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Targeted Drug Delivery for Chronic Nonmalignant Pain: Longitudinal Data From the Product Surveillance Registry

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ABSTRACT

Objectives: To assist in assessment of therapy risks and benefits of targeted drug delivery (TDD) for chronic nonmalignant pain using registry data on product performance, adverse events, and elective device replacement.

Materials and Methods: The Product Surveillance Registry (PSR) (NCT01524276) is an ongoing prospective, long-term, multicenter registry enrolling consented patients implanted with an intrathecal drug delivery system. Patients are followed prospectively with participating investigators providing pump and catheter performance data for events related to the device, procedure, and therapy. Event descriptions include patient symptoms and outcomes.

Results: Registry data from the 4646 patients (59.7% female) treated with TDD for chronic, nonmalignant pain at 59 registry sites between August 2003 and October 2019, with over 17,000 patient-years (4646 patients with 44 months average follow-up), were analyzed. Registry discontinuation was largely (46.2% of discontinued patients) due to study site closure and patient death; exit due to an adverse or device event was limited to 10.2%.

Conclusions: Treating chronic pain with escalating doses of strong systemic opioids often leads to inconsistent pain control, impaired function, untenable side effects, and reduced quality of life and this practice has contributed to the current opioid crisis in the United States. TDD has been an available therapy for these patients for greater than 30 years, and data from this real-world registry offer supporting evidence to the long-term safety of this therapy as an alternative to systemic opioids, as well as insights into patient acceptance and satisfaction.

Keywords: Chronic nonmalignant pain, Intrathecal therapy, registry

Conflict of Interest: The Product Surveillance Registry is maintained by Medtronic, Inc. Todd Weaver, Robert Spencer, Katherine Stromberg is a full-time salaried employee of Medtronic, Inc, the sponsor of this study. Dr. Schultz reports other from Medtronic, outside the submitted work. Dr. Schultz has been a paid consultant for Medtronic in the past and may be a paid consultant for Medtronic in the future. Dr. Schultz has not received consulting payments from Medtronic in the last two years. Dr. Calodney reports other from Medtronic, outside the submitted work. Dr. Abd-Elsayed is a consultant of Medtronic and Avanos.

INTRODUCTION

Chronic pain is estimated to affect one in five US adults (1) with an associated annual cost in lost productivity, direct health care expense, and disability in excess of $560 billion (2). Additionally, on a global scale, chronic back pain is cited as the leading cause of disability, affecting more than 500 million people at any given point in time (3). Recent data further indicate an expansion of the chronic pain prevalence in the United States over the two decades ending 2014, along with significant increases in the use of strong systemic opioids for treatment (4).

Although chronic pain is simply defined as pain lasting more than six months, within the context of *neuromodulation* the focus is typically on the patient with moderate-to-severe pain that has failed to respond to noninvasive strategies (e.g., physical therapy, exercise, etc.), medical management, surgeries, and interventional pain management procedures (e.g., injections, nerve blocks,

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ablations). Having exhausted pain management alternatives, many patients are offered daily systemic opioids as the next therapy option to treat intractable pain. Once opioids are started, tolerance may develop requiring escalation of opioid dosages over time and this cycle of decreased efficacy and increasing dosage of systemic opioids is considered a partial driver of the US opioid epidemic.

Opioid management often continues until the patient seeks alternatives or is referred to an interventional pain physician that may offer implantable pain control options. Existing implantable alternatives, or in some cases adjuvants, to systemic opioids include stimulation therapies (spinal cord, dorsal root ganglia, peripheral nerve), and intrathecal therapies (targeted drug delivery [TDD]).

Although both stimulation and intrathecal therapies have been available for decades, barriers to access continue to limit availability of options (5). Furthermore, misperceptions of the care burden and risks associated with TDD greatly limit the availability of this option. Although there are continued advances being made in stimulation therapies, many patients either fail a preimplant neurostimulation trial or may be identified as better TDD candidates for a number of reasons, including pain that is primarily nociceptive rather than neuropathic or more diffuse rather than regional (6).

The objective of this article is to review the current state of TDD evidence in the treatment of chronic, nonmalignant pain (NMP), especially within the context of the US opioid epidemic and to provide safety data available from a large patient registry adding to existing safety information, along with additional data on therapy durability and system replacement rates to offer insights into patient benefits.

