743
Pain 90 days	1.666	0.405	6.854	0.4795
Overweight	0.773	0.245	2.440	0.6609
Obese	0.387	0.052	2.874	0.3536
Pain 180 days	1.258	0.284	5.572	0.7628
Overweight	0.948	0.263	3.418	0.9353
Obese	0.425	0.055	3.278	0.4117
Pain 365 days	0.715	0.061	8.375	0.7886
Overweight	0.961	0.238	3.874	0.8690
Obese	0.836	0.099	7.031	0.9549
Pain 30 days	0.887	0.261	3.019	0.8481
Diabetes	0.384	0.091	1.632	0.1950
Pain 90 days	1.594	0.392	6.477	0.5149
Diabetes	0.454	0.109	1.887	0.2770
Pain 180 days	1.341	0.323	5.562	0.6857
Diabetes	0.478	0.109	2.094	0.3277
Pain 365 days	0.674	0.056	8.039	0.7549
Diabetes	0.499	0.077	3.242	0.4664
Pain 30 days	1.031	0.295	3.603	0.9617
Insurance	0.224	0.026	1.958	0.1762
Pain 90 days	2.161	0.486	9.621	0.3117
Insurance	0.196	0.021	1.812	0.1509
Pain 180 days	1.377	0.308	6.160	0.6755
Insurance	<0.001	<0.001	>999.999	0.9946
Pain 365 days	0.452	0.0038	5.327	0.5284
Insurance	<0.001	<0.001	>999.999	0.9958
Pain 30 days	0.662	0.175	2.506	0.5438
Hispanic	0.697	0.157	3.087	0.6341
Pain 90 days	0.930	0.186	4.643	0.9300
Hispanic	0.688	0.152	3.118	0.6275
Pain 180 days	0.457	0.073	2.870	0.4039
Hispanic	0.897	0.186	4.319	0.8924
Pain 365 days	0.486	0.043	5.565	0.5622
Hispanic	0.256	0.028	2.331	0.2268
Pain 30 days	1.054	0.319	3.481	0.9313
Smoker	1.625	0.482	5.477	0.4334
Pain 90 days	1.802	0.440	7.378	0.4128
Smoker	1.523	0.416	5.572	0.5251
Pain 180 days	1.190	0.302	4.696	0.8039
Smoker	1.015	0.246	4.184	0.9835
Pain 365 days	0.812	0.065	10.098	0.8712
Smoker	0.364	0.059	2.233	0.2748

A single-factor analysis was also performed to determine the odds of meeting the threshold of any (> 0% difference) in pain scores from baseline when each given factor was controlled for, in cases versus controls (Table 6). None of the variables showed statistically significant differences in odds ratios for meeting the threshold of any difference in pain scores from baseline between cases and controls when analyzed individually.

Table 6. Single-Factor Analyses: More than 0% decrease vs. Less than 0% decrease

	Odds ratio estimates			
Effect	Point Estimate	95% CI		χ^2 p-value
Pain 30 days	1.124	0.367	3.427	0.8376
Overweight	0.429	0.070	2.625	0.3595
Obese	0.867	0.284	2.648	0.8019
Pain 90 days	1.040	0.339	3.189	0.9453
Overweight	0.358	0.049	2.625	0.3123
Obese	0.723	0.232	2.250	0.5753
Pain 180 days	0.695	0.162	2.992	0.6257
Overweight	0.490	0.065	3.690	0.4885
Obese	1.003	0.295	3.419	0.9956
Pain 365 days	0.330	0.065	1.661	0.1787
Overweight	1.587	0.134	18.863	0.7145
Obese	1.187	0.269	5.228	0.8212
Pain 30 days	1.056	0.404	2.764	0.9110
Diabetes	0.685	0.207	2.270	0.5361
Pain 90 days	0.894	0.332	2.406	0.8237
Diabetes	0.818	0.248	2.696	0.7413
Pain 180 days	0.819	0.270	2.479	0.7233
Diabetes	1.106	0.308	3.975	0.8775
Pain 365 days	0.665	0.163	2.716	0.5701
Diabetes	1.291	0.278	5.994	0.7445
Pain 30 days	1.146	0.384	3.423	0.8073
Insurance	0.218	0.025	1.916	0.1694
Pain 90 days	0.920	0.300	2.820	0.8844
Insurance	0.221	0.025	1.951	0.1743
Pain 180 days	0.500	0.108	2.322	0.3763
Insurance	<0.0011	<0.001	>999.999	0.9943
Pain 365 days	0.316	0.058	1.730	0.1841
Insurance	<0.001	<0.001	>999.999	0.9955
Pain 30 days	0.589	0.174	1.989	0.3935
Hispanic	0.598	0.131	2.741	0.5083
Pain 90 days	0.763	0.245	2.380	0.6415
Hispanic	0.687	0.155	3.035	0.6201
Pain 180 days	0.430	0.091	2.031	0.2866
Hispanic	0.953	0.186	4.884	0.9538
Pain 365 days	0.522	0.103	2.637	0.4318
Hispanic	0.330	0.034	3.182	0.3379
Pain 30 days	1.080	0.372	3.136	0.8875
Smoker	1.647	0.482	5.630	0.4266
Pain 90 days	1.122	0.343	3.674	0.8488
Smoker	1.609	0.406	6.367	0.4984
Pain 180 days	0.622	0.150	2.578	0.5128
Smoker	0.973	0.232	4.079	0.9704
Pain 365 days	0.411	0.092	1.838	0.2446
Smoker	0.427	0.064	2.874	0.3820

