REVIEW ARTICLE



Strategies of complementary and integrative therapies in cancer-related pain—attaining exhaustive cancer pain management

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Abstract

Purpose Complementary integrative therapies (CITs) correspond to growing demand in patients with cancer-related pain. This demand needs to be considered alongside pharmaceutical and/or interventional therapies. CITs can be used to cover certain specific pain-related characteristics. The objective of this review is to present the options for CITs that could be used within dynamic, multidisciplinary, and personalized management, leading to an integrative oncology approach.

Methods Critical reflection based on literature analysis and clinical practice.

Results Most CITs only showed trends in efficacy as cancer pain was mainly a secondary endpoint, or populations were restricted. Physical therapy has demonstrated efficacy in motion and pain, in some specific cancers (head and neck or breast cancers) or in treatments sequelae (lymphedema). In cancer survivors, higher levels of physical activity decrease pain intensity. Due to the multimorphism of cancer pain, certain mind-body therapies acting on anxiety, stress, depression, or mood disturbances (such as massage, acupuncture, healing touch, hypnosis, and music therapy) are efficient on cancer pain. Other mind-body therapies have shown trends in reducing the severity of cancer pain and improving other parameters, and they include education (with coping skills training), yoga, tai chi/qigong, guided imagery, virtual reality, and cognitive-behavioral therapy alone or combined. The outcome sustainability of most CITs is still questioned.

Conclusions High-quality clinical trials should be conducted with CITs, as their efficacy on pain is mainly based on efficacy trends in pain severity, professional judgment, and patient preferences. Finally, the implementation of CITs requires an interdisciplinary team approach to offer optimal, personalized, cancer pain management.

Keywords Pain management · Personalized management · Multimorphic pain · Cancer pain · Mind-body therapy · Complementary therapies

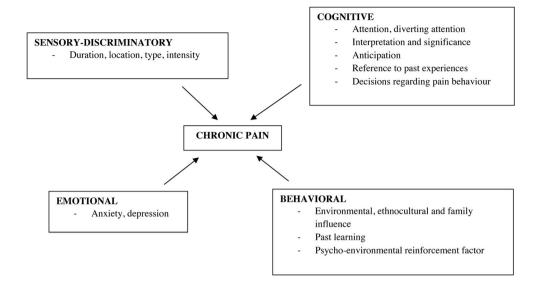
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Introduction

Pain is a subjective symptom defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. Cancer-related pain felt by patients is multimorphic and presents four dimensions (sensory-discriminatory, emotional, cognitive, and behavioral; Fig. 1). Thus, pain is expressed by the "body itself" (suffering experienced by the body) and/or by the "mind" (e.g., depression), and it leads to physical and psychological complications associated with a decrease in patients' vitality and quality of life. Pain impacts social relationships with relatives and caregivers and encourages certain relational behaviors [2, 3]. The behavior of people towards pain is transcultural and is influenced by patients' beliefs and culture.



Fig. 1 Multidimensional model of chronic pain



Cancer pain is one of the major burdens for survivors along with depression and fatigue and has a strong impact on quality of life [4]. Nevertheless, it remains underdiagnosed, poorly evaluated, and undertreated [5–12]. This is mainly due to healthcare professionals' insufficient knowledge of cancerrelated pain, which impedes quality management of this multimorphic disease [13, 14]. The cancer pain requires multimodal, targeted, dynamic, and personalized management (Fig. 2) including, in addition to pharmaceutical strategies and/or interventional therapies, the use of non-pharmacologic, non-invasive approaches, called complementary integrative therapies (CITs), especially when pain control becomes hazardous [15–19]. Due to the multimorphic character of cancer pain, patients experience frequent changes/exacerbations related to evolution and treatment of cancer, and to disruptive events (concomitant treatments, associated disease pains, comorbidities, and complications, modifications of the environment) (Fig. 3). Repeated inappropriate management of these exacerbations may create a vicious circle impacting the four dimensions of cancer pain (Fig. 4). On the other hand, several CITs are already used by cancer patients on their own [20–22] and often without discussing their use with their physician [23]. Thus, clinicians have to handle appropriately this possible desire [24], especially in patients with poorly treated cancer-related pain.

