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Ziconotide for the Management of Cancer Pain: A Budget Impact Analysis

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ABSTRACT

Objectives: Recent recommendations on starting dose, smaller dose increments, and longer intervals between dose increase have the potential to increase the safety of ziconotide administration in addition to improving its value for money. Ziconotide is not routinely commissioned in England, with one of the concerns being whether it represents the best use of resources. The aim of this project is to conduct a budget impact analysis to estimate the costs or savings associated with the changes in ziconotide dosage in addition to its use in combination with morphine for the management of cancer pain.

Materials and Methods: An open, Markov-like cohort decision analytic model was developed to estimate the budget impact of ziconotide in combination with morphine (ziconotide combination therapy) vs morphine monotherapy through intrathecal drug delivery (ITDD) for the management of cancer pain. The perspective adopted was that of the UK National Health Service, with a five-year time horizon. Sensitivity analyses were conducted to evaluate different scenarios.

Results: Ziconotide combination therapy was more expensive than treatment with morphine monotherapy. The total costs of ziconotide combination therapy and morphine monotherapy for the first year were £395,748 and £136,628 respectively. The estimated five-year cumulative budget impact of treatment with ziconotide combination therapy for the five-year time horizon was £2,487,539, whereas that of morphine monotherapy was £913,804. 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.

Conclusions: The results of this budget impact analysis suggest that although a combination of intrathecal ziconotide in combination with morphine is associated with higher costs to the health care system in England, the incremental costs are not significant. Routine commissioning of ziconotide alone or in combination with morphine would provide an alternative for a population with limited ITDD treatment options.

Keywords: Budget impact analysis, cancer pain, delivery of health care, intrathecal drug delivery, ziconotide

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INTRODUCTION

Cancer Research UK estimates that between 2016 and 2018, there were approximately 375,000 new cancer cases in the UK every year, approximately 1000 cases every day. Breast, prostate, lung, and bowel cancers accounted for more than half (53%) of all new cancer cases in the UK in 2016–2018.[1]

It has been shown that up to one-third of patients with cancer will go on to experience chronic pain.[2] With at least half of people diagnosed with cancer experiencing physical pain to an extent, many patients suffer from severe pain, especially in advanced stages of the disease.[3,4] Depending on stage and type of cancer, the number of patients experiencing pain differs, with 33% of patients undergoing curative treatment to 64% of patients with advanced, metastatic, or terminal disease suffering from pain.[5] Cancer pain may be neuropathic or nociceptive but is often mixed. It may result from local tumor invasion, metastases, or as a side effect of cancer treatment. As a result, the World Health Organization developed the cancer pain ladder, with other guidelines developed subsequently.[6,7] Despite cancer pain guidelines, studies indicate that cancer pain in Europe remains undertreated in 56% to 69% of patients.[8]

Approximately 5% to 15% of patients with cancer develop refractory pain or suffer intolerable adverse effects from systemic analgesics and adjuvants.[9] Intrathecal therapy is one way to provide pain relief for these patients. Intrathecal drug delivery (ITDD) provides analgesics directly into the cerebrospinal fluid (CSF) through a catheter attached to an external or implantable pump. Infusion of drugs into the CSF allows direct delivery of medicines to their site of action in the dorsal horn, thus avoiding the need for medicines to cross the blood-brain barrier and allowing the drugs to evade first pass metabolism. Thus, the intrathecal route allows much lower doses of analgesia, reducing the occurrence of adverse effects[10] and enhancing the analgesic effect.

ITDD is an advanced stage intervention used in patients with cancer. Currently, only morphine, baclofen, and ziconotide are approved for ITDD by the Food and Drug Administration.[11] Intrathecal morphine, baclofen, and ziconotide are also authorized for use in Europe.[12,13] Intrathecal drug combinations are not recommended by pump manufacturers owing to the possibility of corrosion to the infusion system and device failure. However, use of off-label drugs and drug combinations is common and recommended by an international panel of experts.[11] Survival in patients with cancer pain after ITDD has been estimated as 39%, 24%, 16%, 11%, and 5% at 0.5, 1, 2, 3, and 10 years, respectively.[14]

