REVIEW

Neuromodulation techniques for cancer pain management

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Purpose of review
Advanced pain management techniques may be indicated in 5–15% of cancer patients. Despite this, a recent review identified that, over the course of 1 year in England, only 458 patients received a procedure intended to provide analgesia and only 30 patients had intrathecal drug delivery (ITDD) devices implanted. This article describes the emerging evidence for ITDD in cancer pain and provides a narrative review of other neuromodulatory techniques (including spinal cord stimulation, peripheral nerve stimulation and acupuncture), approaches that might be employed to address this area of significant unmet clinical need.

Recent findings
Numerous studies have been published within the last year reporting positive outcomes associated with ITDD in cancer pain management. Neuromodulation represents an important strategy in the management of persistent pain. Whilst the nonmalignant pain evidence-base is rapidly growing, it remains sparse for cancer pain management. The growing cohort of cancer survivors may significantly benefit from neuromodulatory techniques.

Summary
ITDD and other neuromodulatory techniques for cancer pain management appear underutilised in the UK and offer the prospect of better treatment for cancer patients with refractory pain or intolerable side-effects from systemic analgesics.

Keywords
cancer, intrathecal drug delivery, neuromodulation, pain

INTRODUCTION

Advances in cancer diagnosis and treatment have resulted in increasing numbers of cancer survivors. Those living with and beyond cancer often develop a number of pain states with varied phenotypes [1] and pain is a major area of unmet clinical need in this population [2]. The challenge of managing cancer pain has been recognised for decades; in 1986 the World Health Organization (WHO) published specific guidelines. Central to the suggested approach was the pharmacotherapeutic 'step-ladder', which, whilst simple and highly successful [3], does not fully address the complexity of cancer pain [4]. Additionally, potentially harmful practice may result, in particular a reliance on the use of opioids, a situation that has permeated the management of nonmalignant pain alongside acute cancer pain and end-of-life pain [5]. Oral opioid analgesia is associated with a number of adverse effects, which, whilst justifiable in acute pain management and palliative care, limit its deployment in chronic cancer pain management [4].

It is imperative, therefore, to explore opioid-sparing strategies to manage more persistent pain in cancer patients. The shift from opioid based management of chronic nonmalignant pain is well established and neuromodulation rather than systemic analgesia is arguably a cornerstone of modern pain management. Defined as 'the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites of the body'

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KEY POINTS

- Advanced interventional analgesic techniques may benefit 5–15% of those with cancer.
- Data published last year suggest that there is a significant unmet clinical need for such techniques for cancer patients in England.
- Increasing data is being published regarding the efficacy and safety of ITDD systems.
- The body of evidence for neuromodulation in cancer pain management remains light.
- Ongoing prospective data collection using validated PROMs are integral to providing large-scale data to help guide information provided to patients and clinical decision making.

[6], neuromodulation can be effective in a wide variety of chronic pain conditions [7] and a growing body of evidence supports its use in cancer-related pain.

The prevalence of cancer pain is approximately 40–60%, with over a third of subjects experiencing moderate to severe pain [1]. A pan-European survey conducted over a decade ago indicated that 41% of those with at least moderate intensity cancer pain took strong opioid analgesia [8]. NHS England estimates that approximately 5–15% of cancer patients have pain refractory to pharmacological management and require advanced pain management techniques [9]. A recent analysis estimated that this represents approximately 15,000 patients per year, approximately half of whom might be suitable for intrathecal drug delivery (ITDD) [10▪▪]. Between April 2018 and March 2019, in England, 458 cancer patients underwent a pain management procedure and 30 patients received ITDD [10▪▪]. Although focusing on the substantial gap between the need and provision of ITDD in England, these figures reflect more broadly the sizeable population of cancer patients with refractory pain who may potentially benefit from advanced analgesic techniques. Conducting high-quality trials in this area is challenging due to ethical issues surrounding the use of placebo (or other controls), blinding and randomisation in those with refractory pain impacting on quality of life; and the practical challenges of long-term enrolment and follow-up in this population. It is plausible that the absence of robust evidence contributes to the underuse of these techniques. With a well-defined landscape of unmet clinical need and a small but growing number of supportive studies, it is imperative to review emerging data frequently. A recent publication has comprehensively detailed the evidence surrounding neurosurgical ablative procedures in cancer pain management, including myelotomy, cordotomy, dorsal root ganglion entry zone lesioning (DREZotomy), thalamotomy and cingulotomy [11]. This narrative review consequently aims to present the current and evolving literature for additional advanced analgesic techniques including ITDD and other neuromodulatory approaches in cancer patients. A brief overview of acupuncture that arguably should be considered alongside other neuromodulation techniques is provided. Whilst not an 'advanced' intervention, acupuncture is ideally positioned to play a key role in addressing the substantial shortfall between clinical need and service delivery. Figure 1 represents a schematic of the sites of the interventions detailed within this article.

