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Systemic Opioid Reduction and Discontinuation Following Implantation of Intrathecal Drug-Delivery Systems for Chronic Pain: A Retrospective Cohort Analysis

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Objective: The study evaluated systemic opioid utilization before and after initiation of intrathecal drug therapy in patients with chronic, noncancer pain, as well as the effect of opioid elimination on payer costs.

Methods: This was a retrospective cohort analysis of administrative claims data (2011-2016), evaluating patients using systemic opioids for chronic, noncancer pain, newly implanted with an intrathecal drug-delivery system. Patients were excluded for spasticity, cancer, and device explant. The primary outcome was reduction or discontinuation of systemic morphine milligram equivalents during a 395-day follow-up period. The secondary outcome was total commercial insurer payments.

Results: Of 9223 total patients, 631 met selection criteria. From baseline to 395-day follow-up, average daily morphine milligram equivalents decreased in 81.5% of patients, and 43.3% discontinued systemic opioid therapy entirely. Among patients who continued systemic opioids, average daily morphine milligram equivalents decreased in 74.9% of patients. Logistic regression found that morphine milligram equivalents of <50 mg/day prior to initiation of intrathecal drug delivery was associated with two times the odds of discontinuation vs. ≥90 mg/day (odds ratio = 2.08, 95% confidence interval 1.42-3.02, $p = 0.001$). Mean annual payer costs were reduced 29% for patients who discontinued vs. continued systemic opioids (−$11,115 per patient).

Conclusions: A meaningful proportion of patients discontinue or decrease systemic opioid use following initiation of intrathecal drug delivery. Standard of care should include opioid dose tapering prior to intrathecal drug delivery to maximize the probability of systemic opioid discontinuation.

Keywords: Chronic pain, drug delivery systems, intrathecal analgesia, pain control, prescription opioid drugs

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INTRODUCTION

The current epidemic of opioid abuse, addiction, and overdose mortality represents a complex public health issue. Its origins are multifold and straightforward solutions are lacking; for example, efforts to reduce diversion, abuse, and addiction by more heavily regulating access to prescription opioids have not only driven increasing use of illegal opioids (1) but it also have adversely affected the lives of patients living with chronic pain, whom were estimated to be more than 100 million in the United States alone (2).

The fundamental goal of how to provide pain relief to people who need it cannot be lost in the debate about how to bring the epidemic under control. Ideal solutions for pain relief would have proven efficacy for the specific type of pain being treated (3), would administer the minimum amount of drug necessary to achieve effective analgesia, would not contribute to dependency or addiction, and would not lend itself to abuse or diversion.

Intrathecal drug-delivery systems deliver small doses of medications directly to the spinal canal for the treatment of chronic, intractable pain. Although morphine or ziconotide monotherapy are the only medications approved by the Food and Drug Administration for use with this technology, there also is significant off-label use of other medications. Literature suggests that, by providing targeted drug delivery, intrathecal drug-delivery systems are more effective in controlling pain, with reduced side-effects, at a fraction of the dosing requirements of systemic opioids (4–7).

It has previously been shown that an intrathecal drug-delivery system can eliminate or reduce the use of systemic opioids

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among patients with chronic noncancer pain (4–11). Using commercial health insurance claims data from 2008 to 2011, we examined opioid discontinuation and all-cause healthcare utilization among patients newly implanted with an intrathecal drug-delivery system, finding that 51% of patients had eliminated use of systemic opioids at one year following intrathecal drug-delivery system implantation (9). However, that study only evaluated patients eliminating systemic opioid use, without assessment of dosing levels. Recently, greater focus has been placed on systemic opioid dosing prior to start of intrathecal drug-delivery system therapy and optimal protocols for patient weaning, drug-free holidays, and therapy trialing (6,11).

The present analysis examines both systemic opioid dosing levels and the proportion of patients who were able to eliminate use of systemic opioids in the one year following intrathecal drug-delivery system implant, as well as the downstream cost implications, from a payer perspective, of opioid reduction or discontinuation.

MATERIALS AND METHODS

Data Source and Study Ethics

This was a retrospective data base analysis of healthcare claims data from the IBM Truven MarketScan® Research Databases. These data bases include deidentified, patient-level healthcare claims information from more than 135 million patients with commercial health insurance, including inpatient and outpatient medical and pharmacy claims, basic demographics, and plan enrollment information. Healthcare encounter information is reported via International Statistical Classification of Diseases diagnosis codes and procedure codes, Current Procedural Terminology procedure codes, and medication National Drug Codes. Pharmacy prescription-level details include the number of units, days' supply, strength, and route of administration. Information on the specific drugs used intrathecally was not available in this dataset, given that any compounded medications were not captured in administrative claims. The data base is a deidentified, HIPAA compliant, closed system of administrative claims; therefore, this study did not require Institutional Review Board approval.

