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Multidimensional Treatment of Cancer Pain

Weiyang Christopher Liu[1] · **Zhong Xi Zheng**[2] · **Kian Hian Tan**[1] · **Gregory J. Meredith**[1]

Abstract
Purpose of review Though numerous treatment options are available to address cancer pain, inadequate management continues to be an ongoing problem worldwide.
Recent findings A systematic review of the recent scientific literature was conducted with attention to new therapies along with reports of general consensus that were analyzed.
Summary Pain research continues to be difficult and though numerous guidelines have been developed, adequate powered studies are not common. Good practice would suggest a comprehensive approach to cancer pain management taking into account the many options available and treating each patient with a personalized therapeutic program. Though there is a very low number of randomized control trials, this probably reflects the difficulty in conducting these studies in heterogeneous cancer pain patient populations in sufficient numbers to yield credible study power.

Keywords Cancer pain · Oncologic pain · Multidisciplinary pain management · Persistent post-surgical pain · Cancer pain assessment · Cancer pain survivors

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✉ Gregory J. Meredith
gregory.meredith@singhealth.com.sg

Weiyang Christopher Liu
christopher.liu.w.y@singhealth.com.sg

Zhong Xi Zheng
zhongxi.zheng@mohh.com.sg

Kian Hian Tan
tan.kian.hian@singhealth.com.sg

[1] Pain Management Centre, Department of Anaesthesiology, Singapore General Hospital, Outram Road, Singapore 169608, Singapore

[2] Ministry of Health Holdings Pte Ltd, 1 Maritime Square, #11-25 Harbour Front Centre, Singapore 099253, Singapore

Introduction

Worldwide, more than 10 million people are diagnosed with cancer each year, and nearly half of these patients will suffer from poorly controlled pain [1, 2••]. Suboptimal pain management negatively impacts the lives of these patients, reducing their quality of life, physical functioning, and contribute to psychological distress. Furthermore, it is estimated that half of the cancer population believes that their healthcare provider did not consider their quality of life a priority [3].

A systematic review published in 2016 analyzed the literature from 2005 to 2014 and found that the prevalence of cancer pain was 39.3% after curative treatment, 55% during anti-neoplastic treatment, and 66.4% in advanced cancer [2••]. Interestingly, the results of this study were not much different from an earlier work performed a decade ago [4]. This is rather disappointing given the significant advances in our understanding of cancer pain pathophysiology, increased global attention to cancer pain, and increased opioid consumption and the availability of new medications [2••, 5]. A partial explanation might be the larger numbers of cancer survivors with residual pain and improvements in pain assessment including increased patient's willingness to report pain.

An overview of the recent literature discussing the assessment and treatment options of cancer pain along with non-pharmacologic approaches is presented in this review.

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Assessment of Cancer Pain

Comprehensive pain assessment should note the pain location, characteristics, mechanisms, expression, and function, including assessment of the psychosocial factors and the current analgesic treatment. Such an assessment will allow the physician to determine the sources of pain, taking into account psychosocial factors, quality of life, and functional status [6, 7•]. A reasonable, individualized management plan can then be formed to treat the pain with the appropriate analgesics, setting the treatment goals.

Pain intensity should be regularly assessed to determine the severity of the pain as well as to monitor responses to analgesic treatment. Unidimensional scales such as the visual analog score (VAS), verbal rating scale (VRS), or numerical rating scale (NRS) are the most commonly employed measurements in clinical practice. The use of these tools are also supported by recent guidelines [8]. By themselves, the use of these measurements might be insufficient in that cancer pain is a multidimensional experience [9].

Multidimensional instruments such as the Brief Pain Inventory (BPI) and the McGill Pain Questionnaire (MPQ) are able to overcome some of the limitations of unidimensional pain scores [1, 9], but are time-consuming and are not practical when frequent assessments are required. It might be more practical to employ the MPQ or BPI during the initial consultation and a unidimensional score on follow-up assessments. Additional functional and psychological assessments are helpful to determine if treatment goals have been reached.

Breakthrough pain (BTP) is defined as transient episodes of severe pain causing increased functional impairment, psychological distress, and decreased quality of life [10]. These also are associated with higher healthcare costs, hospital admissions, and longer inpatient stays [11, 12•, 13, 14]. Breakthrough pain may be assessed with the algorithm proposed by Davis et al. [15].

Specific BTP measurements have recently been developed including the Alberta Breakthrough Pain Assessment Tool (ABPAT) and the Breakthrough Pain Assessment Tool (BPAT) [16, 17]. These methods show potential to be used for clinical and teaching purposes, but at present, neither has been adequately validated for clinical use [10, 17–18].

