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Mechanism based cancer pain therapy

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Abstract

Cancer pain remains prevalent and severe for many patients, particularly in those with advanced disease before they die. The effectiveness of treatment in routine practice appears to have changed little in the last 30 years since publication of the WHO approach. Qualitative studies in patients with advanced cancer suggest that key priorities in pain management strategies should be to help patients achieve a balance between pain and adverse effects of analgesia in order to optimise physical function, and support for self-management.

Interventions targeted at physiological, behavioural and health-system mechanisms can improve pain outcomes for patients. Strong opioids have medium to strong effect sizes while most other drug and non-drug interventions have small to medium effect sizes at best. The limitations of current analgesic interventions should encourage greater use of interventions that target patient and healthcare professional behaviour. A framework is proposed for interventions in cancer pain management that target mechanisms and outcomes that are important to patients. This framework might help to broaden management strategies and encourage evidence-based but underused interventions.

Introduction

Pain prevalence and severity

Pain is the commonest presenting feature that leads to a diagnosis of cancer [8] and remains the most feared symptom by patients throughout the course of the disease [9]. This fear is understandable; a systematic review by van den Beuken-van Everdingen [47] showed that pain prevalence rises with disease progression and affects about 64% of patients with advanced cancer. About 45% of all patients with advanced cancer experience pain of moderate to severe intensity (at least 5 on a 0-10 pain rating scale) [8,47]. In an update to this review published almost 10 years later [48], these estimates were 66% and 55% respectively, suggesting that little progress has been made in cancer pain management during this period. Given that 8.2 million people die from cancer worldwide each year, the majority of which are not living in developed countries, there are huge numbers of people suffering with moderate to severe pain from advanced cancer before they die.

Under-treatment

Greco at al [23] estimated the adequacy of treatment for cancer pain and identified that approximately 32% of patients were not receiving analgesia proportionate to their pain severity. This potentially represents an improvement on an earlier estimate [16] which suggested 43% of cancer patients were undertreated. Nevertheless, a significant number of patients with cancer pain are not well managed. A retrospective cohort study from the UK identified for the first time the relatively short duration of strong opioid treatment in patients who died from cancer [55]. This study showed that only 48% of patients received a strong opioid before death and that median treatment duration was 9 weeks, suggesting that earlier pain assessment might lead to improved outcomes for patients.

Meaningful outcomes for patients

Epidemiological data provide useful quantitative information on population level experiences but for individual level experiences, qualitative studies are superior in illuminating how patients manage with pain from cancer and what they need from healthcare professionals. Longitudinal interview studies reveal that pain is very dynamic and

complex for patients, and that pain control is often a trial and error process that requires continuous work [25]. Neither pain relief nor expertise in pain management is secured once and for all. Patients attempt to reduce interference from both pain and the cognitive effects of analgesia in order to maintain as much function as possible [31]. This often leads to trade-offs between pain and analgesia, impacting on medication adherence. This 'trading off' concept has been identified in an acute pain context [21] but it seems much less well known in the context of patient preferences in cancer pain management.

Although patients understandably express that they want to be pain free, in general they do not actually expect their pain to go completely [22]. Most patients seem to determine whether their pain is controlled by whether or not they can perform activities or tasks and maintain relationships with family or friends. This outcome is what determines themselves as individuals [22,25,31]. Bender et al [2] identified that patients are keen to understand the cause of their cancer pain, what to expect, options for pain control (including addressing concerns about strong opioids), and how to cope with cancer pain including talking with others and finding help.

These qualitative studies suggest that key priorities in pain management strategies for patients with advanced cancer should be to help them achieve a balance between pain and adverse effects of analgesia in order to optimise physical function, and support for self-management. In this context, a simple numerical rating of pain intensity has less meaning as an outcome measure. Instead, determining interference from pain or analgesia in daily activities and the degree of self-efficacy (ability to cope) are more relevant measures of pain management.

Assumptions about cancer pain and management

Before examining approaches to improve the management of cancer pain, it is important to identify some assumptions held by healthcare professionals regarding cancer pain. First, the assumption that 'cancer pain' represents a homogenous and clearly understood pathological process. In reality it is simply an umbrella term for a large range of different cancer types that initiate different pain states and mechanisms, each requiring individual assessment and tailored treatments. Second is the assumption that any pain in a cancer

patient is related to active tumour. In practice, around two thirds to three quarters of pains are related to tumour, and around 10-20% are related to cancer treatments (particularly chemotherapy and surgery), with around 10% related to co-morbid diseases [7,24]. So assessment should clearly distinguish tumour-related pain from treatment-related pain or co-morbid pain. Third is the assumption that a focus on drug development alone will solve the problem of widespread under-treatment of pain. More diverse strategies need to be implemented in parallel to optimizing analgesia. These should enable healthcare professionals to improve the assessment and monitoring of pain, and provide better support for self-management, and for healthcare systems to facilitate better access to skilled help and analgesia for patients.

