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Engineering the extraordinary

**HEALTH SYSTEM & PAYER VALUE**

SynchroMed™ II Drug Infusion System

# Targeted drug delivery for refractory cancer pain

Together, let's help patients take control of their cancer-related pain

Refractory cancer pain
Prevalence
Breakthrough pain
Burden of cancer pain
Current treatment management
Intrathecal drug delivery
References

# Cancer pain is a significant problem -

## And it's growing

Pain persists throughout the cancer lifecycle, reported in:

- 55% of patients undergoing active treatment;
- 39% of patients with cancer in remission;
- 66% of patients with advanced, metastatic, or terminal disease[1].

**Refractory pain is suffered by people who have inadequate pain control, despite optimized use of systematic analgesics[3].**

Cancer pain can be episodic with no pain in between or with lesser background pain.

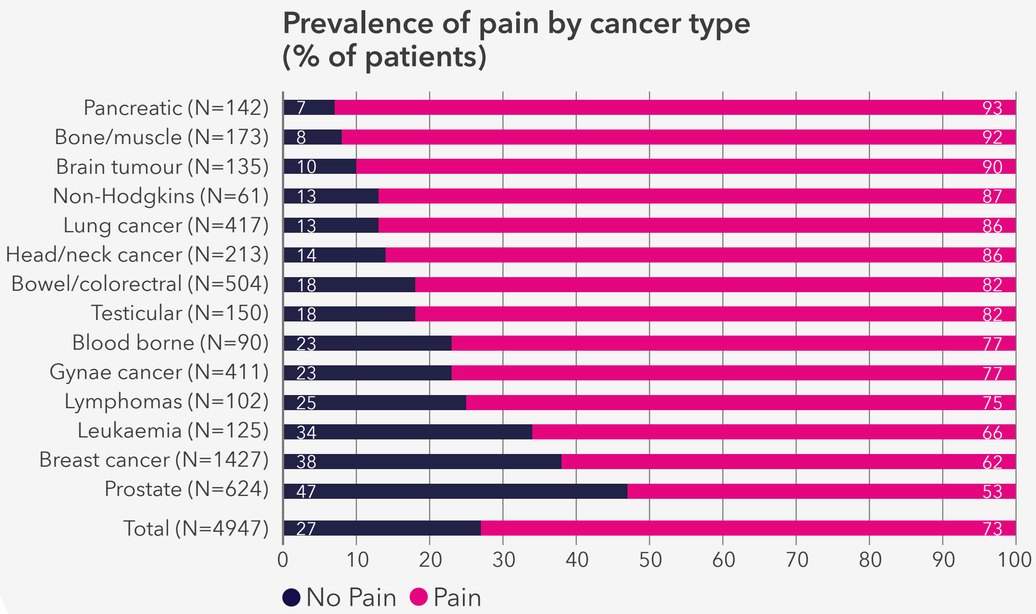
**With better treatments, cancer patients are surviving longer – however chronic pain can persist in patients many years from diagnosis [4-6].**

About
25%
of cancer patients die in pain[2]

Breakthrough cancer pain

Click for more

**Cancer pain has a high incidence in the cancer population[9]**

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# Cancer pain has a high incidence in the cancer population[9]

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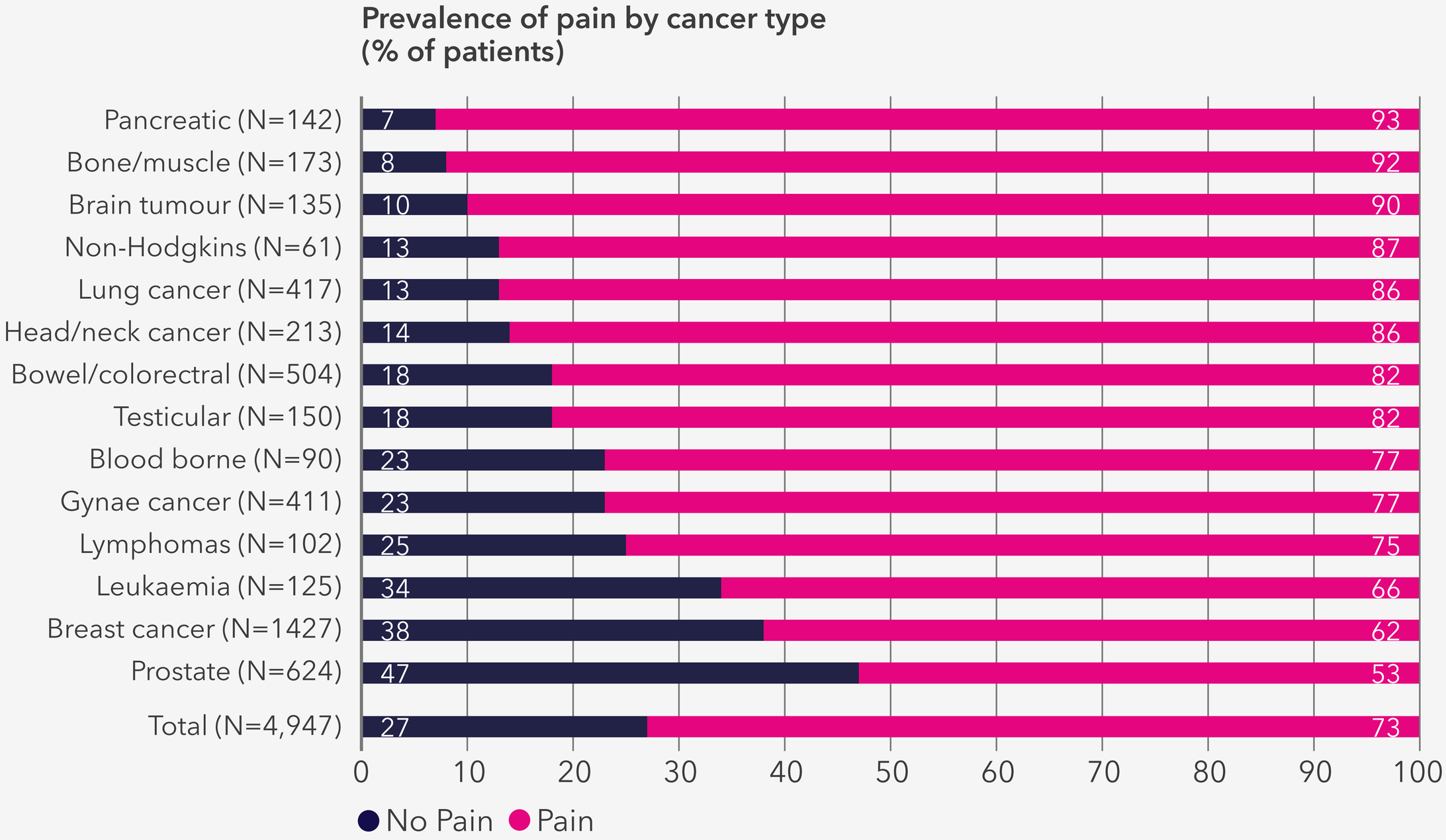




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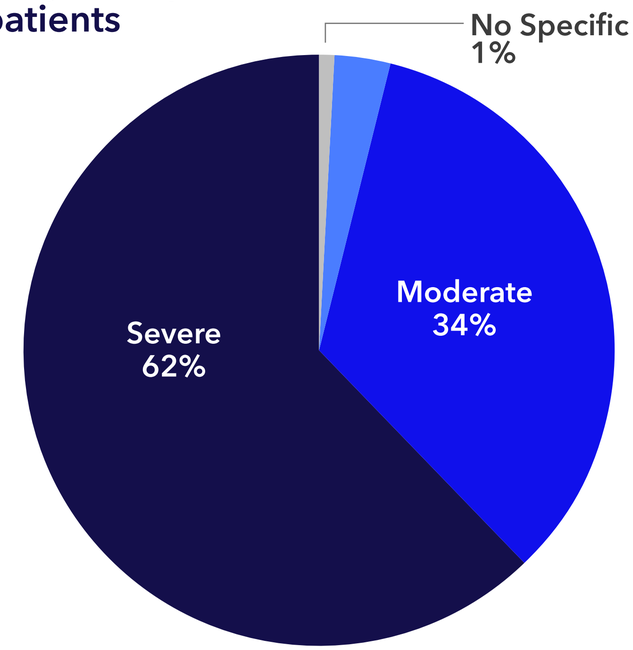
# Breakthrough cancer pain

Breakthrough cancer pain (BTcP) is a complex, heterogenous symptom described as a transitory flare of pain in the setting of chronic pain[10,11].

In a European cohort of 1,000 cancer pain patients, a daily median of three BTcP episodes was reported, with the majority (61.8%) describing their BTcP as 'severe'[12].

**BTcP Intensity: European cohort of 1,000 patients**



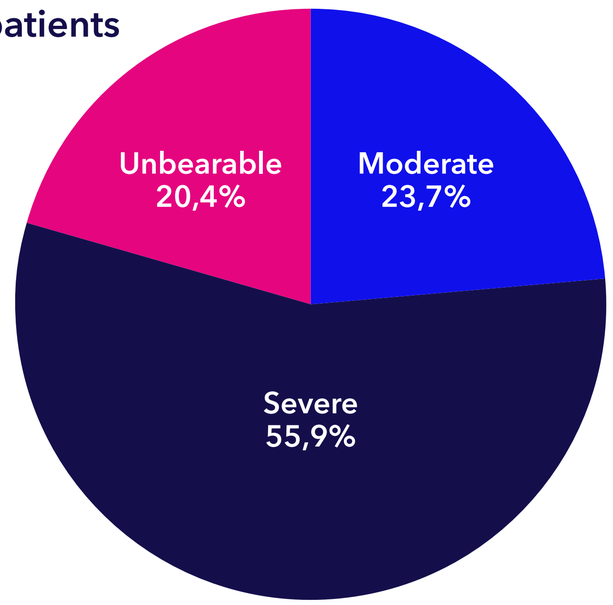

Study Demographics: 51% male, median age of 62 years. Tumor location: gastrointestinal (26.4 %), lung (17.2%), urological (16%), breast (12.5 %), other body locations (23.9%), unknown (1.6%), not stated (2.4%)[12].

*8 pain units; 8 palliative care units; 1 oncology department[13]

A 2018 study from 17 centers* across 16 provinces throughout Spain examined the impact of BTcP and found[13]:

- Patients experienced a mean of 3.1 episodes of BTcP/day (mean duration of 30.6 min[13]).
- 20% described their BTcP intensity as "unbearable"[13].
- Almost two-thirds indicated that their BTcP was "unpredictable" in its occurrence[13].

**Intensity of BTP in cancer patients (N=152)**




Study demographics: 65.8% male with mean age of 66.8 years. Tumor location: gastrointestinal tract (23%), lung (22.4%), breast (9.2%), prostate gland (5.3%), other body locations (40.1%)[13].