Ziconotide is an analgesic drug licensed only for intrathecal use. It is a synthetic peptide, derived from the venom of the marine snail *Conus magus,* ω-conotoxin MVIIA. It selectively blocks the N-type voltage gated calcium channels found in the dorsal horn of the spinal cord.[15] The inhibition of these channels results in suppression of pronociceptive neurotransmitter release (including substance P), thus curbing pain signals. Ziconotide has been shown to provide effective pain relief in numerous studies, including cancer-related pain.[16–18] In the United States, intrathecal ziconotide and morphine are considered first line options for both cancer- and non–cancer-related pain.[11] Ziconotide has poor ability to cross the blood-brain barrier, hence intrathecal administration. Ziconotide is known to have a long-lasting analgesic effect, reportedly lasting hours to days in animal studies.[15]

Although intrathecal ziconotide is commonly used for the management of cancer pain in countries such as the United States and France,[19–21] its use is not routinely commissioned in England.[22] One of the considerations for not routinely commissioning ziconotide in England was uncertainty whether the use of ziconotide represented the best use of National Health Service (NHS) resources. The recommended starting dose, dose increments, and recommended intervals between dose increases in the European Medicines Agency Summary of Product Characteristics are 2.4 μg/day, ≤ 2.4 μg/day, and ≥ 48 hours, respectively.[13] However, recommendations based on recent evidence suggest a reduced starting dose (ie, 0.5–1.2 μg/d [0.02–0.05 μg/h] or initiation with ≤ 0.5 μg/day [0.02 μg/h]), smaller dose increments (ie, ≤ 0.5 μg/d [≤ 0.02 μg/h]), and a longer recommended interval between dose increases (ie, not more than once weekly).[23] These recommendations have the potential to increase the safety of ziconotide administration in addition to improving its value for money. Furthermore, the combination of ziconotide with morphine has been shown to result in statistically and clinically significant improvements in pain intensity for a population with cancer pain.[20] Recent estimates suggest that at least 8000 people with cancer pain may be eligible for ITDD in England.[24] The use of ziconotide as an adjuvant in a target population with a great need and a limited life expectancy may potentially affect the cost of the drug to the NHS. The aim of this study is to conduct a budget impact analysis to estimate the costs or savings associated with the changes in ziconotide dosage in addition to its use in combination with morphine for the management of cancer pain.

MATERIALS AND METHODS

An open, Markov-like cohort decision analytic model was developed in Microsoft Excel to estimate the budget impact of ziconotide in combination with morphine (ziconotide combination therapy) vs morphine monotherapy through ITDD for the management of chronic cancer pain. The budget impact analysis also includes a scenario considering ziconotide monotherapy. The budget impact analysis was conducted from the UK NHS perspective.

Model Structure

A Markov model is a mathematical framework to represent the movement of hypothetical patients across predefined health states. The health states represent relevant events that need to be captured in the evaluation of a condition. Hypothetical patients who reside within a specific health state will experience the events that are associated with that health state, for example, accrue costs, experience health improvement or deterioration, or acquire certain characteristics relevant for decision-making.[25] The model in this analysis consists of four mutually exclusive health states. The starting health state was "all-cancer" health state. The model is termed an open Markov-like model because it enables unrestricted entry into the starting health state as new patients are diagnosed with cancer and experience cancer pain. At the end of each cycle, patients who are eligible to receive ITDD progress to an "incident-ITDD" health state, which is a tunnel health state as all patients become prevalent cases at the next cycle (ie, move to the "prevalent-ITDD" health state). Death is an absorbing health state, as shown in Figure 1.

