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# OPIOIDS, SUBSTANCE ABUSE & ADDICTIONS SECTION

## *Original Research Articles*

# Prospective Study of 3-Year Follow-Up of Low-Dose Intrathecal Opioids in the Management of Chronic Nonmalignant Pain

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### Abstract

**Objective. Long-term follow-up with the use of low-dose opioids in intrathecal (IT) drug delivery system (DDS) for the treatment of intractable, severe chronic nonmalignant pain.**

**Design. This is a prospective, cohort long-term outcome study.**

**Intervention. The intervention was the implantation of DDS.**

**Method and patients. A total of 61 consecutive patients (60% females, 40% males) with a mean age of 59.2 years and a mean duration of symptoms prior to implant of 6.2 years were referred for implant of DDS for severe intractable noncancer pain. After adequate patient evaluation, each underwent a trial with IT opioids. Three patients failed the trial and 58 patients were implanted. Follow-up was 36 months, with intervals at 6, 12, 18, 24, and 36 months. The Brief Pain Inventory was used for follow-up assessment criteria at baseline prior to implant as well as throughout the duration of the study.**

**Outcome Measures. Outcome measures included self-reported pain scores (worst and average), functional improvement, and IT dose, and oral opioid consumption.**

**Results. We observed a statistically significant reduction in both worst and average pain from baseline (8.91 and 7.47 at baseline) throughout the duration of the study (4.02 and 3.41, respectively, at 36 months) ($P = 0.012$ and $P < 0.001$, respectively). We also documented a statistically significant improvement in physical and behavioral function. All subjects showed a significant reduction in the oral opioid consumption. The dose of IT opioids remained low and virtually unchanged for 36 months of follow–up: 1.4 morphine equivalent/day at 6 months and 1.48 at 36 months. Oral opioid averaged 128.9 mg of morphine equivalent/patient/day at baseline to 3.8 at 3 month and remained at the same level throughout the study.**

**Conclusion. Low-dose IT opioid can provide sustained significant improvement in pain and function for long-term follow-up in chronic noncancer pain.**

**Key Words. Chronic Noncancer Pain; Intrathecal Drug Delivery System; Low Dose; Long-Term Follow-Up**

### Introduction

Chronic noncancer pain has been defined as pain that extends beyond the usual healing time and can include conditions such as low back pain, osteoarthritis, complex regional pain syndrome (CRPS), abdominal/pelvis pain, and fibromyalgia. The estimated total health care expenditure for low back pain alone in 2004 and 2005 has ranged from 85 to 100 billion US dollars [1]. In addition,

noncancer pain is a leading cause of disability in North America [2,3]. It can have deleterious effects on the ability to work, functional status, and other quality of life domains [2–4].

The use of oral/transdermal opioids in the treatment of noncancer pain has accelerated over the last two decades. The efficacy of opioids in the treatment of chronic nociceptive and neuropathic pain has been demonstrated in short-term trials [5–7]. However, little is known about the long-term (greater than 2 years) use of these agents. Concerns over the long-term use of opioids include opioid-related side effects, tolerance, and opioid-induced hyperalgesia. One systematic review noted drop-out rates due to adverse events as high as 32% at 6–12 months [8]. The most commonly reported adverse events were gastrointestinal (constipation, nausea, vomiting, dyspepsia, and dysphagia), headache, lethargy/fatigue/somnolence, hormonal effects, and urinary complications (hesitancy, retention). The increased use of oral opioids has also been associated with aberrant drug behavior, diversion, and, in some instance, opioid-related fatalities secondary to unsanctioned use.

Thimineur et al. [9] in the meta-analysis examining the effectiveness of oral opioid therapy determined that many patients do not achieve long-term analgesia with oral opioids, and lack of increase in functional capacity with oral opioid therapy [10]. It appears based on those findings that achieving analgesia with oral opioids may not return the patient to a more functional state.

The efficacy and safety of long-term opioid therapy can be influenced by the route of administration. The discovery of the dorsal horn μ-receptors has been an important factor in the development of neuraxial administration of opioids and better pain relief [11]. The increased magnitude of analgesic efficacy of intrathecal (IT) opioid in comparison to systemic oral and transdermal opioids has been demonstrated. Since the introduction of a programmable drug delivery system (DDS) in 1991, there has been an increase in the use of IT opioid for the control of chronic intractable pain [12,13]. Many reports have documented the efficacy of the use of IT opioids for controlling chronic nonmalignant pain. These range from case reports to retrospective reviews, with varying degrees of effectiveness and follow-up durations [12–15].