CITs may directly act on certain aspects of cancer pain (Fig. 5). Their initiation allows not only supporting patients in their daily life (at their demand) but also to prevent or avoid worsening chronic cancer-related pain within a holistic strategy.

This review is an endeavor to highlight several non-pharmacologic, non-invasive interventions with proven efficacy on pain, or at least trends for it. Facing cancer patients often suffering from undertreated pain, at their consultations, the authors have carried out a critical reflection based on a

literature analysis and their clinical practice. For each domain, the literature search was set up on recent reviews and the latest publications on Medline.

Background to complementary and integrative therapies

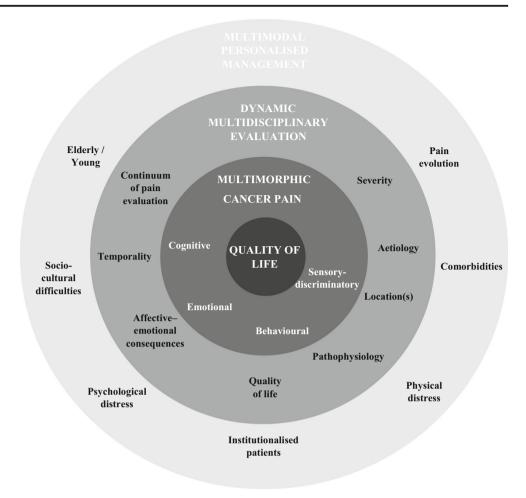
Due to cancer's potential life-threatening character, cancerrelated pain has long been considered as a minor secondary endpoint in clinical trials, and, when studied, it was mainly along with or as a component of quality of life. Thus, there is little room for clinical trials in mainstream pain therapies, and even less for CITs. Only trends for CIT efficacy or minor evidences of it have been obtained or even searched for in cancer-related pain. Furthermore, only few studies have addressed these issues in a longitudinal fashion, comparing patients with and without a history of cancer to differentiate between the effects of cancer and those of aging [25].

The implementation of the CITs requires the participation of specialists and of an interdisciplinary team to propose the appropriate complementary therapy to patients and answer any questions they may have. CITs can be classified in natural products (e.g., herbs, vitamins and minerals, probiotics), Mind and body practices (procedures or techniques administered or taught, e.g., yoga, chiropractic and osteopathic manipulation, meditation, and massage therapy; and other practices such as acupuncture, relaxation techniques, tai chi/qi gong, healing touch, hypnotherapy), and other complementary health approaches (e.g., Ayurvedic medicine, traditional Chinese medicine, homeopathy, and naturopathy) [26]. The effective CITs on pain address different dimensions of pain and often overlap.

Certain factors that initially appear non-modifiable strongly influence chronic pain and must be taken into account when envisaging the best cancer pain management [27]. These



Fig. 2 Model of the multimodal, targeted, personalized management of the multimorphic cancer-related pain



factors include age, sex, cultural and socio-environmental aspects, and inherited factors.

In this article, CITs potentially effective against multimorphic cancer pain are presented according to the dimensions of chronic pain they target primarily. The authors chose to focus mainly on mind and body practices, and not to cover the other two aspects (natural products and other complementary health approaches).

Sensory-discriminatory dimension

Physical exercise

Physical activity acts at a sensory-discriminatory level [28–31] and appears to both reduce stress and anxiety [32], and improve depression [33], as shown in general elderly populations [34]. The type of exercise must be adapted to the patient's physical condition and limits in order to avoid damage [35]. Thus, for patients with advanced disease, the physical therapist will look for a task to be completed instead of focusing on correction of individual impairments.