All patients with ITDD by definition will have an implanted device. For each model cycle, new patients requiring an ITDD (ie, patients in incident-ITDD health state) were expected to incur the

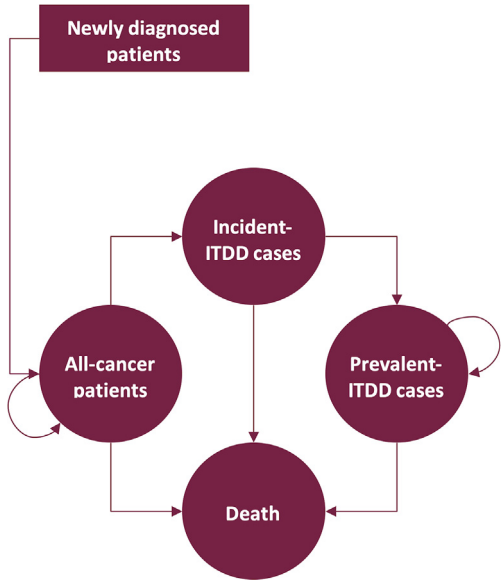

Figure 1. Model structure. [Color figure can be viewed at www.neuromodulationjournal.org]

device cost, device implantation cost, and the drug costs, whereas patients with existing ITDD (ie, patients in prevalent-ITDD health state) will only incur treatment costs (ie, refill procedure and drug costs). Therefore, it was important to distinguish patients with incident-ITDD from those with prevalent-ITDD in the model structure.

The time horizon, in line with published guidance for conducting budget impact analysis,[26] was five years. The cycle length was set to one week to allow important events such as weekly escalation of starting treatment doses or ITDD refill intervals to be captured. Costs were presented for the 2019–2020 price year. Costs were not discounted over time as recommended in National Institute for Health and Care Excellence guidelines and best practice recommendations for budget impact analysis.[27,28]

Study Population

The initial model population comprised all patients with cancer, although the subpopulation that would incur the relevant treatment costs in the analysis was those receiving ITDD. This approach was taken to differentiate incident cancer cases from prevalent cancer cases, which can be obtained from large, readily available data sets containing information about all patients with cancer but not specifically for patients with cancer with an ITDD. Consequently, the distribution of incident cases and prevalent cases in the entire cancer population can be applied to patients with ITDD. For this study and for simplicity of design, we assumed that the ratio of incident-to-prevalent patients in the entire population with cancer would be the same in the population with ITDD.

The distribution of patients with cancer into incident and prevalent cases was obtained from an assessment of the Hospital Episode Statistics (HES) data base by Duarte et al.[24] The analysis of the HES data base identified the total number of patients with cancer and the number of deaths among patients with cancer, from which the proportion of incident and prevalent cases can be estimated. Furthermore, Duarte et al present the number of patients who were potentially eligible to receive an ITDD device and the number of patients with cancer who received ITDD over a six-year period (2014–2015 to 2019–2020).

The starting population in this model was assumed to be the 727,607 patients with cancer in the UK for the 2014–2015 year. In the base-case analysis, the number of patients with cancer who received an ITDD (Supplementary Data Table S1) based on historical data was used to derive the transition probabilities for the base-case analysis (Supplementary Data Table S2). The weekly health-state transition probabilities used in the model are presented on Table 1. Because the use of ziconotide combination therapy is expected to lead to a modest increase in the use of ITDD, it was essential to capture the projected maximum cost impact of the use of ITDD with ziconotide.

Using data reported in the HES data analysis,[24] the number of incident cancer cases for a given year was estimated by considering the annual difference in the total number of patients with cancer after accounting for the number of deaths. The ratio of patients who were incident-to-prevalent in the cancer population was then applied to the population with ITDD to obtain the number of incident cases.

The following weekly probabilities/proportions were derived from the numbers directly reported in or calculated from the HES data analysis:

- Percentage increment in the number of patients with cancer: transitions from newly diagnosed to all-cancer health state
- Proportion of patients with cancer requiring ITDD and proportion of patients with ITDD with a new device: transitions from all-cancer health state to incident-case health state
- Mortality risk in patients with cancer: transition to the absorbing health state "Death" from other health states.

Resource Use and Unit Costs

Costs considered were for drug acquisition, implantation procedure, ITDD device, and refill procedure. The unit costs of drugs

Table 1. Weekly Transition Probabilities Used in the Model.

From	Newly diagnosed	All-cancer	Incident-ITDD	All-cancer, incident ITDD, and prevalent-ITDD
To	All-cancer	Incident-ITDD	Prevalent-ITDD	Death
Cycle 0	100.00000%	100.00000%	0.0000000	0.0000000
2014–2015 (year 1)	0.02389%	0.53100%	100.00000%	0.58176%
2015–2016 (year 2)	0.02389%	0.60552%	100.00000%	0.58301%
2016–2017 (year 3)	0.10058%	0.68300%	100.00000%	0.55920%
2017–2018 (year 4)	0.06118%	0.62004%	100.00000%	0.54287%
2018–2019 (year 5)	0.04527%	0.58789%	100.00000%	0.52500%

Table 2. Unit of Resources.