IT delivery has several advantages over the more traditional oral or transdermal routes, including the use of a fraction of the dose, decreased systemic exposure, potential for reduced side effects, and reduced reliance on systemic medications. The pharmacodynamics, pharmacokinetics, and flow dynamics of IT delivery continues to evolve. A relatively new concept is that of "microdosing," which is characterized by the use of low opioid dosing [16], often less than 1 mg of morphine or its equivalent. In such cases, it is recommended that the patient be withdrawn from all opioids prior to the IT trial. This approach could result in lower doses of opioid to achieve adequate pain control as a result of eliminating tolerance and possibly reversing opioid-induced hyperalgesia.

Postimplant management of the IT therapy has become of great concern. A report from 2008 ECRI summarizing the IT literature noted increases in IT dosing by a factor of 5–10 times that of baseline dose over the span of 24–36 months, often without any improvement in pain relief. Furthermore, the rate of dosage acceleration did not appear to decrease over time. The degree to which this represents tolerance or opioid-induced hyperalgesia is unclear. Some data have also suggested that greater higher baseline levels of IT opioid and ongoing use of systemic opioids may be associated with less desirable outcomes. In addition, attending to only pain rating or percent improvement on subjective pain provides an incomplete picture of patient overall functioning [17].

The present study was designed to evaluate a specific protocol for the trialing and long-term management of IT therapy in a cohort of 58 chronic noncancer pain patients. The trial focused on functional as well as pain reduction outcomes. Patients were withdrawn from their systemic opioids prior to implant and their use was very restricted to postimplant. All patients were followed up for 36 months. Follow-up assessment parameters included worst and average pain scores visual analog score (VASs), physical and behavioral functional improvement, the dose of oral and IT opioids (expressed in morphine equivalent), and patient global assessment.

## Methods

### *Patients*

This prospective study was approved by the Institutional Review Board. All patients had severe intractable and chronic nonmalignant pain, and failed multiple lines of conservative and invasive care. We included all patients referred to our service for consideration for implantation of DDS. Each patient underwent a detailed medical history, physical examination with special attention to previous treatments. All patients reported having failed multiple medical management approaches, including anti-inflammatory, antidepressant, antiepileptic, and opioids either as a result of unacceptable pain relief or undesirable and dose-limiting side effects. Imaging and electrodiagnostic studies were reviewed. Patients underwent a surgical consultation to rule out the presence of any pain relevant surgically correctable lesion. The patients received 1) educational material outlining IT therapy; 2) a clinic handout explaining the protocol and rationale of IT therapy; 3) information as to the method of trialing; 4) strategy for the management of systemic oral opioids; and 5) details of the postoperative care and follow-up frequency. Specifically, patients were informed that systemic opioids would be very limited and daily use will be discouraged. All patients were then referred for a psychological evaluation 1) to ensure adequate understanding of the provided material; 2) rule out any psychogenic barrier to long-term improvement; and 3) to establish appropriate expectations. We included all patients who had their pump implant between 2005 and 2006.

*Weaning Protocol*

All patients underwent a weaning program for opioids. Over 3–5 weeks, 50% of baseline opioid were weaned, a trial was then undertaken, all patients who had a positive trial continued to wean down to off all opioids over 3–5 weeks. After coming off all opioids for 7–10 days, pump implant was then undertaken.

*Trial Protocol*

The IT trial involved an inpatient, single-blinded, placebo-controlled, dose-escalating protocol. The IT catheter was implanted under fluoroscopic guidance. In general, the catheter entered at about L4-L5 interspace with the tip located at T12—L1. The catheter was bolused with 0.25 mg of morphine, 0.5 mg of morphine, or 0.5 mL of normal saline. All patients were informed that opioids and normal saline would be used during the trial. However, they were not informed of the order, except at the completion of the trial. They were informed that this was done in an effort to ensure that improvement was due to the medication rather than a placebo response. IT injections during trial were done every 24 hours. Pain relief, as well as physical functional improvement, was recorded by the patient and observed by the staff for 24 hours after each bolus. Three patients reported greater relief with the saline injections compared with opioid and were considered as a trial failure and did not proceed to implant. The remaining 58 patients were determined to have had a "positive" trial based on 1) pain reduction; 2) improved function; and 3) no or very minimal response to saline, and higher level response with the higher IT opioid dose. They were discharged to complete the weaning protocol.

*Implant Protocol*

Under general anesthesia, a Synchromed II programmable pump (Medtronic Inc. Minneapolis, MN, USA) was implanted. Catheter entry site at L4-L5 interspace, catheter tip at T11-T12 interspace. Pump was placed in a subcutaneous pocket in the abdominal region. Incisions were closed in two layers, subcutaneous running absorbable suture, skin approximated with staples. Initial pump dose was started based on the trial dose. The patients were discharged with short-acting opioid for incisional pain, and instructions for wound care. All patients were seen 10–14 days postoperative for assessment of healing, removal of staples; they were seen back about 8 weeks later to further ensure adequate healing and pump increase as needed and then commencement of physical therapy. The physical therapy was started as aquatic physical therapy twice per week for 6 weeks, followed by floor exercises and work hardening twice per week for 6 weeks. A home-based exercise program was developed for each patient. About 15% of patients were not able to attend the structured physical therapy program, those followed a walking program. IT opioids were titrated by 10–25% as needed throughout the phase of physical therapy dose titration, and continued throughout the physical therapy. The patients were offered participation in a patient-guided and managed support group that met quarterly.