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# Quality of life impact

## Cancer patients perceptions of their pain:

**67%**

describe it as distressing[9]

**32%**

describe their pain as so bad they wish they would die[9]

**36%**

describe their pain as an unbearable aspect of their disease[9]

Pain is often the most tangible sign of disease that cancer patients and their families perceive[7]



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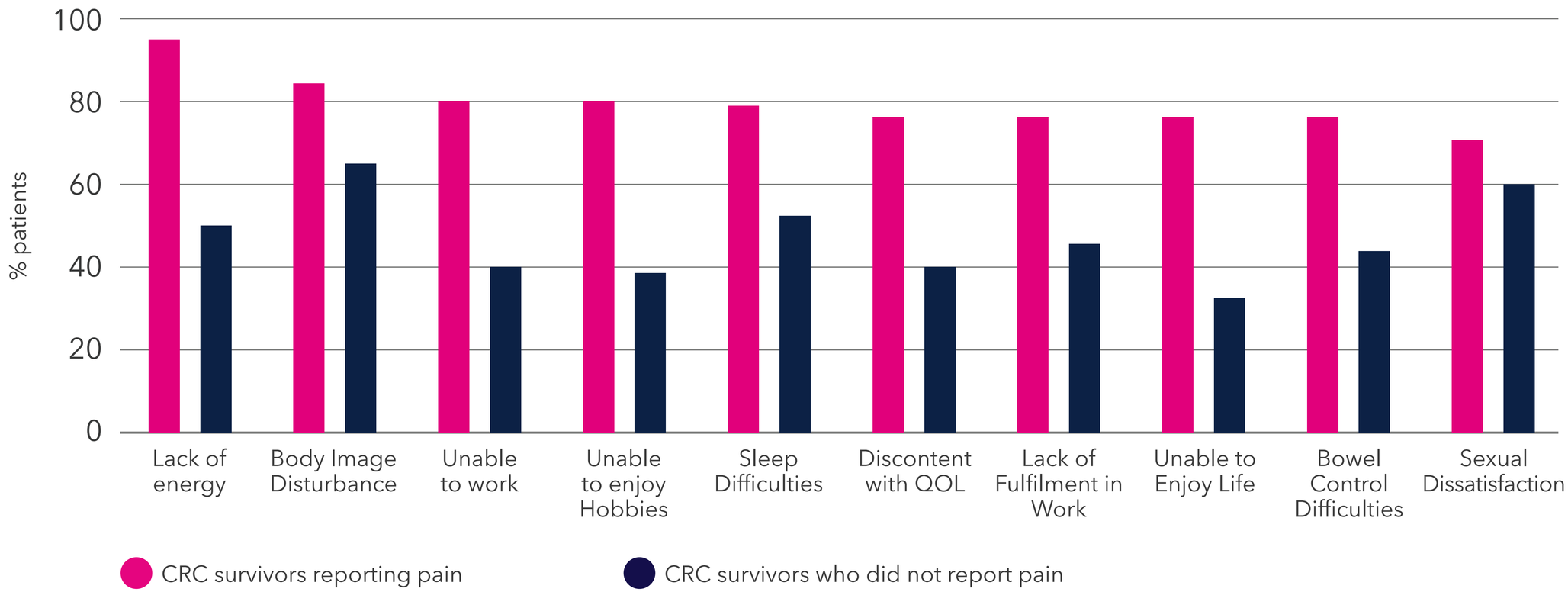
# Cancer pain has a detrimental impact on patients & their families

Cancer pain contributes to impaired performance of daily activities, disability, negatively affects mental health, and reduces health-related quality of life[9].

The 10 most common symptoms experienced by colorectal cancer (CRC) survivors with pain are almost twice as prevalent in comparison to those without pain who report these symptoms[14].



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# Barriers to seeking cancer pain analgesia

Barriers to seeking adequate cancer pain relief include:

- **Reluctance** to report pain, due to the belief that healthcare professionals must be focused on the cancer itself [15];
- **Beliefs** that pain is an inherent part of cancer and fears that higher pain levels, increased analgesia needs, and the symbolic significance of opioids indicate disease progression, deterioration and approaching death[16];
- **Fears** of side effects and addiction associated with perceptions of opioids use[15].

"... I don't want to let them see I'm in pain, so I have to hide it."

Patient-reported extract from a study of narrative interviews with severe chronic cancer pain patients, from a single centre in Italy[23]

Family members of end-of-life cancer patients report anxiety about giving correct and timely dosages of analgesia, and concerns about keeping the patient comfortable without causing harm[16].



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# The cost of unmanaged cancer pain

## High dose opioids

- Cancer pain patients prescribed conventional medical management (CMM) with strong opioids have an increased prevalence of opioid-induced constipation (OIC) or bowel dysfunction, despite the use of laxatives[17,18].
- 2017 data from a Danish national registry found total healthcare costs were 25% higher for cancer patients with OIC vs. without OIC*[19].

* adjusted for age, gender, opioid usage, marital status, ($p<0.001$)

## Ability to work

- 78% of cancer pain patients reported inability to work, compared to 40% of cancer patients without pain[14].
- A Norwegian study found increased pain to be significantly associated with long-term cervical cancer survivors holding disability pensions, compared to those holding paid work[20].

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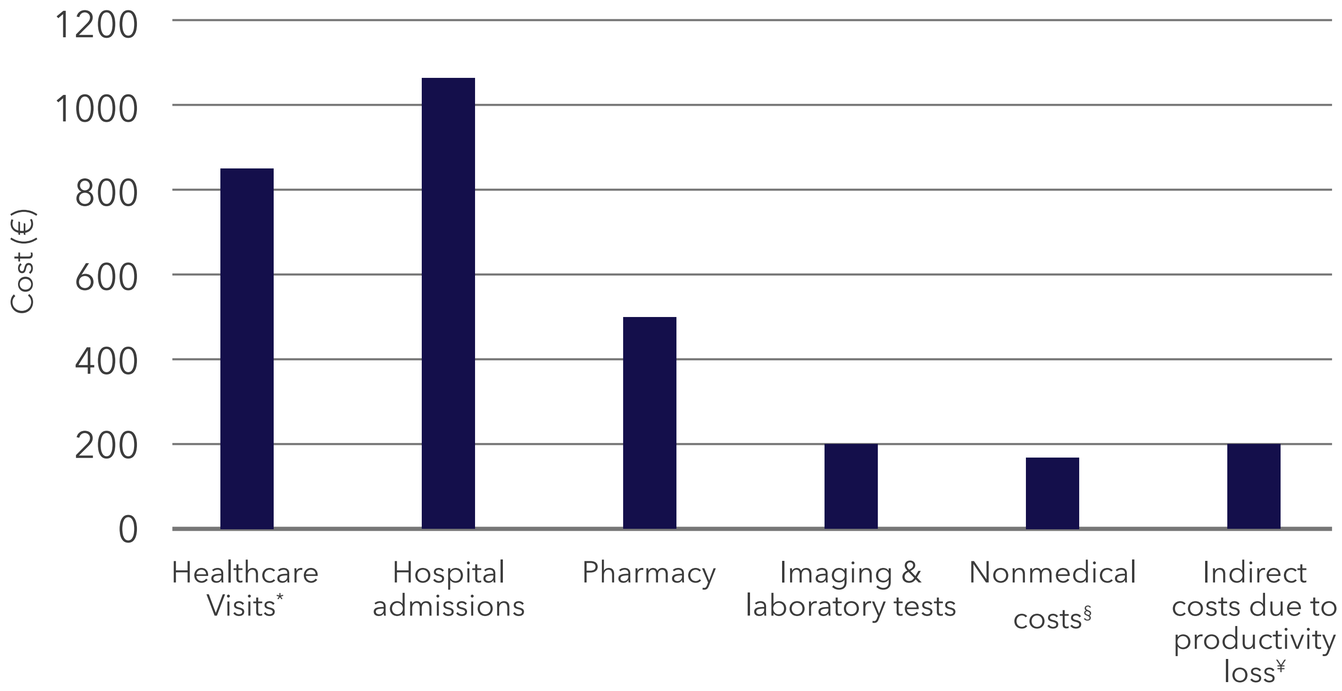
# The cost of unmanaged cancer pain

## Breakthrough cancer pain

- The monthly cost per breakthrough cancer (BTcP) patient in Spain was estimated at €2,941 (2017 values)[13].
- Assuming the annual distribution of cost is proportional, this translates to a cost of €35,000/year/patient for the management of BTcP alone.

### Monthly cost drivers for a BTcP patient




* primary care, specialist physician, emergency unit, day hospital, visit by home hospitalization, radiotherapy session;

§ nonhealthcare resources, psychotherapy, physiotherapy, caregiver (paid and unpaid);

¥ patient and caregiver leave[13].

Multicentre study (17 centers) – 8 pain units; 8 palliative care units;1 oncology department – across 16 provinces throughout Spain (2017)[13]



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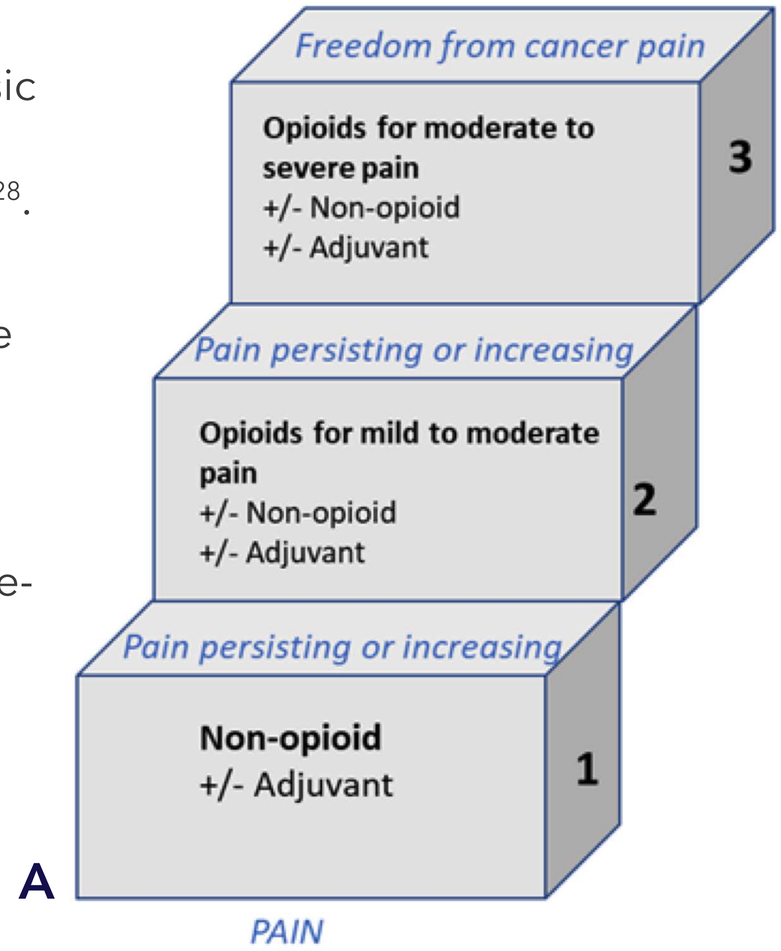
# Management of cancer pain is frequently suboptimal[21,22]

## With undertreatment for those with moderate to severe pain[9,24-27]

- Since 1996, The World Health Organization's (WHO) 3-step analgesic ladder (Figure 3, left) has been the stalwart of cancer pain management[28].
- However, in real-life clinical practice, the likelihood of clinical success if the WHO steps are followed is low (12%, 74% and 14% at Steps 1,2 and 3, respectively)[29]
- For patients at stage 3 (with moderate-severe pain), 25% do not respond to recommended treatment, or are poor responders to pain relief with transdermal and oral opioids[30].




