

Retrospective Analysis

Transition from Compounded to Monotherapy Intrathecal Pain Medication Reduces Drug Costs: Retrospective Analysis of Patient Billing Data

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Background: Chronic pain accounts for several hundred billion dollars in total treatment costs, and lost productivity annually. Selecting cost-effective pain treatments can reduce the financial burden on both individuals and society. Targeted drug delivery (TDD), whereby medications used to treat pain are delivered directly to the intrathecal space, remains an important treatment modality for chronic pain refractory to oral medication management. These medications can be administered alone (monotherapy), or in conjunction with other medications to give a synergistic affect (compounded therapy). While compounded therapy is often prescribed for pain refractory to both oral management and intrathecal monotherapy, compounded administration has not been approved by the United States Food and Drug Administration (FDA), and is thought to be more expensive. In this study, we hypothesized that TDD delivering monotherapy vs compounded therapy would differ significantly in cost.

Objectives: In 2015, a pharmacy-led initiative resulted in an institution-wide policy requiring that all TDD patients, being treated with compounded therapy, be transitioned to FDA-approved intrathecal monotherapy. The intent of this new policy was to eliminate use of non-FDA approved, "off-label" medications. During this transition, our practice used the opportunity to retrospectively analyze and compare the costs of monotherapy vs compounded therapy.

Study Design: Billing, drug dosing, and pain data were collected from 01/2015 to 01/2019, and reviewed retrospectively for patients originally on compounded intrathecal medication therapy, and compared before and after transition to monotherapy.

Setting: A multidisciplinary hospital-based spine center within an academic tertiary care facility.

Methods: Electronic medical records from the institutional TDD program were retrospectively reviewed to identify all patients on compounded drug therapy before the transition period (2015-2016). Patients were excluded from the study if they chose to switch their care to another practice rather than transitioning from compounded therapy to monotherapy. Cost per medications refill, cost per year, and reported pain scale before and after the transition were computed, and differences were compared using unpaired t tests. Refill costs of individual drugs were also compared.

Results: Of 46 patients originally on compounded therapy, 26 patients met inclusion criteria. The most common pre-transition drugs administered as compounded therapy were bupivacaine (n = 17), morphine (n = 15), and clonidine (n = 14), while hydromorphone (n = 10), baclofen (n = 5), and fentanyl (n = 1) were less common. There was a 51.3% decrease in cost per refill ($P = 0.135$) and a 50.0% decrease in cost per year ($P = 0.283$) after transition. Morphine and clonidine were both significantly more expensive than hydromorphone and bupivacaine ($P < 0.05$). After removing cases in which hydromorphone was the baseline opiate, there was a 64.8% decrease in cost per refill ($P = 0.041$) and a 66.8% decrease in cost per year ($P = 0.190$). There was no significant difference in the average reported pain scale across the transition ($P = 0.323$), suggesting stable pain management efficacy.

Limitations: This retrospective study is limited by its small cohort size and lack of a control group.

Conclusions: Based on single-institutional billing data, transition from compounded therapy to monotherapy TDD resulted in cost savings, dependent on the specific combination of drugs initially used for therapy. A larger multi-institutional study is indicated.

Key words: Low back pain, intrathecal pain management, implantable drug pump, cost analysis, morphine, hydromorphone, fentanyl, clonidine, baclofen, bupivacaine

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The treatment of chronic pain, in particular chronic low back pain (LBP) affects over 100 million adults in the United States (US) and carries significant personal and societal costs. The economic burden, excluding lost productivity, ranges from \$200 to \$300 billion US dollars annually with indirect costs associated with lost productivity exceeding \$300 billion US dollars. The total cost for treating pain (1) exceeds the annual cost for heart disease, diabetes, and cancer. Prior studies (2-6) have established that targeted drug delivery (TDD) may be more cost effective than long-term administration of opioids via other routes. Amidst high drug prices in the US, we hypothesized that prescribing compounded therapy for TDD may increase the cost barrier to further implementation of TDD as health care continues shifting towards a cost-benefit model.

TDD utilizes an implantable medication reservoir (pump) to deliver pain medication to the intrathecal space. Numerous previous studies (7-12) have demonstrated the safety and efficacy of TDD for achieving symptom relief in patients with nonmalignant chronic pain from a variety of etiologies, and especially for pain refractory to medication therapy administered by other methods. Studies have suggested additional opportunities to incorporate TDDs (12,13), including treatment of intractable back pain in the setting of advanced cancer. TDD systems are easily refilled, carry favorable risk profiles, and produce demonstrable benefit for many patients (14), even after long-term use (15).