Based on the single-factor analysis, none of the variables met criteria for mandatory inclusion in the final multivariate model for ≥ 30% decrease in pain scores from baseline. When all factors were simultaneously controlled (Table 7), the odds for meeting the 30% pain reduction threshold at 30 days after baseline pain scores in cases versus controls was not significant (odds ratio point estimate = 0.171, p = 0.1370). When all factors were controlled, Hispanic ethnicity reduced the odds of meeting the threshold of 30% pain reduction at 30 days (point estimate = 0.537) and these results were not significant (p = 0.5509). Too little data were available to assess the effect of Non-Hispanic ethnicity on meeting the 30% threshold at 365 days when all other factors were controlled. The odds of cases versus controls for meeting the 30% pain reduction threshold were not significant at any of the fixed time intervals when all factors were controlled for simultaneously.

Table 7. Full Model: ≥ 30% decrease vs. < 30% decrease

	Odds ratio estimates			
Effect	Point Estimate	95% CI		χ^2 p-value
Pain 30 days	0.171	0.017	1.752	0.1370
Pain 90 days	0.367	0.028	4.735	0.4424
Pain 180 days	0.192	0.010	3.724	0.2754
Pain 360 days	<0.001	<0.001	>999.999	0.9962
Pain 30 days				
Overweight	1.929	0.300	12.404	0.4888
Obese	0.856	0.077	9.586	0.8999
Pain 90 days				
Overweight	1.047	0.147	7.451	0.9632
Obese	0.574	0.034	9.806	0.7015
Pain 180 days				
Overweight	1.278	0.163	10.013	0.8154
Obese	0.715	0.043	11.858	0.8149
Pain 365 days				
Overweight	1.765	0.141	22.009	0.6591
Obese	2.195	0.032	150.159	0.7154
Pain 30 days				
Diabetes	1.016	0.117	8.816	0.9883
Pain 90 days				
Diabetes	1.182	0.131	10.677	0.8814
Pain 180 days				
Diabetes	2.351	0.170	32.589	0.5240
Pain 365 days				
Diabetes	1.731	0.017	171.486	0.8149
Pain 30 days				
Insurance	<0.001	<0.001	>999.999	0.9956
Pain 90 days				
Insurance	<0.001	<0.001	>999.999	0.9940
Pain 180 days				
Insurance	<0.001	<0.001	>999.999	0.9960
Pain 365 days				
Insurance	<0.001	<0.001	>999.999	0.9946
Pain 30 days				
Hispanic	0.537	0.069	4.149	0.5509
Pain 90 days				
Hispanic	0.519	0.073	3.692	0.5123
Pain 180 days				
Hispanic	1.413	0.125	15.946	0.7798
Pain 365 days				
Hispanic	0.223	0.014	3.663	0.2933
Pain 30 days				
Smoker	1.335	0.221	80.54	0.7530
Pain 90 days				
Smoker	1.304	0.178	9.562	0.7938
Pain 180 days				
Smoker	1.413	0.125	15.946	0.7798
Pain 365 days				
Smoker	4.934	0.147	165.829	0.3735

Based on the single-factor analysis, none of the variables met the criteria mandatory for inclusion in the final multivariate model for any decrease in pain scores from baseline. The odds of cases versus controls for meeting the > 0% pain reduction threshold were not significant at any of the fixed time intervals when all factors were controlled for simultaneously (Table 8).