*Outcome Measures*

Follow-up visits were conducted at 6, 12, 18, 24, and 36 months postoperative. The Brief Pain Inventory (BPI) was completed at each visit, including baseline visit prior to weaning oral/transdermal opioids, the initial introduction of educational material, and every follow-up. The BPI assesses worst pain, average pain, and has a physical functioning scale (general activity, walking activity, and normal work), behavior scale (mood, relations, and sleep), and enjoyment scale. A 0–10 scale was used. The limitations in function and behavior are also reported as degree of pain interfering with such function. The global Patient Reported Pain and Functional Improvement were assessed on a 0–100% scale. IT and oral opioids use was monitored and converted to morphine milligram equivalents. We reported starting at 6 months as to allow for titrating and stabilization of IT opioids throughout healing, physical therapy, and work hardening phase.

*Statistical Analyses*

SAS v.2 (SAS Institute Inc., Cary, NC, USA) was used for all data analysis and all graphics were created using Microsoft® Office Excel® 2007. Descriptive statistics including means/standard deviations (SDs) or medians/interquartile range (IQR) for continuous variables and frequency counts and percentages for nominal variables were computed to describe the characteristics of the sample. Linear mixed-effects models were used to model the changes in the outcome variables (worst BPI, average BPI, and physical functioning, behavior, and enjoyment BPI subscales) over time from baseline to 36 months follow-up (0, 6, 12, 18, 24, and 36 months). All models assumed an unstructured covariance structure for the repeated measures over time within a subject. A similar mixed-effects model was used to model the changes in IT dose over time 6–36 months postimplant. A paired *t*-test was used to test for a change in systemic opioid dose from baseline to 3 months postimplant.

The mixed-effects model was selected to account for both within- and between-subject sources of variation. Furthermore, there was very little missing data due to dropout, pump explanation, or death. The losses occurred can be assumed to be missing at random, making the mixed model the preferred choice because data available from other time points for the subjects with some missing data can still be incorporated into the model.

## Results

*Patient Demographics*

Baseline patient characteristics (age, gender, diagnosis, and duration of symptoms at time of presentation) are summarized in Table 1. Some 60% of the patients were

**Table 1** Patient demographics

| | | |
|---|---|---|
| Female count (%) | 35 | (60.3) |
| Age (years), mean (SD) | 59.2 | (13.5) |
| Duration of symptoms (years), mean (SD) | 6.2 | (1.8) |

SE = standard deviation.

**Table 2** Patients presentations

| Diagnosis | Number | % |
|---|---|---|
| FBSS | 35 | 60.3 |
| LBP | 16 | 27.5 |
| CRPS | 3 | 5.1 |
| Abdominal pain | 2 | 3.4 |
| Pelvic pain | 2 | 3.4 |

CRPS = complex regional pain syndrome; FBSS = failed back surgery syndrome; LBP = low back pain.

female. The average age for the entire cohort was 59.2 years (SD 13.5) and average duration of pain was 6.2 years (SD 1.8). Approximately 88% of patients were diagnosed with either failed back surgery syndrome or low back pain. Presenting diagnoses are summarized in Table 2.

*Average and Worst Pain*

There were significant changes in both BPI worst ($F$[5, 51.7] = 119.8, $P < 0.001$) and Average ($F$[5, 51.4] = 95.2, $P < 0.001$) scores over time from baseline to 36 months follow-up. The mean BPI worst and average scores at baseline were 8.91 and 7.47, respectively, and initially decreased (improved) to 3.93 and 2.97 by 6 months follow-up. The BPI worst scores continued to change significantly from 6 to 36 months follow-up ($P = 0.012$), but remained low and between 3.93 and 4.18 (mean = 4.02). This change represents mean percent reduction from baseline of 36 months of 54.2% and 47.4%, respectively. Similarly, BPI average scores continued to change significantly from 6 to 36 months follow-up ($P < 0.001$), but remained low and 2.97 and 3.78 (mean = 3.41). BPI worst and average scores were significantly higher (worse) at baseline as compared with all follow-up time points, with decreases (improvements) from baseline at each follow-up month ranging from 4.73 to 5.05 and from 3.69 to 4.25, respectively (see Figure 1).