MATERIALS AND METHODS

We analyzed data from the ongoing Product Surveillance Registry (PSR) to assess the safety (adverse events related to the device, implant surgery, or infusion therapy), durability (duration of pump implants, and freedom from registry exit due to device events), and patient satisfaction (elective pump replacement, therapy discontinuation) with TDD for patients with chronic nonmalignant pain across the therapy lifecycle. The PSR comprises the largest multicenter cohort of TDD-treated patients worldwide, covering aggregate prospective follow-up time for all pumps across all indications of 28,058 patient years (7) (e.g., 17,000 patient years for chronic nonmalignant pain and 11,000 patient years for other indications).

Registry Description

The Medtronic Implantable Systems Performance Registry (ISPR; ClinicalTrials.gov Identifier: NCT01524276), initiated in 2003, is described by Konrad et al. (8), Stearns et al. (9), and Schiess et al (10). Results presented in these studies include product performance data collected under the ISPR protocol across all patients enrolled, data specific to patients enrolled for the treatment of cancer-related pain, and data specific to patients enrolled for the treatment of severe spasticity, respectively. In 2013, the registry expanded data collection with a corresponding name change to the Product Surveillance Registry (PSR). The PSR platform was designed to conduct ongoing nonrandomized, active prospective post-market surveillance under a common protocol, with specific appendices for neuromodulation products/therapies, by enrolling patients with an eligible product—in this case, an implanted intrathecal pump and catheter system. Prior to patient enrollment, all sites obtained Ethics Committee/Institutional Review Board approval to allow tracking of the device performance in each consented patient. The PSR sites contributing to these data are noted in the Acknowledgments.

Patients

Each site followed local standards regarding patient selection for TDD implant. Within the cohort of patients analyzed here, patients with chronic, nonmalignant pain who successfully pass site-specific criteria (i.e., psychological screening and successful intrathecal trial) are considered candidates for SynchroMed™ II infusion system (Medtronic, Inc. Minneapolis, MN, USA) implant. The patient or legally authorized representative provided written authorization and/or consent per institution and geographical requirements prior to data collection. Patients are enrolled with consent, which must be completed before initial implant (''therapy naïve'') or pump replacement; patients unwilling to provide consent, inaccessible for follow-up, excluded per local law, or currently enrolled in or planning to enroll in any concurrent drug and/or device study that may confound results are not included in the registry. Excluded from this specific analysis were registry patients enrolled/implanted for the treatment of severe spasticity or cancer pain. After enrollment, patients were followed longitudinally per standard of care, with status updates obtained every six months with no predefined duration. Data for all global registry centers and all patients enrolled are reported.

Data Collection

As previously reported (8,9,10), because the original intent of the registry was to monitor performance of the implanted infusion systems, reporting of device-related product performance issues has remained consistent throughout the course of the registry and across all patients enrolled. In 2010, the collection of safety data expanded to include all adverse events (AEs) related to implanted or external components of the infusion system, the implant procedure, or the infusion therapy; these events have only been collected for patients active in the registry or enrolled since that time. Although not a prespecified outcome in the PSR, elective pump replacement was assessed here as a surrogate for patient satisfaction as reported in Schiess et al (10). The patients know that pump replacement requires surgery with a painful post-surgical recovery period. With pump replacement, patients also indicate they are willing to continue to accept the inconvenience and potential risks associated with periodic pump refills at the clinic. In contrast to the passive, voluntary reporting of adverse events to regulatory authorities, the prospective registry design includes active data monitoring and allows for analysis of adverse event occurrence relative to a defined sample size and implant duration.

Analytic Methods

Data included in this analysis specific to patients enrolled for the treatment of chronic nonmalignant pain were collected from August 2003 through October 31, 2019. Summary statistics are presented either as percentages for categorical variables or as mean (standard deviation, SD; or minimum/maximum) for continuous values.

SynchroMed II pump performance, reported as ''Pump Survival,'' was defined as freedom from product performance events (7), where product performance events are physician-

reported pump issues or failures of pump function which have been confirmed through returned product analysis. Although not all product performance events result in therapy discontinuation, pump replacement, or pump explant, this analysis is reported as "survival" through specified durations of pump implant—an indication of the probability a patient will experience a pump performance-related event through specific timepoints. Product performance as a function of real-world clinical use is particularly relevant with regard to nonmalignant pain and the use of drugs other than those tested and approved for use in the SynchroMed II infusion system (Infumorph®, Prialt®). Information collected in the registry allows for conservative classification of device use as either "On-label" (morphine or ziconotide monotherapy) or "Off-label" (all other medications or medication admixtures, and drugs reported as compounded) (7).

