REVIEW

Management of pain in cancer patients with depression and cognitive deterioration

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Abstract
Patients with cancer are burdened with pain, ranging in prevalence from 14 to 100% in this population, and with comorbid behavioural symptoms such as depression and cognitive decline. However, the complex relationships between cancer pain, depression and cognitive decline, as well as their causes, still need to be clarified.

Here, the existing literature on pain and its relationships with depression and cognitive decline in adult patients with cancer is reviewed, in order to understand the impact of pain on these interrelated symptoms, and the importance of its correct assessment and management.

From the literature, it emerges that pain in cancer patients has a multidimensional phenomenology, which is the final product of a complex process involving emotional, cognitive, and sensory components. There is a substantial agreement that cancer patients with pain are at higher risk of having depression and cognitive decline. However, it is still controversial if these symptoms may fit into the same cluster, due to the paucity of studies exploring the simultaneous impact of pain on the psychological and cognitive well-being of patients with cancer, which would be consequential on their treatment and management. Finally, recent advances in immunology/oncology have provided novel insights into the pathophysiologic mechanisms supposedly underlying pain-related symptoms. Particularly, immune dysfunction may represent a common pathogenic ground of pain, depression and cognitive decline in cancer patients. In clinical practice, an appropriate assessment of pain should take into account the relationships with depression and cognitive decline, in order to develop more personalised and effective therapies for its management.

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Introduction

In the last few decades, growing attention has been given to the burden of cancer pain and its management, especially since the application of the World Health Organization guidelines for pain control [1]. Furthermore, cancer patients with chronic pain often report depressive symptoms and complain of decreased cognitive function. Indeed, failure to manage pain and its comorbid psychological distress may lead to serious consequences such as depression and cognitive decline. Thus, understanding the complex relationships between cancer pain, depression and cognitive decline appears relevant in order to assist patients and caregivers, potentially improving their quality of life.

Bearing these considerations in mind, the objective of this paper is to review the existing literature regarding the phenomenology of cancer pain and its relationships with depression and cognitive decline in oncological patients.

Methods

Search limits

In order to clarify the state of the art in the topic of pain, depression and cognitive decline in cancer patients, we conducted detailed searches of the published medical literature with a review of the Medline (PubMed) databases. Article inclusion criteria were as follows: (1) period of publication between January 1980 and January 2009; (2) English language only; (3) human studies. Exclusion criteria were: (1) articles with a primary focus on medical symptoms (e.g. sexual dysfunction; anorexia or malnutrition; dysphonia or hearing disorders, etc.), social factors (e.g. social support or social stigma), or other conditions that can be secondarily associated to pain, depression or cognitive decline (e.g. hopelessness, symptom beliefs, coping resources); (2) articles with a primary focus on the outcome (e.g. quality of life or adjustment); (3) animal studies.

For our purposes we used various combinations of the following keywords: "pain", "depression", "cognition", and "cancer".

Selection process

Search terms were used to extract records limited to the issue of pain, depression and cognitive decline in patients with cancer. A paper was considered for inclusion if all the above-mentioned criteria were satisfied. For each citation identified, we scanned titles and/or abstracts. We searched bibliographies of published articles for relevant titles, considering cross-references and review articles reported in the different papers collected. All articles cited in this manuscript were judged by I.S. and G.S. to meet the scientific and conceptual criteria listed.

Results

Matching all the keywords, 31 articles were selected. Other combinations such as "pain, cognition and cancer" highlighted 229 papers, whereas "pain, depression and cancer" highlighted 1007 articles. The articles highlighted in our searches and selected for this review spanned the period March 1986–December 2008.

Pain and depression in oncological patients: epidemiology and phenomenology

Pain prevalence ranges from 14 to 100% in cancer patients [2], with higher percentages found in advanced stages of the disease [3]. Cancer pain is often severe enough to impair a patient’s ability to function [4,5], and its significant impact on the overall quality of life has been described [6]. Particularly, sub-optimally controlled pain remains a common cause of diminished quality of life [7].

Cancer pain has been conceived as the final product of a complex and multifaceted process involving emotional, cognitive and sensory components [8]; consequently, different taxonomies have been proposed to explicate its multidimensional phenomenology. A common taxonomy of cancer pain parses different, but sometimes overlapping, dimensions into nociceptive, somatic, visceral, and neuropathic subtypes [9], as summarised in Table 1. Pain may be due to cancer itself (e.g. tumour infiltration) or be the...
Pain in cancer patients with depression and cognitive deterioration

Table 1  Subtypes of cancer pain according to Foley’s taxonomy (1998).