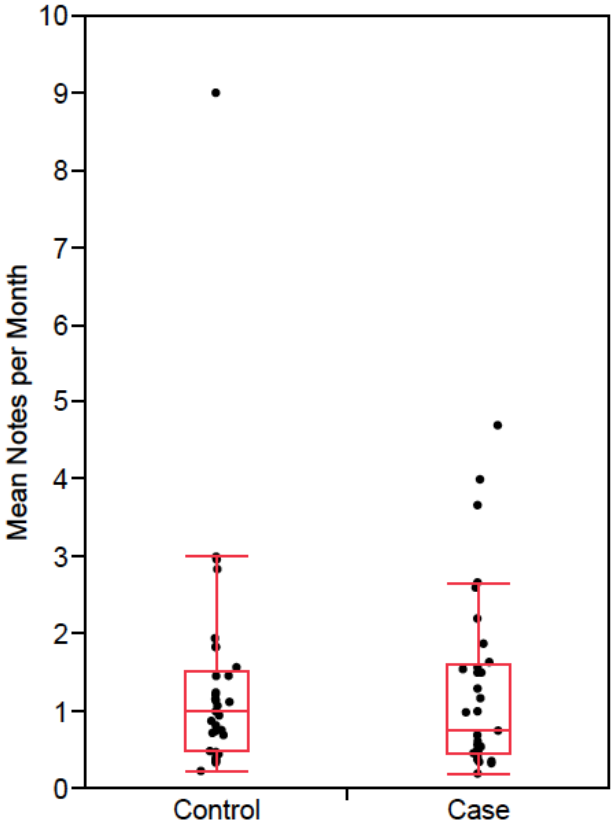
Table 8. Full Model: More than 0% decrease vs. Less than 0% decrease

	Odds ratio estimates			
Effect	Point Estimate	95% CI		χ^2 p-value
Pain 30 days	0.549	0.130	2.323	0.4156
Pain 90 days	0.532	0.124	2.277	0.3951
Pain 180 days	0.256	0.034	1.942	0.1875
Pain 360 days	0.051	<0.001	4.044	0.1825
Pain 30 days				
Overweight	2.326	0.364	14.881	0.3725
Obese	1.366	0.135	13.871	0.7920
Pain 90 days				
Overweight	1.360	0.188	9.847	0.7605
Obese	0.868	0.060	12.621	0.9176
Pain 180 days				
Overweight	1.810	0.219	14.980	0.5821
Obese	1.625	0.089	29.823	0.7435
Pain 365 days				
Overweight	5.944	0.247	143.092	0.2721
Obese	24.577	0.077	>999.999	0.2767
Pain 30 days				
Diabetes	0.625	0.077	5.107	0.6614
Pain 90 days				
Diabetes	1.117	0.123	10.114	0.9213
Pain 180 days				
Diabetes	1.039	0.123	8.777	0.9719
Pain 365 days				
Diabetes	1.291	0.031	53.434	0.8931
Pain 30 days				
Insurance	<0.001	<0.001	>999.999	0.9940
Pain 90 days				
Insurance	<0.001	<0.001	>999.999	0.9941
Pain 180 days				
Insurance	<0.001	<0.001	>999.999	0.9959
Pain 365 days				
Insurance	<0.001	<0.001	>999.999	0.9940
Pain 30 days				
Hispanic	0.384	0.052	2.822	0.3471
Pain 90 days				
Hispanic	0.580	0.079	4.259	0.5919
Pain 180 days				
Hispanic	1.420	0.139	14.489	0.7672
Pain 365 days				
Hispanic	1.878	0.063	55.803	0.7517
Pain 30 days				
Smoker	1.639	0.274	9.812	0.5886
Pain 90 days				
Smoker	1.086	0.140	8.457	0.9369
Pain 180 days				
Smoker	0.999	0.111	9.014	0.9994
Pain 365 days				
Smoker	5.307	0.130	216.634	0.3774