Proposed 4th step

Click for more

A. WHO 3-step analgesic ladder reported in 1996. Adapted from[28].

**With the rise in cancer survival rates[4-6] the treatment of cancer pain is shifting from short-term analgesia to long-term pain management[8]. Yet, there is little evidence of the safety or long-term efficacy of opioid therapy in cancer patients with chronic pain[33].**

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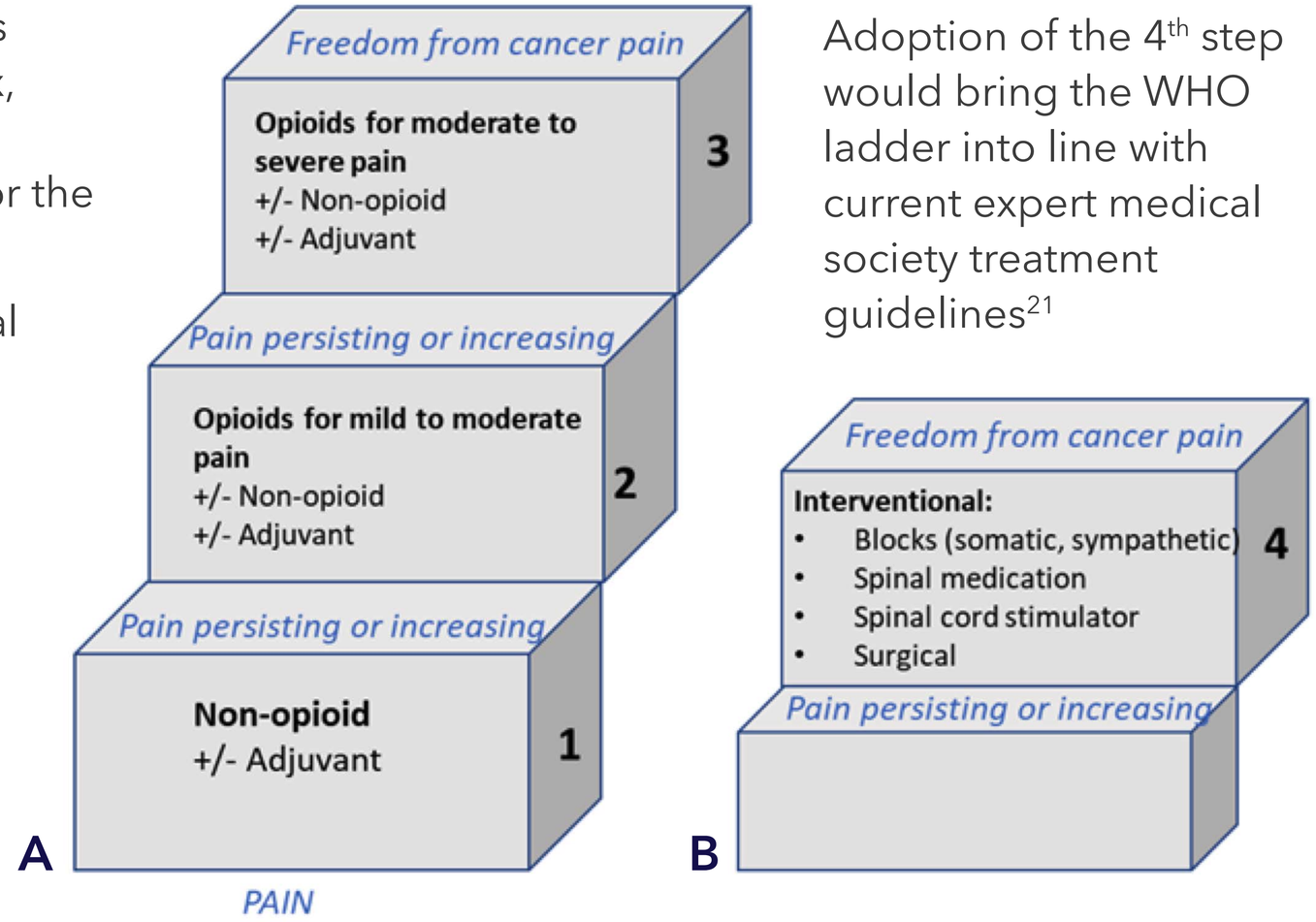
# Management of cancer pain is frequently suboptimal[21,22]

## With undertreatment for those with moderate to severe pain[9,24-27]

- As the management of cancer pain is now considered to be more complex, the WHO ladder is under review for adults[34], and has been abandoned for the management of children[35].
- A fourth step, including interventional techniques, has been proposed (Figure B, right)[31].




Adoption of the 4th step would bring the WHO ladder into line with current expert medical society treatment guidelines[21]

A. WHO 3-step analgesic ladder reported in 1996. Adapted from[28].
B. The proposed 4th step, as reported by Miguel et al, 2000[31], Adapted from[31].

**In the last decade, intrathecal drug delivery has been recognized as a treatment option for cancer patients in whom the expected clinical outcome of systemic treatments is not obtained, or who present intolerance to low doses of these treatments[8,9].**



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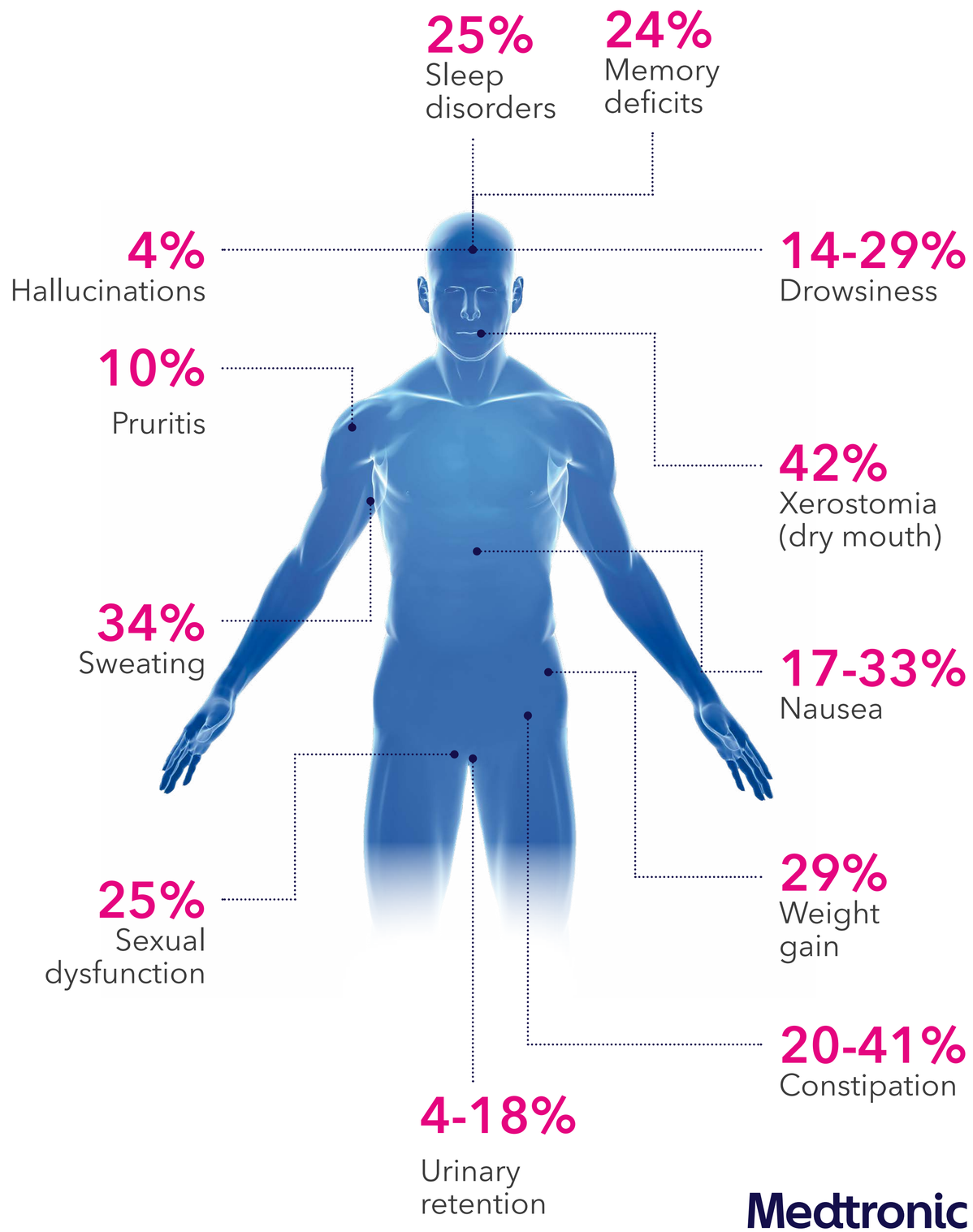
# Management of cancer pain is frequently suboptimal[12,13]

## High dose opioids: patient impact

Evidence supports pain as a key prognostic variable associated with a shorter survival in cancer patients[36-39]. Furthermore, high level opioid use is significantly associated with shorter overall survival[40].

High dose opioids prescribed for cancer pain have well-established adverse events[41]:

- Increased prevalence of opioid-induced constipation or bowel dysfunction (OIC, OIBD) despite the use of laxatives - which can negatively impact on cancer patients' already reduced quality of life[17,42].
- OIC may be indicative of poor opioid tolerability, which could lead patients lowering their opioid dose, resulting in inadequate pain control[42].



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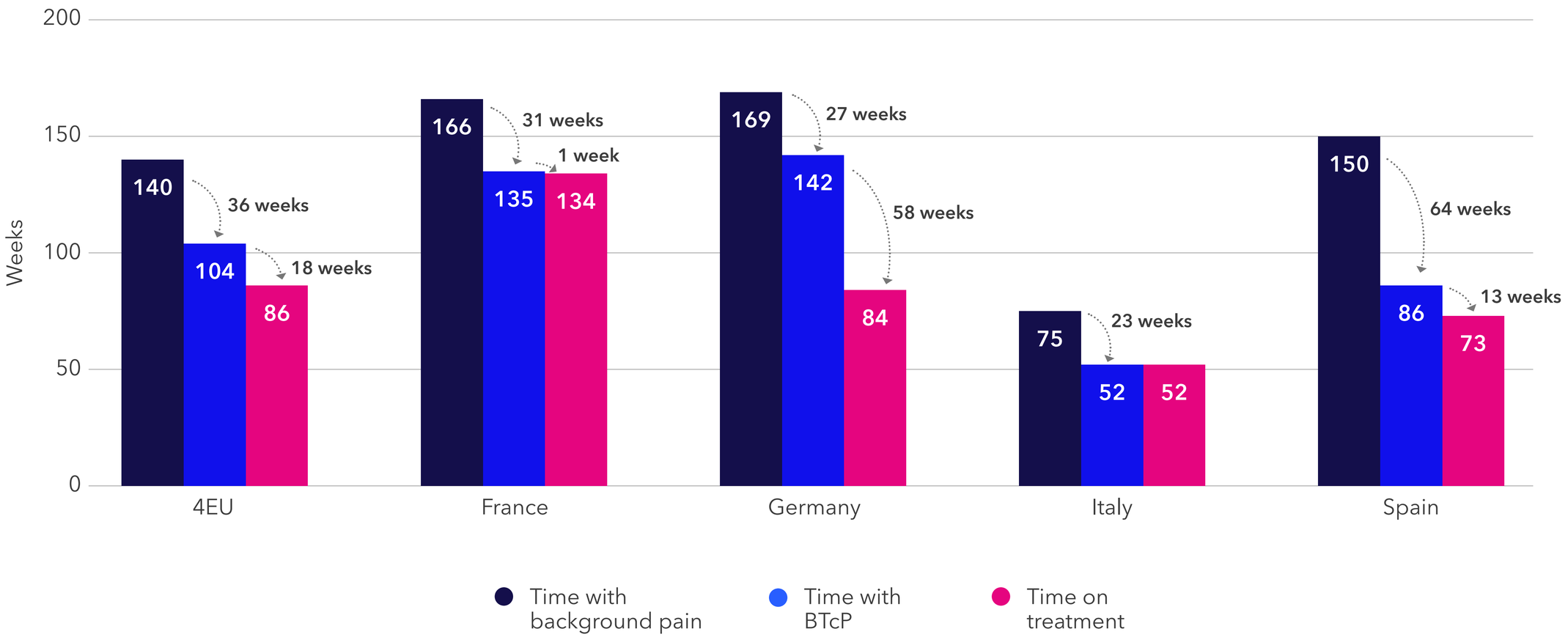
# Inequalities of access to optimized cancer pain treatments