Pain assessment research has been conducted in the fields of cancer pain pathophysiology, pain genetics, computer-based assessment tools, and quantitative electrophysiological techniques [19]. It is hoped that as these assessment measures develop, better, individualized treatment plans could be formulated.

Principles of Cancer Pain Treatment

Many authors hold that a comprehensive and holistic approach to the treatment of cancer pain is a standard of care [20, 21]. This would include pharmacologic as well as non-pharmacologic modalities [22, 23]. Numerous methods of controlling cancer pain have been described with varying degrees of success.

Treatment methods are broadly divided into pharmacologic and non-pharmacologic. Modalities that are non-pharmacologic encompass interventional procedures, physiotherapy, occupational therapy, and treatment by behavioral medicine specialists. Pain procedures by the surgical and interventional radiology teams can be helpful in selected patients.

Additional options that have varying degrees of scientific support include acupuncture [24, 25], massage [26, 27], and music therapy [28]. Finally, noted by many authorities, patient education is essential for adequate care, but is often overlooked [29•, 30, 31].

Non-pharmacological Approaches to Pain

Behavioral Medicine Treatment Options

The biopsychosocial model acknowledges that a person's pain experience is affected not only by the degree of tissue injury, but also by psychological and social factors [32]. This model is supported by numerous studies that have demonstrated the relationship between cancer pain and psychosocial factors. For example, persistent post-mastectomy pain was found to be associated with anxiety, depression, catastrophizing, and somatization [33, 34]. Increased cancer pain has also been linked with lower levels of social support and avoidant attachment styles [35–37]. However, as these studies are largely cross-sectional in nature, it is difficult to ascertain that the pain caused the psychosocial problems or vice versa.

As a result of the close association between psychosocial problems and cancer pain, a broad variety of treatments has been developed to target the psychological processes thought to be exacerbating pain and distress [38]. These treatments include education, cognitive-behavioral therapy (CBT), stress management, relaxation training, education, hypnosis, and other experimental techniques. The effects of these psychosocial interventions on cancer pain were analyzed in a systematic review by Sheinfeld Gorin et al. Data from 37 papers were pooled and found that psychosocial interventions had a moderate effect on pain severity (weighted average effect size of 0.34), concluding that there is a role for the use of psychosocial intervention as part of a multimodal approach to cancer pain management [39].

The effective management of cancer pain is largely dependent on pharmacotherapy. Barriers to effective pain control must be identified. These might include inadequate reporting of pain, fear of the consequences of pain such as disease progression, and fear of analgesic usage especially opioids. This may result in non-adherence to medications and therefore, inadequate pain management [40, 41]. Educational interventions have been used in an attempt to improve these barriers. Unfortunately, the last systematic review looking at these interventions was performed in 2009. This report found that compared to usual care or control, educational interventions improved average pain intensity by a mean of 1.1 points (over an 11-point rating scale) and maximal pain intensity by a mean of 0.78 points [42].

Cognitive behavioral therapy (CBT) refers to a broad range of treatments that aim to address maladaptive thinking, resulting in an improvement in mood and behavior [43]. Although this technique was first described for depression, its application has now expanded to other disorders such as anxiety, schizophrenia, eating disorders, and chronic pain. In a systematic review, the authors pooled the results of 20 studies that used CBT for the treatment of pain arising from breast cancer. They found that CBT is an effective technique for reducing pain, with an effect size of 0.49 [44].

Hypnosis has been used to provide palliation of cancer pain for over 200 years. This therapy involves inviting the patient to focus on his awareness and use his imagination to experience beneficial changes in symptoms and emotional responses [45•, 46]. There have been multiple RCTs studying the efficacy of hypnotherapy in a variety of situations. Hypnotherapy has been demonstrated to reduce anxiety and pain during diagnostic procedures, cancer treatment such as percutaneous treatment of tumors as well as in reducing pain in patients with advanced breast cancer [47–49]. In a recent systematic review, looking at the efficacy of hypnosis in breast cancer care, it was noted that hypnosis is beneficial in reducing cancer pain and was not associated with increased adverse effects. It should be noted, however, that the primary limitation of this paper is the small number of RCTs that were included [50].

Relaxation with imagery and meditation training has also been used for the management of cancer pain. In this training, the patient is taught to focus on letting go of muscle tension through the use of imagery and suggestions for shift in pain perception. The evidence behind relaxation therapy is sparse. Small RCTs have been performed, demonstrating a statistically significant but clinically insignificant (1.16 decrease in pain score measured by an 11-point numeral rating score) improvement in pain score [51].