INTRATHECAL DRUG DELIVERY

NHS England supports the routine commissioning of ITDD for the treatment of severe cancer pain [9]. This policy, published in 2015, identified one systematic review of clinical effectiveness and safety [12], comprising one randomised controlled trial (RCT) and four observational studies. The multicentre RCT analysed 200 patients with refractory cancer pain despite at least 200 mg oral morphine equivalent (OME) opioid use, and compared comprehensive medical management (CMM) to ITDD and CMM [13]. The addition of ITDD to CMM was associated with a significant reduction in toxicity scores ($P = 0.004$), a nonsignificant reduction in pain scores ($P = 0.055$), reduced median systemic opioid use (statistical significance not discussed), and, perhaps most surprisingly, increased 6-month survival (53.9% vs. 37.2%) although this was not statistically significant ($P = 0.06$). Serious adverse events were evenly distributed between the two groups, although 14 of the 99 complications in the ITDD group were related to the 'implanted pump or related procedure' [13]. The four observational studies included a total of 250 patients receiving intrathecal morphine therapy alone and reported a number of positive outcomes [14–17].

These studies highlight two cohorts of patients who may benefit from ITDD: those with inadequate pain management despite high or escalating doses of opioids; and those experiencing intolerable opioid dose-related adverse effects. Although costs of device insertion are initially high, it is reported that these attenuate over time. A recent study matching 73 pairs of patients reported that ITDD therapy saved $3195 per patient at 1 year and became cost effective at two months [18]. A recent review has

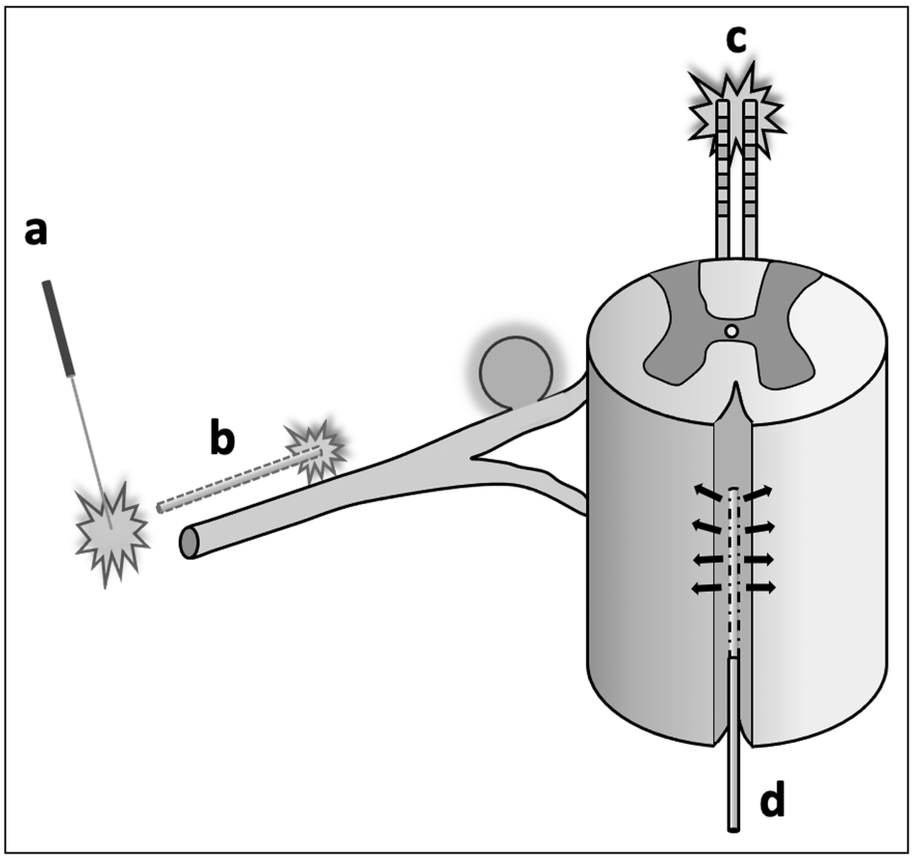

FIGURE 1. A schematic representing the anatomical sites of action of interventions detailed throughout this publication. (a) Acupuncture, (b) Peripheral nerve stimulation, (c) Epidural spinal cord stimulation and (d) Intrathecal drug delivery (Nb shown ventrally for illustrative purposes but normally dorsally placed).

effectively detailed advances in understanding of cerebrospinal fluid drug diffusion, drug management and technical features [19]. The remainder of this section will focus on summarising efficacy-relevant clinical studies or safety data published within the last year.