*BPI Physical Functioning*

The BPI physical functioning scale (BPI-PFS) is a composite of the scores from the BPI general activity, walking activity, and normal work items. There were significant changes in BPI physical functioning composite scores over time from baseline to 36 months follow-up ($F$[5, 51.6] = 103.3, $P < 0.001$). The BPI-PFS score was, on average, 25.41 at baseline and initially decreased (improved) to 14.27 by 6 months follow-up. The BPI-PFS scores did not change significantly from 6 to 36 months follow-up ($P = 0.31$), and remained between 14.27 and 14.83 (mean = 14.58). The BPI-PFS scores were significantly higher (greater interference) at baseline as compared with each follow-up. The magnitude of the decreases (improvements) from baseline to each follow-up month ranged from 10.58 to 11.15. The estimated mean BPI-PFS scores and the estimated decreases from baseline are summarized in Figure 2. Figure 2 summarizes the mean scores and 95% confidence intervals over time for each of the BPI-PFS items. All of these individual items exhibited significant decreases from baseline to each follow-up time points (all $P$ values < 0.001).

*BPI Behavior*

The scores from the BPI mood, relations, and sleep items sum to form the composite score for the BPI behavior scale (BPI-BS). There were significant changes in BPI-BS

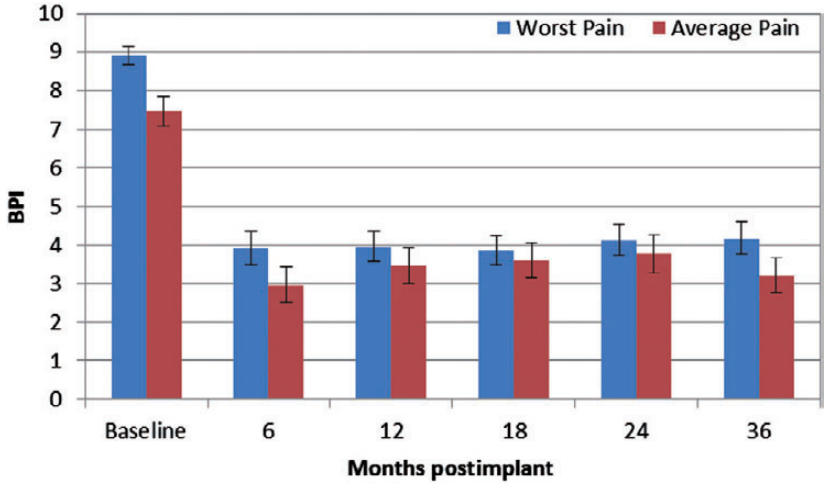


**Figure 1** Mean worst and average pain (Brief Pain Inventory [BPI]) over time postimplant (±95% confidence intervals).

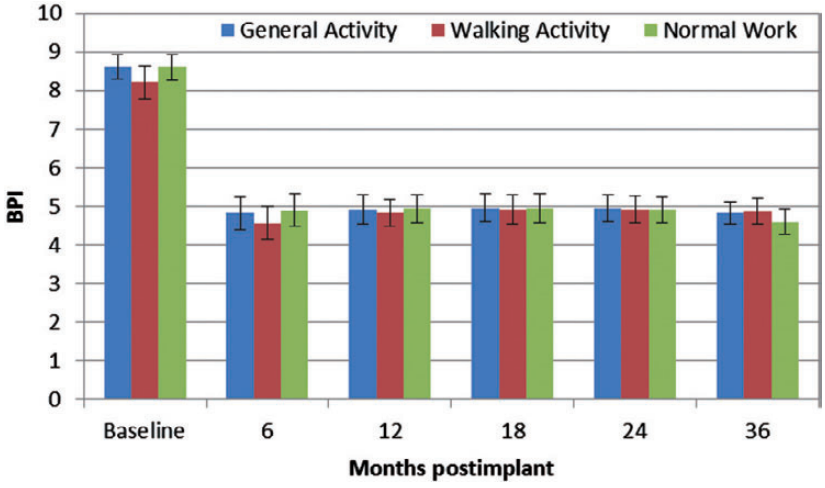


**Figure 2** Mean Brief Pain Inventory (BPI) physical functioning items over time postimplant (±95% confidence intervals).

scores over time from baseline to 36 months follow-up ($F[5, 51.2] = 99.0$, $P < 0.001$). BPI-BS scores were, on average, 23.21 at baseline and initially decreased (improved) to 13.44 by 6 months follow-up. The BPI-BS scores continued to change significantly from 6 to 36 months follow-up ($P = 0.026$), but remained low and between 13.44 and 14.64 (mean = 14.20). BPI-BS scores were significantly higher (greater interference) at baseline as compared with all follow-up time points, with decreases (improvements) from baseline to each follow-up month. Figure 3 summarizes the mean scores and 95% confidence intervals over time for each of the BPI-BS items. All of these individual items showed significant decreases from baseline to each follow-up time points (all $P$ values < 0.001).