Taken together, psychosocial interventions may be helpful, when they are used in conjunction with conventional pharmacotherapy. However, the evidence for psychosocial interventions is sparse; therefore, no recommendation can be made presently with regards to the types of intervention or patient selection. Further research is necessary to define which patients will benefit from psychosocial interventions.

Physical Medicine Considerations

Often overlooked, physiotherapy and occupational therapy can provide a very valuable role in both cancer patients as well as cancer survivors. Orthotics and other braces can help reduce pain and improve function. Manipulation, soft tissue manipulation, heat, and massage have been reported to reduce discomfort in these patients. A recent review of the physical medicine and rehabilitation literature has described the numerous reports discussing treatment options that are underemployed [52••].

Interventional Procedures

The WHO pain ladder has been shown to be highly effective, providing satisfactory analgesia to most cancer pain patients (71–86%) [53, 54]. One of the limitations is that it does not address situations in which there is a failure to achieve satisfactory analgesia despite the use of high doses of opioids or the development of intolerable side effects. As such, there have been suggestions for an addition of a fourth step (use of interventional procedures) to the ladder [55].

Interventional cancer pain procedures can be broadly classified into soft tissue injections, neuraxial analgesia, nerve blocks, and neuroablative procedures. Though there is increasing amount of literature suggesting that these procedures are helpful, there is also a lack of adequately powered randomized controlled trials (RCT) [56•]. This may reflect the difficulty recruiting a large homogenous group of patients.

Persistent post-surgical pain (PPSP) can be a problem following cancer surgery and has recently received increased attention, especially in cancer survivors. Defined as continued pain, 2 months after a procedure, local anesthetic infiltration by indwelling central or peripheral nerve catheter is often helpful [57]. These catheters can be placed before or after surgery and are postulated to ablate the peak noxious pain barrage in the perioperative period and therefore, minimize the pathological neural plasticity that is responsible for PPSP. Recent systematic reviews have concluded that there is moderate evidence that the use of paravertebral blocks decreases the incidence of post-mastectomy and post-thoracotomy pain [58, 59].

Neurolytic blocks are achieved through the destruction of nerves that transmit pain. Most commonly, these procedures are performed using alcohol or phenol, but may also be performed by surgery or radiofrequency ablation of these nerves. Though neurolytic blocks provide longer pain relief, serious side effects such as deafferentation pain or motor weakness limits the use of this therapy [56]. It might be prudent to limit the use of these techniques to patients who have focal

intractable pain despite the application of the WHO ladder and also have a life expectancy of less than 6 months.

Neuraxial analgesia may be achieved through the delivery of drugs (local anesthetics, opioids, or coanalgesics) into the intrathecal or epidural space via a percutaneous or implanted catheter. This is then connected to an externally or internally implanted pump. The objective is to provide analgesia with much lower doses thereby minimizing side effects and medicine toxicity. A systematic review in 2010 examined 12 randomized, controlled trials and found that intrathecal analgesia provided better analgesia and less side effects compared to standard analgesia [60]. Unfortunately, most of the RCTs were found to have poor methodology and were industry funded.

Given that neuraxial analgesia is costly and associated with potentially serious complications (such as infection, catheter dislodgement, and granuloma formation), more independently funded and well-designed RCTs would be helpful [61]. It might be prudent to limit neuraxial infusions to patients with intractable focal cancer pain in the absence of any contraindications to intrathecal catheter placement such as coagulopathy. It has been reported that in selected patients, intrathecal analgesia provided a significant pain reduction of 67% with a very low rate of complications [62].

In recent years, there have been calls to perform neuroablative interventional pain procedures earlier to minimize the complications of long-term opioid use [63]. It might be logical to defer more liberal performance of neurolytic procedures until more evidence becomes available with regards to the outcomes and safety.

Pharmacological Approaches to Pain

First proposed in 1986, the WHO pain ladder describes a stepwise increase in analgesia until adequate pain control is achieved [64••]. The first step involves treating pain with non-opioid medication. Weak opioids are introduced in the second step while strong opioids are reserved for the third step. Despite its utility, there have been several debates regarding its scientific validity [65–67]. Several studies and meta-analyses have concluded that significant proportions of cancer patients still suffer from poor pain control despite established pain management founded on the ladder [2••, 68].