Kaplan–Meier survival methods were used to estimate product performance for SynchroMed II pumps overall and by device use group (On- or Off-label). A Cox proportional hazards model was used to calculate the hazard ratio (HR) and test the difference in overall survival between the On- and Off-label device use groups. Additionally, a chi-square test was used to compare the survival values between the device use groups at the six-months time point with the largest observed difference in product performance (72 months post-implant).

The percent of subjects who continue with TDD therapy following initial pump implant (Therapy Retention) is presented over the observed duration of therapy. This analysis only included those patients enrolled in the PSR with their initial pump implant to eliminate the potential bias of nontherapy naïve patients. Long-term therapy retention was assessed using time-to-event Kaplan–Meier survival estimates, where patients were evaluated as failures if they exited from the registry due to therapy discontinuation. Patients who were active in the registry or who exited from the registry due to nontherapy discontinuation reasons were statistically removed from analysis (i.e., censored) at their last visit. Study exit due to an adverse event or device event or due to an inactive system (i.e., therapy abandoned for greater than six months or system explanted without replacement) was the event of interest. These study exits were considered a discontinuation from the registry due to dissatisfaction with the therapy. The length of time a patient remained on TDD therapy, or duration of therapy retention was defined as months from implant to therapy discontinuation, if applicable, or last visit.

RESULTS

Enrollment Summary and Patient Demographics

A total of 8997 TDD patients were enrolled at 76 sites across the United States, Europe, and Latin America, with 4646 patients (59.7% female) from 59 sites implanted and treated for chronic, nonmalignant pain (Supporting Information Fig. S1). No single site represented more than 17% of cumulative enrollment. Within these patients, 3845 were active in the registry following the adverse event collection expansion in 2010 and are included in the analysis of adverse events. The most common pain condition treated was back pain with leg pain (33.8%), followed by back pain without leg pain (27.2%). Table 1 provides patient demographics and pain indication, and Fig. 1 provides pain indication for patients implanted. At the time of enrollment, 43% (2013/4646) of patients were implanted with their initial pump and were naïve to infusion therapy; the remaining 57% (2633/4646) of patients were either enrolled with a pump replacement (18%, 835/4646), or the status of their pump (initial or replacement) was not collected in the registry (39%, 1798/4646).

Table 1. Patient Demographics and Pain Indication.

Gender	*N* (%)
Female	2773 (59.7%)
Male	1873 (40.3%)
Mean age at enrollment (min/max, SD)	59 years (11/96, 14)
Pain indication	*N* (%)
Back pain with leg pain	1570 (33.8%)
Back pain without leg pain	1263 (27.2%)
A general neuropathic condition	200 (4.3%)
CRPS I	146 (3.1%)
Peripheral neuropathy	70 (1.5%)
Joint pain/arthritis	61 (1.3%)
A general nociceptive condition	44 (0.9%)
CRPS II	35 (0.8%)
Osteoporosis	13 (0.3%)
Unknown/not provided	831 (17.9%)
Other	413 (8.9%)
Total	4646
Status at enrollment	*N* (%)
Therapy naïve	2013 (43%)
Pump replacement/not reported	2633 (57%)
Follow-up duration range	Average 44 months (SD = 39) 0 months to 15 years

Product Performance/Survival

Within the analyzed cohort of all SynchroMed II pumps implanted in patients for the treatment of chronic, nonmaligant pain and available for analysis at five years (n = 1384), 93.5% remained pump product performance event-free. Figure 2 graphically displays the survival curve through 84 months, the point at which all pumps are replaced due to end of battery life.

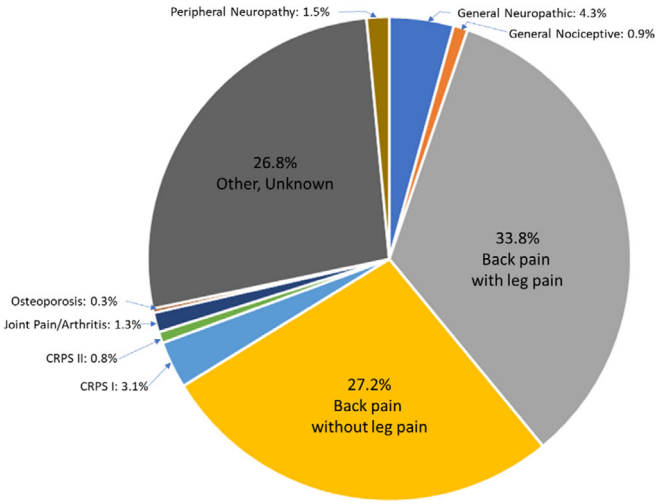

Figure 1. Pain indication.