There is ample evidence supporting the efficacy of TDDs for treating chronic pain across multiple clinical scenarios. Compounded therapy is often utilized to enhance pain control for patients in whom monotherapy has failed; however, compounded therapy has never been approved by the US Food and Drug Administration (FDA) for use within TDD. Furthermore, some of the medications used in compounded therapy (e.g., clonidine) have not been approved individually for intrathecal use. This practice, despite being the standard of care, is considered an "off-label" use. While there is data to suggest that local anesthetics (LAs), such as bupivacaine, work synergistically with opiates to provide improved pain control for nociceptives as well as neuropathic pain when compounded for carefully selected

LBP subpopulations (2,16-17), there are older studies which suggest that, in general, off-label usage of LAs compounded with morphine in the intrathecal setting does not provide additional benefit (18,19).

Our institution implemented a policy, in 2015, requiring that all patients undergoing TDD treatment with compounded therapy, who wished to continue treatment at our institution, be transitioned to monotherapy over a 2-year period (01/2015-12/2016). This policy change was a pharmacy-based decision to eliminate off-label drug usage. We conducted a retrospective review of patients with TDD systems who underwent the transition to monotherapy. Compounding of drugs was outsourced to a 503B certified pharmacy and monotherapy was Duramorph. We tested our hypothesis by comparing pharmaceutical billing data from before and after the transition, as well as assessing any differences in reported pain levels over the same period of time.

METHODS

This study was conducted as a retrospective review of the institutional electronic medical record (EMR) and Institutional Review Board authorization for this retrospective chart review was obtained (#1190729).

The study population comprised a series of consecutive patients managed at a single hospital-based outpatient multidisciplinary spine center within an academic regional tertiary care facility between 01/2015 and 12/2016. The patients' care were transitioned from a private neurosurgery practice to a hospital-based practice. These TDD patients had previously been established on compounded therapy using a Medtronic SynchroMed™ II pump, for a diagnosis of chronic LBP refractory to standard of care. The intent was to transition all patients from compounded therapy to monotherapy, as per updated institutional policy. A list of all patients who were receiving compounded therapy was collected from clinic records, and the EMR was retrospectively searched for relevant demographics, billing data, drug dosing data, and reported pain on a numeric rating scale (NRS-11) from 0 to 10. Billing data were obtained from the hospital pharmacy's billing records associated with individual patient EMR accounts; reimbursement data were unfortunately not available for review. Drug dosing data were obtained

from clinic notes containing templated intellectual and developmental disability (IDD) readouts. The data collected spanned from 01/2015 to 01/2019 in an effort to capture the compounded to monotherapy transition period-to-monotherapy transition period. Individual patients were excluded or subcategorized based on availability of data points for completing target cost analyses according to the flowchart in Fig. 1.

Demographic data included age, gender, and diagnosis. Billing data included cost per refill for each drug dispensed, as obtained from individual refill expenses billed to individual patient accounts and recorded on the pharmacy billing record. Drug dosing data included TDD pump size and daily dose of each drug, which were computed from pump settings and recorded in each follow-up medication refill and clinic note. This data was then extrapolated to calculate the number of refills per year. Notably, in cases where data were present from multiple pre- and post-transition time points, representative billing and dosing data were selected from the periods when the patient reached optimal pain control, so as to avoid predictable fluctuations immediately prior to and immediately following transition from compounded therapy to monotherapy (i.e., periods of dose taper before and/or pain relief optimization after). From this data, costs per refill and per year were computed in US dollars for comparison between the pre- and post-transition period. The average overall cost per refill, cost per year, and cost per refill for individual drugs were also computed across the full study population, as were the average change in costs from before transition to after. Unpaired t tests were performed on raw data to assess the statistical significance of these differences, and P values were reported. Hospital billing data were used to represent the cost

billed to insurance, and differences were reported to represent comparative findings between drugs. There were no data indicating which charge, or which portion of each charge, was covered by the patient vs. their insurance plan, and there was no data on the actual reimbursements received by the hospital for the bills issued.