Two-step models have been proposed that start with weak opioids or low-dose morphine. In addition, fast-track guidelines, which start therapy at step 3, have also been described. The European Association for Palliative Care or EAPC 2012 recommendations suggested low-dose strong opioids in place of step 2 weak opioids [69]. This follows the conclusion of Bandieri et al. who found in patients with cancer and moderate pain, low-dose morphine reduced pain intensity significantly compared with weak opioids, with a similarly good tolerability and an earlier effect [70].

At the inception of the WHO pain ladder, morphine was chosen to be the recommended initial opioid due to its availability, cheap cost, and ease of administration by multiple formulations. The side effect profile of morphine and the availability of newer opioids such as oxycodone and hydrocodone resulted in EAPC updating their guidelines. It was found that no significant differences exist between morphine, oxycodone, and hydrocodone and any of these three drugs can be used on the third step of the analgesic ladder as a first choice opioid for moderate to severe cancer pain [69].

Treatment can also be directed at the underlying cause of pain. Osteogenic pain from bony metastasis might be better treated with nonsteroidal anti-inflammatory [71] drugs while neuropathic pain from damaged central or peripheral nervous system tissue might be addressed with antidepressants or anticonvulsants [23].

Non-opioid Adjuvants

Paracetamol (acetaminophen) and nonsteroidal anti-inflammatory drugs [NSAIDs] are described in all three steps of the WHO analgesic ladder, being coupled with an opioid in steps 2 and 3 [64••].

The evidence for use of paracetamol as an add-on analgesic in steps 2 and 3 may be limited or equivocal [72]. A meta-analysis by Nabal et al. [73] concluded that there was insufficient evidence to support use of paracetamol in combination with step 3 opioids as most studies were limited by small sample sizes and were relatively underpowered. Although the 2012 EAPC guidelines acknowledge these limitations, it supports a weak recommendation for use of paracetamol over NSAIDs due to a more favorable side effect profile.

In contrast, the evidence for use of NSAIDs, especially in combination with opioids for severe cancer pain, is more established [73, 74]. The side effect profile of the NSAIDs varies widely but is a concern for high-risk groups that are not dissimilar to the palliative care population. While newer generation selective COX-2 inhibitors have shown equal efficacy in terms of analgesia while having lower rates of GI toxicity, concern about renal and cardiovascular toxicity remains. It is for this reason, as mentioned above, that the EAPC weakly recommends the use of paracetamol over NSAIDs for use as an additional analgesic despite evidence of its efficacy [69].

Opioids for Mild to Moderate Cancer Pain—Step 2

The original WHO pain ladder classified opioids for mild to moderate cancer pain as “weak” opioids. They include a heterogenous group of opioids including tramadol and codeine, which is the prototypical weak opioid of step 2 [64••].

Buprenorphine is a mixed partial mu-agonist, with some kappa-antagonist effects, and many authors consider as a

strong opioid for step 3 of the analgesic ladder. A transdermal patch is available with some studies demonstrating promising results for moderate to severe cancer pain [75]. A Euromed Panel noted the ceiling effect for buprenorphine side effects and antihyperalgesic properties but were unable to recommend more widespread use due to limited evidence [76]. A recent meta-analysis reviewing multiple formulations of buprenorphine was also unable to provide evidence for its use, noting that most of the studies were small and at risk of bias [77]. A Cochrane Database review noted that studies were underpowered and no recommendations could be made [78]. Limitations of the use of buprenorphine include cost, antagonism of other opioids, and the risk of QT prolongation.

Tramadol is metabolized by the CYP2D6 cytochrome p450 isozyme to its major active metabolite O-desmethyltramadol. Up to 10% of patients are slow metabolizers and derive a weaker analgesic effect. Apart from having mu-receptor agonist effects, however, Tramadol also has provided analgesia by serotonin and norepinephrine reuptake inhibition and might be useful in the treatment of neuropathic pain [79]. Despite this, few studies have been done to show any difference compared to the other step 2 opioids [80].

Tapentadol is a comparatively newer oral opioid similar to tramadol. Comparatively, it is a more potent mu-receptor agonist and a noradrenaline reuptake inhibitor, although a much weaker serotonin reuptake inhibitor. Unlike tramadol, tapentadol is not a prodrug, and its analgesic properties are dependent on action of the parent drug. This provides a more reliable dose-response range among a larger patient population although patients who inherit the ultra-rapid metabolizer phenotypes of certain cytochrome P450 isoenzymes (e.g., CYP2D6) may have reduced analgesic efficacy [81, 82].

The most recent Cochrane review on Tapentadol focused on four studies involving 1029 patients [83]. Overall, there were insufficient data for pooling and statistical analysis, and the authors could only conclude that there was low-quality evidence that for pain relief, tapentadol was no more and no less effective than oxycodone or morphine. Since then, a few cohort studies were conducted which showed generally favorable results albeit in a small selected study population [84, 85].