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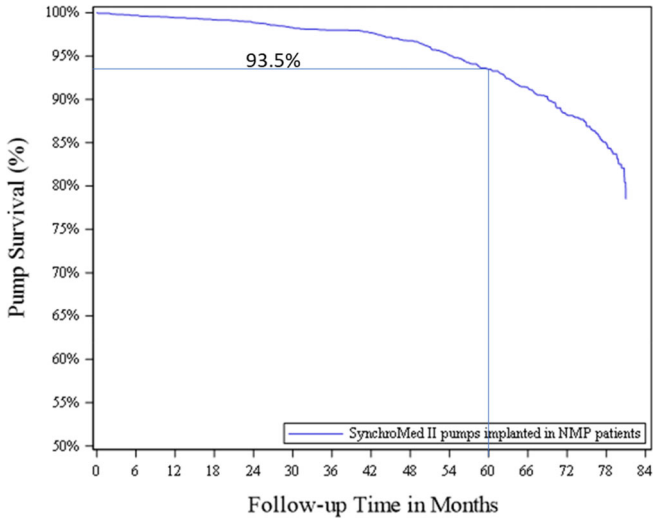

Figure 2. SynchroMed II pump survival from PPE (nonmalignant pain patients).

Figure 3 presents survival from product performance events for pumps by device use group through 81 months. Off-label pump survival (95% CI) at 60 months is 93.3% (92.1%, 94.3%) and 84.4% (82.2%, 86.4%) at 78 months, compared to on-label survival of 95.9% (92.6%, 97.8%) and 90.0% (80.2%, 95.1%), respectively. In overall survival, there was no statistically significant difference in the risk of a product performance event occurring between the two groups (HR [95% CI] for off-label vs. on-label pumps: 1.5 [0.9–2.6], p = 0.12). The difference in survival at 72 months (the six-months timepoint with the largest difference in survival between the two groups), however, was statistically significant (p = 0.001). Within the full cohort of patients (n = 4646) being treated with TDD for nonmalignant pain there were a total of 318 product performance-related events with a pump etiology reported in 253 (5.45% of total cohort) patients (Supporting Information Table S1).

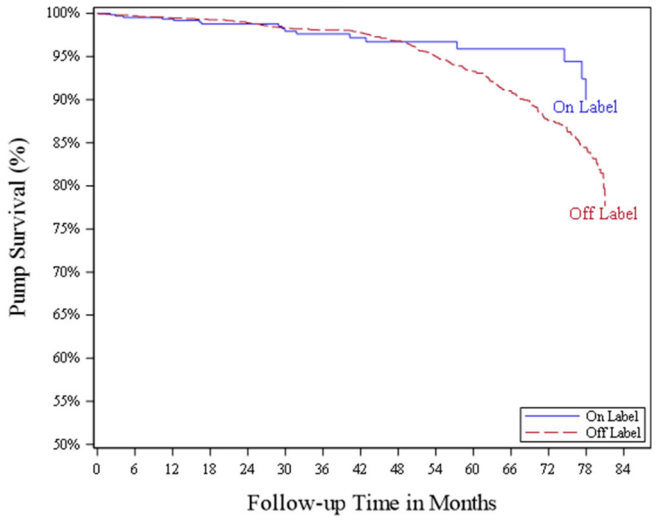

Figure 3. SynchroMed II pump survival from PPE (nonmalignant pain patients, on and off label).

Patient Retention/Study Exit

Registry enrollment and patient follow-up do not follow the model typically seen with prospective, controlled clinical studies. Within the registry design, enrollment is not a precondition to receiving the proposed treatment, and the duration of follow-up is not defined by a study protocol. As such, enrollment is an indication of a patient's agreement with the importance of supporting data collection relating to a therapy, and their long-term continuation in a registry provides interpretable data beyond what is typically seen with a fixed time-point outcome measure. Although registry discontinuation appears high (2835, 61%; Table 2), only 6.2% (290/4646) of all patients (10.2% of exited patients, 290/2835) did so due to an adverse or device event. The majority of registry discontinuations were due to causes unrelated to the therapy itself: death (23%, 655/2835), site closure (23%, 655/2835), and transfer of care to another physician (19%, 538/2835). Discontinuation from the registry does not equate to discontinuation of therapy although some discontinued subjects may have stopped therapy. With an average duration of patient follow-up of 44 months (SD = 39, range 0–15 years) and an accumulated follow-up of over 17,000 patient-years, available PSR data allow for assessment of study exit reason as an indication of patient satisfaction with TDD.