Adverse Events Outcomes

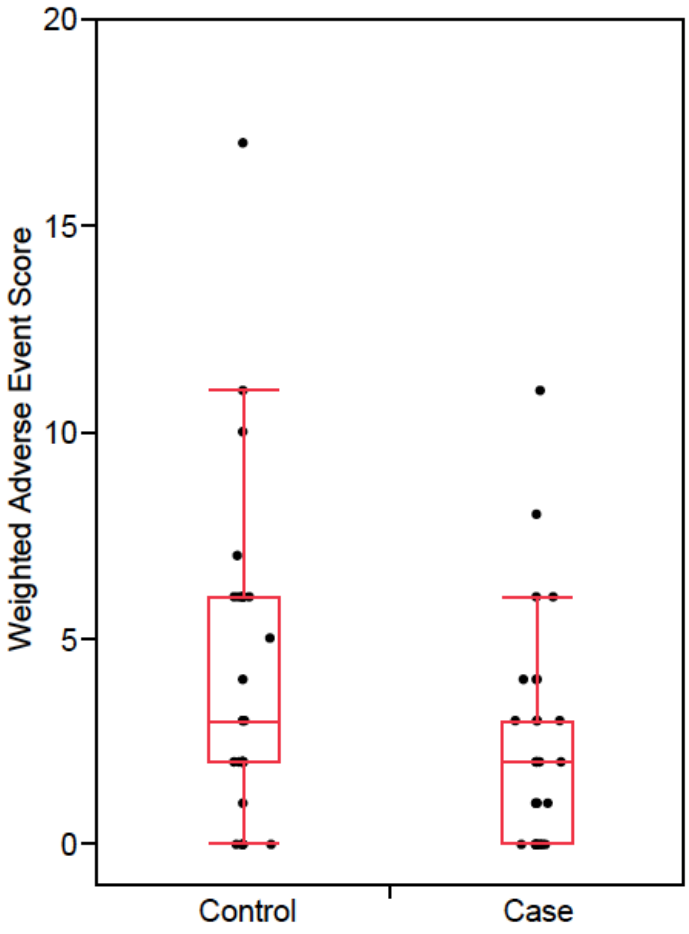
Differences in mean notes per month were analyzed for the cases and control groups and displayed in a boxplot where each dot represents the mean number of notes per month for a patient (see Figure 2). The mean number of notes per month for all patients in the control group together was of 1.36 ±1.56 compared with a mean of 1.27 ±1.14 for all the cases together, and these differences were not statistically significant between groups (p = 0.788).

Figure 2: Mean notes per month



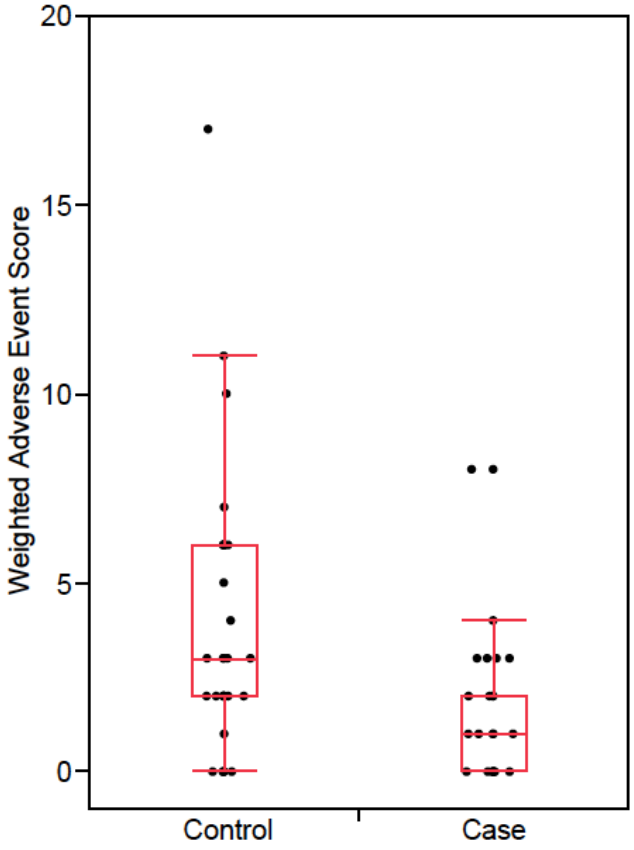
Weighted adverse events were calculated by multiplying each adverse event for a patient by the CTCAE severity score and summing the total for each patient. A boxplot was generated to compare differences in weighted adverse events scores between groups, where each dot represents the weighted score for one patient (see Figure 3). The control group had a lower mean-weighted adverse-events score (3.82 ± 3.63) compared with the cases (2.18 ±2.58) and these differences were statistically significantly (p = 0.026).