Most studies on the impact of physical exercise in cancer patients have focused on its benefit in terms of survival and quality of life, with cancer-related pain being a minor secondary endpoint. Nevertheless, physical exercise modifies the levels of circulating hormones (e.g., insulin, estrogens) and cytokines (e.g., IL-6, TNF- α), and induces other metabolic changes [36]. The changes in adipokine balance may impact the nociceptors with potential benefits in pain control [37].

Physical exercise (including community-based exercise programs, strength or resistance training, walking, cycling, stretching) has been associated with improved overall psychological, behavioral, and physical conditions [2, 36, 38, 39]. Higher levels of physical activity are associated with lower pain levels [40]. The efficacy of progressive resistance exercise training has been demonstrated in shoulder pain and disability and upper extremity muscular strength and endurance in head and neck cancer survivors [28]. Few other studies have shown a positive impact on pain of physical exercise combined with cognitive-behavioral therapies (CBT) or lifestyle programs [41–43]. Physical exercise must be tailored to obtain appropriate duration and intensity [31], but treatment-related activity barriers often need to be removed [44].



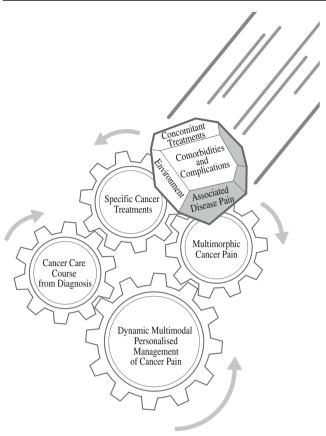


Fig. 3 Disruption key elements in the dynamic, multimodal, targeted, personalized management of multimorphic cancer pain

Physical therapy

Of the various applications of physical therapy, multifactorial physical therapy and active exercise are effective for treating postoperative pain after breast cancer treatment and impaired range of motion [45]. No such results have yet been obtained with passive mobilization, stretching, or myofascial therapy as part of the multifactorial treatment [45].

Therapeutic massage has been poorly studied in cancerrelated pain [46]. Exercise and manual lymphatic drainage have shown efficacy for lymphedema [38], as well as massage therapy in patients with metastatic bone pain [47]. In patients receiving chemotherapy, massage was beneficial for reducing pain, inducing physical relaxation, and improving mood disturbances and fatigue [48]. The significant effect of massage in reducing immediate pain was associated with an important decrease in nonsteroidal anti-inflammatory drugs use, and a trend for reduced opioid use. The evidence for analgesic effects of massage in non-cancer and cancer patients is nevertheless debated [49-51]. Massage may be perceived negatively by some women due to altered body image, modesty, or ethnocultural considerations [45]; on the other hand, tai chi/qi qong is more accepted nowadays in Western countries than it used to be [52]. Healing touch (energy therapy with light hand contact) has shown benefits on several symptoms in cancer patients during chemotherapy, especially reducing pain with significant short-term effect (less than a month), compared with the therapist presence alone or standard care [48].

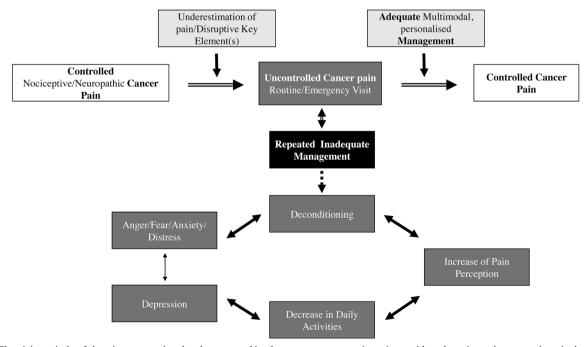


Fig. 4 The vicious circle of chronic cancer pain related to repeated inadequate management in patients with underestimated cancer pain or in the presence of disruptive key element(s)