Recent retrospective studies

One study of ITDD morphine therapy ($n = 43$) reported a significant reduction ($P < 0.001$) in median pain scores [20] with complications related to insertion limited to two postdural puncture headaches. Estimated cost equivalence was achieved at 2.89 months in those taking higher doses of opioids, but as long as 28.83 months in others [20]. A retrospective review of a variety of different intrathecal drug therapies ($n = 173$), reported reductions from median daily OME of 240 mg (interquartile range [IQR] 130–390 mg) to 0 mg (IQR 0–0 mg, $P < 0.0001$) following ITDD [21]. Another ($n = 50$), used a combination of bupivacaine with morphine or hydromorphone, reporting a gradual decline in mean Visual Analog Scale (VAS) pain scores from 6.6 pre-procedure to 3.4 after 6 months (statistical significance not reported) and reduction in median daily OME from 503 mg (range 35–5560 mg) to 105 mg (range 0–2880 mg) [22]. Additionally, it is reported that, despite 79.3% ($n = 217$) receiving at least one anticancer therapy within 30 days prior to ITDD device implantation, only 2 patients developed a surgical site infection within 6 months of implant, representing an overall infection rate of 0.9% (95% CI, 0.1–3.3%) [23].

Recent prospective studies

A prospective study of combination intrathecal therapy (morphine, ziconotide and levobupivacaine) in patients with cancer-related refractory pain ($n = 60$) reported a significant reduction in mean visual analogue scale of pain intensity (VAPSI) from 88 ± 6 to 49 ± 17 mm ($P < 0.001$) two days after starting ITDD therapy [24]. This reduction persisted at 56 days (mean VASPI 44 ± 9, $P < 0.001$) and all patients stopped regular oral opioids and

gabapentinoids [24]. Another prospective study ($n = 51$) of ITDD therapy with morphine or hydromorphine, reported that 92% of patients (median OME 240 mg, IQR 150–405 mg) had discontinued all nonintrathecal opioids at two months [25]. There were no infectious complications reported but two patients developed postdural puncture headaches [25]. Another prospective study of 33 patients receiving morphine ITDD reported significant improvement in mean pain scores, Karnofsky performance scores (KPS), self-rating anxiety and depression scale scores at 1 year follow-up ($P < 0.001$) [26]. No serious adverse events were observed in this study [26].

Recent randomised controlled trials

One randomised controlled, multicentre, single-blinded noninferiority trial published in 2020, enrolled 233 patients with intolerable side effects or unsatisfactory analgesia despite greater than 200 mg OME daily [27]. The study compared hydromorphone with morphine ITDD, reporting noninferior 'clinical success rates' (>50% pain relief) in both groups. Multiple secondary outcome measures did not demonstrate any significant differences, but the authors reported significantly less change in ITDD dose from baseline and patient controlled boluses were required in the hydromorphone group [27].

Additional significant publications in 2020

Finally, a prospective, long-term, multicentre registry published data of 1403 patients receiving ITDD for cancer pain [28▪▪]. Although the registry was established in 2003, pain numerical rating scales (NRS) were not incorporated until 2010 and other patient-reported outcome measures (PROMs) added in 2013. Of the 283 patients for whom baseline pain scores were available, mean preinsertion NRS pain scores were 6.8 (SD 2.4). Data were available for fewer patients at later time points but significant reductions in pain scores were reported at 6 months (NRS 5.5, SD 2.6, $n = 103$, $P = 0.0007$) and 12 months (NRS 5.4, SD 2.5, $n = 55$, $P = 0.0026$). A significant improvement in the quality of life was observed at 6 months but the increase was not statistically significant at 12 months. In 1403 patients, infections requiring surgical intervention were reported in 3.2% of patients. In total two deaths were possibly associated with ITDD therapy: one postoperative pneumonia following device implantation and one pulmonary embolus possibly attributed to drug withdrawal as a result of missed pump refill [28▪▪].