Figure 3: Greater adverse events were present in the controls



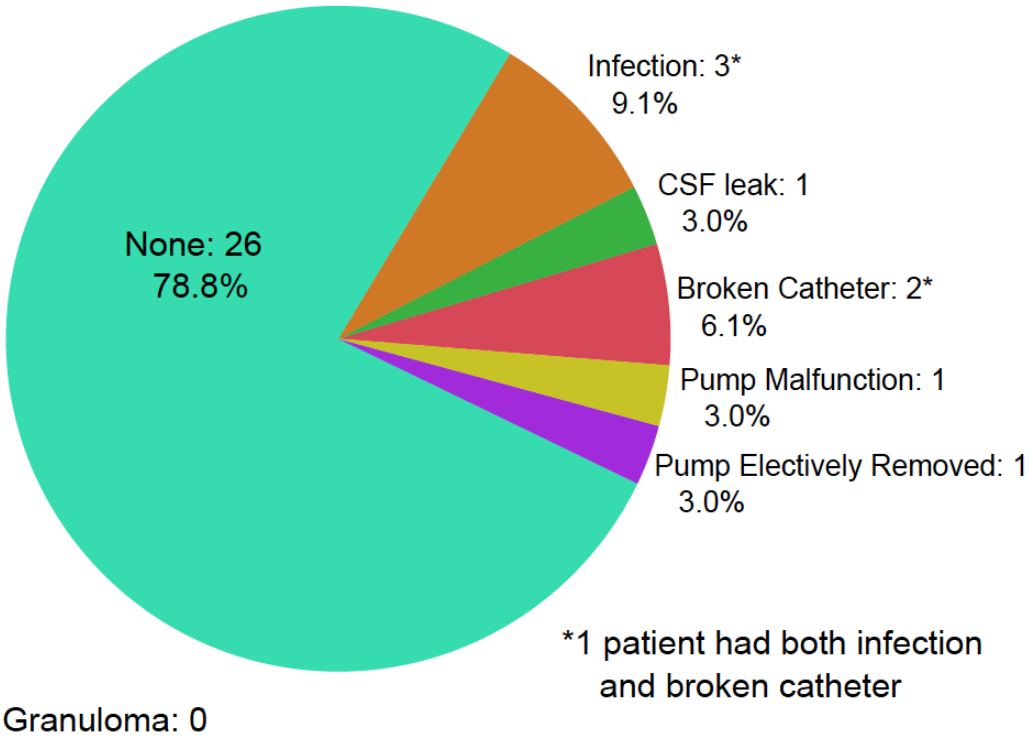
A boxplot was generated to compare differences in weighted adverse events scores between groups when IDDS-related adverse events were omitted (see Figure 4). The cases had a statistically significantly lower mean weighted adverse event score (1.52 ±2.03) compared with control group, and this effect was stronger than when IDDS-related adverse events were included in the analysis (p = 0.001).

Figure 4: The effect was stronger when looking at systemic opioids effects only



IDDS-related adverse events in our sample cases were looked at alone and displayed in the form of a pie chart (see Figure 5). These results show that 78.8% of our cases had no IDDS-related events. Infection was reported in 3 cases (9.1%), broken catheter was reported in 2 cases (6.1%) pump malfunction was reported in 1 case (3%) and elective removal of the device was reported in 1 case (3%).

Figure 5: IDDS-related adverse events were very low



*Percentages do not add to 100% both because of rounding and because 1 patient appears in two places.

Chapter 4

Discussion

Even after 25 years of empirical use, due to lack of supporting evidence, the use of IDDS for nonmalignant pain is still considered experimental by some (46, 47). There are inherent challenges in designing a randomized controlled trial for IDDS implantation due to the invasiveness of the procedure and their infrequent use. This study aimed to present the effectiveness and adverse event profile of IDDS through the use of a clinical data warehouse, which combines electronic healthcare data from multiple sources (48) to accelerate this research (49) in our select group of patients treated for chronic neuropathic pain at UNM.

The most important finding of our study was that significantly fewer adverse events were found among patients treated with IDDS compared to patients treated with traditional oral medications. This effect was stronger when the analysis was limited only to opioid-induced adverse events (excluding IDDS-related adverse events). Though adverse events associated with systemic oral opioid use are also reported with IDDS, these results suggest that they are less severe and less frequent when administered intrathecally and/or with synergistic medications.

We examined the differences in recorded pain scores over time, but did not have statistically significant findings due to too many missing data points in the warehouse database. The reduction in initial assessments of available pain scores in the database was due to: 1) errors in how pain scores were initially entered into the medical record

and 2) exclusion of initially eligible patients based on lack of matching demographic and other information.

We did not find a significant difference in notes per month between cases and controls. Differences in management strategies potentially exist between PCTC providers, who manage chronic pain conditions for most of the patients with IDDS, versus primary care providers, who manage the overall care of patients with and without IDDS. For example providers focusing on chronic pain management at the PCTC might convey more realistic expectations with treatment or have more defined algorithms for unscheduled appointments when compared to primary care providers who treat patients for a variety of different health issues. However, these potential differences were not captured in looking at differences in notes per month between the two groups.