Patient Selection

All codes used for patient selection are summarized in Supporting Information Table S1. We identified all patients in the data base with record of intrathecal drug-delivery system implantation between 2012 and 2015, which allowed for a full one-year baseline and follow-up for all patients (2011 as first baseline and 2016 as last follow-up years). Patients were additionally required to have at least one pump-medication refill during follow-up and to be enrolled in their health plan continuously from baseline through the end of follow-up, allowing for up to a 30-day gap in coverage during baseline. Finally, patients were required to have filled at least one opioid prescription within six months prior to initiation of the intrathecal drug-delivery system to permit evaluation of discontinuation and/or dose reduction in follow-up.

Because this was a study of intrathecal drug-delivery systems in the management of chronic, noncancer pain, subjects were excluded who had active non-skin-cancer diagnosis, with active cancer defined as at least one inpatient or two outpatient visits with a non-skin-cancer diagnosis during baseline through follow-up. Other exclusion criteria included any history of prior intrathecal drug-delivery system implant as evidenced by a pump implantation, explantation, or revision procedure, any device programming or refill visit during baseline, evidence of an intrathecal drug-delivery system explant procedure during follow-up, and any evidence of a baclofen injection as a surrogate marker for a spastic condition.

Study Definitions and Measures

The index date for analysis was defined as the intrathecal drug-delivery system implantation date. The baseline period was defined as one full year prior to the index date. The first 30 days after implantation were defined as a "washout" period, which was included to account for the time required to wean patients off systemic opioid therapy, especially in scenarios in which opioid dosing was not weaned prior to the index date. Follow-up was defined as one year after washout, ending on day 395 after the index procedure.

All systemic opioid prescription fills were evaluated from one year baseline through 395 days follow-up. A patient was considered to have discontinued systemic opioids when the last documented prescription fill was calculated to run out on or before day 366 of follow-up. The discontinuation date was defined as the date of the last days' supply according to the quantity and dosing information for the last systemic opioid prescription fill observed.

To account for any patients who had a gap in systemic therapy during follow-up, followed by a final prescription fill during follow-up days 366 to 395 (potentially indicating an acute event), we applied the following algorithm: if the last day of the opioid prescription fell during days 366 to 395 of follow-up and the total number of treated days during washout plus follow-up was ≤30 days, then the patient was considered to have discontinued systemic opioids, with the discontinuation date also set as the last day of supply observed during this time period (Supporting Information Table S2). "Treated days" was defined as the total number of days a patient was in possession of an opioid supply.

All other patients with evidence of a prescription fill with the supply ending during days 366 to 395 of follow-up, with the total number of treated days in washout and follow-up >30 days, were considered to have continued opioid therapy.

To compare systemic opioid dosing levels before and after intrathecal drug-delivery system use, all systemic opioid prescriptions were converted to the morphine equivalent dose, expressed in morphine milligram equivalents, using published conversion factors (Supporting Information Table S3). Morphine milligram equivalents was calculated by multiplying prescription strength by quantity by morphine conversion factor and divided by the prescription-days' supply. Average daily morphine milligram equivalents per patient was calculated by summing the total morphine milligram equivalents for all prescriptions filled within a given time period, divided by the number of days in the time period of interest. Patients were categorized as "low" (0-50 morphine milligram equivalents/day), "moderate" (51-89 morphine milligram equivalents/day), or "high" (≥90 morphine milligram equivalents/day) dose based on Centers for Disease Control and Prevention (CDC) prescribing guidelines (12).

Total commercial insurer payments (costs) were evaluated during days 31 to 395 in the follow-up period. The initial pump implant procedure and costs incurred during washout were analyzed separately to allow for direct comparison of the incremental cost savings associated with opioid discontinuation, instead of therapy implantation and systemic opioid weaning-related costs. All-cause total costs to the payer (medical visits plus all pharmacy costs) and opioid-specific pharmacy costs were summarized. Among patients discontinuing systemic opioid therapy, we compared payer costs among patients who discontinued systemic