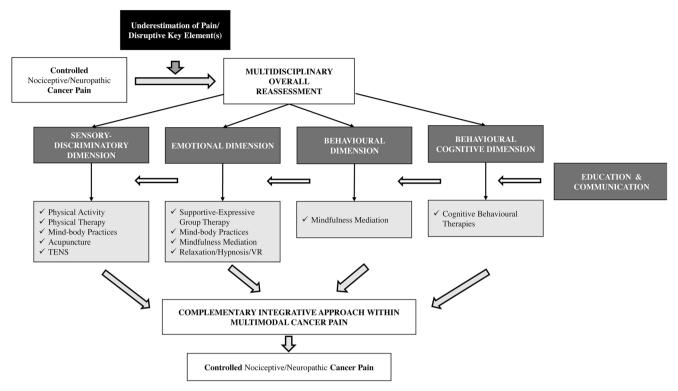


Fig. 5 Instauration of complementary integrative therapies within multimodal, personalized management of cancer pain according to their primary targeted domains after a multidisciplinary assessment. CBT,

cognitive-behavioral therapy; TENS, transcutaneous electrical nerve stimulation; VR, virtual reality

Yoga, tai chi, and qi gong

Even though interest in mind-body interventions such as yoga is growing for minimizing the deleterious effects of cancer-related symptoms [53–56], few studies have been conducted on pain. In cancer survivors, the variability of yoga efficacy on pain ranged from non-significant to considerable (in two of four studies) [57]. Yoga awareness programs including CBT elements and meditation and breathing exercises improved joint pain in breast cancer survivors [58]. Relaxation, breathing exercises, and/or yoga programs focused on cancer-related pain are often successfully associated with CBT interventions [45]. Furthermore, yoga appeared to be particularly efficient in aromatase inhibitor-associated arthralgia [58, 59].

Qi gong and tai chi studies have reported positive findings for both physical and psychological functions, including reducing non-cancer pain and perceived stress [60]. In cancer survivors, tai chi and qi gong significantly improved fatigue, sleep difficulty, depression, and quality of life [61, 62], but only a trend for pain improvement was observed. Otherwise, compared to health education control, tai chi did not provide further improvement to pain [63].

Acupuncture

Literature review showed that acupuncture plus drug therapy is more effective than conventional drug therapy alone for cancer-related pain, while the reduction in cancer-related pain with acupuncture alone was not greater than that of conventional drug therapy [64, 65]. Somatic and auricular acupuncture plus drug therapy resulted in benefits in cancer pain, and better quality of life (when measured) without serious adverse effects, the quality of all outcomes being mainly low [64]. A recent meta-analysis showed the efficacy of acupuncture in malignancy-related and surgery-induced pain as part of a multimodal management, but not for chemotherapy- or radiation therapy-induced pain [66]. Acupuncture may be considered for pain related to aromatase inhibitor-associated musculoskeletal symptoms [67–70]. As for other CITs, high-quality clinical trials with larger sample sizes should dispel any doubt about its efficacy [71].

Electrical nerve stimulation

For more than two decades, transcutaneous electrical nerve stimulation (TENS) has been used without clear evidence of



efficacy in any type of chronic pain, including chronic cancer treatment-related pain. Its effectiveness might be explained by supportive environment or a placebo effect [72, 73]. Clinical experience supports a trend for efficacy in some patients. A new electrocutaneous nerve stimulation device has been designed to "scramble" afferent pain signals and replace them with "non-pain" stimuli through conventional lines of neural transmission (scrambler therapy), above and below the site of pain. Trends for efficacy have been reported in patients with neuropathic or mixed pain [74]. Scrambler therapy has also shown a trend for efficacy in patients with cancer pain (pilot studies) [75, 76].

Emotional dimension

As shown in breast cancer survivors, depression is highly associated with other cancer-related symptoms such as pain, fatigue, and insomnia [77]. Mind-body interventions (e.g., relaxation, meditation, imagery, hypnosis, music therapy, virtual reality) may help relieve depression, stress, anxiety, and other mood disturbances associated with pain, and reduce cancer-related pain [45, 78].