Limitations of our study included ambiguity in measuring pain outcomes. Measuring pain outcomes in chronic pain patients is particularly challenging due multiple situational and environmental factors associated with the experience of pain (50-52) and to the complexity involved in treatment for patients with chronic pain. Psychiatric comorbidity, for example, can predict higher doses of opioids and less improvement in pain (53). In an attempt to determine a clinically significant reduction in pain scores, we used ≥ 30% difference (54) as our criteria for comparison between groups. We also analyzed the data for any reduction at all in pain scores between cases and controls, but we were unable to appreciate a statistically significant difference in

either case. In some situations, we did not have enough data points to run a statistical analysis, which amplified the challenge of determining a clinically significant difference.

Our pain outcomes data analysis was also limited by power. Initially, we matched cases to the eligible controls in our database based on the predetermined criteria most relevant to this patient population. Therefore, we chose the diagnoses of anxiety and depression as comorbidities most relevant for matching. This strategy was implemented to decrease variability among groups and ultimately increase power. However, due to the unexpectedly small final sample size, the study was not powered appropriately. The sample size of our study may have been adequate if pain scores were consistently reported at regular intervals in order to have enough data points. We had originally expected this to occur based on our observation at PCTC that pain scores, as the "fifth vital sign" (55), are entered into the electronic medical record as part of clinic intake procedures. Our criteria for including patients, if they did not have IDDS implantation that requires regular clinic visits for maintenance, included that they had been seen at least 3 times for a primary complaint of neuropathic pain (non-IDDS patients). However, even with these criteria in place, usable pain scores in the database were far below what we expected. When analyzing a large dataset for use in the future, our first objective would be to carefully analyze the usable pain data for completeness prior to merging patient information from the database. In addition, a small probing analysis with approximately 10% of the usable data after merging patient information would be helpful in predicting the feasibility of seeing a difference in pain scores.

Additional limitations in our study include those inherent in a retrospective trial

such as lack of blinding and selection bias. For example, our select population studied may not be representative of the neuropathic pain patients across the rest of New Mexico or the United States. There also may be a difference in reported adverse events based on the provider variability in dictating the notes, which could confound our adverse events data.

Since the recent application of clinical data warehouses for research purposes (56), several challenges associated with medical research have been documented (57) that include problems with the quality of the data (58). This pilot study, utilizing our local clinical database to determine pain outcomes, underlines how: 1) the inputting pain scores needs to be improved by clinical staff and 2) how a greater breath of data (multi-center) needs to be accessed to achieve sufficient power. Defining the criteria of acceptability prior to actual data mining may help in producing less biased and a more objective evaluation of data mining results (59).

Future directions of our research include using the newly-introduced extensive new informatics resource for accessing de-identified electronic health record data, CTSC Health Facts (60). This resource collects data from over 600 hospitals and clinics and represents more than 106 million patients. A database of this breath could be used to: 1) recruit patients meeting eligibility criteria for multi-center randomized trial and/or 2) to improve amount of accessed data to increase power when looking at pain outcomes. After understanding to challenges faced in missing data, we plan to utilize the this national database to enhance the sample size and target our research question towards existing data that can provide meaningful pain outcomes.

References

1. van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: A systematic review of epidemiological studies. Pain. 2013.

2. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;132(3):237-51.

3. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2010;17(9):1113-e88.

4. Hunt SP, Mantyh PW. The molecular dynamics of pain control. Nat Rev Neurosci. 2001;2(2):83-91.

5. Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. Nature reviews Neuroscience. 2009;10(1):23-36.

6. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpaa ML, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc. 2010;85(3 Suppl):S3-14.

7. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010;150(3):573-81.

8. Cousin MJ GM, Jamison RN, McGrath PA, Rajagopal MR , Smith MT, Sommer C, Wittink HM. Pharmacological Managment of Neuropathic Pain: International Association for the Study of Pain; November 2010, Vol XVIII, Issue 9.

9. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA. 2005;293(24):3043-52.

10. Centers for Disease Control and Prevention (CDC). CDC grand rounds: Prescriptoin drug overdoses-A U.S. epidemic. MMWR Morb Mortal Wkly Rep. 2012;61(1):10-3.

11. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, CDC WONDER Online Database [Internet]. 2012.

12. The Federation of State Medical Boards of The United States, Inc. Model guidelines for the use of controlled substances for the treatment of pain. South Dakota journal of medicine. 1999;52(1):25-7.

13. Rudd RA AN, Zibbell JE, Gladden RM. Increases in Drug and Opioid Overdose Deaths - United States, 2000-2014. 2015.

14. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Res Ther. 2005;7(5):R1046-51.