Mechanism based therapies

Conventionally, a mechanism-based discussion of pain therapies is confined to pathophysiological processes occurring at a molecular or cellular level, and the consequent biological targets for treatments. However, the definition of mechanism as 'a system of parts working together in a machine', or 'the interconnection of parts in any complex process, pattern, or arrangement' [37] enables a wider and more creative perspective on cancer pain therapy. This review will focus on physiological, behavioural and health-system mechanisms in order to understand and prioritise effective interventions for patients with pain from advanced cancer, Table 1.

Physiological interventions

Physiological mechanisms in cancer pain are broadly described as nociceptive, inflammatory or neuropathic [19], with analgesia tailored to these. The principal approach to cancer pain management has been based on the World Health Organisation's Method for Cancer Pain Relief [53]. The foundation of this approach is the concept of matching the strength of analgesia to severity of pain, ranging from basic analgesics to strong opioids. Other approaches, including adjuvant analgesia, corticosteroids, radiotherapy and interventional procedures are also highlighted. With good adherence, this approach can result in

satisfactory pain control for around 73% of patients with cancer pain, leaving at least a quarter of patients with inadequate control [3, 54].

Closer scrutiny of the effectiveness of specific analgesic drugs in cancer pain reveals an evidence base that is generally of low quality with few studies providing strong evidence of effectiveness. For example, systematic reviews of basic analgesics suggest that paracetamol is likely to be ineffective, particularly in patients already treated with strong opioids, whereas there are no good quality studies of non-steroidal anti-inflammatory drugs (NSAIDs) to guide practice [33,34]. Strong opioids are generally effective with about 75% of patients achieving satisfactory pain control after first or second line opioid treatment, with no significant differences in efficacy between morphine, oxycodone, fentanyl or buprenorphine [10, 41, 42, 52]. This translates into approximately a 3 point mean reduction on a 0-10 pain rating scale at a group level [10], though these data are not compared with response to placebo. Interestingly, these data imply that the effectiveness of the WHO approach is based entirely on strong opioids, with no substantial contribution from other approaches.

Disappointingly, data supporting the use of adjuvant analgesia in tumour-related cancer pain are weak, particularly for antiepileptic and antidepressant drugs targeted at neuropathic mechanisms. One recent review concluded that the evidence base was of low to very low quality which prevented firm recommendations regarding adjuvant analgesia in cancer pain [49]. Another review highlighted the increase in adverse effects when adjuvants were combined with opioids, which could outweigh any benefits [4]. This is despite good evidence of effectiveness in non-cancer contexts [20].

The forthcoming update of the International Classification of Diseases (ICD-11) will include diagnostic codes covering cancer related pain (caused by tumour) and cancer treatment related pain [44]. Cancer related pain is coded by anatomical origin into visceral, bone or neuropathic, with separate codes for continuous (background) pain and intermittent (episodic) pain. This standardized approach to classification of cancer pain is designed to help clinicians and researchers. Improvements in cancer pain classification may promote more rigorous evaluations of interventions within more homogenous populations.

Vardeh at al [50] have recently proposed a concept for pain assessment for all aetiologies which forms a hierarchy comprising pain state (e.g. inflammatory or neuropathic), pain mechanism (e.g. peripheral or central sensitisation) and finally, molecular targets (e.g. nerve growth factor (NGF) or NMDA receptors). This concept is attractive and potentially allows more precision in tailoring analgesic treatments. However, basic science research in cancer pain has demonstrated a complex and incompletely understood picture. Boney metastases are the most common cause of cancer pain [32] and animal models of cancer bone pain represent the most studied of cancer pain mechanisms [14]. This type of pain is a unique mixture of inflammatory and neuropathic mechanisms [46], with a large number of potential molecular targets [29]. Treatments developed against these molecular targets include denosumab, which interferes with receptor activator of nuclear factor Kb ligand (RANK-L) and tanezumab which inhibits nerve growth factor (NGF). The evidence to support an analgesic effect of these compounds remains weak [40]. In routine clinical practice, and based on numbers-needed-to-treat derived from clinical trials, effective cancer bone pain therapy remains centred on strong opioids, radiotherapy and bisphosphonates [26]. Interventional procedures may have a role for selected patients, but strong evidence of effectiveness is lacking [51].

Behavioural mechanisms

The behaviour of a healthcare professional or a patient can influence the outcome of pain management when measured by patient reported pain intensity or satisfaction with treatment.

Classroom style teaching to healthcare professionals can improve knowledge of cancer pain management but there is good evidence that this has no significant impact on patient outcomes [1,6,18]. Encouraging a change in healthcare professional behavior (activity) is needed. Patients report greater satisfaction with cancer pain management when professionals state the importance of pain control, provide instructions to manage pain at home including managing side effects, and allaying fears about addiction [15,40]. A recent

meta-analysis emphasised the effectiveness of inducing expectations of improvement for patients with pain, particularly with verbal suggestion [38].

