Psychological and non-pharmacologic treatments for pain in cancer patients: a systematic review and meta-analysis

Running tittle: Pain in cancer patients

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Abstract

Context. Pain is the most fearful symptom in cancer. Although there is a relationship between psychosocial variables and oncologic pain, psychological and non-pharmacological treatments for pain management in cancer patients are not very widespread.

Objectives. To analyse the efficacy of psychological and non-pharmacological treatments for reducing pain in cancer patients.

Methods. We performed a systematic review following the PRISMA protocol. In January 2021, data were extracted from PubMed, Web of Science and Scopus, including randomised controlled trials (RCT) published in the last five years (from 28th January 2015 to 15th December 2020), in the English language and whose sample was patients with cancer pain. The database search used the following keywords: cancer, cancer-related pain, psychological intervention, non-pharmacologic intervention. The Cochrane risk of bias assessment for randomised trials (RoB 2) was used for quality appraisal.

Results. After the inclusion and exclusion criteria were applied, ten papers were fully screened. The evidence suggests that the most effective interventions to reduce cancer pain were mindfulness-based cognitive therapy, guided imagery and progressive muscle relaxation and emotional and symptom focused engagement (EASE). Music therapy and brief cognitive behavioural strategies (CBS) require more research, while coping skills training and yoga did not show positive effects. Overall, we obtained a moderate size effect (d = 0.642, 95% CI: 0.125 to 1.158) favourable to psychological and non-pharmacologic treatments at post-treatment, which increased at follow-up (k = 5, d = 0.826, 95% CI: 0.141 to 1.511).

Conclusion. This study provides insight into psychological interventions which might be applied and contribute to cancer-related pain reduction in adults. Although the results are

not completely consistent, they may shed a light on psychology applications in the oncology environment.

Keywords: cancer; pain; psychological treatment; systematic review; meta-analysis

Introduction

Cancer is a health problem worldwide. According to recent data, it is one of the principal causes of morbi-mortality in the world. Populations estimates indicate that the number of new cases in the next two decades will increase up to 30.2 million in the world. Regarding to the worldwide incidence, the most frequently diagnosed tumours in 2020 was breast, lung, colon and rectum, prostate, and stomach.[1]

Pain is the most fearful symptom in cancer and, frequently, it is not well evaluated and treated, despite the current control possibilities.[2] Despite these control efforts, according to different authors,[3,4] pain is present at the time of diagnosis in 30-50% of cases and, as the illness progresses to advanced stages, between 70-90% (within this last percentage, the 70% belongs to a kind of pain related to illness progression and the remaining 30% is linked to the treatments used or other diseases). Although there has been considerable progress in the study, diagnosis, and treatment of cancer-related pain. It is calculated that 30% of cancer patients are diagnosed in an early stage while the diagnosis is delayed in 70%. Of these oncology patients, 58% present with pain; of these patients, 33% refers to only one type of pain, another 33% to two types and the remaining 33% to three or more types.[5]

Pain has important consequences in the patients' daily life. The quality of life (QoL) seems diminished, causing a devastating effect on many daily life aspects of the patient.[6] Several investigations have demonstrated that cancer-related pain is associated with sleep disorders,[7] isolation,[8] and lack of appetite or activity reduction.[9] According to some authors, approximately 69% of patients with cancer experience pain during their

daily activities, which may have dangerous psychosocial consequences, such as anxiety or depression.[10] Around 50-70% of cancer patients suffer from uncontrolled pain which, in many cases, leads to anxiety, depression, suicidal tendencies, and more fear of pain than of their own death.[11,12]

There is also a relationship between psychosocial variables and oncologic pain.[13] Previous studies have pointed out the correlation between depression and oncologic pain; specifically, they observed a significant relationship between both variables when pain is referred to in a short gap of time. The connection between pain and depression, according to these authors, appears to be in the physiological mechanism behind both processes.[14] The neurotransmitter concentration imbalance (serotonin and noradrenaline) that causes depression is also the responsible for the cancer-related pain sensitivity threshold reduction.[15] Although the prevalence of depression varies considerably in this group of patients (from 0-58%), cancer is linked with a high level of depression.[16] O'Mahony et al.[17] claim that, under intense pain, oncologic patients have the desire for advancing their death. Furthermore, these authors observed that this desire tends to improve if strategies focusing on the state of mind are applied.

Regarding to Pozo-Kaderman and Pirl,[18] oncologic pain is underdiagnosed and undertreated. Also, poor pain management might cause depression and anxiety. Accordingly, considering the different treatments and interventions developed for reducing cancer-related pain, it is necessary to highlight that, although pharmacological/medical treatment is very effective, adverse side effects such as constipation, dizziness, or sickness are very common and result in a lack of adherence to treatment. Moreover, the highly addictive potential of some analgesics like opioids is a serious disadvantage. It is important to say that, even though the proper use of drugs reduces pain, a lot of patients express that it is uncontrollable. In addition, surgical

interventions employed at present are very expensive and they are not universally accessible.