Resource use	Unit cost	Reference
ITDD implantation	£3,118	NHS ref cost: HRG code AB13Z
Intrathecal device	£11,000	Medtronic

were obtained from the British National Formulary[29] whereas ITDD implantation and refill procedure costs were derived from the NHS schedule of reference costs (Table 2).[30]

The starting dose of ziconotide was 0.5 μg per day, which is then increased weekly by 0.5 μg until a median dose of 3.5 μg per day is reached at week 6. Thereafter, patients continued to receive the median daily dose until death. Chemical and physical in-use stability for ziconotide alone or in combination with other drugs has been demonstrated for 14 days at 37 °C in Synchromed pumps.[31,32] As such, in the base-case analysis, it was assumed that a refill takes place every two weeks. The ziconotide dose used in the base case was informed by evidence that suggested a starting dose of 0.5 to 1.2 μg per day and dose increment of ≤ 0.5 μg per day, with an interval between dose increments that is not more than once weekly.[23] Clinical advice was that when ziconotide is being used in combination with morphine, ziconotide is considered the primary drug whereas the dose of morphine is titrated as required. Given the narrow therapeutic range of intrathecal ziconotide, in the absence of unified guidance on intrathecal morphine dosage in combination with ziconotide and for simplicity, morphine dosage and dose escalation were assumed to be equivalent to those of ziconotide. The dosages used in the model are shown in Table 3.

Based on clinical advice considering the conservative nature of UK physicians and the lack of experience with ziconotide in the UK, it was assumed in the base-case analysis that the market share of ziconotide combination therapy and morphine monotherapy/or other combinations could be 30:70 throughout the five-year time horizon. The ITDD implantation cost (£3118) was obtained from NHS reference costs.[30] These costs did not cover the cost of the device, which was assumed to be £11,000.

RESULTS

Base-case Result

A total of 109 patients entered the model as prevalent cases according to the results generated by the HES analysis.[24] Using the growth rate shown in Table 1, the total number of new patients with ITDD from the first year to fifth year is 40, 55, 64, 61, and 59, respectively (Table 4). Ziconotide combination therapy was more expensive than treatment with morphine monotherapy. The total costs of ziconotide combination therapy and morphine monotherapy for the first year were £395,748 and £136,628 respectively.

The estimated five-year cumulative budget impact of treatment with ziconotide combination therapy for the five-year time horizon was £2,487,539 whereas that of morphine monotherapy was £913,804. A significant proportion of the cost difference was due to the higher drug cost of ziconotide.

A scenario was conducted whereby ziconotide monotherapy was considered. The associated year 1 (£374,577), year 2 (£466,845), year 3 (£489,905), year 4 (£506,456), to year 5 (£517,892) costs were lower than the equivalent cost of ziconotide combination therapy but expectedly higher than the costs of morphine monotherapy.

Deterministic Sensitivity Analysis

The five-year cumulative deterministic results are shown in Table 5. The results show that cumulative cost was most sensitive to an increase in the refill interval from two weeks to one month, the use of a more expensive vial of ziconotide and morphine, and the possibility of vial sharing.

Of note, no overhead cost for ITDD pump refill was incurred in the base-case analysis. A sensitivity analysis was conducted using alternative ITDD refill overhead costs. The first estimate was obtained from a previous cost-effectiveness study of intrathecal drug therapy in the Canadian health system.[33] The unit cost in that study ($120 Canadian) was subsequently used in a Canadian health technology assessment of ITDD systems.[34] It was therefore considered that using the inflation-[35,36] and currency-adjusted[37] value (£91.98) was appropriate. A second estimate that reflects the current NHS refill cost (£671) as detailed in the NHS reference costs was used. These two overhead cost estimates did not significantly change the base-case results (Table 5).