15. Turner JA, Sears JM, Loeser JD. Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications. Clin J Pain. 2007;23(2):180-95.

16. Xenidis M, Pandya N, Hames E. Effects of intrathecal opioid administration on pituitary function. Pain medicine. 2013;14(11):1741-4.

17. Duarte RV, Raphael JH, Labib M, Southall JL, Ashford RL. Prevalence and influence of diagnostic criteria in the assessment of hypogonadism in intrathecal opioid therapy patients. Pain physician. 2013;16(1):9-14.

18. Maino P, Koetsier E, Perez RS. Fentanyl overdose caused by malfunction of SynchroMed II intrathecal pump: two case reports. Reg Anesth Pain Med. 2014;39(5):434-7.

19. Peccora CD, Ross EL, Hanna GM. Aberrant intrathecal pump refill: ultrasound-guided aspiration of a substantial quantity of subcutaneous hydromorphone. Reg Anesth Pain Med. 2013;38(6):544-6.

20. Hnenny L, Sabry HA, Raskin JS, Liu JJ, Roundy NE, Dogan A. Migrating lumbar intrathecal catheter fragment associated with intracranial subarachnoid hemorrhage. J Neurosurg Spine. 2015;22(1):47-51.

21. Daniel JW, Haft GF. Progressive adult spinal deformity following placement of intrathecal opioid pump: a report of four cases. Iowa Orthop J. 2014;34:144-9.

22. Williams BS, Wong D, Amin S. Case scenario: self-extraction of intrathecal pump medication with a concomitant intrathecal granulomatous mass. Anesthesiology. 2011;114(2):424-30.

23. Yaksh TL, Allen JW, Veesart SL, Horais KA, Malkmus SA, Scadeng M, et al. Role of meningeal mast cells in intrathecal morphine-evoked granuloma formation. Anesthesiology. 2013;118(3):664-78.

24. Yaksh TL, Steinauer JJ, Veesart SL, Malkmus SA. Alfentanil: correlations between absence of effect upon subcutaneous mast cells and absence of granuloma formation after intrathecal infusion in the dog. Neuromodulation. 2013;16(5):459-66; discussion 66.

25. Duarte RV, Raphael JH, Southall JL, Baker C, Ashford RL. Intrathecal granuloma formation as result of opioid delivery: systematic literature review of case reports and analysis against a control group. Clin Neurol Neurosurg. 2012;114(6):577-84.

26. Duarte RV, Raphael JH, Haque MS, Southall JL, Ashford RL. A predictive model for intrathecal opioid dose escalation for chronic non-cancer pain. Pain physician. 2012;15(5):363-9.

27. Duarte RV, Raphael JH, Sparkes E, Southall JL, LeMarchand K, Ashford RL. Long-term intrathecal drug administration for chronic nonmalignant pain. J Neurosurg Anesthesiol. 2012;24(1):63-70.

28. Rizvi S, Kumar K. History and present state of targeted intrathecal drug delivery. Curr Pain Headache Rep. 2015;19(2):474.

29. Rauck R, Deer T, Rosen S, Padda G, Barsa J, Dunbar E, et al. Long-term follow-up of a novel implantable programmable infusion pump. Neuromodulation. 2013;16(2):163-7.

30. Gulati A, Puttanniah V, Hung J, Malhotra V. Considerations for evaluating the use of intrathecal drug delivery in the oncologic patient. Curr Pain Headache Rep. 2014;18(2):391.

31. Lin CP, Lin WY, Lin FS, Lee YS, Jeng CS, Sun WZ. Efficacy of intrathecal drug delivery system for refractory cancer pain patients: a single tertiary medical center experience. J Formos Med Assoc. 2012;111(5):253-7.

32. De Andres J, Asensio-Samper JM, Fabregat-Cid G. Intrathecal delivery of analgesics. Methods Mol Biol. 2014;1141:249-78.

33. Hamza M, Doleys D, Wells M, Weisbein J, Hoff J, Martin M, et al. Prospective study of 3-year follow-up of low-dose intrathecal opioids in the management of chronic nonmalignant pain. Pain medicine. 2012;13(10):1304-13.

34. Godsi SM, Saadatniaki A, Aghdashi MM, Firoozabadi NK, Dadkhah P. Outcome of continuous intrathecal opioid therapy for management of chronic pain in Iranian veterans of the imposed Iraq- Iran war. Acta Med Iran. 2011;49(7):456-9.

35. Anderson VC, Burchiel KJ. A prospective study of long-term intrathecal morphine in the management of chronic nonmalignant pain. Neurosurgery. 1999;44(2):289-300; discussion -1.