*Patient Reported Pain and Function Improvement (Patient Global Assessment)*

All patients were asked to assess their global impression of improvement at the end of the study compared with baseline. The patient's reported, on average, an improvement in pain of 65.2% (SD = 21.8%, range = 20–95) and an improvement in function of 42.7% (SD = 19.4%, range = 10–80). The distribution of the percentage of improvement in pain and function (0–25%, 26–50%, 51–75%, and 76–100%) are shown in Figures 4 and 5. Nearly 38% of patients reported more than 75% improvement in pain and 72.4% reported more than 50% improvement in pain. Only 1.7% of patients reported more than 75% improvement in function, 31.0% reported more than 50% improvement in pain, and 75.9% reported more than 25% improvement in function.

*BPI Enjoyment*

There were significant changes in the BPI enjoyment item scores over time from baseline to 36 months follow-up ($F[5, 50.9] = 69.5$, $P < 0.001$). BPI enjoyment scores were, on average, 8.47 at baseline and initially decreased (improved) to 4.87 by 6 months follow-up. The BPI enjoyment scores did not change significantly from 6 to 36 months follow-up ($P = 0.35$), and remained between 4.76 and 5.07 (mean = 4.89). BPI enjoyment scores were sig-

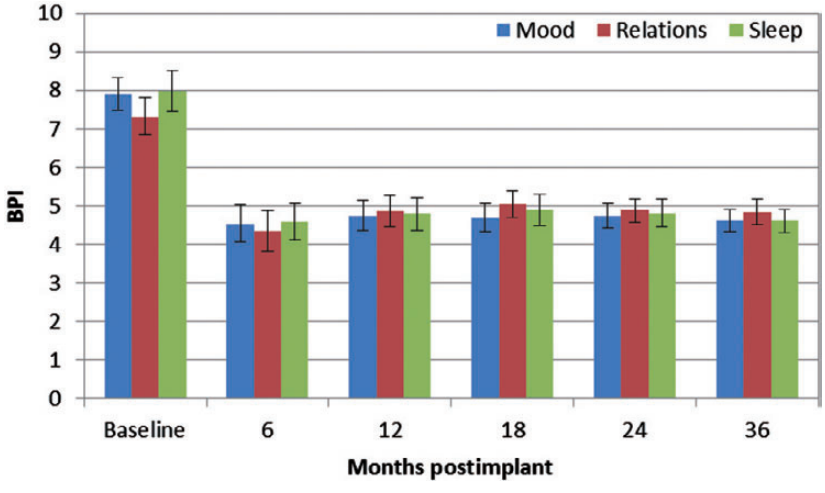


**Figure 3** Mean Brief Pain Inventory (BPI) behavior items over time postimplant (±95% confidence intervals).

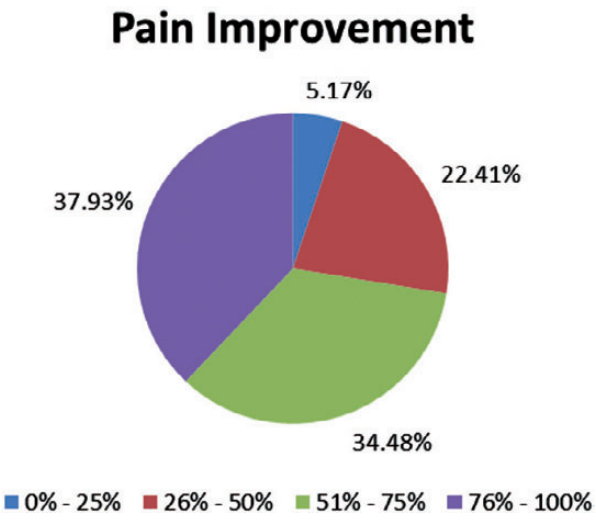


**Figure 4** Patient global assessment of pain improvement.

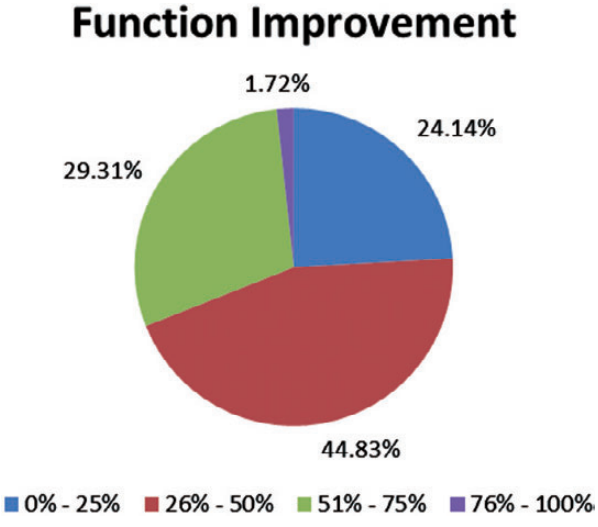


**Figure 5** Patient global assessment of functional improvement.

nificantly higher (greater interference) at baseline as compared with all follow-up time points, with decreases (improvements) from baseline to each follow-up month ranging from 3.39 to 3.70 (Figure 6).