DISCUSSION

We provide a budget impact analysis from the NHS perspective over a five-year time horizon that reflects a patient population with cancer pain in England. 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.[38] The results were robust to sensitivity analyses, with only the use of a more expensive vial of ziconotide (5 ml vial at a unit cost of £1086.94) resulting in a budget impact superior to £1 million per year. A lighter burden on health care resources would occur if vial sharing was a possibility. Vial sharing would require several patients to be scheduled to have a refill on the same day, which may not always be feasible if a center has a small number of patients receiving ziconotide. A large center in France that provides ziconotide and averages 256 refills per month estimated savings of €68,411 during the year 2021 by sharing ziconotide vials.[39]

Table 3. Treatment Dosage and Unit Cost of Drugs Used in the Model.

Drug name	Dosage	Quantity per unit	Units per pack	Cost per pack	Source
Ziconotide	0.5 μg/d on day 1, then 0.5 μg weekly increment until 3.5 μg/d	100 μg/ml	1 ml vial	£302.48	BNF[29]
Ziconotide	Pump rinse at ITDD implantation with 3 syringes containing 2 ml	25 μg/ml	2 ml vial	£75.62	BNF[29]
Morphine	0.5 mg/d on day 1, then 0.5 mg daily increment until 2.5 mg/d	40 mg/ml	1 ml vial	£9.60	BNF[29]

BNF, British National Formulary.

Table 4. Budget Impact of Ziconitide Combination Therapy vs Morphine Monotherapy.

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Mean number of patients/wk	146	175	181	189	195
Total number of new patients/y	40	55	64	61	59
ITDD placement					
Ziconotide with morphine*	£44,906	£59,922	£69,564	£66,083	£64,671
Morphine monotherapy	£87,767	£119,623	£140,080	£132,696	£129,699
ITDD refills					
Ziconotide with morphine	£350,842	£433,088	£447,414	£468,697	£482,352
Morphine monotherapy	£48,861	£60,316	£62,311	£65,275	£67,177
Total cost					
Ziconotide with morphine	£395,748	£493,009	£516,978	£534,780	£547,023
Morphine monotherapy	£136,628	£179,939	£202,391	£197,971	£196,875

*ITDD placement cost includes the cost of rinsing device with ziconotide in the ziconotide with morphine model arm.

A limited number of expert centers currently provide ITDD for cancer pain in England, which is largely due to a limited number of practitioners in addition to operating room access constraints. Additional reasons for limited access to this intervention include the interface required between a number of specialties, making treatment delivery complex and only possible in large centers, the patient referral system that stipulates referrals from networked secondary care pain services or other tertiary specialties, and the lack of licensed ITDD-compatible therapeutic alternatives to morphine.[24] A recent study reported on the feasibility of conducting pump refills at the patient's home, with 95% of patients and physicians/nurses feeling safe during the procedure.[40] The possibility of pump refills at the patient's home may improve access to ITDD, particularly in a population with cancer pain who often present with advanced ill health due to cancer and other comorbidities, limiting their ability to travel to bigger centers for implantation/pump refills and subsequent care.

Recent systematic reviews with meta-analysis have shown that ITDD is an effective and safe intervention for the management of cancer pain, with statistically and clinically significant reductions in pain intensity observed.[41,42] Improvements in quality of life were observed in the included studies that evaluated this outcome. Several studies in the systematic reviews included patients who received a combination of ziconotide with morphine.[20,21,43–46] A meta-analysis focused solely on patients who received ziconotide with morphine was not possible because the studies only provided aggregate data and results were not available for those specific patients alone. However, all studies reported significant pain relief in patients with cancer pain after ITDD.

Many patients with cancer pain who present for ITDD are already receiving high doses of oral and systemic opioids, rendering them refractory to intrathecal opioids alone. Candidates for ITDD and clinicians are presented with very few evidence-based therapy options. Celiac plexus neurolysis, an intervention commonly practiced in pancreatic cancer, was found to be associated with worsened survival compared with treatment with opioids (adjusted hazard ratio 1.69; 95% CI, 1.59–1.79).[47] Other drugs may be combined with opioids to improve efficacy of ITDD, such as local anesthetics and alpha-2 agonists.[48] These, however, are not approved for use in the ITDD device, and have limited evidence of efficacy and several limitations including cardiovascular side effects and the need for precise catheter tip placement. Besides morphine, ziconotide is currently the only other intrathecal analgesic drug approved for management of cancer pain with ITDD.[11] Although

Table 5. Sensitivity Analysis Results.