There were 2013 patients who were naïve to infusion therapy at the time of enrolment in the registry. The therapy retention rate within these patients (i.e., percent of subjects who have not exited from the registry due to therapy discontinuation) is shown in Fig. 4. By the 5-year time point postimplant, 14.1% of patients had experienced adverse or device events resulting in therapy discontinuation or opted for therapy discontinuation; 85.9% continued with TDD therapy for nonmalignant pain.

Pump Replacement at End of Service

As noted in earlier PSR publications (8,9,10), implanted, battery powered pumps eventually require replacement due to battery depletion. In the case of the SynchroMed II infusion system, the designed performance life is capped at 84 months, with a typical time to replacement of 75 months for the currently available infusion system. The clinician-programmer displays an anticipated end of service (EOS) date with each pump interrogation; and an elective replacement indicator (ERI) message is displayed 90 days in advance of the EOS. This lead time for a necessary surgical intervention to continue therapy, in contrast to the more acute decisions needed in cases of system complications, allows for a thorough patient assessment of therapy benefits in deciding whether to undergo the replacement procedure.

There were 770 SynchroMed II pumps explanted due to normal battery depletion, representing the sub-cohort of patients progressing to this point who did not discontinue therapy or exit from the registry due to previously discussed reasons. Within these, 763 (99.1%) were replaced on the same day as the explant procedure (Table 3). The median time to explant for the 770 pumps was 78 months. For the seven pumps that were explanted without replacement due to normal battery depletion, there was no plan to replace five of the pumps at a future date. The reasons given for nonreplacement included: stopped using the device in favor of alternate therapy (2), patient improvement (1), TDD initially controlled symptoms but lost effectiveness (1), and infected abdominal wall (1). For the remaining two pumps, a future pump implant was planned, but one patient was exited from the registry (care transferred to another physician) before a

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Table 2. Study Exit Reasons.

Exit reason	No. of patients	% of exited patients
Adverse event or device event	10*	0.4
All enrolled Medtronic products are inactive†	460*	16.2
Care transferred to another physician	538	19.0
Death	655	23.1
Eligibility criteria not met	9	0.3
Lost to follow-up	74	2.6
Other	7	0.2
Patient is no longer available for follow-up	259	9.1
Patient withdrawal of consent	92	3.2
Site closure	655	23.1
Sub-study exit	5	0.2
Withdrawal of patient by physician	71	2.5
Total	2835	100

*Of the 460 patients who exited due to inactive products, 280 patients had their system explanted or therapy abandoned due to an adverse event or device event. Therefore, 10.2% (290/2835) of patients who exited from the registry discontinued due to an adverse or device event.
†Includes TDD systems that were explanted without replacement or where TDD therapy was abandoned for greater than six months.

Table 3. Battery Depletion Replacement Rates.

Explant category	No. of pumps	% of pumps	No. of patients
Explanted with replacement on same day	763	99.1	724
Explanted without replacement	7	0.9	7
Total	770		730*

*The 770 pump explants due to battery depletion occurred in 730 patients: 684 patients had one pump explanted with replacement, 39 patients had two pumps explanted with replacement, six patients had one pump explanted without replacement, and one patient had one pump explanted with replacement and one pump explanted without replacement.

replacement pump implant was reported in the registry and the other received a non-Medtronic pump.

Patient Safety

Expanded adverse event reporting has been consistently collected for the subset of patients active in the registry after April 2010 (n = 3845). There were 4445 adverse events reported in 1657 patients from April 2010 through October 2019 (Supporting Information Table S2); 425 of these events (reported in 344 patients, 8.9%) were serious. The most common serious adverse events were medical device site infection (1.6%), drug withdrawal syndrome (1.5%), and adverse drug reaction (1.0%). The remaining serious adverse events occurred in fewer than 1% of patients (Table 4). The nonserious adverse events that occurred in at least 5% of patients were adverse drug reaction (15.1%), pain (8.2%), and medical device site pain (7.9%). When considering all types of infections (MedDRA System Organ Class of Infections and infestations), the rate of infections was 4.9% (208 infections in 188 patients), and the rate of serious infections was 2.7% (114 events in 105 patients). The rate of infections requiring surgical intervention was 3.7% (153 events in 142 patients).