<table>
<thead>
<tr>
<th>Types of cancer pain</th>
<th>Sources of cancer pain</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptive</td>
<td>Stimulation of pain receptors in cutaneous and musculoskeletal structures</td>
<td>Tissue injury from surgery, trauma, inflammation</td>
</tr>
<tr>
<td>Somatic</td>
<td>Metastatic bone pain, postsurgical incisional pain, musculoskeletal inflammation and spasm</td>
<td>Direct injury to bones, tissue or tendons. Aching, dull, stabbing pain. Focal pain</td>
</tr>
<tr>
<td>Visceral</td>
<td>Organ damage or tumour infiltration, compression or distortion of organs within the pelvis, abdomen, or thorax</td>
<td>Pressure-like sensation, internal squeezing or cramping. Vague, diffuse pain. Associated with nausea, vomiting, sweating. Possibly referred to superficial locations distant from the affected organ</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>Tumour infiltration of peripheral nerves, plexi, roots, or spinal cord. Effect of treatment as surgery, chemotherapy, drug-induced neuropathy or neuritis. Causes sensory changes caused by injury in the central nervous system or peripheral nervous system</td>
<td>Burning, shooting, pins/needles, electrical or numbness. Radiates over dermatomal distributions. May be unresponsive to opioid therapy</td>
</tr>
</tbody>
</table>

Adapted from Christo and Mazloomdoost (2008).

indirect consequence of treatments [10]. Also, the great variability of cancer pain phenomenology depends on the type of cancer, stage of disease, and location of tumour. Finally, in the perception and expression of pain, learned responses and sociocultural factors may play a key role [10]. Particularly, the presence of comorbid psychological distress must be taken into account.

Indeed, one out of two cancer patients report psychiatric disorders, especially depressive symptoms [11–13] (depressive symptoms according to the Diagnostic and statistical manual of mental disorders, 4th ed., text revised [14], are described in Table 2). Notably, the moderate rate of major depressive disorder (five or more depressive symptoms), which is around 25% during the clinical course of the illness [15], is accompanied by a much higher rate of minor depressive disorder and subthreshold forms of depression, which are characterised by a minor number of symptoms. Unfortunately, the diagnostic criteria for mood disorders which are currently applied in oncological research are often inadequate to detect these subtle forms of depression [16], which are consequently at risk of being underecognised and untreated in cancer patients. Also, in the diagnostic assessment of mood disorders in cancer patients, it should be considered that many somatic symptoms of depression, such as anorexia, weight loss, low energy and sleep disturbances, are similar to those of cancer itself [17]; therefore, they may be easily misattributed to cancer and not to depression [18]. For this reason, several authors have proposed to exclude these somatic symptoms from depression diagnosis in cancer patients [19] or to substitute them with other non-somatic symptoms [20].

Further complicating their phenomenologies and diagnoses, depression and pain often co-occur [21]. Indeed, the relationship between depression and pain is a complex issue both in medical and psychiatric settings. Some studies point out the presence of a direct relationship between pain and severity of depression in the depressed non-cancer population [22] with a higher risk of suicide in those patients with pain complaints [23]. Thus, if pain is conceivable as a component feature of depression, this issue appears to be particularly relevant in patients with cancer.

Relationships between pain and depression in oncological patients

Interestingly, some studies [17,24,25] have consistently shown that the prevalence of depression is significantly higher in cancer patients suffering from pain. Particularly, the presence of pain has been shown to increase the prevalence of depression in cancer patients [26] who complain not only of more depressive disorders, but also of anxious and somatic symptoms, compared to patients without pain [27,28]. Specifically, a study [29] showed that 39% of cancer patients with a psychiatric diagnosis (15% of whom were diagnosed with major depressive disorder) reported severe pain, compared to only 19% of patients without a psychiatric diagnosis. Furthermore, Gaston-Johansson et al. [24] found that depression and pain had a significant impact on the global health status. Also, even in the absence of a major depressive disorder, the risk of suicidal ideation is higher in depressed cancer patients who reported uncontrolled pain [30]. Specifically, a study on patients with lung carcinoma [31] found that pain was the best predictive factor for suicidal ideation. Thus, earlier pain management and psychiatric intervention appears to be pivotal in preventing suicidal risk. Finally, it is well-described that antidepressant medications can help treat neuropathic pain in cancer patients, offering analgesic effects independent of their antidepressant effects [10,32,33].

From the above-reported data it is clear that there is a relationship between cancer pain and depression. However, the direction and the nature of this relationship have still to be clarified. On the one hand, it has been argued that pain causes depression in cancer patients [26,34,35] and there is also evidence of pain as a predictor of depressive disorders in this population [25]. On the other hand, the link between pain and depression appears to be bidirectional, considering that depression and anxiety, in

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particular during the course of illness, reinforce pain by increasing its intensity [27,36–38]. Thus, it is reasonable to suppose that pain in cancer patients may lead to depression but also that depression sensitises patients to feel pain. Finally, further supporting the link between pain and depression, and their potential common neurobiological basis [39] (see paragraph 6), another cancer-related symptom often associated with pain and depression in oncological patients is cognitive decline.