*IT Dose*

There were significant changes in the IT dose from 6 to 36 months postimplant ($F[4, 51.7] = 10.5$, $P < 0.001$). The mean IT dose for 6–36 months postimplant is illustrated in Figure 7. As can be seen in Figure 7, the IT dose remained between 1.40 and 1.43 from 6 to 18 months postimplant and then increased to between 1.57 and 1.58 from 24 to 36 months postimplant. This represents an average increase of only 11.4% across the 3 years of treatment. The largest increase appeared to occur between 18 and 24 months and stabilized between 24 and 36 months.

*Oral Opioid Utilization*

A paired *t*-test was used to compare the change in the mean opioid dose (mg/day morphine equivalent) from baseline to 3 months follow-up. There was a significant decrease in opioid usage from baseline to 3 months follow-up (paired *t*-test = 9.7, degrees of freedom [df] = 57, $P < 0.001$). The mean opioid dose at baseline and at 3 months postimplant is summarized in Table 3 along with the average decrease in opioid dose. The dose of systemic opioids was unchanged throughout the duration of the study.

## Discussion

This study examined the effects of a specific protocol in the treatment of severe chronic noncancer pain using low-dose IT opioid monotherapy. In general, the patients reported clinically significant improvements of pain, mood, function, enjoyment, and overall global improvement. These changes persisted over the 3-year follow-up period. Unlike many previous studies, the IT medication remained relatively low and stable. The use of systemic opioids was extremely low. No correlation was found between the type of pain, duration of symptoms, or the initial IT dose and outcomes.

Implantable DDS has established a significant position in the treatment of chronic noncancer pain. Many different medications have been utilized. Morphine remains one of the few Food and Drug Administration (FDA)-approved preparations and perhaps the most commonly used drug in IT therapy [18,19]. It is common for other opioids and various mixtures to be employed. Despite increases and adjustments in the IT medication(s), the number of patients reporting benefit decreased and the degree of improvement noted worsened, also the intake of systemic opioids medications significantly increased [20–29]. In other reports, dose escalation over 12–25 months in patients started at 2.5 mg morphine and progressed to 12 mg morphine. Additionally, these two reports [21,30] did not report any systemic guidelines for the management of oral systemic opioids. Similar reports have

**Table 3** Mean opioid dose (mg/day) from baseline to 3 months postimplant

| | N | Estimate | SE | 95% CI |
|---|---|---|---|---|
| Baseline | 58 | 126.71 | 12.92 | (100.83, 152.58) |
| 3 months | 58 | 3.80 | 0.90 | (2.01, 5.60) |
| Decrease | | 122.91 | 12.61 | (97.65, 148.16) |

SE = standard error; CI = confidence interval.

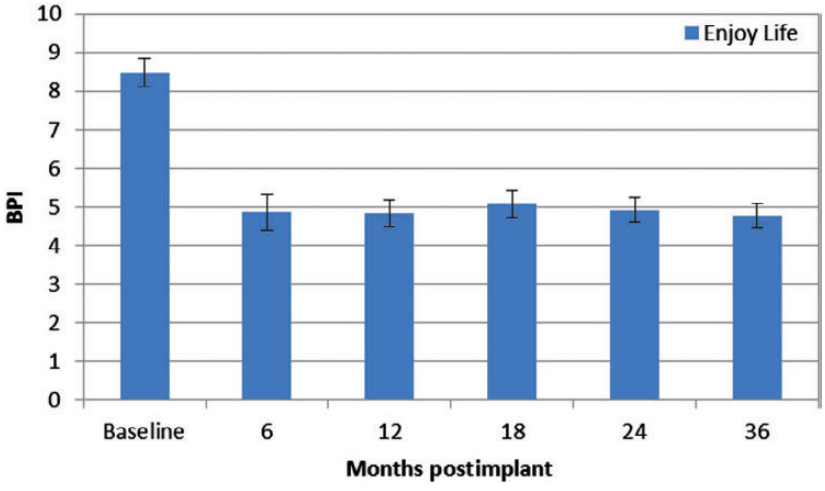


**Figure 6** Mean Brief Pain Inventory (BPI) enjoyment item over time postimplant (±95% confidence intervals).

reported progressively increasing IT dose by up to 100% of baseline doses [14,21,25–27,31].