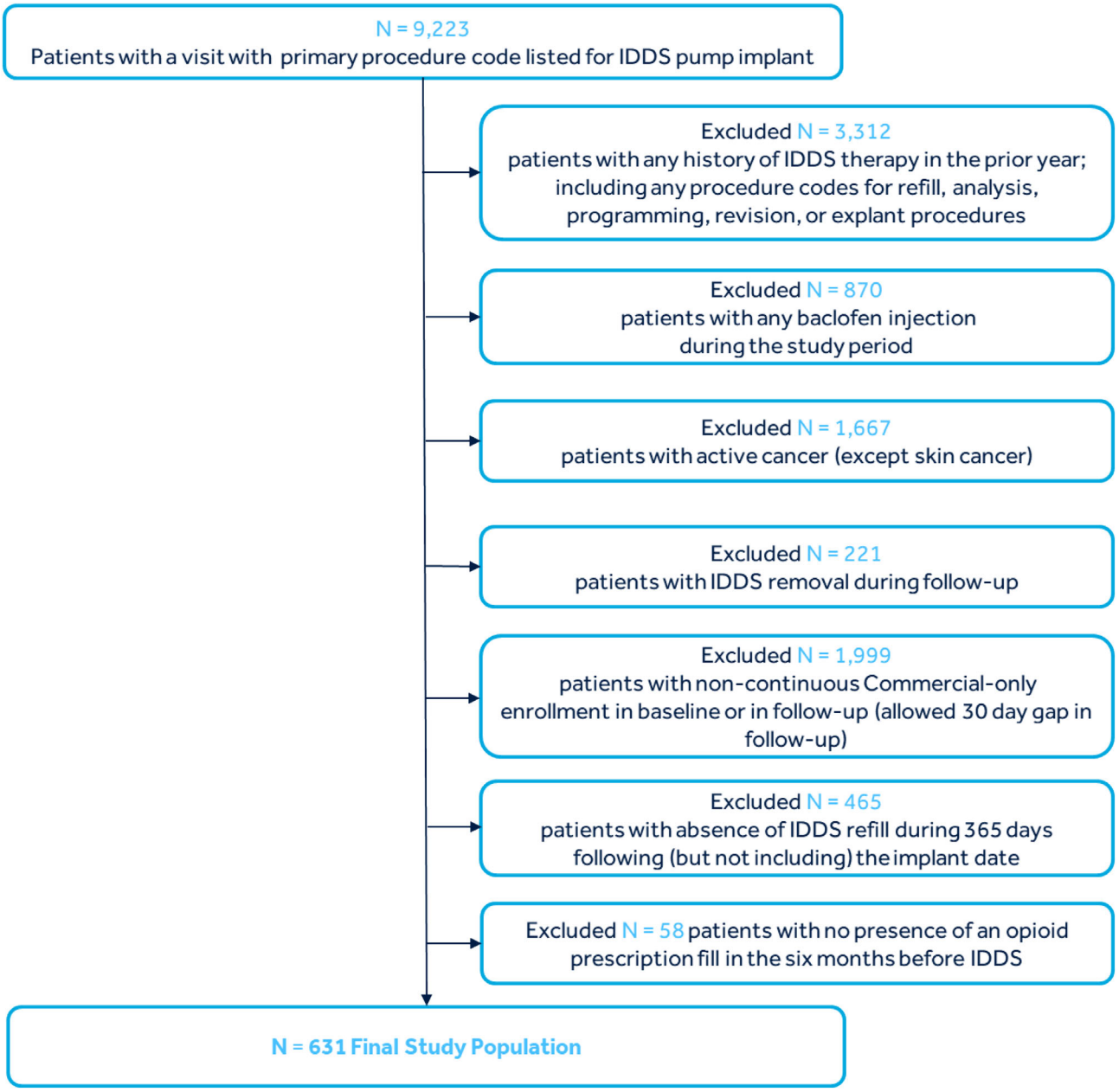

Figure 1. Patient selection. [Color figure can be viewed at wileyonlinelibrary.com]

opioids during baseline or washout (early discontinuation) vs. all others (late discontinuation). Separately, total patient out-of-pocket costs, defined as total copay, deductible, and coinsurance payments, were summarized over days 31 to 395 of follow-up. The 1st and 99th percentile of costs were excluded from all cost measures to eliminate potential outliers due to miscoding. All costs were inflated to 2017 USD using the Medical Care Component of the U.S. Consumer Price Index.

Statistical Analyses

Comparison of statistical significance among patients continuing vs. discontinuing systemic opioid therapy was calculated with the *t*-test for normally distributed continuous variables, the Wilcoxon-Mann-Whitney test for skewed (cost) variables, and the chi-squared test for categorical variables. Paired *t*-tests were used for comparison of average morphine milligram equivalents values at different baseline and follow-up time points. Sample selection, creation of analytic variables, and significance testing was performed using the Instant Health Data platform (BHE, Boston, MA, USA). Regression analyses were performed in SAS, version 9.4.

A multivariate logistic regression model with binomial distribution and logit link function was constructed to evaluate factors correlated with opioid discontinuation following start of intrathecal drug-delivery system therapy. Covariates included patient age, gender, region, Charlson score group, baseline morphine milligram equivalents level, history of diagnosis of mood disorder, psychoses, tobacco use, or opioid abuse, and baseline average daily morphine milligram equivalents category (low, medium, or high).

Generalized linear models (GLM), using a gamma distribution and log link, were developed to calculate adjusted mean one-year postwashout follow-up costs, controlling for the same covariates

Table 1. Patient Demographics and Clinical Characteristics.