### Cognitive decline and its relationships with pain and depression in oncological patients

Cognitive decline in cancer patients is characterised by a slight comprehension deficit, loss of ability to think abstractly, anomies, memory loss, mental fatigue, and difficulties in concentrating [40]. Due to this subtle and peculiar phenomenology, accurate estimations of cancer-induced cognitive impairment are difficult to obtain. Indeed, cognitive decline in cancer patients has been ascribed to a variety of aetiologies, which might be dichotomised in disease- and treatment-induced causes [41].

Focusing on the former category, cognition may be directly affected by cancer itself (e.g. brain metastases) or indirectly (e.g. metabolic disturbances) [41]. Indirectly, cognition may also be affected by the presence of depression and pain. Indeed, a diminished ability to think or concentrate, or make decisions, is among the depressive symptoms (Table 2). Thus, due to the overlap between cognitive deficits and depressive symptoms, the former might be misattributed to depression. As well as for depression, the relationships between cognitive decline and pain in cancer patients have been explored, although the neuropsychological studies on this topic are sparse. A study [42] found that higher pain scores were associated with poorer working memory performances in cancer patients, concluding that pain is likely to influence cognition in this population. Another line of evidence for the deleterious effect of unrelieved pain on cognitive function arises from studies that concluded that cognitive performance improved after successful treatment of pain [43,44].

The category of treatment-induced cognitive decline has been much more explored in cancer patients. Indeed, the influence of long-term opioid therapy (which is primarily used in the treatment of moderate to severe pain) on cognition in cancer patients has been described, although with controversial findings. Indeed, some studies suggest that opioids may cause neuropsychological impairment (i.e. episodic verbal memory or attention) in cancer patients [45–47], whereas other studies fail to demonstrate such impairments or even claim that opioids have beneficial effects on neuropsychological performance [40,48,49]. Finally, it has been argued that cognitive deficits may be caused by unrelieved pain rather than opioids, considering that long-term opioids for cancer pain do not affect neuropsychological performances by themselves, whereas pain causes greater neuropsychological impairment [40].

These inconsistencies may be explained in different ways. Firstly, methodological limitations such as the paucity of randomised, controlled trials, and inadequate sample sizes, must be taken into account [50]. Secondly, the subjective report of cognitive dullness and mental slowness may refer to phenomena markedly different from what is formally measured by objective tests [50].

Taken all together, these findings seem to indicate that stable opioid therapy is associated with minimal cognitive

### Table 2 Depressive symptoms for mood (depressive) disorder diagnoses according to DSM-IV-TR.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Description</th>
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<tr>
<td>1. Depressed mood&lt;sup&gt;a,d,e&lt;/sup&gt;</td>
<td>Significant unpleasant mood with feelings of sadness or emptiness and/or appearance of tearfulness</td>
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<tr>
<td>2. Anhedonia&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>Significantly reduced level of interest or pleasure in most or all activities</td>
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<td>3. Appetite&lt;sup&gt;b,d,e&lt;/sup&gt; or weight change&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>Substantial increase or decrease in appetite nearly every day or unintentional weight loss or gain (e.g. 5% or more change of weight in a month when not dieting)</td>
</tr>
<tr>
<td>4. Sleep disturbance&lt;sup&gt;b,d,e&lt;/sup&gt;</td>
<td>Difficulty falling or staying asleep (insomnia), or sleeping more than usual (hypersomnia)</td>
</tr>
<tr>
<td>5. Increased or decreased psychomotor activity&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>Behaviour that is agitated or slowed down. Others should be able to observe this</td>
</tr>
<tr>
<td>6. Decreased energy&lt;sup&gt;b,d,e&lt;/sup&gt;</td>
<td>Feeling fatigued, or diminished energy</td>
</tr>
<tr>
<td>7. Guilt or feelings of worthlessness&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>Feelings or thoughts of worthlessness or excessive guilt (not about being ill)</td>
</tr>
<tr>
<td>8. Decreased concentration&lt;sup&gt;c,d,e&lt;/sup&gt;</td>
<td>Diminished ability to think or concentrate, or make decisions</td>
</tr>
<tr>
<td>9. Suicidal ideation&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>Frequent thoughts of death or suicide (with or without a specific plan), or attempt or suicide</td>
</tr>
<tr>
<td>10. Low self-esteem&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>Feelings of being uninteresting or incapable</td>
</tr>
<tr>
<td>11. Hopelessness&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>Feelings of discouragement and pessimism, i.e. no hope for the future</td>
</tr>
</tbody>
</table>


<sup>a</sup> Psychological symptom.