A 2018 survey of European healthcare professionals and cancer patients suffering from breakthrough cancer pain (BTcP) found significant time lags of (58 and 13 weeks in Germany and Spain, respectively) between diagnosis of BTcP and initiation of specific treatment.[44]

**Time with cancer pain (weeks)**



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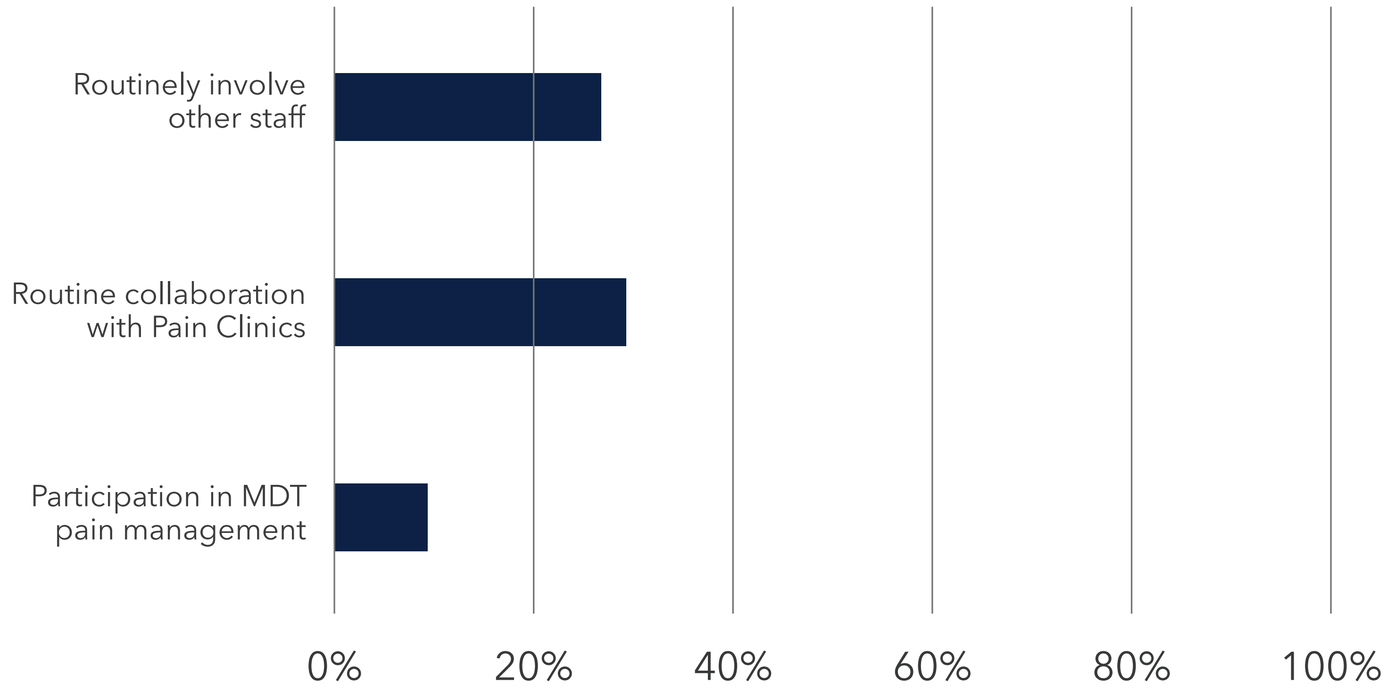
# Inequalities of access to optimized cancer pain treatments

Multidisciplinary management and collaboration between oncologists and other specialists remains uncommon.[44]

**Survey of oncologist involvement in cancer pain management***




* Nationwide survey of medical oncologists in Spain, carried out through a self-administered, written questionnaire (conducted in two waves over Sept-Oct 2015 and Dec 2015-Jan 2016. Total of 73 and 82 oncologists participated in the first and second wave, respectively. The study participants were from 15 of the 17 Autonomous Communities of Spain. All respondents (155 in total) fulflled the questionnaires completely.



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# Inequalities of access to optimized cancer pain treatments

**Access to effective palliative pain management for cancer patients is a European priority[41].**

**In the 2018 Resolution for the Provision of Palliative Care in Europe[45]**, The Council of Europe (the continent's leading human rights organization) calls on member states to:

"ensure access to pain treatment and management as a crucial component of palliative care…. including address educational and attitudinal barriers by raising awareness of appropriate and effective pain management, including opioid-based treatments, among health-care professionals and the general public"[45]

- Integration of palliative medicine in oncology improves patient outcomes and decreases healthcare costs[46].
- Early involvement of palliative medicine after the cancer diagnosis is supported by national guidelines [46].

**Multi-disciplinary collaboration between Oncology, Pain Management, Nursing & Palliative Care are essential to achieving effective and timely pain relief for cancer pain patients and survivors[43,47].**



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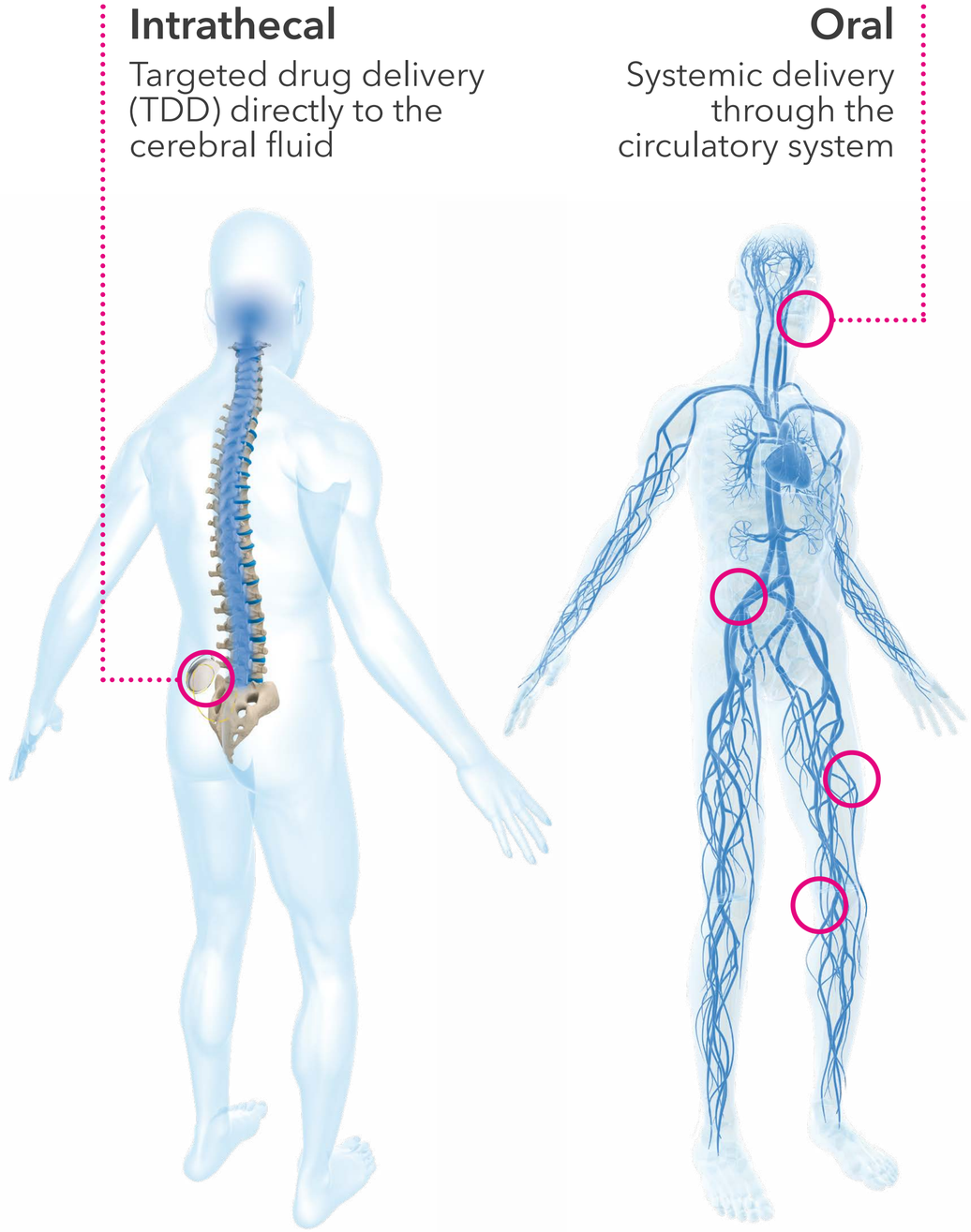
# The benefits of intrathecal targeted drug delivery for cancer pain patients

- A lower morphine equivalent dose is needed via intrathecal application[48].
- Targeted drug delivery (TDD) via the intrathecal route offers significant benefits to cancer pain patients who are not optimally managed on oral or transdermal analgesia. The smaller doses may reduce the systemic side effects[49,50].

| Route of Administration | Conversion Ratio |
|---|---|
| **Oral** | 300 |
| **Intravenous** | 100 |
| **Epidural** | 10 |
| **Intrathecal** | 1 |

**Morphine equivalent dose across different routes of morphine administration[48]**



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# The procedure: clinical considerations

## Trial implant and refill management[62]

### Trial

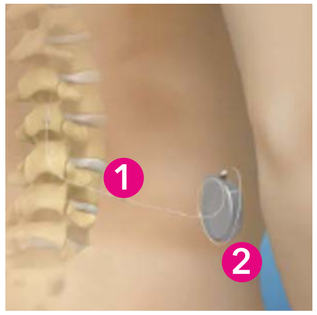
- Simple lumbar puncture
- Medications delivered via needle or catheter
- Evaluate therapy efficacy

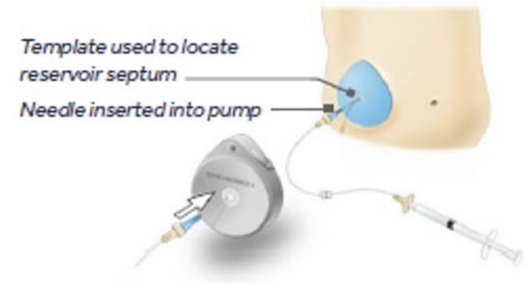
### Implant

- Time: 1-2 hours
- May be performed under general/local MAC
- Two incisions: Catheter 1 and Pump 2
- Relative size of the pump