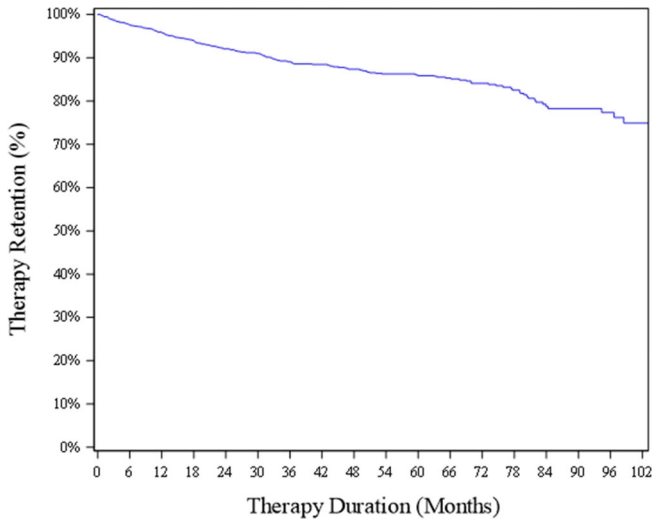

Figure 4. Patient survival from therapy-related study exit.

DISCUSSION

TDD with a fully implanted programmable pump and intrathecal catheter system designed to target pain-relieving medications directly to spinal cord pain receptors (11) was first introduced in the early 1980's and has evolved and expanded since. Opioids applied directly to the spinal cord provide powerful analgesia while minimizing systemic opioid uptake, thus reducing drug effects on the brain. Spinally administered opioids have been shown to produce powerful analgesia at significantly reduced opioid doses compared to those used with oral or intravenous (IV) administration (12,13).

With regards to initiation of intrathecal opioid therapy, current best practice is to start at a low intrathecal opioid dose and titrate slowly to effect (14), in patients who have reduced or discontinued their systemic opioids prior to pump implant. Once spinal drug delivery is initiated, systemic opioids are gradually tapered if not already discontinued.

Treatment of chronic nonmalignant pain with TDD involves the use of a fully implantable pump connected to an intrathecal catheter. Programmable infusion systems additionally allow for the use of a clinician programmer to interrogate and program the pump, along with a patient programmer to provide patient-controlled analgesia for selected patients who want more control over their analgesia. Programming parameters for the pump can be set at a constant daily dose, variable (flex) dosing by time of day, a fixed basal infusion rate with periodic programmed bolus doses, or a fixed basal infusion rate with on-demand bolus doses using the patient programmer. Although current data do not prove a specific benefit of one drug delivery approach over

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Table 4. Serious Adverse Events ($n \geq 5$ patients).

Adverse event*	Number of events	Number of patients with event	Percent of patients with event ($N = 3845$) (%)
Medical device site infection	62	60	1.6
Drug withdrawal syndrome †	61	58	1.5
Adverse drug reaction	42	40	1.0
Pain	23	23	0.6
Cerebrospinal fluid leakage	20	18	0.5
Overdose	16	16	0.4
Wound infection	15	15	0.4
Meningitis	13	13	0.3
Wound dehiscence	9	9	0.2
Medical device site extravasation	9	8	0.2
Mental status changes	7	7	0.2
Vomiting	6	6	0.2
Inflammatory mass (confirmed)	5	5	0.1
Medical device site cellulitis	5	5	0.1
Medical device site pain	5	5	0.1
Therapeutic product ineffective	5	5	0.1
All other events (<5 patients)	122	117	3.0
Overall total	425	344	8.9

*Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term.
†Includes Drug Withdrawal Syndrome and Withdrawal Syndrome.

another, the flexibility of the TDD platform allows patients to choose from among several modes of drug delivery and to change this mode over time as pain management needs and desires change.

Krames (15) and Kumar (16) have each published recent thorough overviews of TDD outlining the history of intraspinal analgesia with review of TDD evidence. In addition, the periodic Polyanalgesic Consensus Conference (PACC) publications provide regularly updated, evidence-based recommendations and guidelines for the use of TDD in the treatment of pain. Whereas PACC guidelines outline more traditional and standard dosing practices for TDD, three recent studies of TDD in chronic pain focused on utilization of ultra low-dose intrathecal morphine monotherapy as the sole treatment for nonmalignant pain with emphasis on the weaning and total elimination of all systemic opioids prior to pump implant. Work by Hamza (12) and Grider (13) recently replicated by Wilkes et al. (17) indicate the potential for long-term (up to three years) pain management with intrathecal morphine doses of less than 1.0 mg/day in select patients.