36. Kumar K, Kelly M, Pirlot T. Continuous intrathecal morphine treatment for chronic pain of nonmalignant etiology: long-term benefits and efficacy. Surg Neurol. 2001;55(2):79-86; discussion -8.

37. Rainov NG, Heidecke V, Burkert W. Long-term intrathecal infusion of drug combinations for chronic back and leg pain. J Pain Symptom Manage. 2001;22(4):862-71.

38. Kumar K, Hunter G, Demeria DD. Treatment of chronic pain by using intrathecal drug therapy compared with conventional pain therapies: a cost-effectiveness analysis. J Neurosurg. 2002;97(4):803-10.

39. Anderson VC, Burchiel KJ, Cooke B. A Prospective, Randomized Trial of Intrathecal Injection vs. Epidural Infusion in the Selection of Patients for Continuous Intrathecal Opioid Therapy. Neuromodulation. 2003;6(3):142-52.

40. Deer T, Chapple I, Classen A, Javery K, Stoker V, Tonder L, et al. Intrathecal drug delivery for treatment of chronic low back pain: report from the National Outcomes Registry for Low Back Pain. Pain medicine. 2004;5(1):6-13.

41. Mekhail N, Mahboobi R, Farajzadeh Deroee A, Costandi S, Dalton J, Guirguis M, et al. Factors that might impact intrathecal drug delivery (IDD) dose escalation: a longitudinal study. Pain Pract. 2014;14(4):301-8.

42. Gogia V, Chaudhary P, Ahmed A, Khurana D, Mishra S, Bhatnagar S. Intrathecal morphine pump for neuropathic cancer pain: a case report. Am J Hosp Palliat Care. 2012;29(5):409-11.

43. Bolash R, Mekhail N. Intrathecal pain pumps: indications, patient selection, techniques, and outcomes. Neurosurg Clin N Am. 2014;25(4):735-42.

44. ICD-90CM Expert for Physicians. 2014 Edition ed: Optum-Ingenix; 2014.

45. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03: National Institutes of Health; June 24, 2010.

46. Harden RN, Argoff CE, Williams DA. Intrathecal opioids for chronic pain: a call for evidence. Pain medicine. 2014;15(11):1823-4.

47. Harden RN, Argoff CE, Williams DA. Intrathecal opioids for chronic pain: a call for evidence. Pain medicine. 2012;13(8):987-8.

48. Odgers DJ, Dumontier M. Mining Electronic Health Records using Linked Data. AMIA Jt Summits Transl Sci Proc. 2015;2015:217-21.

49. Blumenthal D, Tavenner M. The "meaningful use" regulation for electronic health records. N Engl J Med. 2010;363(6):501-4.

50. Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011;3(70):70ra14.

51. Borsook D, Edwards R, Elman I, Becerra L, Levine J. Pain and analgesia: the value of salience circuits. Prog Neurobiol. 2013;104:93-105.

52. Levine JD, Gordon NC. Influence of the method of drug administration on analgesic response. Nature. 1984;312(5996):755-6.

53. Wasan AD, Michna E, Edwards RR, Katz JN, Nedeljkovic SS, Dolman AJ, et al. Psychiatric Comorbidity Is Associated Prospectively with Diminished Opioid Analgesia and Increased Opioid Misuse in Patients with Chronic Low Back Pain. Anesthesiology. 2015;123(4):861-72.

54. Rowbotham MC. What is a "clinically meaningful" reduction in pain? Pain. 2001;94(2):131-2.

55. American Pain Society. Section II: Assessment of Pain [December 22, 2015]. Available from: http://americanpainsociety.org/uploads/education/section_2.pdf.

56. Prather JC, Lobach DF, Goodwin LK, Hales JW, Hage ML, Hammond WE. Medical data mining: knowledge discovery in a clinical data warehouse. Proc AMIA Annu Fall Symp. 1997:101-5.

57. Mohammed RO TS. Clnical Data Warehouse Issues and Challenges. International Journal of u-and e-Service, Science and Technology. 2014;7(5):251-62.

58. Dewitt JG, Hampton PM. Development of a data warehouse at an academic health system: knowing a place for the first time. Acad Med. 2005;80(11):1019-25.

59. Bellazzi R, Zupan B. Predictive data mining in clinical medicine: current issues and guidelines. Int J Med Inform. 2008;77(2):81-97.

60. UNM Health Science Center Clinical and Translational Science Center. CTSC Heatlh Facts and Tableau [cited University of New Mexico December 20, 2015]. Available from: hsc.unm.edu.