### Refill

- 22 gauge needle
- No sedation required



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# Clinical evidence supports TDD for chronic cancer pain

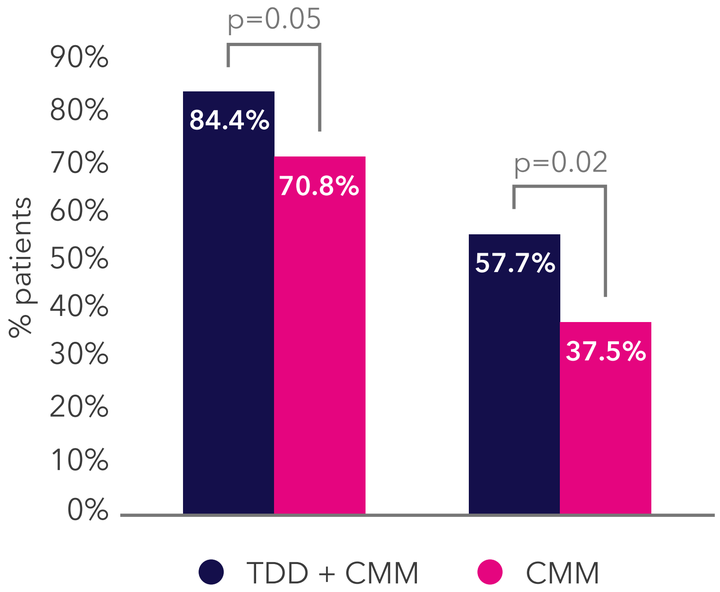
## International, multicenter RCT assessing TDD + conventional medical management

The safety and efficacy of targeted drug delivery (TDD) for the treatment of cancer-related pain have been demonstrated in randomized controlled clinical trials[49,50].

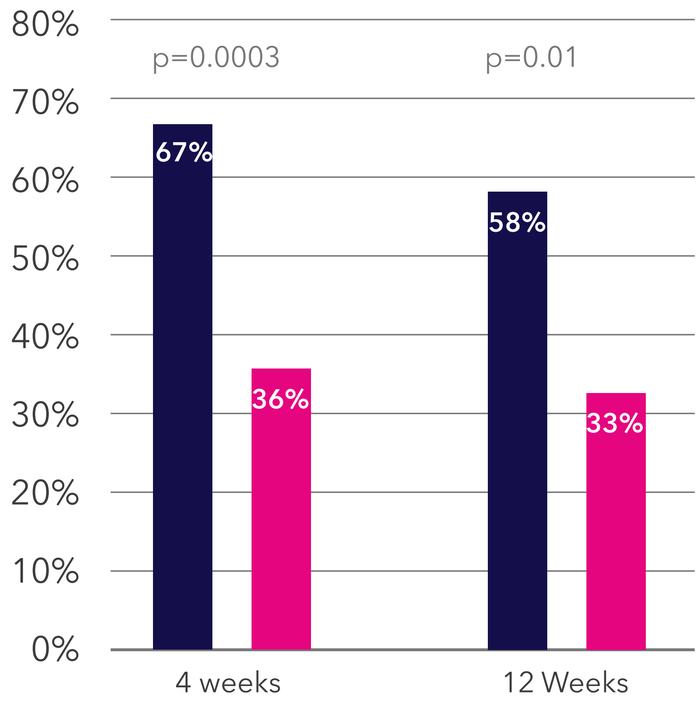
**More patients with increased pain control and reduced toxicity[49].**

Reduction of pain by 20% regardless of increased toxicity, or equal pain with 20% reduction in toxicity at 4 weeks

Reduction of both pain and toxicity by 20% at 4 weeks




**% of patients with a reduction in both pain & toxicity**




Study Details: International, multicenter RCT (Evidence Level II), assessing TDD + Conventional Medical Management (CMM) for treating chronic cancer pain vs. CMM. A total of 202 patients (Randomization: 101 in TDD arm; 99 in CMM arm) were enrolled at 21 centers (16 in the United States, 4 in Europe, and 1 in Australia). Clinical success was defined as>20% reduction in VAS scores, or equal scores with > 20% reduction in toxicity[49,50].



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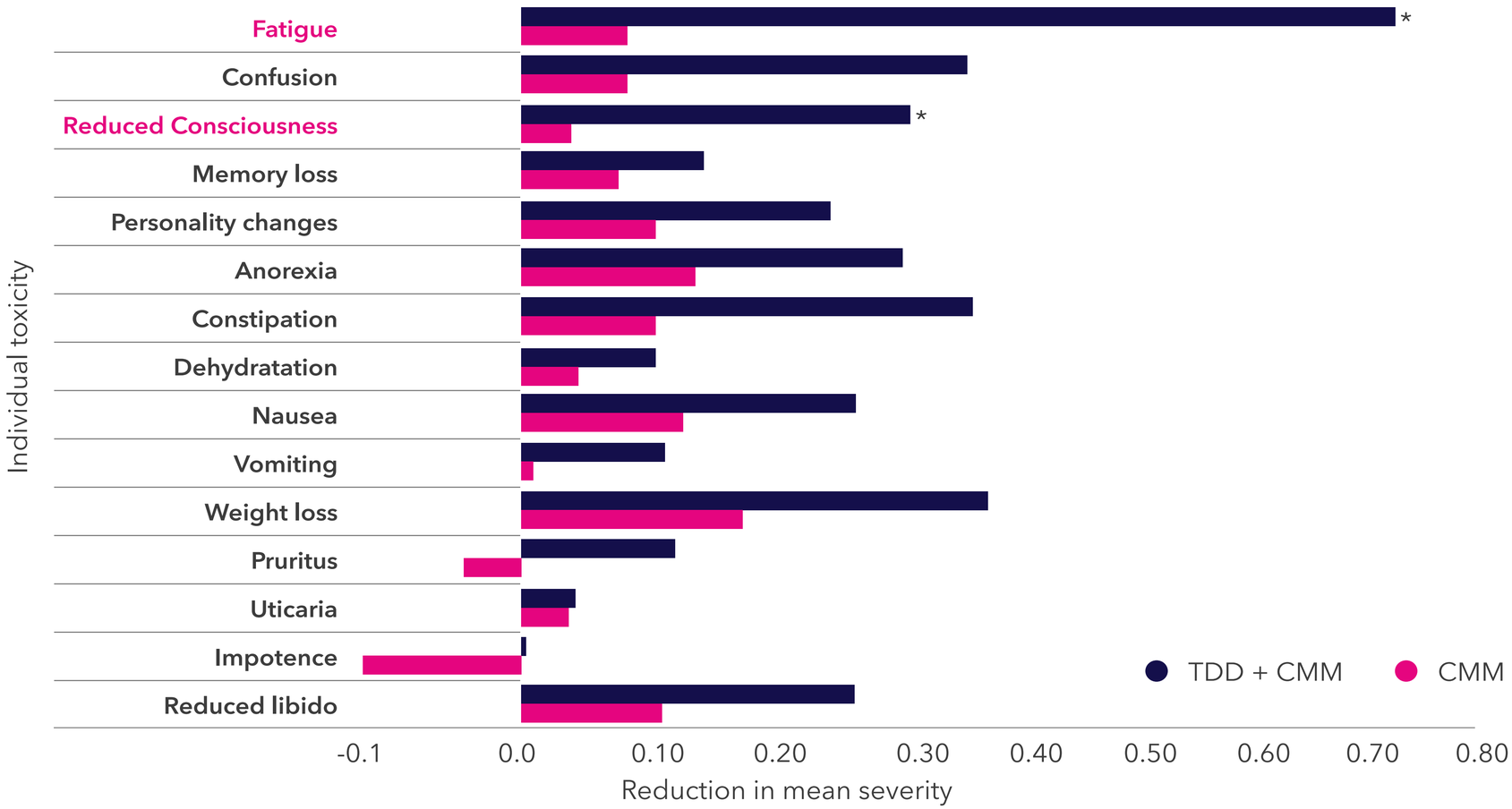
# Clinical evidence supports TDD for chronic cancer pain

## International, multicenter RCT assessing TDD + conventional medical management

**More patients with less fatigue and reduces consciousness[49].**

Reduction in individual toxicities from baseline to 4-week follow-up.

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# Clinical evidence supports TDD for chronic cancer pain

## International, multicenter RCT assessing TDD + conventional medical management

**The safety and efficacy of targeted drug delivery (TDD) for the treatment of cancer-related pain have been demonstrated in randomized controlled clinical trials[49,50].**

## Safety outcomes

- The 194 serious adverse events (SAEs) reported were evenly distributed between the two study groups; 49% were reported in the CMM group and 51% in the TDD+CMM group[49].
- The frequency of two common adverse events associated with opioid use, fatigue and depressed level of consciousness, was significantly lower in the TDD+CMM group compared to the CMM group from baseline to 4 weeks ($p<0.05$)[49].

Study Details: International, multicenter RCT (Evidence Level II), assessing TDD + Conventional Medical Management (CMM) for treating chronic cancer pain vs. CMM. A total of 202 patients (Randomization: 101 in TDD arm; 99 in CMM arm) were enrolled at 21 centers (16 in the United States, 4 in Europe, and 1 in Australia). Clinical success was defined as>20% reduction in VAS scores, or equal scores with > 20% reduction in toxicity[49,50].



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# Clinical evidence supports TDD for chronic cancer pain

## Systematic Review & Meta-Analysis: Management of intrathecal drug delivery (Perruchoud et al. 2021)[32]

### Objectives

To examine the efficacy of managing cancer-related pain with IDD with external pump or implanted infusion systems. Secondary objectives included the effects of IDD on systemic opioid use (oral morphine equivalent [OME]) and infection rates.

### Results

Twenty-nine studies, 17 for calculating pain levels and 13 for weighted mean morphine dose, were identified.

Pain levels significantly decreased postintervention from baseline. Mean differences (on a 0 to 10 scale) were:

- −4.34 ($p < 0.001$) at 4 to 5 weeks (short-term)
- −4.34 ($p < 0.001$) at 6 to 12 weeks (mid-term)
- −3.32 ($p < 0.001$) at >6 months (long-term)

Mean systemic opioid use (OME) was reduced by 308.24 (SE = 22.72) mg/d. (54% reduction of OME).

Mean infection rates were ~3% for intrathecal pumps, which is similar to that found in other populations treated with IDD implanted systems.

Survival - The pooled weighted mean survival time was 130.68 (SE = 1.50) days. This may have been possible due to reduced toxicity and a general improvement in the patients' QoL post-IDD.

### Study Design

A systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

### Limitations

Meta-analysis could not be performed based on control group values because of the heterogeneous designs of the selected studies.

A substantial intertrial heterogeneity was found, as anticipated from the variability in study designs.

Complications, adverse events, and drug side effects were not consistently collected and/or analyzed across selected studies.

### Key Insights

This 2021 published meta-analyses showed a statistically significant and sustained decrease in cancer pain with IDD, compared with baseline.

Systemic opioid consumption was reduced on average by >50% after IDD. Infection rates were comparable with other indications.



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# Clinical evidence supports TDD for chronic cancer pain

## Effectiveness and Safety of Intrathecal Drug Delivery Systems for the Management of Cancer Pain: A Systematic Review and Meta-Analysis (Duarte et al. 2022)[51]

### Objectives

To evaluate the effectiveness and safety of IDD and SCS for cancer pain.