The beliefs of many health professionals and patients about pain are inseparable from the suffering human beings experience; oncologic pain is unavoidable and very common.[19] Ironically, these same professionals have expressed the difficulty related to pain treatment, and there are problems in recognising that this pain has a psychological component, which also needs treatment. For all of this, in addition to pharmacological treatment for cancer-related pain management, non-pharmacological options and complementary therapies are being contemplated.[20]

The American National Comprehensive Cancer Network recommends the use of non-pharmacological interventions if the pain level is at 4 or above (on a scale of 10) after pharmacological treatment has been evaluated and readjusted.[21] The aim of non-pharmacological interventions is to treat the affective, cognitive/psychological, behavioural, and socio-cultural dimensions of oncologic pain. Generally, within this category, there are physical, cognitive-psychological, and behavioural methods, both invasive and non-invasive.

Oncologic patients are affected by a different ethology of pain; for this reason, there is clear evidence for the necessity and importance of this intervention. Due to pain multidimensionality, it affects many areas of patient life, and has a negative impact on many different levels of their lives. For this reason, therapies targeted to cancer patients must include resources directly generated from psychology with demonstrated efficacy and utility to provide patients with tools that help with symptom management, like acceptance and commitment therapy, mindfulness, or some versions and techniques based on cognitive-behavioural therapy.

The psychological intervention must not be understood as an alternative intervention when other therapies have failed, but as a complementary therapy that provides and complements the positive effect of other treatments.[22] Non-pharmacological therapies, as well as psychological treatments, are an important addition to pharmacological therapies in the development and relief of pain; in some cases, they can also be used as unique therapies.[23]

The previous evidence suggests the need to conduct multimodal interventions that include psychological aspects and treatments for patients with cancer, combining the medical and pharmacological experience with non-pharmacological interventions, physical therapy, and social approaches.[24]

Non-pharmacological therapies are frequently used as complementary therapies. When these strategies are used in conjunction with conventional therapies, the term integrative medicine is used.[25] Little by little, this strategy has become more present in practice, with a wide spectrum of components including psychological treatments that are very helpful to palliate this pain in patients. There is evidence for the efficacy of these treatments in cancer patients and survivors, leading to an increase in sleep QoL, state of mind, stress levels, and anxiety.

In this sense, different investigations have focused on non-pharmacological interventions for cancer-related pain management, but the current literature lacks systematic reviews related to this topic of investigation.[26]

Aim

Based on what has been presented about the benefits of combined therapies, which include psychological and non-pharmacological interventions, the avoidance (to the greatest extent possible) of drug use, in addition to the limited evidence for non-pharmacological treatments, the aim of this systematic review and meta-analysis was

evaluate, analyse, and systematise the efficacy and quality of the current empirical evidence about psychological and non-pharmacological interventions for reducing cancer-related pain in adult patients.

Method

Protocol and Registration

This systematic review and meta-analysis were developed according to the PRISMA statement.[27] The PRISMA checklist was applied (see Supplementary material 1). The inclusion and exclusion criteria were identified prior to the document search and the review protocol was registered in PROSPERO with number CRD42021251472.

Search strategy

In January 2021, the search was done in databases including PubMed, Web of Science, and Scopus. Furthermore, the grey literature, which was found using browsers such as Google Scholar, was finally excluded, due to the scarce validity and heterogeneity of the results. It focused on the evidence published between 28th January 2015 to 15th December 2020; the search was performed in English. For better precision in the search strategy, the structure was adapted to each database. For example, the PubMed search was: ((‘cancer’ OR ‘cancer-related pain’ OR ‘cancer pain’ AND (‘psychological intervention’ OR ‘non-pharmacologic’ OR ‘alternative medicine’ OR ‘pain management’)). For Web of Science (WoS) similar descriptors were used: ((‘cancer pain’ OR ‘cancer-related pain’ AND (‘psychological intervention’ OR ‘complementary therapies’)). For SCOPUS, the search was limited to ((‘cancer-related pain’ AND (‘psychological intervention’ AND (‘systematic review’)).

All the authors decided, jointly, on the inclusion and exclusion criteria, and developed the search strategy. The search and data extraction were accomplished by two independent reviewers blinded to each other. It was previously established that possible

discrepancies would be solved by discussion. If there was no agreement after the discussion between reviewers, a third author could be consulted to solve the discussion. Data about the objective of the research, design, participants, interventions, and main results were obtained in each document.

Selection of studies

Inclusion criteria

The PICOS criteria were: (P) adult patients with cancer aged from 19 to 70 years, including women and men, (I) non-pharmacological and/or psychological interventions, (C) control group: waiting list, placebo, treatment as usual (TAU), or other intervention different to the principal, (O) pain reduction as a principal aim of the intervention, (S) randomised and controlled clinical trials (RCT) published in English or Spanish.

(1) Studies in English or Spanish published after 2015, more specifically randomised clinical trials including a control group in which the efficacy comparison could be done or where the difference between the application of the main therapy and the control group intervention could be significant (either by placebo, usual treatment, or any different intervention to the principal one). In cases where there was no control group, the study must show that the target intervention has higher efficacy in the sample compared to the other one applied.