RESULTS

A total of 46 patients (representing a cohort of the total number of compounded IDD patients originally in the practice was seen from 01/2015 to 12/2016) were receiving compounded intrathecal pain medication at baseline. Upon searching the EMR for key dosing and cost data, 3 of these patients were excluded due to inadequate baseline pump dosing data (probably due to EMR implementation occurring in March of 2015). An additional 17 patients were excluded from the study population because they ultimately decided to transfer their care to another local provider rather than undergo further IDD that did not involve compounded medication. Our study cohort, therefore, included 26 patients (n = 26). Of these, 6 patients went on to choose non-

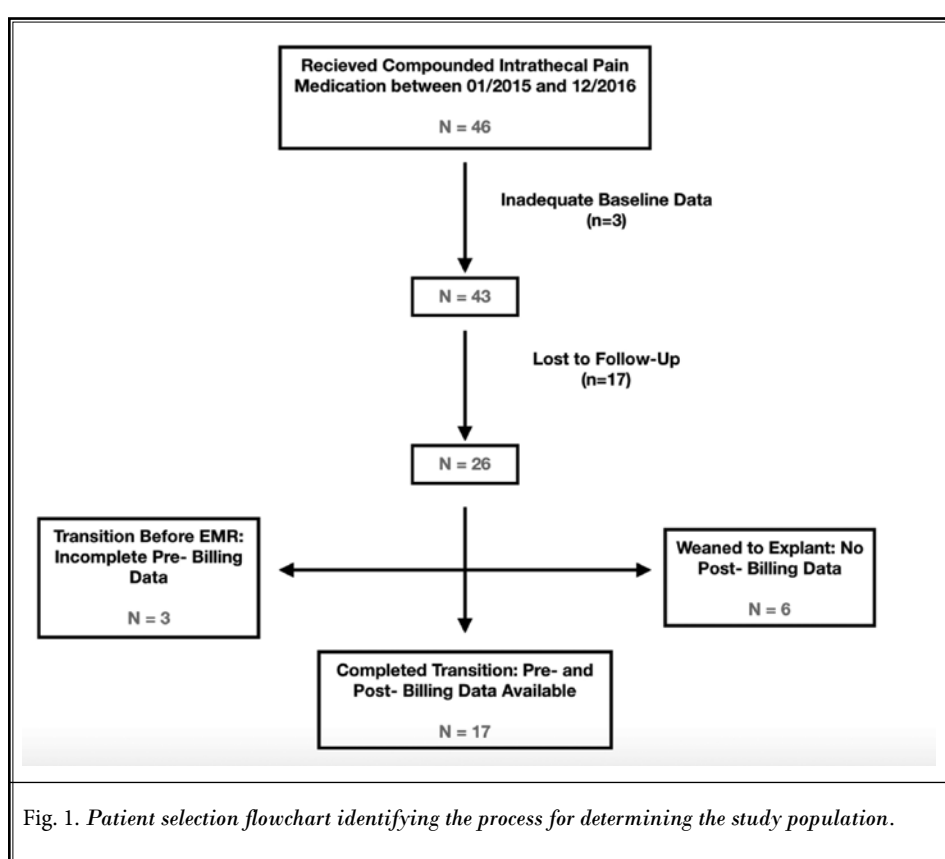


Fig. 1. Patient selection flowchart identifying the process for determining the study population.

intrathecal pain management and were weaned to explant. No follow-up billing data were available for these patients. An additional 3 patients did not have compounded dosing billing data available. Complete data (all pre- and post-transition dosing and billing data) were available for the remaining 17 patients (Fig. 1).

The average age of our cohort was 63 (SD \pm 11.7) years, including 15 men and 11 women patients. The most common pre-transition drugs administered as compounded therapy were bupivacaine (n = 17), morphine (n = 15), and clonidine (n = 14), while hydromorphone (n = 10), baclofen (n = 5), and fentanyl (n = 1) were less popular. Almost all patients of the 20 who transitioned to monotherapy were transitioned to morphine (n = 16). Two patients transitioned to hydromorphone alone, and 2 patients transitioned to baclofen alone. The number of patients receiving each drug, along with pre- and post-transition average and range dosing for all 6 drugs, are summarized in Table 1.