Supportive-expressive group therapy

Of psychological interventions, supportive-expressive group therapy significantly improved cancer pain scores at 12 months compared with usual practice, in a meta-analysis of three studies [79].

Guided imagery

Relaxation with imagery (or mental rehearsal imagery) mainly consists in patients mentally creating a peaceful comfortable physical place. In several studies, there were small to moderate improvements in cancer-related pain; however, these studies were of low methodological quality [80–83].

Virtual reality

Virtual reality (VR) has been used to manage pain and distress associated with a wide variety of known painful medical procedures, such as burn pain and wound care, chemotherapy, lumbar puncture, and port access in cancer patients, with very few, only mild, short-term side effects [84–88]. VR has been used with success in rehabilitation systems to treat cancer survivors coping with upper body chronic pain [89]. In hospitalized patients, pain relief was obtained with VR in significantly more patients than with control distraction conditions (high-definition, 2D video), and mean pain reduction was significantly greater [90]. Participants immersed in a VR experience reported reduced pain levels, general distress/

unpleasantness and a desire to use VR again during painful medical procedures [91].

Hypnosis

During the treatment period, several meta-analyses and randomized clinical trials have shown beneficial effects of hypnosis on cancer-related pain relief, treatment procedures, and concomitant disease (e.g., mucositis), in addition to its activity against distress or anxiety [2, 45, 92]. In survivors, hypnosis has been studied to a lesser extent and a recent study has shown great improvements in symptoms using the Valencia model of waking hypnosis with cognitive-behavioral therapy (VMWH-CBT), including alleviating cancer-related pain [93]. The efficacy of hypnosis is well established and is the only non-invasive CIT recommended in France [94]. Hypnosis has been used in a group therapy context for more than two decades, and greater benefit on pain relief related to advanced breast cancer was reported in highly hypnotizable participants [95–97].

Music therapy

Music therapy is either passive or active (i.e., with patient participation in creating live music) and it seems to act through neurologic, psychological, behavioral, and physiologic pathways [45]. The efficacy of interactive or passive music therapy in relieving cancer-related pain is supported by moderate evidence, and music therapy may reduce anesthetic and analgesic consumption and the length of hospitalization [92, 98–102].

Behavioral dimension

Patients with cancer often present frailty and build attitudinal barriers to cancer pain management. Fear of addiction to opioids is the strongest barrier in patients, and these attitudinal barriers are associated with less effective pain control [103]. Attitudinal barriers to pain and the use of analgesics are shared by patients and their family caregivers [104], often based on cultural and religious barriers [105–107]. The perceived barriers appear to be significantly higher in Asian patients than Western patients with no differences between other ethnic groups [108, 109].

Mindfulness mediation

During exposure to pain, meditators exhibited modifications on magnetic resonance imaging [110], leading to the conclusion that changes in the perception of pain were facilitated through the cognitive and affective components of the pain matrix, rather than through the sensory properties of pain. Mindfulness-



based methods, including mindfulness-based stress reduction (MBSR, a structured group program), are deemed effective for conditions such as chronic pain by increasing mindfulness and pain acceptance, as well as improving emotional functioning [111-113]. MBSR programs have shown effects on some chronic pain conditions, but not all, and compliance with home meditation practice did not favor pain improvement [114]. However, in chronic pain, the benefits of mindfulness-based meditation strategies remain controversial as in recent reviews and meta-analyses pain reduction during treatment was not clearly and unambiguously demonstrated [115, 116]. Considering cancer patients, MBSR has shown benefits on sleep disturbance and fatigue [92], but no clear benefit is established on cancer pain [117, 118]. Relaxation training was found to significantly improve pain and other treatment-related symptoms in a meta-analysis in cancer patients undergoing acute non-surgical cancer treatments [119].

Cognitive dimension

Most of the performed studies focused on both the behavioral and cognitive dimensions of pain and do not distinguish the cognitive dimension solely. Therefore, the interventions presented in this section cover cognitive dimension associated with behavioral one.