Codeine is another prodrug that is metabolized to its active metabolite morphine, and again, about 10% of patients are slow metabolizers yielding poor analgesic response. Several studies since have shown that the efficacy of codeine in relieving mild to moderate cancer pain varies widely, with 5 to 10% of patients having no clinical benefit. Conversely, there have been reports of patients who have the ultra-rapid metabolizer phenotype that have unexpectedly high morphine levels with significant side effects, and unfortunately shorter duration of action [86•, 87].

Some authorities have proposed using low-dose strong opioids at stage 2, omitting weak opioids [88, 89], though scientific support for this is weak. Because of issues with study design, there is only weak evidence that these studies show elimination of step 2 of the WHO study or at least using low dose step 3 opioids is appropriate. This is reflected in recent guidelines by the EAPC and the National Comprehensive Cancer Network [NCCN].

Opioids for Moderate to Severe Pain—Step 3

Morphine is the most widely used opioid for severe cancer pain and is classically described for step 3. There are, however, reports and systematic reviews that have not shown any difference between strong opioids such as oxycodone, fentanyl, hydromorphone, and morphine [90, 91].

Oxycodone is a strong opioid with both mu- and kappa-receptor agonist activity. Hepatic metabolization to oxymorphone and subsequent active metabolites also partly accounts for its analgesic efficacy. The analgesic effect seems to have less individual variability compared to codeine. Oxycodone is available in formulations that prevent misuse or diversion in addition to the combination with naloxone to prevent constipation [92, 93]. Several authors have noted that there is a lack of good evidence to support the use of oxycodone over the less expensive and more widely available morphine [90, 91].

Hydrocodone undergoes hepatic metabolism into hydromorphone, which largely accounts for the analgesic effects. As with codeine, some patients are slow or fast metabolizers causing problems of variability with analgesic efficacy and toxicity. Hydrocodone is commonly combined with paracetamol, limiting the maximum allowable dose that can be administered. An extended action and tamper resistant formulation are now available [94].

Hydromorphone itself is widely used as a step 3 pure mu opioid. The increased lipophilicity compared to morphine accounting for its rapid onset and increased potency. Unlike other opioids, hepatic metabolism is independent of the CYP450 isoenzymes [95]. The renally excreted metabolite hydromorphone-3-glucuronide has no analgesic effects, but can accumulate in patients to produce excitatory neurotoxic effects including myoclonus and restlessness.

Fentanyl is a versatile synthetic opioid with a much rapid onset and greater potency due to its lipophilicity. It can be administered intravenous, subcutaneous, as well as intrathecally. The sustained release transdermal patch is frequently used when analgesics cannot be administered orally. Several preparations are available for the management of breakthrough pain including transmucosal, sublingual, and intranasal [96–98].

Though not a first line agent, methadone is another alternative, frequently selected in opioid rotation. The d-isomer has additional antagonism of NMDA receptors which is thought to effect non-opioid analgesia and reversal of opioid tolerance. Thus, remarkably smaller doses and equianalgesic

doses are needed to provide the same effect. Additional advantages include the liquid formulation, long duration of action, and inactive hepatic metabolites, which make it suitable for patients in renal failure [99]. The main drawback is individual variability in metabolism and the difficulty in titrating the correct dose. EAPC recommends that use of methadone be limited to experienced professionals [69].

Future Directions

One of the consequences of improved treatment of cancer is the burgeoning population of cancer survivors, many with ongoing chronic pain [100••]. This type of pain may be from treatments such as surgery persistent post-surgical pain (PPSP) mentioned above [65], radiation therapy, chemotherapy, or the actual cancer process. Recognition of these patients is essential and measures can be taken to improve their pain and quality of life.

Summary and Conclusions

Though significant progress has been made in recent years with regard to the understanding and treatment of cancer pain, there are still large numbers of patients with poorly controlled pain. A comprehensive, holistic treatment plan which includes a team of trained specialists employing both pharmacological as well as other treatments would be most beneficial. Though numerous modalities are available, care plans must be individualized for each specific patient. Few adequate studies evaluate current treatments of cancer pain, but this is probably a reflection of the difficulty in conducting adequately powered randomized controlled trials in this heterogeneous patient population.

Compliance with Ethics Standards

Conflict of Interest Weiyang Christopher Liu, Zhong Xi Zheng, Kian Hian Tan, and Gregory J. Meredith declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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