The cost per refill was found to vary significantly between individual drugs given as compounded therapy (Tables 2 and 3). The most expensive drugs per refill were fentanyl (\$5,022.00, n = 1) and baclofen (average \$3,443.52, range \$163.20-\$13,056.00), while the least expensive were bupivacaine (average \$17.71, range \$3.88-\$50.95) and hydromorphone (average \$28.50, range \$10.43-\$85.80). The range in billed expense for each drug varied widely across all 6 drugs, was directly proportional to drug concentration, and was billed at standardized cost per unit of drug. Baclofen, morphine, and clonidine were approximately 2 orders of magnitude (100x) more expensive on average per refill than hydromorphone and bupivacaine. Fentanyl, which was only given to one patient included in the final cohort, was also more than 100x more expensive per refill than hydromorphone and bupivacaine. The differences between

hydromorphone and morphine, hydromorphone and clonidine, bupivacaine and morphine, and bupivacaine and clonidine were all statistically significant ($P < 0.05$). The differences in average refill cost between baclofen and both hydromorphone and bupivacaine trended towards significance ($P < 0.1$), but these comparisons were limited by sample size; only 5 patients received baclofen as part of their compounded medication.

Across the 17 patients for whom both sets of billing data were available, the average pre-transition cost per refill was \$3,990.39 (\$30.26-\$17,120.18), and the average cost per year (extrapolated based on number of refills per year for each patient) was \$16,836.74 (\$76.08-\$122,415.28). The post-transition costs per refill and per year were \$1,944.79 (\$28.60-\$13,056.00) and \$8,421.88 (\$93.79-\$59,362.49), respectively. The total cost per refill from pre- to post-transition decreased on average by 51.3% ($P = 0.135$), and the total annual drug cost decreased by 50.0% across the same population ($P = 0.283$). Since it was noted that 1 of the 3 opioids (morphine, hydromorphone, or fentanyl) was included in the compounded drug regimen for all patients, and since hydromorphone was found to be significantly cheaper per refill than the other 2, the subpopulation of patients receiving hydromorphone pre-transition was excluded for a secondary analysis of overall cost difference across the transition. The remaining group (n = 13) did experience a more significant decrease in both refill cost (64.8%, $P = 0.041$) and annual cost (66.8%, $P = 0.190$) after transition to monotherapy.

Pain data were reported on NRS-11 and documented in the EMR for 9 patients pre-transition and 16 patients post-transition. The average pre-transition pain score was 7.2, and the average post-transition score was 5.9. The decrease in pain from pre- to post-transition (although important to show no loss of ef-

Table 1. Distribution of intrathecal pain medications administered among the patient cohort pre- and post-transition from compounded therapy to monotherapy, with average (and range) doses reported for each drug. Note that a range is not reported for fentanyl (n = 1).

	Pre-Transition (Compounded, n = 26)	Pre-Transition Daily Dosage	Post-Transition (Monotherapy, n = 20)	Post-Transition Daily Dosage
Intrathecal Medications	No of Patients	Mg or Mcg	No of Patients	Mg or Mcg
Morphine	15	8.6 (2.4-16.5) mg	16	7.7 (1.8-14.6) mg
Hydromorphone	10	5.0 (3.0-7.8) mg	2	8.5 (8.0-9.0) mg
Baclofen	5	473.2 (20.8-1992.6) mcg	2	1.2 (0.3-2.0) mg
Bupivacaine	17	3.0 (0.9-7.0) mg	-	-
Clonidine	14	106.0 (15.1-423.4) mcg	-	-
Fentanyl	1	790.4 mcg	-	-

Table 2. Average cost per refill for each drug administered as compounded therapy:

Medication	Average Cost / Refill (\$)	Range Cost / Refill (Min-Max, \$)
Morphine	\$2,320.07	\$352.42-\$10,069.00
Hydromorphone	\$28.50	\$10.43-\$85.80
Baclofen	\$3,443.52	\$163.20-\$13,056.00
Bupivacaine	\$17.71	\$3.88-\$50.95
Clonidine	\$1,469.78	\$231.38-\$4,627.50
Fentanyl	\$5,022.00	-

ficacy) did not rise to statistical significance ($P = 0.323$), due to the small sample size.