	Discontinued opioid therapy (*N* = 273)	Continued opioid therapy (*N* = 358)	*p* Value*
Age (SD), y	59.3 (14.6)	55.5 (12.1)	0.0050
Age group, *N* (%)			
<50	67 (24.5%)	111 (31%)	
51-59	72 (26.4%)	120 (33.5%)	
60-69	65 (23.8%)	80 (22.4%)	
70-79	33 (12.1%)	36 (10.1%)	
≥80	36 (13.2%)	11 (3.1%)	
Woman, *N* (%)	157 (57.5%)	204 (57%)	0.9593
Census region, *N* (%)			
East North Central	74 (27.2%)	92 (25.7%)	
South Atlantic	65 (23.9%)	60 (16.8%)	
West South Central	40 (14.7%)	57 (15.9%)	
Pacific	25 (9.2%)	37 (10.3%)	
Mountain	21 (7.7%)	27 (7.5%)	
East South Central	20 (7.4%)	35 (9.8%)	
Middle Atlantic	17 (6.3%)	28 (7.8%)	
West North Central	9 (3.3%)	18 (5%)	
New England	1 (0.4%)	4 (1.1%)	
History of diagnosis, *N* (%)			
Radiculopathy	225 (82.4%)	299 (83.5%)	0.7961
Chronic pain disorders (general)†	203 (74.4%)	258 (72.1%)	0.5807
Postlaminectomy syndrome	151 (55.3%)	200 (55.9%)	0.9537
Peripheral neuropathy of lower extremity	18 (6.6%)	20 (5.6%)	0.7205
Complex Regional Pain Syndrome Type I	15 (5.5%)	26 (7.3%)	0.4656
Opioid abuse	30 (11%)	49 (13.7%)	0.3717
Tobacco use	41 (15%)	77 (21.5%)	0.0490
Mood disorder	61 (22.3%)	82 (22.9%)	0.9436
Psychoses‡	34 (12.5%)	38 (10.6%)	0.5527
Charlson score group, *N* (%)			0.1295
0	125 (45.8%)	176 (49.2%)	
1	63 (23.1%)	87 (24.3%)	
2	52 (19%)	44 (12.3%)	
≥3	33 (12.1%)	51 (14.3%)	
Baseline (1 y) total medical plus pharmacy payments			
Mean	$30,971	$43,300	
SD	$42,672	$53,282	
Median	$16,153	$25,790	<0.001
Interquartile range	$7365-$34,837	$11,893-$50,398	

**t*-test for normally distributed continuous variables, Wilcoxon-Mann-Whitney test for skewed (cost) variables, and chi-squared test for categorical variables.
†Chronic pain disorders (general) diagnoses included: central pain syndrome, other chronic pain, and chronic pain syndrome.
‡Psychoses included diagnosis of any of the following: dementias, alcohol- or drug-induced mental disorders, transient mental disorders, persistent mental disorders, or schizophrenic, episodic mood, delusional, other nonorganic psychoses, or pervasive development disorders.

listed above, additionally including baseline total cost. We constructed several models to calculate the adjusted mean follow-up total cost, opioid-related pharmacy costs, and patient out-of-pocket costs. In models calculating adjusted systemic opioid-related pharmacy costs, we employed a two-part model to account for zero/null costs among patients who discontinued during baseline or washout (thereby incurring no systemic opioid-related costs in follow-up). The two-part model consisted of a logistic regression to determine the probability of positive opioid payments, followed a GLM with gamma distribution to calculate adjusted opioid-related pharmacy payments (13).

RESULTS

Of the 9223 patients initiating therapy with an intrathecal drug-delivery system between 2012 and 2015, 631 met selection criteria (Fig. 1). Mean age was slightly higher among patients who discontinued vs. continued systemic opioids 59.3 (14.6) vs. 55.5 (12.1), $p = 0.001$ (Table 1).

Overall, 43.3% of patients discontinued systemic opioid therapy in the year following implantation of the intrathecal drug-delivery system (Fig. 2). Of those, six had experienced acute use of systemic opioids in follow-up but still met our algorithmic definition of discontinuation. Relatively few patients discontinued systemic opioids during baseline (3.3%) or washout (8.1%). Among patients who discontinued systemic opioids, median (interquartile range) time to discontinuation was 175 (27-307) days following the start of intrathecal drug-delivery system therapy. Median (interquartile range) number of treated days in washout through follow-up for patients discontinuing was 30 (6-87) days vs. 314 (204-368) days among patients continuing systemic opioids.

Across all patients, regardless of discontinuation status, the average daily morphine milligram equivalents during baseline