Cognitive-behavioral therapy

Cognitive-behavioral therapies (CBTs) have a common base of behavioral and cognitive models of psychological disorders and utilize a set of overlapping techniques that can be used to improve chronic pain problems by decreasing patient catastrophizing and increasing patient self-efficacy for managing pain [112, 120, 121]. CBT has proven its efficacy in chronic pain and its cost-effectiveness for several decades [122]. More recently, the third wave of CBT approaches integrate strategies such as mindfulness exercises, acceptance of unwanted thoughts and feelings, and cognitive diffusion [123]. Psycho-education on stress and coping have been added to cognitive-behavioral stress management (CBSM) [124, 125].

CBT, CBSM, or similar mind-body combination interventions produced improved cancer-related pain in most studies [2, 82, 83, 92, 126–129]. Their effects seem mainly due to improved pain catastrophizing [130]. During post-treatment survivorship, CBT showed some promising results in a small study in improving chronic pain and coping with pain [131].

A recent review found some evidence for potential predictors or moderators of outcomes in contextual CBT for chronic non-cancer pain [132]. Using mindfulness-based interventions, patients with higher psychological distress or a history of depression tended to obtain the greatest improvements in

chronic pain [133–135]. However, two studies on online interventions of acceptance and commitment therapy found that lower psychological distress led to greater improvements in pain-related interference [136], and found no association between baseline depression diagnosis and outcomes [137]. A study on pre-surgical stress management training in cancer patients revealed no effect on pain, or anxiety and sleep problems [138]. The outcomes of CBT interventions depend on the methodology and approach used (e.g., face-to-face vs online). Nevertheless, such outcomes again emphasize the need for high-quality clinical trials.

Education and communication

Educational interventions are generally defined as information, behavioral instructions, and advice on pain management delivered by a health provider or peer (such as an expert patient) using any medium (for example, verbal, written, taped, or computer-aided) [126]. The intervention significantly improved knowledge and attitudes towards cancer pain and analgesia, but high heterogeneity has been reported [126]. No pain reduction in daily activities or improved medication adherence was observed. In advanced-cancer patients, a combined intervention that included oncologist communication training and coaching for patients improved only patientcentered communication [139]. Conversely, a patientcentered approach combining pain consultations and pain education programs improved pain intensity, daily interference, and adherence to analgesics [140]. Similarly, patient-centered tailored education and coaching improved communication self-efficacy and enhanced patient involvement in care compared to education only, with analgesic adjustment associated with better sustained pain control [141].

Self-management education interventions have been shown to improve pain and other cancer-related symptoms (and quality of life) [142]. Self-management is the capability of a patient to manage pain, analgesic treatments, and the physical and psychological consequences of living with cancer-related pain [19]. However, Howell et al. were not able to determine the components or elements of these interventions impacting the strength of the effects. Different potential levels of intervention may affect pain intensity, such as coaching, nursing support, and the use of a diary on pain intensity and analgesic intake [143, 144].

The systematic use of patient-reported outcome (PRO) measurements with feedback to increase discussions between patients and professionals may improve cancer pain management [145]. However, only modest reductions have been reported in cancer pain intensity when PROs were used with other coaching tools [146, 147]. PROs may be of interest when patients make tradeoffs between opioid side effects, physical activity, cognitive function, and pain relief [148].



Finally, as shown by Street et al., cancer patients who need to communicate with their physician prescribing pain medication are keen to discuss pain-related matters, and state preferences which can elicit changes in their pain management regimen leading to better pain control [149]. In addition to the direct advantages of self-management over attitudinal barriers, truly balanced communication between patients and healthcare teams, leading to informed choice, must be part of the patient healthcare pathway.