Atli et al. reported the efficacy of IT opioids for control of chronic noncancer pain. However, they also reported significant IT dose escalation by about 50% or more with initial drop in oral opioids. Diminished reduction in reported initial pain improvement was documented over the duration of follow-up for 36 months [28].

Grider et al. [16] reported a retrospective series of 22 patients. This group had a 6-week opioid-free period prior to the IT pump implantation. They also reported two trial failures secondary to urinary retention and lack of efficacy of morphine. Followed up with VAS for 12 months. However, no functional or behavioral outcome assessments were obtained. Previous reports have commented on series with number of patients between 10 and 38 with approximate follow-up period of up to 2 years. IT morphine on those studies reported efficacy with expressed analgesia. None of those studies commented on specific opioid trialing technique. Variable trialing techniques have been reported with outpatient/inpatient IT vs epidural catheters (from [9,20,25,26,31,32]).

Recent reports, reviews, and consensus guidelines emphasize the fact that no particular approach to trialing has proven more predictive than another. Indeed, Webster [33] questioned the need for a trial as it would be virtually impossible to trial all analgesics and their combinations, thus resulting in a high likelihood of a "false-negative" trial. Doleys and Kraus [34] emphasized an individualized trial constructed on the basis of "what one is trialing for," i.e., analgesia, side effects, function, patient acceptance, etc. Given the emphasis on improved function and quality of life as desirable therapeutic outcomes, a functionally oriented trial would merit consideration. What is often overlooked is the role of the postimplant management strategy. Inappropriate management, rapid dosage acceleration, and overreliance on IT and systemic opioids in the absence of a complementary rehabilitation therapies may result in a successful trial becoming a poor long-term outcome.

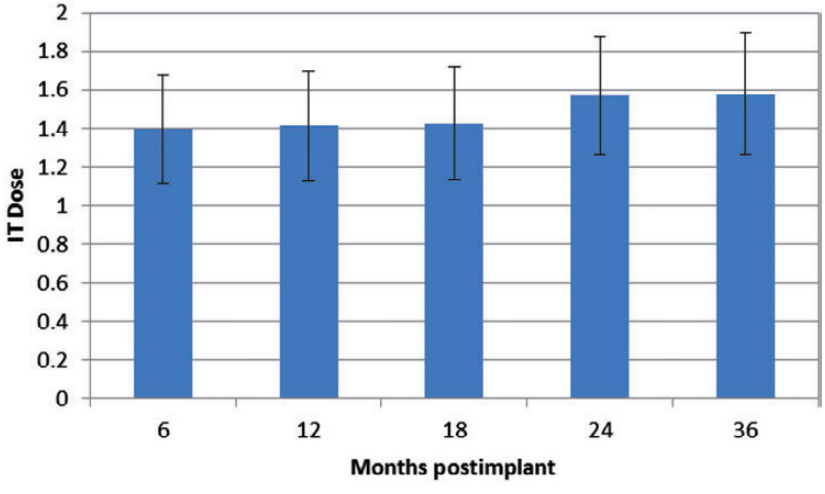


**Figure 7** Mean intrathecal (IT) dose (±95% confidence intervals) over time postimplant.

It is noteworthy that each of the patients in our study responded to opioids monotherapy without the need for increased dosing, medication changes, or the use of combination medications. The trialing protocol, expectations, specification of a management strategy, and the virtual absence of oral opioids may account for this. Whatever the case, it is clear that chronic pain can be effectively managed over a long period without frequent changes and adjustments in the IT medication. Although the level of IT morphine in this study may not be seen as "microdosing," it is substantially less than that reported in most studies and well within the consensus guidelines for minimizing complications.

Consensus guidelines have provided recommendations with regard to patient selection and trialing techniques in the setting of noncancer pain [19]. The polyanalgesic consensus panel outlined an evidence-based algorithm regarding the utilization of different medications in an IDDS [19]. These documents represent a major advance toward the goal of establishing best practices with IT therapy. However, several questions remain. These include 1) the management of systemic opioids during the trial and postimplantation; 2) the appropriate starting dose; and 3) determining when to change or combine medications. The "dose–response" relationship of IT opioids, especially as it relates to various outcome domains, has not been established in humans with chronic noncancer pain. The existing conversion ratio from systemic to IT was established in the acute and/or postoperative setting and may or may not generalize to the chronic pain setting. Therefore, the use of discrete dosing of differing amounts during the trial may have some advantages.