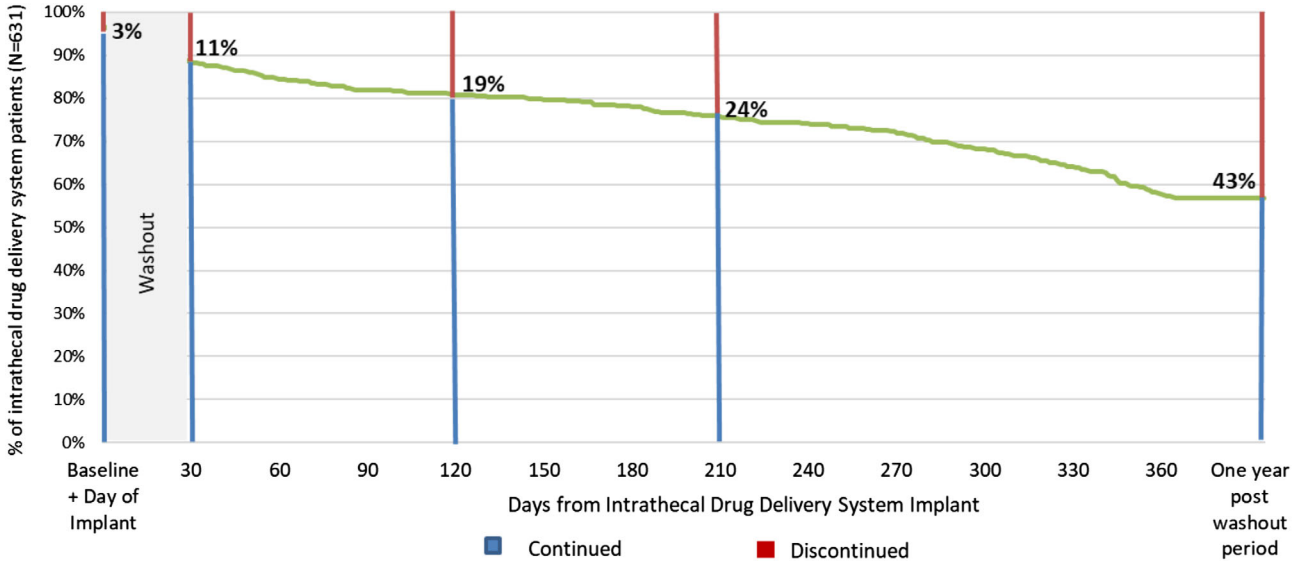

Figure 2. Proportion of patients discontinuing systemic opioid therapy following implantation of an intrathecal drug-delivery system.

was 100.4 mg/day. Average daily morphine milligram equivalents decreased to 45.0 mg/day over one-year follow-up ($p < 0.001$), a 55% reduction in average daily dose of systemic opioid. Overall, 81.5% of intrathecal drug-delivery system patients reduced their average daily morphine milligram equivalents in the postwashout follow-up period relative to baseline levels. Among patients who continued systemic opioids, average daily morphine milligram equivalents decreased in 74.9% of patients.

For patients discontinuing systemic opioids, the average daily morphine milligram equivalents from baseline month −12 to −1 decreased slightly from 71.4 mg to 66.7 mg; however, it was not statistically significant (Fig. 3; $p = 0.77$). Similarly, among patients continuing in follow-up, the change in average daily morphine milligram equivalents from baseline −12 to −1 months was not significant (Fig. 3; 81.7 mg vs. 86.1 mg, $p = 0.23$). In the subgroup of patients continuing systemic opioids in follow-up, there was a significant reduction in average daily morphine milligram equivalents from 86.1 mg during the last month of baseline to 45.7 mg at the end of follow-up (Fig. 3; $p < 0.001$).

In a logistic regression model controlling for age group, gender, census region, Charlson score group, history of opioid abuse, alcohol abuse, or diagnosis of psychoses or mood disorders, the average baseline morphine milligram equivalents category was significantly correlated with odds of systemic opioid discontinuation following initiation of intrathecal drug-delivery system therapy. Specifically, patients in the lowest dose category (morphine milligram equivalents of <50 mg/day) prior to intrathecal drug-delivery system therapy were at two times greater odds of discontinuing systemic opioid therapy following intrathecal drug-delivery system therapy