SPINAL CORD STIMULATION

Spinal cord stimulation (SCS) is an established treatment for persistent pain, particularly that which meets the definition of localised neuropathic pain with surgically refractory spinal pain and complex regional pain syndromes being the most common indications. Stimulation of the dorsal columns of the spinal cord via electrodes in the epidural space is thought to modulate neuronal function and reverse both the neuronal hyperactivity and maladaptive changes that occur in persistent pain states, consequently resulting in analgesia. More recently, non-paraesthesia SCS modalities such as high frequency (e.g. 10,000 Hz) have been introduced. Benefits include improved tolerability compared to 'conventional' (60–200 Hz) SCS due to the absence of paraesthesia. The exact mechanisms by which non-paraesthesia SCS lead to analgesia remain unclear but they are thought to differ from conventional SCS. Postulated mechanisms include decreases in central sensitisation and hyperpolarisation of superficial dorsal horn neurons, suggesting segmental mechanisms that diverge from the 'gate control' mechanisms that are thought to underpin conventional SCS [29], alongside increased activation of medial, affective pathways of the pain brain neuromatrix [30].

Chemotherapy induced peripheral neuropathy (CIPN) is a common and disabling consequence of oncological treatment which often proves refractory to conventional pharmacological management. For painful diabetic peripheral neuropathy, a phenotypically comparable condition, significant reductions in pain scores and improvements in quality of life have been demonstrated with SCS [31]. In contrast, the evidence for SCS in CIPN is limited to case reports and pain behaviour changes in animal models [32–34]. The case reports include neuropathy caused by a number of different agents, which, whilst of interest do not yet provide a particularly robust justification for its use in this condition. Further work to better delineate those patients most likely to benefit from this treatment is required.

Another persistent pain state commonly experienced by cancer patients is persistent postsurgical pain (PPSP), which often has well localised, neuropathic features. SCS is well suited to help manage treatment-refractory PPSP and a number of observational studies have included patients with PPSP affecting a range of anatomical locations including the trunk and lower limbs [35].

Whilst attractive conceptually and showing early promise in observational studies, the evidence base for SCS in the management of cancer pain is limited. A systematic review, published in 2015, was only able to identify four case series and no

randomised studies for inclusion [36]. These four case-series, identified a total of 92 participants with cancer-related pain. Despite various outcome measures utilised, all reported an analgesic benefit associated with SCS. Two studies reported mean VAS scores were reduced 12 months post implantation from 7.07 to 1.867 ($n = 15$) and 7.43 to 2.07 ($n = 14$) respectively [37,38]. The two remaining studies reported that 48 out of 63 individuals with cancer-related pain achieved at least a 50% reduction in pain intensity (reported using VAS) with SCS [39,40]. A Cochrane review in 2015 concluded that the existing evidence base was insufficient to establish the role of SCS in persistent and cancer pain [36]. A literature review published in 2020 presented no evidence of a level exceeding case reports published since 2015 and, therefore, this conclusion still stands [41▪]. The need for systematic research is all the more important.

PERIPHERAL NERVE STIMULATION

Peripheral nerve stimulation (PNS) is a technique whose clinical use is rapidly increasing thanks to advances in available equipment. It is indicated in cases where SCS is contraindicated or where a distinct anatomical area of pain more suited to PNS exists. A small electrode bearing lead is inserted subcutaneously in close proximity to a peripheral nerve and can be connected to a small implantable pulse generator. As its name suggests, PNS works in a fashion analogous both to acupuncture and transcutaneous electrical nerve stimulation to modulate neuronal activity with evidence that peripheral stimulation may modulate the function of central neuronal circuits [42].

A recent systematic review of the use of PNS identified 14 RCTs, and concluded that PNS is safe and relatively effective for the treatment of a variety of persistent pain states [43]. This systematic review does not clearly identify any studies specifically exploring cancer-related pain. However, one of the studies was a randomized, double-blind, partial crossover study investigating the use of PNS in posttraumatic or postsurgical neuralgia [44], relevant to cancer patients given the prevalence of PPSP in this population. This study reports numerous positive outcomes associated with the intervention including a mean pain reduction of 27.2% after 3 months, higher reported satisfaction and quality of life. Additionally, it reports no serious adverse events related to the intervention [44].

Application to cancer pain is a relatively nascent field and the evidence base for PNS in cancer pain is light, with the majority of publications being retrospective case reports and case series. One such series has been published which reports positive outcomes in 7 out of 12 oncology patients with pain that had not been managed adequately with other medical and interventional techniques [45]. In these 7 patients, mean pain scores were reduced from 9.0 (SD 1.0) to 3.1 (SD 1.6) following extraction of devices 60 days after insertion. Interestingly, analgesic benefits were reported to last many months beyond removal of PNS devices [45].