### Results

Twenty-two studies were included on either IDD or SCS for cancer pain. Eight studies were included in the meta-analysis of pain intensity. Pain levels significantly decreased postintervention from baseline.

Mean differences (on a 0 to 10 scale) were:

- −3.31 ($p < 0.001$) at the latest posttreatment follow-up time
- −3.53 ($p < 0.001$) up to one month after treatment.

Studies with either an IDDS or an SCS device showed similar results.

Improvements were also observed in survival, HRQoL or functional outcomes, and use of systemic opioids.

Postdural puncture headache was the most reported complication, whereas urinary retention, nausea, and vomiting were commonly reported side effects.

### Study Design

A systematic review method according to the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

### Limitations

- Substantial unexplained heterogeneity was present within the meta-analyses, meaning that the magnitude of pain intensity reduction with IDDS therapy is uncertain.
- Limited evidence was identified evaluating the effectiveness of SCS for patients with cancer pain.

### Key Insights

This 2022 published meta-analyses showed a statistically and clinically significant reduction in pain intensity up to one month and the latest posttreatment follow-up, compared with baseline.

The evidence also suggests that IDD results in improvements in other outcomes, such as survival, HRQoL or functional outcomes, and use of systemic opioids.

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# Budget impact of ziconotide through IDD for cancer pain

## Ziconotide for the Management of Cancer Pain: A Budget Impact Analysis (Lambe et al. 2022)[52]

### Objectives

To conduct a budget impact analysis from the NHS perspective over a five-year time horizon that reflects a patient population receiving IDD ziconotide or morphine therapy for cancer pain in England.

### Study Design

Markov-like analytic modelling to estimate the budget impact of ziconotide monotherapy vs morphine monotherapy through intrathecal drug delivery (IDD) for the management of cancer pain. The perspective adopted was that of the UK National Health Service, with a five-year time horizon.

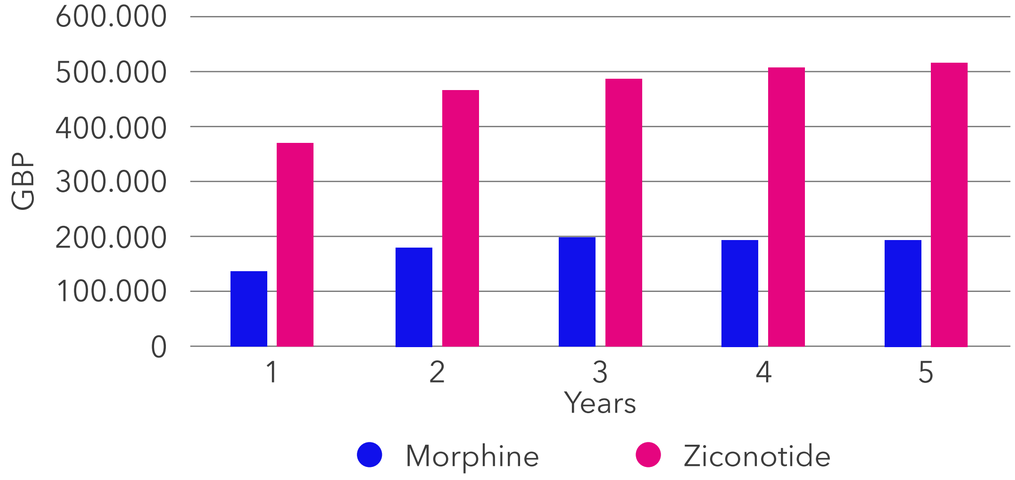
Patients requiring an ITDD were expected to incur the device cost, device implantation cost, refill procedure and the drug costs. The time horizon was five years.

### Results

The total costs of ziconotide monotherapy and morphine monotherapy for the first five years are shown in Figure 1. The estimated five-year cumulative budget impact of treatment with ziconotide monotherapy for the five-year time horizon was £2,355,675 whereas that of morphine monotherapy was £913,804.

The results of this study suggest that the use of ziconotide is associated with higher costs to the health care system. However, the additional costs in any of the first five years are below the resource impact significance level of £1 million for medical technologies in England.

**Budget impact of Morphine vs Ziconitide monotherapy**




### Key Insights

This budget impact analysis suggest that although intrathecal ziconotide is associated with higher costs to the health care system in England, the incremental costs are not significant.

Routine commissioning of ziconotide would provide an alternative for a population with limited IDD treatment options.



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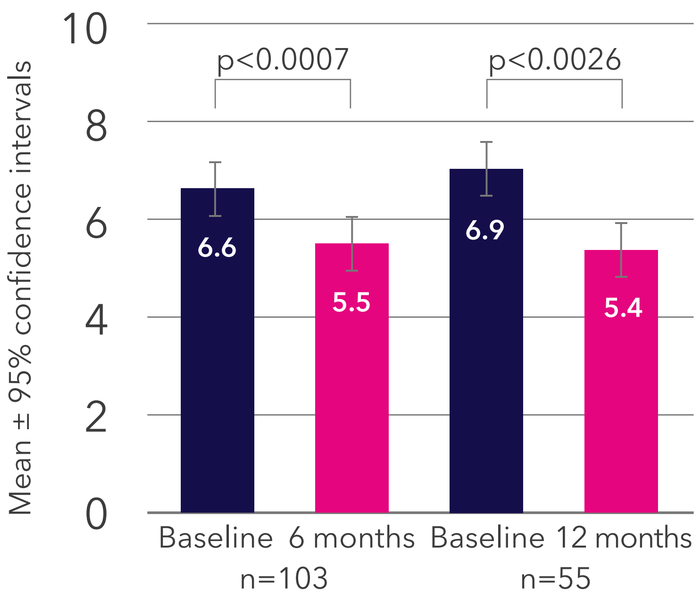
# Clinical evidence supportsTDD for chronic cancer pain

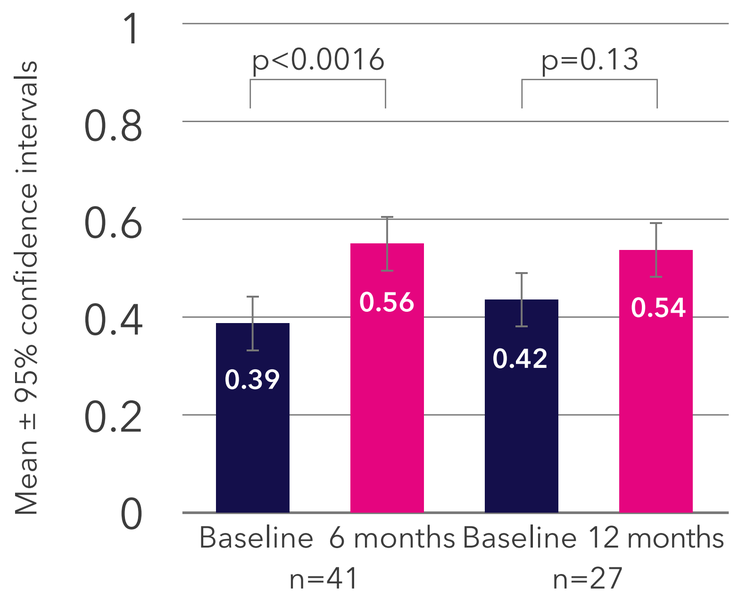
## Real world clinical effectiveness

A 2019 publication based on data from a prospective, long-term multicenter registry (Medtronic's Product Surveillance Registry) report on the **largest cohort of TDD cancer pain patients to date** (1,403 patients included).

**Significant Reduction of Pain at 6- and 12-months post-implant**[53]
Paired pain scores




**Improvement in Health-related Quality of Life at 6 months, and maintained at 12 months***[53]
Paired EQ-5D utility scores




Results support the benefits of TDD as an effective therapeutic option with a positive benefit–risk ratio in the treatment of chronic cancer pain[53].



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# Clinical evidence supportsTDD for chronic cancer pain

## Real world safety

- Infection rates following TDD system implants in cancer pain patients are low, ranging from 0.9%* to 3.2%**

**Medtronic actively tracks and annually publishes the performance reports for the Synchromed II™ drug infusion system.[66]**

**Find these available at:**
https://professional.medtronic.com/ppr


* Retrospective chart review of 217 TDD implants from a single center. Surgical Site infection risk after TDD placement for cancer pain is low, despite frequent concurrent antineoplastic therapy and leukopenia in the perioperative period.[54]

** Prospective, long term, multicenter registry on 1,403 patients suffering from cancer-related pain implanted with TDD. 3.2% experienced infection requiring surgical intervention (e.g., explant, replacement, revision, or debridement).[53]



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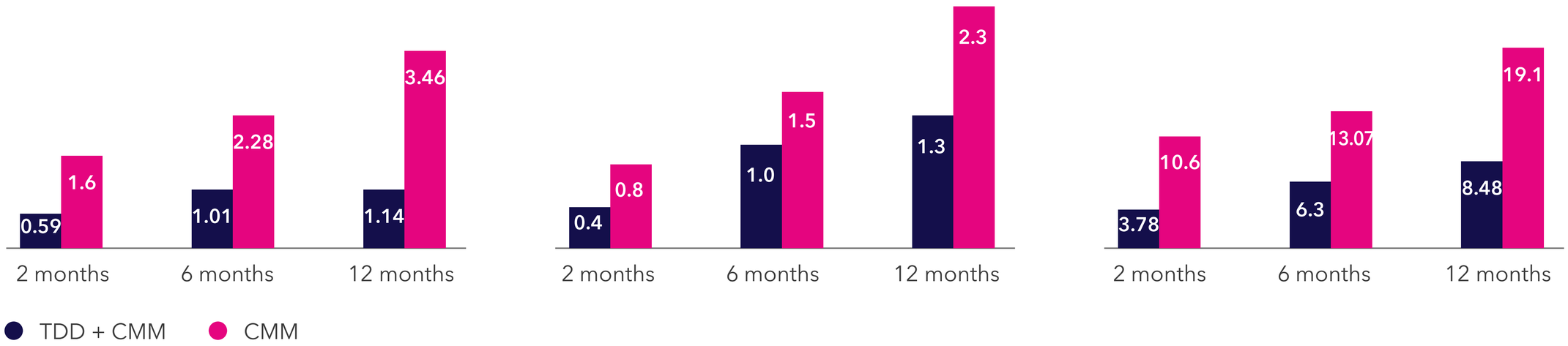
# Economic value of TDD for cancer pain

## Compared to conventional medical management

Recent published evidence has shown that compared to CMM alone, TDD+CMM significantly reduced healthcare utilization as early as 2 months and through 12 months ,in the form of lower inpatient visits, inpatient days and emergency department visits[55].




- From a separate study, in selected patients prescribed high-cost conventional opioid regimens, TDD management of cancer-related pain resulted in cost savings as early as 7.6 months compared with conventional opioid therapy, from a US payer perspective[56].