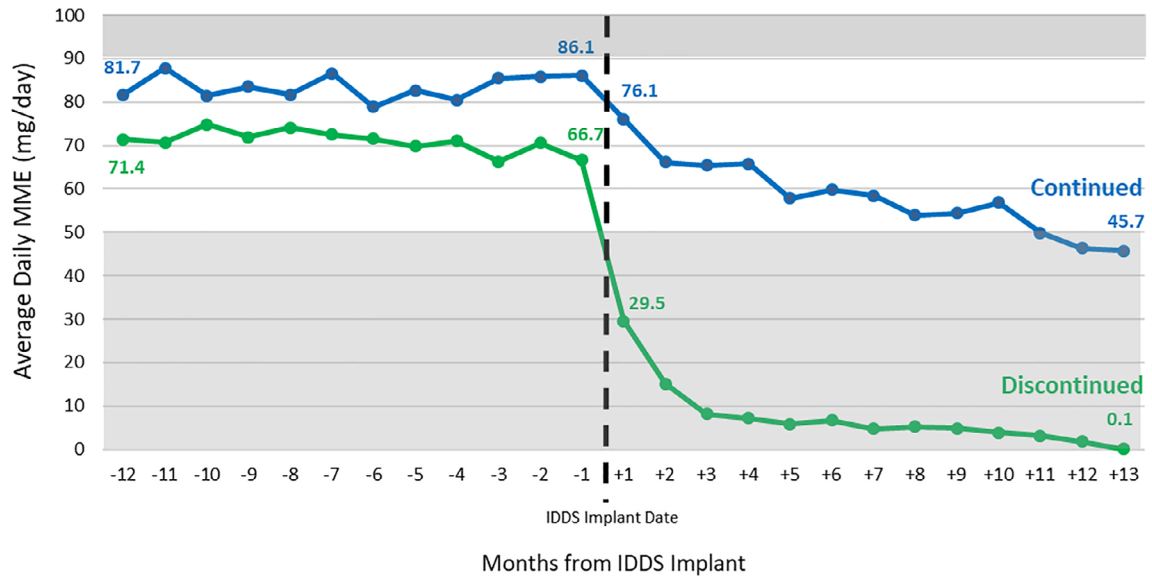

Figure 3. Average daily morphine milligram equivalents in the year prior to and following implantation of intrathecal drug-delivery system therapy, by follow-up systemic opioid discontinuation status. Note: Figure shading reflects low dose (0-50 morphine milligram equivalents/day), moderate does (51-89 morphine milligram equivalents/day), and high dose (≥ 90 morphine milligram equivalents/day) based on CDC guideline.

Table 2. Adjusted Commercial Payer Costs and Patient Out-of-Pocket Costs During One-Year (Postwashout) Follow-Up

#	Cost perspective	Dependent variable*	Comparison†	Adjusted mean (95% CI) cost discontinued	Adjusted mean (95% CI) cost comparator	Mean difference	*p* Value
1	Commercial payer	Total payments	Discontinued anytime (*N* = 250) vs. continued (*N* = 340)	$27,092 ($24,810-$29,373)	$38,207 ($35,669-$40,745)	−$11,115	0.0117
2	Commercial payer	Total payments	Discontinued early (*N* = 63) vs. late (*N* = 187)	$20,423 ($16,699-$24,146)	$28,842 ($26,099-$31,586)	−$8,419	0.2918
3	Commercial payer	Total payments	Discontinued early (*N* = 63) vs. continued (*N* = 340)	$21,733 ($16,674-$26,791)	$38,059 ($35,439-$40,678)	-$16,326	0.0068
4	Commercial payer	Opioid-related pharmacy	Discontinued anytime (*N* = 250) vs. continued (*N* = 340)	$288 ($231-$345)	$2,197 ($1,870-$2,524)	-$1,909	<0.001
5	Out-of-pocket	Total payments	Discontinued anytime (*N* = 266) vs. continued (*N* = 352)	$2,374 ($2,099 -$2,649)	$2,813 ($2,099 - $2,649)	-$439	0.4753
6	Out-of-pocket	Opioid-related pharmacy	Discontinued anytime (*N* = 266) vs. continued (*N* = 352)	$27 ($24-$30)	$180 ($159-$180)	-$152	<0.001

All results in this table are output from GLM with a gamma distribution and log-link, adjusting for patient age, gender, baseline costs, presence of a home intrathecal drug-delivery system refill, region, Charlson score group, baseline morphine milligram equivalent group, Medicare Advantage coverage type, intrathecal drug-delivery system insertion procedure year, and history of diagnosis of mood disorder, psychoses, tobacco use, or opioid abuse. Medical and pharmacy costs were modeled in a single-stage GLM; opioid pharmacy costs were modeled in a two-stage logistic plus GLM model. Out-of-pocket (sum of patient copays, deductibles, and coinsurance).

*Dependent variable: Total payments reflect total medical and pharmacy payments (opioid and non-opioid related); whereas opioid-related pharmacy payments include only payments for opioid prescription fills made in a pharmacy setting.

†Comparisons include: Discontinued anytime (baseline, washout, or one-year follow-up), discontinued early (during baseline or washout), discontinued late (during one year follow-up), or continued systemic opioids.

relative to patients in the high-dose category of ≥90 mg/day (odds ratio [OR] = 2.08; 95% confidence interval [CI] 1.42-3.02, $p = 0.001$). Additionally, patients aged 80 or older were at approximately five times greater odds of discontinuation relative to patients younger than 50 (OR = 5.32, 95% CI 2.41-11.77, $p < 0.001$).

In GLM controlling for patient-level demographic and clinical factors mentioned above, total adjusted mean payer costs during the one year follow-up, excluding implantation and washout related costs, were significantly lower for patients who discontinued systemic opioid therapy relative to patients remaining on systemic opioids (Table 2). Mean annual per-patient medical plus pharmacy costs were $11,115 lower, a 29% reduction, for patients discontinuing vs. continuing systemic opioids ($27,092 vs. $38,207, $p = 0.0117$). Of these total cost savings associated with discontinuation, systemic opioid-related prescription costs accounted for $1909 (17%; $p < 0.001$) of the total savings. In exploratory analyses examining the potential savings associated with early vs. later discontinuation, the difference was not statistically significant; however, when comparing patients who discontinued early and those who continued systemic opioids, the cost savings associated with early discontinuation was $16,326, a 43% reduction ($21,733 vs. $38,059; $p = 0.0068$).

A separate set of GLM evaluating patient out-of-pocket costs (total copays, coinsurance, and deductible amounts paid) showed a modest ($439) but nonsignificant average adjusted per-patient total medical plus pharmacy out-of-pocket cost savings for patients who discontinued systemic opioids vs. those who continued opioids ($2,374 vs. $2,813). When evaluating out-of-pocket costs related to systemic opioid prescriptions, patients who discontinued systemic opioids saved an average of $152 in out-of-pocket costs over postwashout follow-up compared with those who continued systemic opioids ($27 vs. $180 vs. $p < 0.001$; Table 2).