ACUPUNCTURE

Acupuncture may predate the therapeutic use of electrical stimulation [46] yet, by contrast, acupuncture is commonly classified (often with associated scepticism) as a 'complementary' therapy [47]. Arguably, however, acupuncture should be considered a form of neuromodulation: research since the 1950s has established various mechanisms which affect the activity of peripheral nerve terminals, input and descending inhibition within the spinal cord and the activity of higher centres within the brain [48,49]. Whilst the neurobiology is by no means clear, this is no more the case for acupuncture than for other forms of neuromodulation [50].

Clinically, there is evidence for the use of acupuncture in the management of cancer pain. A randomised-controlled trial of electro-acupuncture using thoracic paravertebral needles in 60 patients with pancreatic cancer reported a significant ($P < 0.001$) difference in NRS pain scores in the acupuncture group (−1.67, 95% CI −1.46 to −1.87) compared to sham-acupuncture placebo (−0.37, 0.08 to −0.35) [51]. A recent systematic review and meta-analysis of six sham-controlled randomised trials ($n = 398$) reported a similar effect size (−1.38, 95% CI −2.13 to −0.64) with moderate certainty. Meta-analysis of two included studies that reported analgesic dose ($n = 106$) derived a mean OME reduction of 30 (95% CI 22.5–37.5) mg [52].

Another recent systematic review [53] identified 19 randomised-controlled trials investigating the use of acupuncture for the management of CIPN. Whilst the quality of evidence was limited, with high risk of bias associated with blinding, the authors concluded that acupuncture increased the 'effective rate' of treatment compared to sham acupuncture or pharmacotherapy. Moreover, four studies included nerve conduction velocity outcomes and pooled analysis suggested a significant improvement in patients receiving acupuncture compared with controls. Four studies included pain scores, albeit using different measures (VAS, NRS, Brief Pain Inventory). Pooled ($n = 162$), these show a significantly lower 'pain score' (mean difference −1.64, 95% CI −1.58 to −1.71, $P < 0.00001$) in patients

receiving acupuncture compared to controls but with very high heterogeneity ($I^2 = 99\%$) and heavily weighted (80.3%) towards a single study [54].

Beyond pain control, acupuncture has a wide range of effects that may benefit people living with and beyond cancer. Notably, it has been shown to be an effective treatment for cancer-related fatigue [55,56], breathlessness [57] and, more generally, for anxiety, mood and sleep disturbance [56,58,59], aromatase inhibitor-induced arthralgia [60,61] and vasomotor symptoms associated with hormonal therapy [62,63]. Whilst the quality of evidence for these is variable, with rare and rarely severe adverse effects and low resource costs, acupuncture is a valuable component of comprehensive cancer pain and symptom management. In addition, in our practice acupuncture patients attend weekly for 6 weeks in the initial 'induction' phase of treatment and this provides an excellent opportunity to develop a deeper understanding and therapeutic relationship with patients, affording an insight into their psychology which is recognised to be an important factor in the success of more invasive and more expensive neuromodulation interventions [64,65].

CONCLUSION

It has long been accepted that advanced interventional techniques may significantly benefit a well-circumscribed population of patients with treatment refractory cancer-related pain. A recent publication has highlighted that only a small proportion (1.7–5.0%) of these candidates ever receive any such interventional procedure [10▪▪], meaning that over 95% of these patients with cancer experience moderate and severe pain, potentially during the last few months of their lives. This review highlights a growing body of evidence for the efficacy and safety profile of a number of neuromodulatory approaches in cancer pain. Whilst the evidence for spinal cord and peripheral nerve stimulation in cancer pain management remains limited, evidence for its use in nonmalignant pain suggests a potential role in the management of chronic cancer-related pain, particularly in the growing population of cancer survivors.

NHS England stipulate collection of 10 outcome measures within the commissioning framework for ITDD and submission of data to the National Neuromodulation Registry [9]. The use of these outcome measures is critical for ongoing evaluation of services and interventions, particularly those which are undertaken with limited frequency. The value of registry-based datasets is evident [28▪▪] and will play an important role in guiding clinical decisions and patient choices in the future.

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Conflicts of interest

M.R.D.B. has undertaken paid consulting work for Sativa Wellness Group, Spectrum Therapeutics and Medtronic. The rest of the authors do not have any conflicts of interest.

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