In this context, new opportunities are becoming available to cancer patients in geographically dispersed urban and rural oncology practices. Centralized telecare management through physician and nurse or physician and clinical pharmacist [150] collaboration facilitated optimized medication management by assessing symptom response and medication adherence, and providing pain and depression-specific education. This centralized telecare management coupled with automated symptom monitoring resulted in improved pain and depression outcomes in these cancer patients [147, 151]. In this context, digital technologies may soon offer new opportunities of communication, helping patients share individual symptom experiences and goals, thus enhancing tailored care [152]. Regular, balanced communications between patients and their clinicians, as well as within the interdisciplinary team, are thus necessary for long-lasting cancer pain control.

Discussion

Cancer-related pain requires multimodal, targeted, dynamic, and personalized management (Fig. 2), which can include non-pharmacologic, non-invasive approaches, in addition to pharmaceutical strategies and/or interventional therapies. The CITs address the different dimensions of pain and they often overlap (Fig. 5).

Some of the CITs represent alternative therapies already used by cancer patients on their own without informing their health professionals [20, 21, 23]. Their use is often caused by dissatisfaction with conventional medicine, desperation, and compatibility between the philosophy of alternative therapies and their own beliefs [22]. Therefore, there is a need to establish a truly balanced communication between patients and healthcare teams in order to propose the most appropriate CIT and in adequacy with the ethnocultural and sociological expectancies of patients.

On the other hand, healthcare professionals' attitudes still compromise the delivery of quality care to patients with chronic cancer pain [13]. Primary care physicians report a lack of knowledge in the management of chronic pain in cancer survivors [14]. Because of the multimorphic nature of cancer pain the need for multimodal management, which requires interdisciplinary teams, is another barrier [153]. Six-month educational programs for healthcare professionals,

implemented to alleviate these barriers, led to a significant improvement in their knowledge and attitudes resulting in improved cancer pain management [154].

In this context, the personalized management of cancerrelated pain is particularly sensitive when proposing CITs to reach optimal holistic care in agreement with patients' beliefs and preferences [117]. That being said, choosing CIT(s) is complex due to the overlap between cancer-related pain dimensions. Complementary body-oriented therapies for pain, at every stage of the disease, may result in "body" and/or "mind" improvement. In addition, this improvement may parallel an important benefit regarding cancer evolution or quality of life leading to difficulties in recognizing the benefits on cancer-related pain unless specifically designed RCTs are set up. Physical activity thus participates in the increase in overall survival observed in most cancers with a dose-response relationship [36]]. Regular sustained or intense exercise also presents physiological and psychological benefits [31, 155, 156]. Nevertheless, the principles of physical activity vary greatly in randomized clinical trials, and reporting of the exercise actually performed was incomplete [157]. Methodologically stronger clinical trials of CITs are still needed to provide clinicians with accurate resources for managing cancer-related acute pain [158].

Keeping in mind these methodological weaknesses in the available studies, choosing the appropriate CIT(s) may be driven by the dimensions of cancer pain impacted by genuinely balanced communication between patients and healthcare teams. The formalized informed choice must be part of the patient healthcare pathway and evolve as the conditions change. CIT use may result in better acceptance of pharmacologic therapies due to control of adverse effects and overall positive feelings supported by a more constructive patient-health professional relationship [149].

Even though the levels of evidence may sometimes be moderate or low, the improvement in the patients' overall psychological, behavioral, and physical conditions observed with the different CITs should lead to better-designed RCT to comfort their efficacy if any. The already observed improvements and patients' demands strengthen the need for multidisciplinary teams in oncology settings to integrate analgesic care and expertise in CITs to offer personalized management [2].

Conclusions and perspectives

Few clinical trials have been conducted in the different stages of cancer to assess complementary and integrative therapies, and their efficacy is mainly based on professional judgment and patient preferences. CITs should be chosen in adequacy with the ethnocultural and sociological expectancies of patients. Proposing the CIT(s) by the clinicians might prevent patients turning to uncontrolled (pseudo or non) therapies,



independent of pain level. Finally, implementation of CITs require an interdisciplinary team to offer optimal patient-centered pain management.

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Compliance with ethical standards

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