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# Recommendations:

## Intrathecal drug delivery for cancer-related pain

| Guideline and society (year) | Recommendations for intrathecal drug delivery |
|---|---|
| **European Pain Federation (EFIC) (2018)[58]** | Patients should be referred to specialist advice and treatment if pain is not improving within a short time or if they are experiencing intolerable side effects of analgesia [GRADE 1C]<br>This includes access to advanced pain management techniques such as intrathecal pumps |
| **European Society for Medical Oncology (ESMO) (2018)[21]** | Level II B - Intraspinal techniques delivered and monitored by a skilled team should be included as part of the cancer pain management strategy |
| **Polyanalgesic Consensus Conference (PACC) convened by the International Neuromodulation Society (2017)[59]** | Localized pain can be adequately covered with intrathecal therapy (II B Strong)<br>Diffuse pain can be adequately treated with intrathecal therapy (III C Moderate)<br>Global pain can be adequately treated with intrathecal therapy (III D Moderate) |
| **European Association for Palliative Care (EAPC) (2012)[60]** | Spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered for patients in whom analgesia is inadequate or who have intolerable adverse effects despite the optimal use of oral and parenteral opioids and non-opioid agents. (Weak Recommendation) |



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# Recommendations:

## Intrathecal drug delivery for cancer-related pain

| Guideline and society (year) | Recommendations for intrathecal drug delivery |
|---|---|
| **Federatie Medisch Specialisten - The Netherlands: Pijn bij patiënten met kanker (2019) (Pain in Patients with Cancer, 2019)[57]** | Neuraxial (intrathecal or epidural) administration of opioids in cancer pain<br><br>Recommendation: In cancer patients in the palliative phase: Consider intrathecal opioid administration, if necessary in combination with a local anesthetic and / or clonidine, for the treatment of pain in cancer patients when oral, transdermal or parenteral treatment with opioids has insufficient analgesic effect and / or is associated with severe side effects (1D).<br><br>If neuraxial administration of opioids is expected to be necessary for longer than a few weeks, it is preferable to opt for administration via a Fully Implantable Delivery System (FIDS). This reduces the risk of catheter dislocation and infection. |
| **British Pain Society (2015)[61]**<br><br>**Intrathecal drug delivery for the management of pain and spasticity in adults; recommendations for best clinical practice** | The working group believes that there is reasonable evidence supporting the use of ITDD in pain in patients with cancer where this is not controlled by systemic analgesia or where systemic analgesia causes intolerable side effects.<br><br>ITDD has also been found to be a cost-effective alternative to systemic, intravenous or external infusion devices for cancer patients who require pain management for 3 months or more. |



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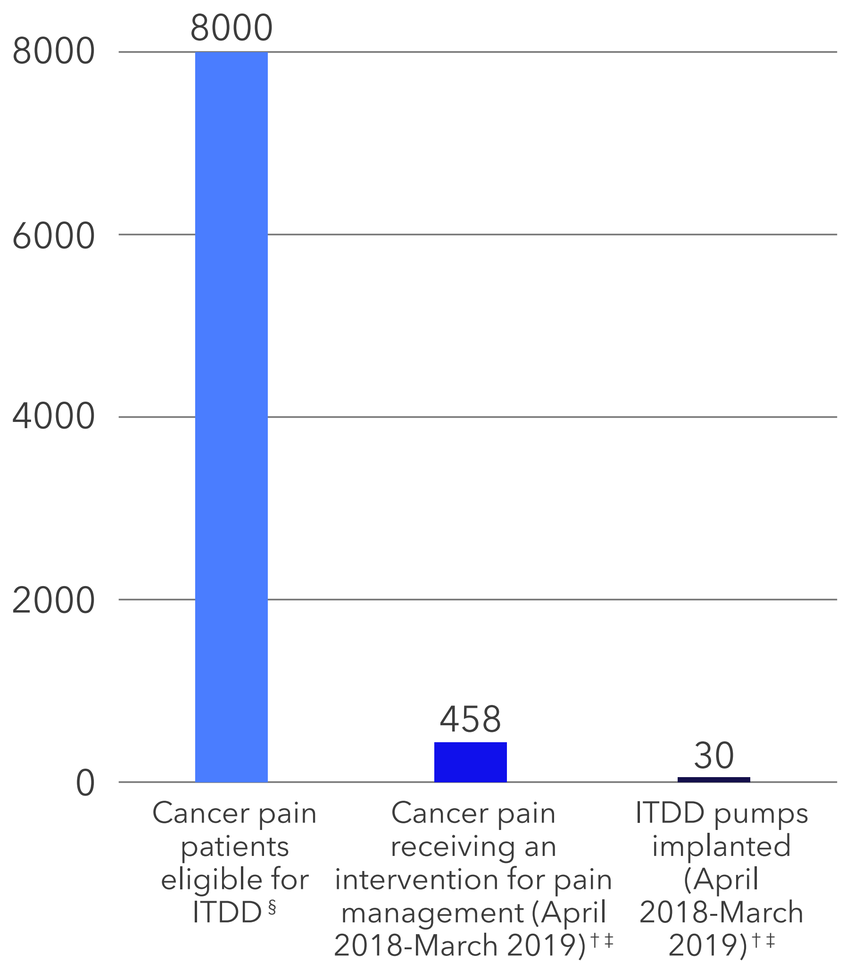
# Gaps in access to intrathecal drug delivery for cancer pain

Despite demonstrated clinical evidence and medical society recommendations, there is a substantial gap between the need and provision of intrathecal drug delivery for patients with refractory cancer pain

**The recent 2019 UK collaborative Framework for Provision of Pain Services for Adults Across the UK with Cancer or Life-limiting Disease[47] has stated the need for its guidance is timely because of:**

"the importance to the public of pain associated with cancer and life-limiting disease, the evidence of under-treatment or poor access to care, the need to show evidence of better pain management in CQC inspections from 2016, and the need to meet new commissioning requirements for managing complex interventions (e.g., intrathecal pumps)"[47]




§ Based on NHS England estimate that 5–15% of cancer patients have refractory pain and require advanced techniques which may include: chordotomy, spinal injections, nerve root ablation, ITDD, radiofrequency ablation, chemical destruction of nerve, cryotherapy (7)

*2014–2019 includes ITDD for management of spasticity; 2014 and 2015 includes ITDD for noncancer pain.

† Patients with an ICD10 C code up to 180 days prior to receiving an ITD

‡ Up to January 2020.

HES, Hospital Episode Statistics; ITDD, intrathecal drug delivery device device



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# Considerations for appropriate patients

## Patient selection recommendations

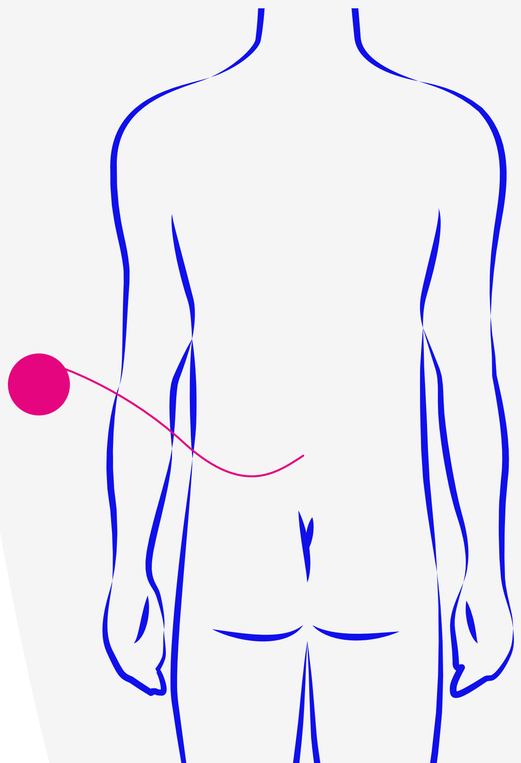
1. **Medium to long-term life expectancy** (typically ≥ 3 month)[49,65]
2. **Visual analogue score (VAS) ≥ 5 despite 200 mg/day** of oral morphine or analgesic equivalent[49,50]
3. **Consider those on lower dose analgesics** if opioid side effects are not well tolerate[49,50,59]
4. **In your assessment, consider the patient perspective on mobility** (i.e. preferred place of treatment – home or specialized care service)

## Try the therapy with your patients

**Test with injection**

**or**

**Test with external pump**



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# Benefitting patients and clinicians for more than 30 years

Medtronic's global reach enables our intrathecal drug delivery therapy to be available in many countries across the world.


Wireless Communicator | SynchroMed™ II Pump | Clinician Programmer

**1988**
SynchroMed™ pump (first used for pain management)

**1992**
SynchroMed™ pump for severe spasticity of spinal origin

**1996**
SynchroMed™ pump for severe spasticity of cerebral origin

**1999**
SynchroMed™ EL pump

**2003**
SynchroMed™ II pump


**2007**
myPTM™ Personal Therapy Manager


**2017**
SynchroMed™ II pump with durable design*

**2018**
New clinician programmer (CLP)

**2018**
New MyPTM™ Personal Therapy Manager for patient


* Design changes to address causes of motor stalls; Product Performance Report 2021, v1.0 03Mar2022. The implementation of these changes does not imply equivalent percent reductions of motor stall.

Note: This timeline only shows extracts of the Medtronic TDD product portfolio.



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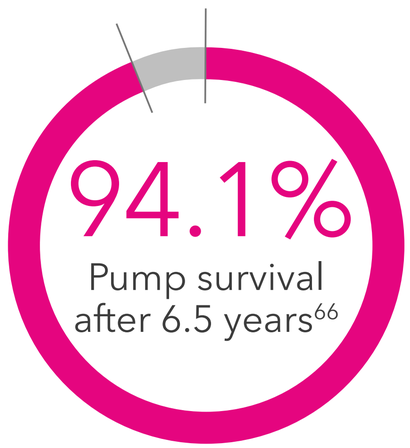
# Performance and reliability

The SynchroMed™ II Programmable Infusion System[62]:

- available with a 20ml and 40ml reservoir size
- precisely moves medication through a peristaltic action
- constant and flexible infusion modes with bolus dosing
- allows patient to self administer a therapeutic bolus with myPTM™
- safe 1.5T and 3.0 full body MRI possible*[64]
- designed to resume therapy shortly after MRI scan
- replacement after 6-7 years[66]
- an alarm is activated 90 days before battery life ends

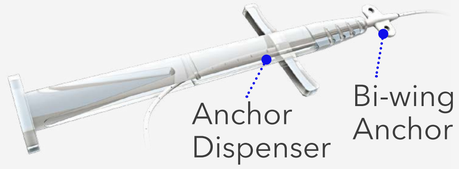

19.6mm thickness (20ml pump)
26.1mm thickness (40ml pump)



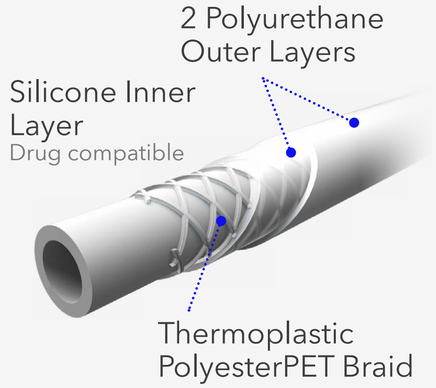

**Confidence year after year**

## Design Enhancements Ascenda™

### Anchor dispenser tool with bi-wing anchor




### Catheter design




### Guide wire interlock handle

* Under specific conditions for 1.5T and 3.0T MRI scans. Requires interrogation to confirm pump status.