Cost benefits and efficacy for TDD as a treatment for nonmalignant pain have also been demonstrated. Guillemette et al. (18), in an analysis of claims data, documented a first-year cost increase of $17,317 for TDD compared to conventional medical management, with a break-even point of approximately two years and a subsequent annual savings of $3111. Hatheway et al. (19) analyzed commercial claims data, comparing total payer medical and pharmacy costs (reimbursed amounts) among TDD patients who discontinued systemic opioid use compared to those who did not. In this analysis, mean annual payer costs were reduced by 29% (−$11,115) for patients treated with TDD who eliminated systemic opioid use in the first year of therapy vs. patients treated with TDD who continued systemic opioids.

TDD requires surgical implant of a medical device with long-term intrathecal delivery of medications and therefore has significant risks. Over 30-year history of TDD with extensive published research, understanding of significant therapy risks has grown, leading to better awareness and improved risk mitigation. For example, inflammatory mass (IM) was first identified as a serious TDD-specific risk in 1991 (20). Researchers subsequently evaluated IM through animal research to isolate root causes (21) and then broadly communicated IM risk mitigation strategies to clinicians through publication and product recall. These efforts appear to have reduced IM incidence from early reported rates as high as 3% (22) to the current 0.5% IM rate within this patient cohort following adjudication (review of medical records and imaging, when available, for all reported events indicative of IM). Similarly, in 2006, Medtronic scientists identified a cluster of three deaths, which circumstances suggested were opioid-related, within one day after replacement of intrathecal opioid pumps for non-cancer pain. Medtronic then convened an investigatory panel which culminated in a landmark 2009 article in Anesthesiology (23) identifying that tolerance to intrathecal opioid is quickly lost after infusion cessation, and that intrathecal doses used after reimplant surgery for catheter or pump failure were too high in certain cases, resulting in fatal overdose. Subsequent education and published practice recommendations for implanters (start low, go slow) were intended to reduce these patient events.

In choosing the best therapy for any specific patient, risks associated with TDD must be compared to risks associated with alternatives including oral and/or transdermal (systemic) opioids. Interventional pain doctors typically proceed down an interventional algorithm of pain-relieving procedures starting with therapeutic spinal injections and culminating in neuromodulation trials when simpler treatments fail. With reduced risk associated with SCS (absence of additional drug risks) pain physicians often trial SCS prior to trialing TDD. The therapy failure rate of SCS trials (40% trial failure) and implants (30% explant rate), however, may lead some pain doctors to trial and implant TDD and avoid SCS altogether for selected pain syndromes. Although neurostimulation has evolved over the years and is sometimes indicated for intractable pain that fails to respond to more conservative treatments, stimulation is ineffective for many nociceptive pain conditions and does not consistently result in discontinuation of systemic opioids (24,25). In the current US opioid crisis, long-term use of systemic opioids for chronic pain has decreased as a result of increased awareness of opioid risks, published guidelines and reimbursement constraints. Unfortunately, opioids are frequently reduced or eliminated without initiation of viable alternative therapies which may lead to intense patient suffering (26,27,28). In addition, some medical providers and payers misunderstand the nature of TDD and consider intrathecal opioids equivalent to systemic opioids with respect to mental effects and addiction potential. Intrathecal delivery of morphine is unique in its brain-sparing effects and, by eliminating opioid-induced euphoria and taking opioid control out of the hands of patients, offers a potentially more effective, safer and better tolerated alternative to systemic opioids especially for patients prone to addiction (29,30).

Data available for our analysis were collected from 4646 patients enrolled into the PSR database and followed over a period of 16 years, with an average duration of follow-up of 44 months (SD = 39, maximum 15 years). The PSR dataset covers a broad range of TDD patients and practices around the world with more than 17,000 accumulated patient-years of experience spanning nearly two decades for patients treated for nonmalignant pain. Pump survival, evaluated as freedom from product performance-related events, is 93.5% at five years, with a

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modest decrease in survival for pumps exposed to off-label drugs becoming apparent at approximately five years after implant. Overall, there was no statistically significant difference in the risk of a product performance event occurring between on- and off-label pumps, but the difference in survival at 72 months was statistically significant, suggesting that differences in performance between on- and off-label pumps develop the longer a pump remains implanted. Design changes to the SynchroMed II pump models were implemented in 2016 to reduce the likelihood of nonrecoverable motor stalls due to component wear or corrosion, a failure in some circumstance associated with off-label drug exposure. Analysis of data from the first 21 months available presented at 2020 North American Neuromodulation Society Meeting (31) indicated a 21-month overall survival from product performance-related events with an underlying reported etiology related to pump function of 99.9%.