DISCUSSION

Amidst poor standardization of pain medication prescribing practices and heterogeneous insurance coverage in the United States, cost can pose a significant barrier to adequate management of chronic pain management. While TDD is a treatment option for refractory chronic pain, clinicians may not regularly consider the cost implications of the specific combination of intrathecal pain medications they prescribe. Over the past decade, there has been an increased focus on rising drug costs. As we look to control health care costs, drug selection often plays a critical role in reducing the long-term cost of TDD. A cost analysis of 555 non-cancer pain patients with TDD over a 3-year period has showed an annual savings of \$3,111 for TDD therapy as compared to conventional pain therapy. Although this study showed significant costs savings for TDD (20), it did not stratify the data based on individual medications delivered. Our study suggests that a deeper analysis into the costs of an individual drug case may provide additional opportunity for savings. In this study, we have used single-institutional patient billing data to highlight the significant cost differences that exist between individual pain medications regularly administered via TDD.

These trends imply that the difference in cost between patients may become especially dramatic over time, depending on doses required for adequate pain relief. For example, one patient on compounded morphine and clonidine pre-transition was billed an estimated \$122,415.28 in drug expenses over the course of one year. After transition to morphine alone, that same patient was charged \$7,192.34 per year. Another patient, who was prescribed intrathecal hydromorphone and bupivacaine, was billed an estimated \$76.08 in drug expenses annually pre-transition, and \$4,558.70

Table 3. Results of unpaired *t* tests of the differences in average cost per refill between medications administered as part of compounded therapy before transition to monotherapy. Data include the full patient population with pre-transition billing data available ($n = 23$). Each difference is represented as a fold difference calculated as the first drug's average refill cost divided by the second, with *P* values indicated.

Intrathecal Medications Administered as Compounded Therapy	Fold Difference (First / Second)	<i>P</i> Value of Difference
Morphine vs Bupivacaine	131.01	0.013*
Morphine vs Clonidine	1.58	0.278
Morphine vs Hydromorphone	81.41	0.009**
Morphine vs Baclofen	0.67	0.563
Hydromorphone vs Bupivacaine	1.61	0.260
Hydromorphone vs Clonidine	0.02	0.002**
Hydromorphone vs Baclofen	0.01	0.063
Baclofen vs Bupivacaine	194.45	0.078
Baclofen vs Clonidine	2.34	0.210
Bupivacaine vs Clonidine	0.01	0.003**

* $P < 0.05$; ** $P < 0.01$

after transition to morphine alone. It is particularly surprising that hydromorphone, the single opiate pain medication prescribed as part of compounded therapy for 10 patients, was much less expensive per refill than morphine or fentanyl. This observation suggests that the financial implications of intrathecal medication prescribing vary within drug classes. For example, the transition of compounded therapy to monotherapy with morphine actually increased the annual drug cost by 58% in this patient population.

It is likely that these trends, including the differences reported between specific medications, may vary across institutions based on local demographics, prescribing practices, reimbursement rates, and availability of insurance plans. Furthermore, our analyses are limited by small cohort size, and by limited availability to collect retrospectively data. As such, our results require validation across larger multi-institutional settings, examining cost prospectively with a larger patient population. Our patient population represents a heterogeneous and typical group of patients seeking TDD for refractory chronic LBP. Each of these patients was transferred to our practice after being maintained on compounded therapy. While our pain score data were inconclusive, it is notable that the subjectively reported pain level of this patient cohort did not increase across their transition, suggesting that monotherapy was not inferior to compounded therapy in terms of symptom relief.

This study suggests it may be important to examine the financial impact on prescribing practices, which might otherwise not be considered. However, it should be noted that there are limitations to this study. Specifically, the study is limited due to small sample size, and data collected were from a single center. Additionally, patients suffering from mechanical LBP tend to have a more positive response to monotherapy as compared to patients whose pain is neuropathic in nature. This may have been a significant factor in our successful transition from compounded therapy to monotherapy and warrants further study. More recently, the FDA issued a clarification with regards to intrathecal drug therapies; health care providers may prescribe a drug for off-label use when determined to be medically appropriate. Of course, providers and patients should note that off-label use has not been reviewed by the

FDA for safety and efficacy. Our study suggests that off-label use of hydromorphone is far more cost effective than FDA-approved morphine. Without regard to cost, TDD remains an invaluable and cost-effective tool in the treatment of refractory pain.

CONCLUSION

In this heterogeneous population of TDD patients with chronic pain at a single center, transition from compounded therapy to monotherapy realized significant cost savings, depending on the specific combination of medications. Medication-specific refill costs were also found to be significantly variable. Arbitrarily switching all patients to intrathecal morphine does not result in overall cost savings and may, in fact, compromise the patient's quality of life and function.

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