Tolerance is a common side effect of oral opioid therapy. Tolerance, along with opioid-induced hyperalgesia, may be responsible for the loss of opioid efficacy [10]. It is possible that an opioid-free interval prior to administering IT opioids may reverse and limit the development of and/or the re-establishment of tolerance. This appeared to be the case in the present study, as indicated by the clinically insignificant escalation for the total dose opioid from 1.4 mg as average daily dose per patient at 6 months to 1.48 mg as average daily dose per patient at 36 months.

The duration of time of opioid withdrawal to reverse tolerance and hyperalgesia is currently unknown. Various lengths of time have been reported. One study reported the need for a 4-week opioid-free period in addicts to reverse tolerance to morphine [35], others have suggested it may take up to 6 months to reverse opioid-induced hyperalgesia [36,37]. Thus, tolerance and hyperalgesia may be reversed; however, the time interval necessary for that is not well understood and/or established.

We elected 7–10 days of abstinence from oral opioids prior to pump implantation based on the fact that the duration of time needed for reversal is not clearly established. Also, weaning patients for 4 weeks or more was deemed to be too demanding in our patient population. Patient acceptance of an opioid taper in our series was achieved by a combination the interview process, explanation of the therapy, outlining the current and potential adverse events of the daily use of oral opioids. Presenting the patient with an IT trial in the middle of the taper seemed to positively impact their acceptance of the tapering. Indeed, all patients presented to our service for consideration of IT therapy agreed to the tapering protocol.

Patients in this study used an average of 3.8 mg of morphine milligram equivalents (range 0–6 mg) orally per day to supplement their IT therapy. We do not believe that such a small dose of oral opioid had a significant impact during the utilization of the IT opioid. However, it allowed patients a sense of control. One recent study [38] demonstrated the potential advantage of patient-determined dosing compared with time-contingent dosing. Furthermore, as oral opioids were not used on a daily basis, there was a reduced likelihood of the development of tolerance which could have an effect on the patient's responsiveness to the IT opioid.

The side effects reported in our study are mild and limited and we believe that is a reflection of the lower dose reported in our series are summarized below.

| | | |
|---|---|---|
| Wound infection | 3/58 | 5% |
| Peripheral edema | 2/58 | 3% |
| Pruritus | 3/58 | 5% |
| Seroma | 2/58 | 3% |

The low rate of complications is a reflection of the low IT dosing. All patients with wound infection presented in the first week post-implant. One patient presented with superficial cellulitis, was treated with oral antibiotics, and responded favorably. Two patients were ex-planted, treated with i.v. antibiotics, then re-implanted in 6 weeks. One patient with peripheral edema responded to a small dose of diuretic and pressure stockings, the second required a change of IT opioid to a more lipid-soluble agent. Seroma responded to conservative care, and pruritus was self-limited, and resolved with no specific treatment. We attribute low drug-related adverse events to the use of low-dose opioids; the use of meticulous attention to operative protocol, a single implant team, we believe, contributed to low surgical complication rate.

Several reports have commented on the cost-effectiveness of IT therapy. It has been suggested that the cost of IT therapy compared with comprehensive medical management with systemic opioids can be recovered over a 3- to 6-year period [39–41]. The estimates were based on the cost of delivering 6 mg of morphine daily. The use of a significantly lower daily dose and very limited systemic opioids would shorten the recovery time. This estimate does not take into account savings that would be accrued by a reduction in the need for other therapies, physician, and emergence room visits. Changes in the health care system in the United States may place a greater financial burden on the patient making cost-efficient therapy even more important.

There are some limitations to our study. There was no control or comparison group. One could consider our study population as being "self-selected" by virtue of their willingness to be withdrawn from systemic opioids. However, the point of this and other such therapies is selecting the patients most likely to have a long-term positive outcome. As all patients were encouraged to participate in some form of post-implant physical rehabilitation program, we are unable to assert its contribution to the positive outcome. The general disconnect between pain relief and increased function is well known. This period of therapy may have served the function of desensitizing the patients to the fear of increased activity, thus limiting the tendency toward "activity-avoidance."

## Conclusion

The present study reports on the use of long-term IT therapy in the treatment of chronic noncancer pain. This study has several unique features, including 1) well-defined trialing technique; 2) easily achievable, gentle program for weaning systemic oral opioids prior to implant; 3) an established initial starting dose without the need for calculations or conversions; 4) assessment of pain, functional, and behavioral improvement; 5) minimal oral medication postimplant; and 6) limited IT dose escalation. The results of our prospective cohort of 58 patients with low-dose IT opioid monotherapy for long-term follow-up noted sustained improvement as reported by pain reduction and functional improvement with very limited IT dose escalation. Weaning patients of oral opioids prior to implantation, as well as engaging patients in a structured postimplant physical rehabilitation program, appeared to be associated with maintenance of low-dose IT administration over a 3-year period and minimal use of oral opioids.

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