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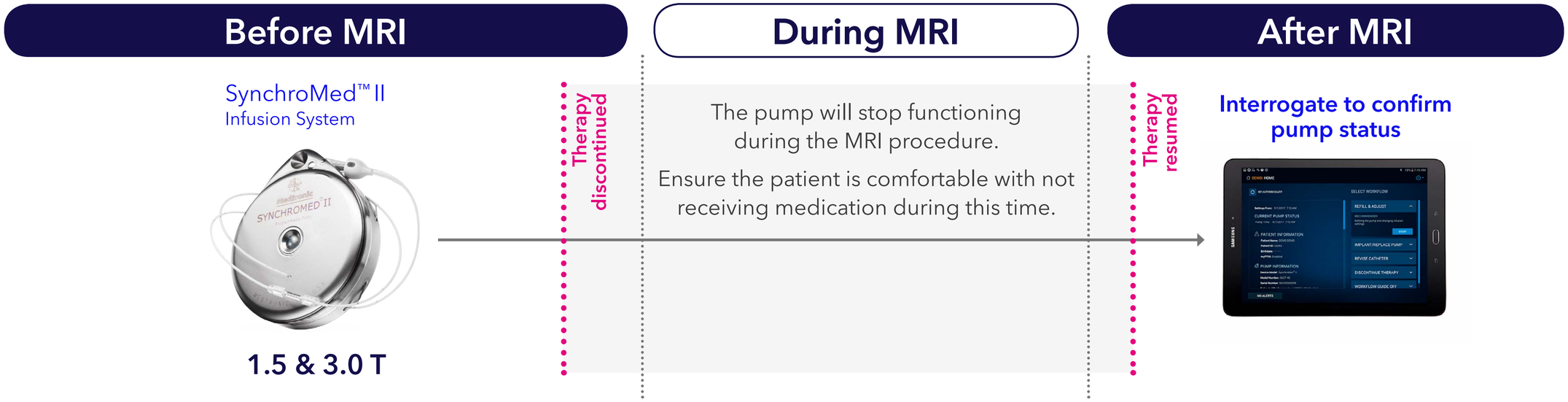
# MRI performance

Medtronic's Product Surveillance Registry, reporting on the **largest cohort of TDD cancer pain patients to date** (1,403 patients included) tracked MRI activity amongst patients implanted with the Synchromed II™ programmable infusions system for cancer pain, and found:

- 3 MRIs were reported in 51 patients[53]
- All MRI-induced motor stalls recovered as expected within 24 hours[53]
- There were no reports of post-MRI drug withdrawal or sequelae[53]

## Synchromed II™ offers a simple protocol to manage MRI in cancer pain patients



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# Benefits for breakthrough cancer pain

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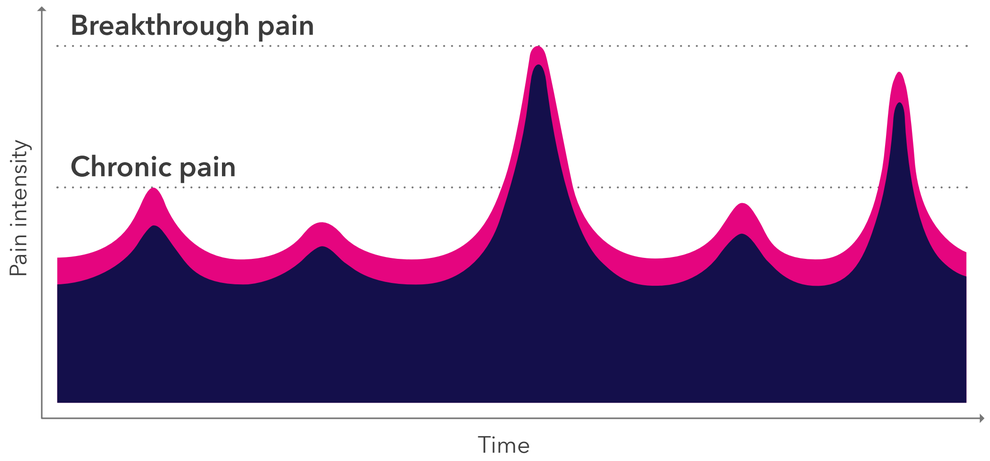
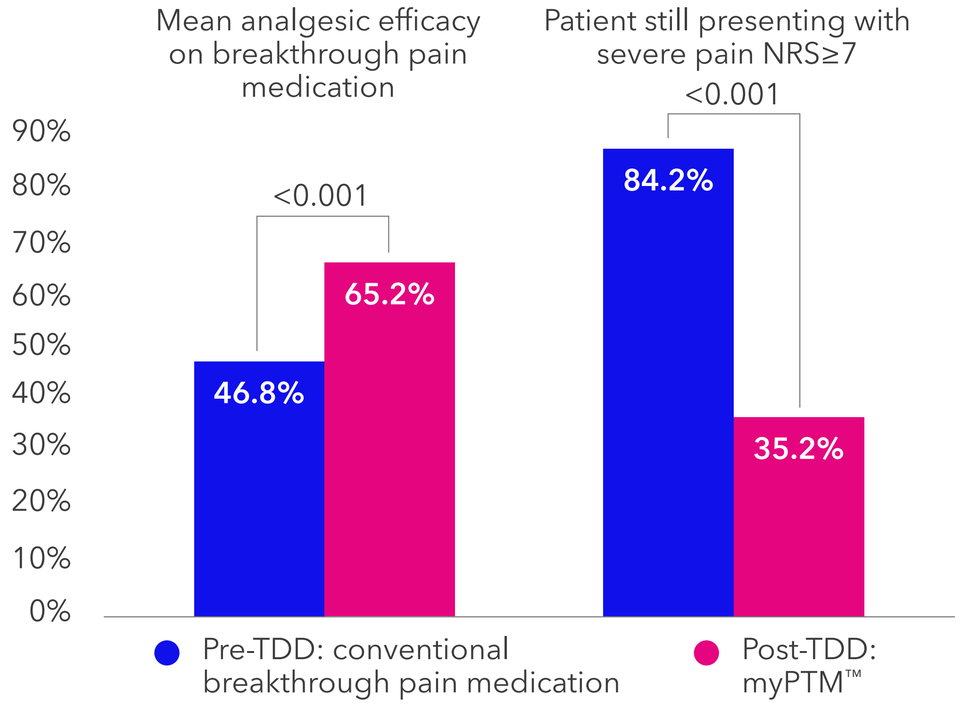
- Onset of breakthrough cancer pain (BTcP) is sudden and reaches a maximum intensity within 1 second to 30 min (median ≈ 3 min)[67]
- Patients can average 4-6 episodes/day, with a median duration of 15-30 min/episode[67]
- Episodes may, or may not, be associated with a precipitating factor and therefore **may not be predictable**. Precipitating factors can be identified in 55-80% of all episodes[67]




**More patients able to better control breakthrough pain and 3x faster with myPTM™ compared to conventional medication.[63]**




- Breakthrough pain reduction was **46.8% before** implant and **65.2% after** implant and with myPTM™[63]
- Patients with severe pain were **84.2% before** implant and **35.2%** after implant and myPTM™[63]
- With myPTM™ patients can manage breakthrough pain **quicker compared to systemic opioids** (10 vs 30 min on average)[63]



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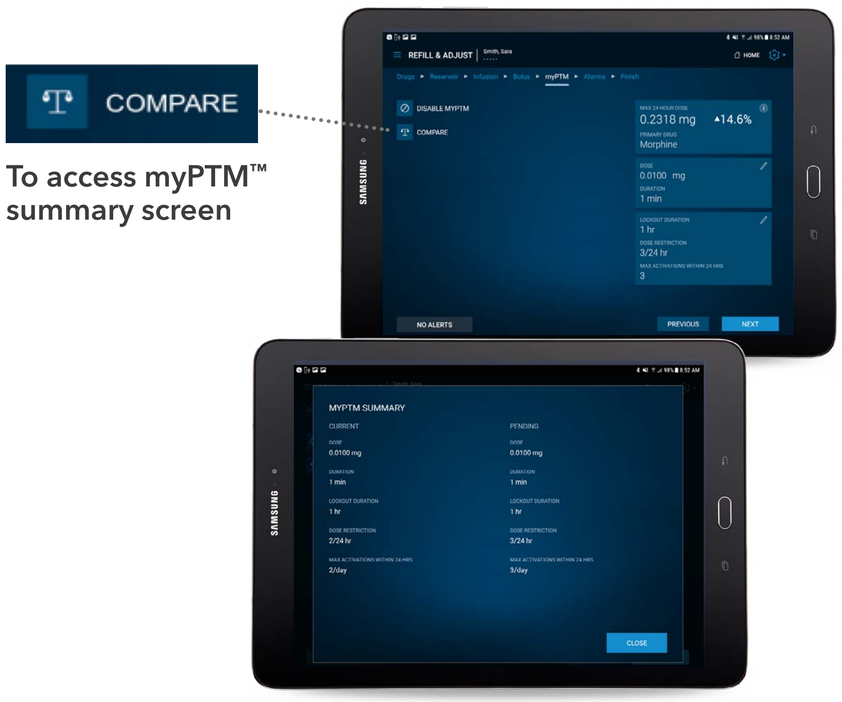
# Easy programming of myPTM™ with clinician programmer

## Compare with ease

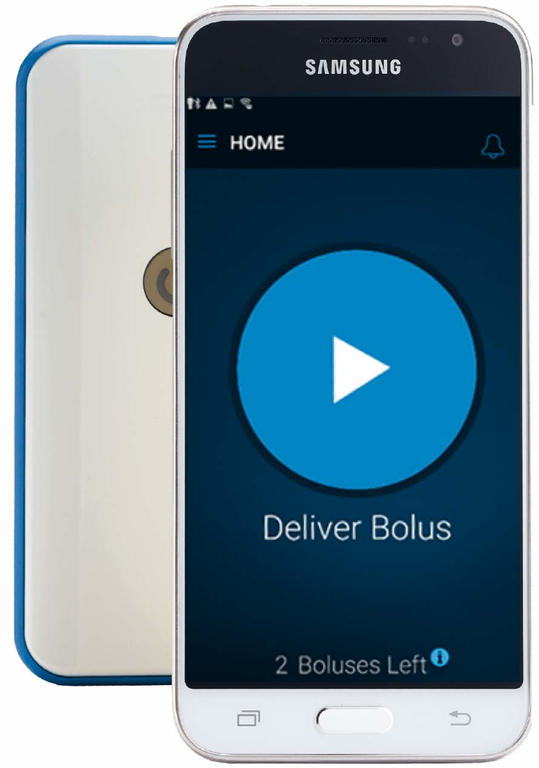
Easily compare current and pending updates while programming simple continuous mode or myPTM™.




**To access myPTM™ summary screen**

## Managing Pain. Managing options.

Targeted drug delivery (TDD) with myPTM™ allows for patient control of breakthrough pain – within programmed parameters – ensuring 100% compliance. When pain is breakthrough, your prescription is right at hand.




**myPTM™**
Personal Therapy Manager



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**Brief Statement**

See the device manual for detailed information regarding the instructions for use, the implant procedure, indications, contraindications, warnings, precautions, and potential adverse events. For further information please contact your local Medtronic representative and/or consult the Medtronic website at www.medtronic.eu.

For applicable products, consult instructions for use on www.medtronic.com/manuals. Manuals can be viewed using a current version of major internet browser. For best results, use Adobe Acrobat® Reader in the browser.

When ITB is mentioned, we are considering Intrathecal baclofen (an antispasmodic) administered by an intrathecal drug delivery pump therapy. Medtronic provides only the intrathecal drug delivery pump and the catheter; the baclofen is provided by an external company.



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