DISCUSSION

The opioid epidemic has had a widespread impact across the United States, with 115 Americans dying from opioid overdoses every day (14). In addition to recommendations on prescribing opioids for pain relief, the CDC recommends nonpharmacologic therapy and nonopioid pharmacologic therapy as alternative treatments for chronic intractable pain (12). Given the intrathecal mode of delivery with intrathecal drug-delivery systems, pain control can be achieved at significantly lower doses compared with epidural or oral routes (8). This has the potential to not only improve the efficacy of analgesia but also the side-effects and associated medical resource use and costs of high-dose chronic systemic opioid use (9). Although intrathecal delivery is not without risk of side-effects, this mode of delivery allows for more

provider control over drug dosing, with a lesser probability of drug diversion issues related to systemic opioids.

Our present analysis expands upon prior work by updating the study period with newer data and by including an evaluation of average daily dose levels (morphine milligram equivalents) prior to and following start of intrathecal drug-delivery system therapy. The results from our study show that 43% of patients initiating intrathecal drug-delivery system therapy discontinued systemic opioids more than a year postwashout period vs. 51% of in the previous analysis (9). The proportion discontinuing systemic therapy in our study is lower compared with the prior analysis, potentially due to variability in patient opioid dosing patterns prior to start of intrathecal drug-delivery system therapy; however, this is conjecture as we would expect average baseline systemic opioid dosing levels to remain relatively consistent prior to 2016 CDC opioid prescribing guidelines (12). Other reasons for the variability in the percent eliminating could be related to slight differences in the patient population definition, with our study more stringently requiring patients remain on intrathecal drug-delivery system therapy through the study period by requiring at least one intrathecal drug-delivery system refill visit, whereas the prior study had no such criteria (9).

As observed in our analysis, patients were two times more likely to discontinue systemic therapy if their average daily morphine milligram equivalents during baseline was in the lowest category (1-50 mg/day) relative to patients in the high-dose category (≥90 mg/day). Interestingly, patients in the moderate-dose category (51-89 mg/day) were not significantly different relative to high-dose patients in their odds of discontinuation ($p = 0.1261$). This may suggest that weaning to levels at least below 50 mg/day is important to maximize a patient's probability of success in systemic opioid discontinuation after start of therapy. Although greater focus has recently been placed on optimizing patient protocols for systemic-opioid dose-weaning prior to start of intrathecal drug-delivery system therapy (6,8), broad adoption of these practice patterns was not observed in our study population. There was minimal dose reduction over baseline prior to start of intrathecal drug-delivery system therapy among patients who discontinued therapy. Conversely, there was an actual increase in average daily dose prior to the start of intrathecal drug-delivery system therapy among patients who continued systemic opioids following intrathecal drug-delivery system therapy. Given the strong correlation between baseline dose levels and systemic opioid discontinuation following intrathecal drug-delivery system therapy, and the variability in dosing patterns and levels observed in our population, it is not surprising that previously reported discontinuation rates are highly variable, ranging from 24% to 100% (4–11).

Not surprisingly, older patients were most likely to discontinue systemic opioids in our analysis, with patients aged 80 and older approximately five times more likely to discontinue relative to patients aged less than 50. This is likely due to age-related considerations associated with prescription opioids including renal function, greater susceptibility to accumulation of opioids in a smaller therapeutic window, and cognitive considerations, among other factors (12).

There are several studies confirming our finding of significant declines in systemic average daily opioid dose following start of intrathecal drug-delivery system therapy (4–11). Overall, regardless of discontinuation status, our study population's average daily morphine milligram equivalents decreased 55% from 100.4 mg/day over the one-year baseline period to 44.5 mg/day over the one-year post-washout follow-up. Similarly, a single-center, retrospective chart review showed a decrease in average daily morphine milligram equivalents from 184 mg/day prior to intrathecal drug-delivery system therapy to 57.6 mg/day at three years follow-up, a 69% reduction ($p < 0.001$) (4). Another single-center study of 40 patients evaluated dosing changes following initiation of intrathecal drug-delivery system therapy among two cohorts following different intrathecal drug-delivery system therapy trialing protocols. Results showed a reduction of greater than 200 average daily morphine milligram equivalents from baseline to six-month follow-up in each cohort, with reductions maintained at 36-month follow-up (7).