Scenario	Ziconotide combination therapy	Ziconotide monotherapy	Morphine monotherapy
Base case	£2,487,539	£2,355,674	£913,804
Overhead cost of refilling pump (£92)*	£2,494,685	£2,362,821	£930,479
Overhead cost of refilling pump (£671)**	£2,539,657	£2,407,793	£1,035,414
Refill interval (1 mo)	£1,419,908	£1,320,659	£835,831
Ziconotide vial size (5 ml)	£7,921,044	£7,789,180	£913,804
Morphine conc. (2 mg/ ml)	£3,468,279	£2,355,674	£3,173,744
Relative dose intensity (80%)	£2,421,606	£2,355,674	£761,834
Relative dose intensity (90%)	£2,487,539	£2,355,674	£913,804
Include vial sharing (Yes)	£1,376,962	£1,296,195	£795,073
Set median survival (3 y)	£2,760,932	£2,614,504	£1,016,171
Set median survival (5 y)	£3,239,853	£3,067,915	£1,195,525
Set median survival (10 y)	£3,686,785	£3,491,041	£1,362,931

conc., concentration.
*Inflation- and currency-adjusted value obtained from a previous cost-effectiveness study.
**Value obtained from the NHS reference cost (health-resource group code DEV18).

ziconotide monotherapy is licensed for use in the pump, a combination of ziconotide and morphine will not be recommended by the manufacturer of the ITDD devices. However, its track record in cancer pain treatment is far superior to either drug in isolation, hence our preference for costing the unlicensed combination vs ziconotide monotherapy. Ziconotide monotherapy or in combination with morphine is recommended by an expert consensus as first- or second-line ITDD treatment options, respectively, for cancer pain.[11]

This study considered several scenario analyses to explore the robustness of the results to variations in the parameters of the model. As recommended by a task force on good practices for budget impact analysis, we used the simplest design to generate credible and transparent estimates.[28] Budget impact analyses, although informative of the impact of implementation of a new treatment in terms of costs to health care systems, do not account for potential improvements in pain control on a population of patients at a critical stage of life and ways this may affect additional resource use consumption, such as cost savings obtained from avoidance of hospital and/or hospice admission near end of life.[49] Furthermore, the budget impact analysis does not account for potential improvements in survival. A randomized controlled trial (RCT) observed a cumulative survival of 53.9% at six months for patients with morphine ITDD compared with 37.2% for patients receiving conventional medical management ($p < 0.06$).[50] The results of this RCT are quite historical and may not reflect current oncologic practices or patient survival; however, they still represent the only comparative RCT evidence for this specific population. We have also not considered the potential economic impact of the adverse events resulting from the addition of ziconotide to opioids in a population with multiple comorbidities because this can only be elucidated from clinical practice within a UK setting, which is currently not feasible.

CONCLUSIONS

The results of this budget impact analysis suggest that although a combination of intrathecal ziconotide in combination with morphine is associated with higher costs to the health care system in England, the incremental costs are not significant. The benefits and consequences of intrathecal ziconotide in combination with morphine should be considered in a full economic evaluation to estimate the cost-effectiveness of this intervention compared with morphine alone in a population with cancer pain.

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Authorship Statements

Rui Duarte and Sam Eldabe conceptualized the study. Tosin Lambe developed the budget impact model, with support from Rui Duarte. Tosin Lambe, Rui Duarte, and Sam Eldabe interpreted the data. Tosin Lambe, Rui Duarte, and Rosie Eldabe wrote the first draft of the manuscript. All authors contributed to and approved the final version of the manuscript.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2022.08.458.

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COMMENTS

This is quite an interesting article as an American. It's actually nice to see international collegial activity in regard to chronic pain. I believe the British community will benefit from this analysis.

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Ziconotide will be a useful drug for treating cancer pain even if it needs more studies to show an adequate evidence.

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