Adverse events that occurred in at least 5% of patients were problematic drug reactions (15.1%), exacerbation of chronic pain (8.2%, unspecified etiology), and medical device site pain (7.9%). The most common serious adverse events were medical device site infection (1.6%), drug withdrawal syndrome (1.5%), and adverse drug reaction (1.0%). Although comparable neuromodulation studies of equivalent size or follow-up duration do not exist, these reported TDD complication rates support the safety of TDD as a treatment for NMP. In addition, the high elective replacement rate of 99.1% for those TDD patients followed from implant through battery depletion provides insight into overall patient satisfaction with TDD. High patient satisfaction with TDD is supported in the recently published study by Schultz et al. (32).

Registry data play an important role in the ongoing evaluation of available therapies. In contrast to controlled observational or randomized clinical studies, registries allow for evaluation of outcomes in a real-world setting. In addition, since predefined outcomes are not assessed at a designated time interval, registries allow for the collection of data over a longer period of time. This extended duration of data analysis also allows for the evaluation of a therapy through changes in general clinical practice for that specific therapy and with respect to concurrent therapies that may be introduced. The PSR, due to its large patient population and long duration of follow-up, complements existing published data on TDD as a treatment for NMP. The safety and elective pump replacement data presented provides evidence-based support for TDD as a beneficial and much needed pain treatment option in an era of increased scrutiny and reduced access to other forms of opioid administration.

Registries such as the PSR are not without limitations. Physicians maintain their standard clinical practice and this lack of a uniform treatment limits the possibility of reproducing study results from randomized trials or studies performed within a clinical practice. Registry patient follow-up continues until a definitive therapy-related event occurs (e.g., therapy discontinuation or death), but patients may discontinue registry participation due to study site closure or transfer of care, leaving their outcomes unknown. The duration of this study (~15 years) additionally spans changes in therapy best practices and general treatment approaches. Not included in the analysis presented here are more details on previous therapies (i.e., failed SCS) and concurrent therapies (i.e., continuation of systemic opioids), which warrants future analysis as these variables may offer additional insight into patient decisions, risk and overall therapy satisfaction. Registry limitations are balanced by the fact that site selection and physician participation include various practice types, including academic medical centers and private practice pain clinics. In addition, high data quality is expected as implanted patients maintain close contact with the prescribing physician to continue/discontinue therapy. Finally, we have used acceptance of pump replacement as a surrogate for patient satisfaction with TDD, but patients may possibly opt for a pump replacement as a routine, or for other reasons not directly connected to therapy effectiveness.

CONCLUSIONS

With 4646 NMP patients being treated with TDD followed over the course of 17 years, these data from the PSR represent the largest global real-world cohort of patients reported to-date. High overall therapy continuation rates and acceptance of surgical intervention for pump replacement at end of battery life were observed in this patient cohort. Although other considerations may lead patients to continue with TDD for NMP, these results provide additional insight into patient satisfaction with TDD and augment other recent publications.

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Dr. Schultz wrote the first draft and participated in statistical analysis execution, review and critique. Dr. Abd-Elsayed, and Dr. Calodney participated in statistical analysis execution, review and critique, and in writing review and critique. R. Spencer participated in statistical analysis review and critique, and in writing review and critique. K. Stromberg participated in statistical analysis design and execution. T. Weaver participated in research conception, organization and execution, in statistical analysis review and critique, and in writing review and critique. All authors approved the final manuscript.

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SUPPORTING INFORMATION

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

COMMENT

This analysis and summary of patient data relating to Targeted Drug Delivery (TDD) provides noteworthy support for this advanced pain therapy. These data reveal high patient satisfaction

and therapy continuation in a population with chronic non-malignant pain. Although complications are possible, there is a low incidence overall and clinician education and device improvement mitigated these risks. The overall benefits to a patient's quality of life merit consideration of TDD and the ongoing data collection presented here only furthers our understanding of the evolution and improvements in this therapy.

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