Our study also evaluated the incremental cost savings associated with systemic opioid discontinuation in the one year postwashout period. Controlling for patient demographic and clinical characteristics, total adjusted mean savings to the payer associated with systemic opioid discontinuation were $11,115 per patient per year, a 29% reduction relative to patients treated with intrathecal therapy who continued systemic opioids. Of these total cost savings associated with discontinuation, $1909 were systemic opioid prescription costs and the remainder medical costs. The total reduction in payer annual expenditures associated with opioid discontinuation observed in our study was similar to the previous analysis of commercial claims data (9), when adjusted to align with the 12 months postwashout follow-up used to observe costs in the present study, and inflated to 2017 dollars (15). In another analysis of commercial claims data specific to patients with cancer-related pain, findings also suggested economic benefit among patients treated with intrathecal therapy plus conservative medical management vs. conservative medical management alone, with a significant reduction in payer all-cause costs at 12 months follow-up (mean difference $63,498, $p = 0.03$) (16).

In secondary analyses of our study dataset, we found the median payer cost for the pump implant procedure was $16,243. When considering that cost relative to follow-up savings associated with systemic opioid discontinuation of $11,115, financial breakeven would occur at 17.5 months of intrathecal drug-delivery system therapy for patients who ultimately discontinue systemic opioids. When considering the greater median savings ($16,326) among patients who discontinued early (prior to intrathecal drug-delivery system therapy or during washout) breakeven would occur after 11.9 months of intrathecal drug-delivery system therapy.

Limitations

Our analysis has several limitations inherent to retrospective administrative claims analyses, first and foremost being the accuracy and completeness of claims submitted. We designed the present study to evaluate trends in systemic opioid utilization among patients remaining on therapy (a proxy for treatment success) to evaluate to what extent intrathecal therapy affects systemic opioid utilization, assuming that adequate pain control was met among the subset of patients continuing intrathecal therapy. Nonetheless, in the future, it would be interesting to analyze trends in morphine milligram equivalents among patients continuing vs. discontinuing intrathecal therapy, similar to a recent analysis of spinal cord stimulation outcomes (17).

Our definition of opioid discontinuation is dependent on pharmacy prescription fill information. If patients did not take prescriptions as prescribed, it is possible that systemic opioid therapy was continued beyond the end of prescribed days' supply, ultimately impacting our definition of discontinuation estimated in this analysis. Given the large difference between median time to discontinuation (175 days) and median number of treated days in follow-up (30 days), we do see a pattern of *pro re nata* dosing. Prospective studies with sophisticated medication tracking methods, such as smart pill packs, would be the only definitive

way to track medication discontinuation. Additionally, we did not evaluate reasons for opioid prescriptions following intrathecal drug-delivery system therapy (such as acute injuries or surgeries) that may have influenced the overall proportion of patients categorized as discontinued or continued. All morphine milligram equivalents calculations are dependent on accuracy of opioid prescription claims, including number of units, strength, and days' supply information listed. In the scenario where a prescription drug days' supply was incorrectly listed as a negative or zero value, we reassigned a days' supply of one, which impacts the prescription level average daily morphine milligram equivalents calculation. Finally, given the nature of retrospective claims, we were unable to assess patient-reported outcomes such as pain severity and other functional measures or the specific mix of medication(s) used intrathecally due to a significant proportion of patients treated with custom compounded medications.

CONCLUSIONS

Our study showed 81.5% of patients with chronic noncancer pain reduced their average daily opioid dose immediately prior to or in the 395 days following implantation of an intrathecal drug-delivery system. Overall, 43% of patients discontinued systemic opioids following implantation of an intrathecal drug-delivery system, with discontinuation associated with significantly lower costs from a payer perspective in the one-year postwashout time period. Patients on lower systemic opioid dose levels (morphine milligram equivalents of 1-50 mg/day) were two times more likely to discontinue systemic opioid therapy relative to patients on high doses prior to start of intrathecal drug-delivery system therapy (morphine milligram equivalents ≥90 mg/day). However, we observed only minimal dose reduction prior to start of intrathecal drug-delivery system therapy in this study population. Our results suggest a need for broader adoption of opioid weaning and/or discontinuation protocols prior to start of intrathecal drug-delivery system therapy to maximize probability of complete systemic opioid discontinuation with intrathecal drug-delivery system therapy and to maximize cost savings in this patient population. Furthermore, complete systemic opioid discontinuation could decrease diversion, addiction, opioid overdose, and overdose-related deaths.

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Authorship Statements

All authors were involved in the study design, analysis, manuscript drafting and critical review, and approved the final manuscript prior to submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

COMMENTS

In our present environment, any article funded by a device manufacturer and research carried out by its employees is going to be suspect, especially with a retrospective study. I know of no way to eliminate this problem.

John Loeser, MD
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This study indicates that IDDS is also a cost effective alternative treatment to systemic opioid pain treatment and could help to fight opioid epidemic.

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A retrospective review of 631 patients who had implanted drug delivery systems using opioids for treatment of chronic non-malignant pain found that 81.5% of patients reduced systemic opioid consumption, with 43% discontinuing use altogether. Those commencing therapy at < 50 morphine milligram equivalents were more likely to be successfully weaned off of systemic opioids than those consuming larger quantities. The cost savings per patient per year was about $11,000.00, with about $2,000.00 representing prescription cost savings; the remainder were for medical costs. This represented about a 29% reduction in costs/patient.

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Comments not included in the Early View version of this paper.