Recording a pain assessment and ensuring that healthcare professionals use this within the consultation with a patient can result in a significant decrease in usual pain [45]. In contrast, simply displaying a pain assessment by the bedside (compared with not displaying the assessment) was ineffective [28]. Pain assessment data needs to be integrated into pain management decisions. Two studies in which patients or clinics (as part of a cluster trial) were randomised to protocol-based physician prescribing and compared with usual care have demonstrated benefits. Du Pen [17] showed that average pain intensity was 1.3 points lower (on 0-10 pain rating scale) following intervention than in control group (3.5 v 2.2, $p=0.02$). Cleeland [11] found that worst pain intensity similarly fell by 0.9 points more in intervention group than in control (1.8 v 0.9, $p<0.05$). Adherence by professionals to analgesic protocols improves patient outcomes.

Interventions to patients with cancer pain that aim to improve self-efficacy or capacity for self-management can be important adjuncts to analgesic treatment. These interventions vary in content but often consist of a needs assessment, provision of information on causes of pain and address common fears about opioids, provide strategies for coping with problems, goal setting, and review. The interventions were usually delivered by face-to-face or telephone coaching sessions combined with written information. A number of meta-analyses have been published on the effectiveness of these types of intervention [5,13,27,43]. While methodology differed between the reviews, all found significant benefits for intervention, equivalent to 1.1 point average pain intensity rating benefit for intervention compared with control [5]. Interestingly while one review found that more intense exposure (more comprehensive content, multiple sessions, greater follow up) resulted in better outcomes [13], this was not supported by other reviews [5,27,43]. While there is likely to be a minimally effective dose, it seems that more intense, longer and complicated interventions are not clearly associated with significantly better outcomes. A single exposure coaching intervention with patients supported by written material might be very cost-effective.

Health system mechanisms

Health systems (the organization of care services) within a country or locality are often complex and unique. While barriers to good cancer pain management have been well documented at the level of patients and healthcare professionals [35], barriers and therefore interventions at the level of the healthcare system are not as well researched. Consequently it is more difficult to identify cause and effect regarding mechanisms in relation to cancer pain at this level. While the availability of, for example, more outpatient clinics or pharmacies with longer opening hours may seem intuitively to facilitate better pain management, demonstrating this in a way that is generalizable is more challenging.

One perspective is to regard health systems as a complex mix of mechanisms involving patient physiology and behavior, combined with the behavior of teams of healthcare professionals. Thus, complex interventions that address multiple components of this mix may be considered as health system interventions [12].

Kroenke et al [29] recruited patients with cancer pain and randomized them to usual care or intervention which consisted of medication management provided by clinicians adhering to a protocol, automated pain monitoring via telephone or computer, and ongoing support from nurses who would telephone patients and checked symptoms and medicines. Nurse calls were also triggered by reports of pain scores above a certain threshold. At 3 and 6 months follow up, average pain scores (0-10 rating scale) in the intervention group were 1.22 and 0.83 points lower than the control group ($p<0.001$). Oldenmenger [36] combined a consultation with a specialist pain physician and a pain education programme delivered by nurses at a face to face coaching session which was then followed up with weekly telephone contact. Over the 8 week follow-up period, average pain intensity was 0.82 points lower in the intervention group than in the control group, ($p=0.03$).

Summary

Cancer pain remains prevalent and severe for many patients, particularly in those with advanced disease before they die. The effectiveness of treatment in routine practice appears to have changed little in the last 30 years since publication of the WHO approach [53]. There are a number of potential explanations for this disappointing state of affairs which include poor assessment and classification of pain in cancer patients, slow translation

of basic science research into effective clinical interventions, and especially from a global perspective, poor access to strong opioids. However, it is also likely that strategies for cancer pain management that focus on promoting effective behavior of healthcare professionals and patients are not taught and not implemented with the same priority as physiologically based strategies. This is particularly important when recent research highlights the needs and outcomes that are most important for patients, and represents a missed opportunity for improvement. From an applied health research perspective, a number of key research questions remain, Table 2.

Strong opioids appear to have medium to large effect sizes (very roughly equivalent to a 2 or more point mean reduction in pain intensity after adjusting for placebo effect), but most other interventions appear to have small to medium effects (mean reduction in pain intensity of roughly 1 point or less). It would make sense to combine a number of these interventions for any individual patient to optimize cancer pain control. However, current evidence does not clearly show either synergistic or even additive effects from this approach. In fact, a simple intervention such as a one-off educational session to a patient on self-management [5] may be as comparable as a complex intervention [29,36] when mean reduction in pain intensity is the primary outcome measure. For healthcare professionals, adopting simple interventions into routine practice could lead to important benefits, Table 1.

One of the challenges in making these comparisons across interventions is that reduction in average pain intensity may not reflect the true benefits (or harms) of these interventions, particularly at an individual rather than group level. Based on experiences of patients with pain from advanced cancer, a new mechanisms and outcomes framework is proposed, Table 3. This framework might help to broaden management strategies and encourage evidence-based but underused interventions. Prioritising an increase in self-efficacy and a decrease in interference and as primary outcomes rather than numerical ratings of pain intensity may enable more accurate assessment of cancer pain management that is congruent with patient priorities.

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