<sup>b</sup> Somatic symptom.

<sup>c</sup> Cognitive symptom.

<sup>d</sup> Major and minor depressive disorder symptom.

<sup>e</sup> Dysthymic disorder symptom.
changes, more evident for parenteral than oral opioids [50], particularly affecting the thinking process and the ability to react to stimuli, as well as psychomotor abilities [51].

**Understanding the relationships between cancer pain, depression, and cognitive decline**

Despite the concept of pain as a multidimensional phenomenon being commonly accepted, greatly influencing its assessment and management [4,52], the simultaneous impact of pain on the psychological and cognitive well-being of patients with cancer has been very underexplored. Indeed, as emphasised by Reyes-Gibby et al. [39] in a recent review (2008), studies in the oncological literature tend to investigate these symptoms as separate entities, with a separate assessment and consequently a parsed treatment. For instance, often the physical symptoms linked to pain are dissociated from its cognitive and affective dimensions. On the contrary, the above-described evidence of the co-occurrence and interrelationships among pain, depression and cognitive decline in cancer patients have led to the hypothesis of a common biological ground [39]. In fact, these cancer-related symptoms may represent a symptom cluster, which is a concept applicable to at least two [53] or three [54] interrelated symptoms, which are observed to occur simultaneously and to influence clinical outcomes [55]. However, only a few studies to date seem to support this recent theoretical supposition. Among these, a study [56] confirmed the existence of a cluster composed by depression and pain in patients with high-grade glioma, whereas cognitive impairment was found to fit in another cluster. This might be due to the fact that brain cancer has a peculiar role in cognitive dysfunctions, which is linked to the cancer site itself. On the contrary, significant correlations were found among pain intensity and both depression and cognitive status in a correlational study in patients with incurable cancer treated for pain-relief and cancer-related symptoms [52]. Interestingly, the correlation between pain and cognitive status remained significant even after controlling for depression, suggesting a specific relationship between the variables despite the above-described overlap with depression.

Considering this preliminary evidence, it has been hypothesised that cancer pain, depression and cognitive decline may share the same pathogenesis [57,58]. Indeed, Cleeland et al. [57] theorised that pain, depression, cognitive impairment and another two cancer-related symptoms (i.e. fatigue and anxiety) may occur as the direct result of proinflammatory cytokine production. Cytokines, such as tumour necrosis factor (TNF)-alpha, IL-1 and IL-6, are released during tissue destruction. Notably, clinical studies have demonstrated that cytokines are also significantly more elevated in depressed than in non-depressed non-cancer patients [59]. Furthermore, animal models showed that cytokine up-regulation induces the so-called ''sickness behaviour'', a syndrome consisting of higher pain sensitivity, cognitive dysfunction, and symptoms like anorexia, sleep alterations, psychomotor slowing, and irritability (which are all depressive symptoms, as shown in Table 2) as well as anxiety and fatigue [60]. Thus, the similarity among the sickness syndrome and cancer pain, depression and cognitive decline has led to the appealing hypothesis that proinflammatory cytokines are an aetiologic factor in forming this peculiar cluster in cancer patients [58]. From a genetic point of view, according to the integrative molecular epidemiology approach [61], it has been proposed that the same genes that are implicated in cancer risk might also be involved in the modulation of these cancer-related symptoms [39]. This recent hypothesis has been substantiated by preliminary evidence showing that, in patients with lung cancer, the same genetic risk factors for cancer (polymorphisms in cytokines genes, IL-1A and IL-1B) were found to be a risk factor for pain severity [62].

**Conclusions and considerations for upcoming studies**

Pain, depression, and cognitive complaints are prevalent and debilitating symptoms in patients with cancer. However, most of the published studies have been focused on selected symptoms instead of defining them as a cluster. Thus, the importance of these interrelated symptoms in clinical practice, i.e. on the treatment response, quality of life and overall survival, still remains unexplored, despite appealing hypotheses on a common aetiopathogenesis. For instance, studies should also include an assessment of cytokine production, focusing on the biological mechanisms underlying these symptoms as therapeutic targets [58]. Indeed, understanding the phenomenology and aetiology of cancer pain and its psychiatric and cognitive correlates may be helpful in determining the most appropriate treatment and management of pain.

Considering the complex phenomenology of pain in cancer patients, its assessment and management require a comprehensive approach in order to identify all the physical, emotional, and cognitive dimensions, toward a significant improvement on patient’s and caregivers’ quality of life.

**Conflict of interest statement**

The authors have no conflict of interest to declare.

**References**


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