(2) Interventions must be psychological or non-pharmacological; in other words, interventions must be non-invasive or not have chemical effects in the participants.

(3) The participants must be adult women and men (aged between 18 and 70 years) with a cancer diagnosis.

Exclusion criteria

Taking into account all of these criteria, studies were excluded that: (1) had been published in other languages; (2) did not have an RCT design, did not have a control group to which a treatment different than the one studied was applied, or did not demonstrate significant target therapy efficacy against the others included; (3) used or apply medical or pharmacological interventions; (4) included patients waiting for a biopsy/diagnosis or who had overcome the disease; (5) included children or young adults exclusively; (6) performed a pain study associated with other pathologies or related to diseases other than cancer; (7) had overly broad inclusion criteria with participants that did not fulfil the criteria of this review; (8) included participants who did not have a basic level of education or whose cognitive abilities were affected by the illness or any kind of mental disability; (9) did not include any of results related to the aim of this review. For that matter, fatigue was excluded as a result of interest for being a broadly defined concept, which may lead to confusion.

Search outcome and data abstraction

The search strategy identified a total number of 5.367 documents from the different electronic databases. After removing duplicates and applying the inclusion/exclusion criteria, 29 documents remained for full text access. Further analysis of the papers led to the exclusion of 19 papers, resulting in the final papers included in the review. After study selection, 10 articles were included; Figure 1 shows an abbreviated summary of this process. During this selection procedure, new inclusion/exclusion criteria were defined, as it was decided to be more flexible with the sample age (at first from 18 to 44 years), because many studies had a mean age of 60 years, and thus conformed to this new range of 18 to 70 years. Studies with overly broad inclusion criteria were excluded. Then, due to the considerable presence of investigations

with this feature, it was decided to include studies in which the sample was exclusively comprised of women, as well as mixed sample studies. A category for biased or inconsistent results was added to the flow diagram, to exclude those investigations where the results were not reliable, ambiguous, or showed some king of bias that invalidated the results. Finally, investigations in which the aim of study was too wide were discarded, as were those that were irrelevant or did not sufficiently investigate our topic (it barely mentioned pain, focused on other oncologic symptoms, or spoke of chronic and long-term diseases other than cancer). Studies in in which the search design was quasi-experimental (samples were not randomised) were also excluded.

Quality appraisal

One reviewer assessed the methodological quality using the Cochrane risk-of-bias tool for randomised trials (RoB 2) from *The Cochrane Handbook for Systematic Reviews of Interventions - the Handbook*[28] while another reviewer re-assessed the domains evaluated and summarised the main results in a graph (Figure 2). The Cochrane Handbook is a revised tool that provides guidance to the authors for the preparation and maintenance of systematic reviews based on health interventions or treatment effects. RoB 2 is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct and reporting. Within each domain, a series of questions ('signalling questions') aim to elicit information about features of the trial that are relevant to risk of bias. Judgement can be 'low' or 'high' risk of bias or 'unclear'. The domains mentioned are (1) random sequence generation, in the particular case of this review, randomisation process, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete of outcome data, (6) selective reporting (reporting bias), (7) other bias. The process allows reviewers to assess the potential risk in these seven areas for validity purposes.

Synthesis

This review is reported using the items of the PRISMA checklist.[27] Data extracted from the reviewed studies were tabulated (Table 1). The study selection process is discussed in detail in terms of study selection, screening, and inclusion. A synthesis of the key characteristics (i.e., country and setting, population, design, and measured outcomes) is also presented in Table 1. Findings from individual studies and each potential risk assessment of the studies are presented in the data extraction table.

Meta-analytic procedure

A meta-analysis was performed to evaluate the overall effect of psychological and non-pharmacological therapies to reduce pain. To do this, we use the values of "intensity" or "severity" included in the studies analyzed for the experimental and control groups at post-treatment and nine to twelve weeks follow-up. First, Cohen's *d* (bias corrected) was calculated for each study as a measure of the differences between the standardized mean changes (pre-post) of the experimental and control groups. To obtain the standardized mean changes, we used the formula $d = c \cdot [(Mpre - Mpost) / SDpre]$, where *c* is the bias correction factor, *Mpre* and *Mpost* are the means of the pre-test and post-test scores, respectively, and *SDpre* is the pre-test standard deviation score[29]. For each study, *d* was calculated for the experimental and control group, providing the *d* index of the general size from the differences between them. The 95% confidence intervals for every effect size were also calculated. By last, the Comprehensive Meta-Analysis software (version 3.3) was used to perform the meta-analysis.

We expected a high heterogeneity among the effect sizes of the studies, due to the variety of interventions included. Thus, a random effects model was used, which assumes that the effect size might vary from one study to another. Effect size heterogeneity was analyzed by means of *Q* and I^2 statistics. The *Q* statistic indicates whether the

heterogeneity is significant and I^2 shows the percentage of heterogeneity. I^2 values around 75%, 50%, and 25% indicate high, moderate, and low heterogeneity, respectively.

Results

The systematic search generated 10 articles published between 2015-2020. Figure 1 represents the PRISMA diagram.[27]

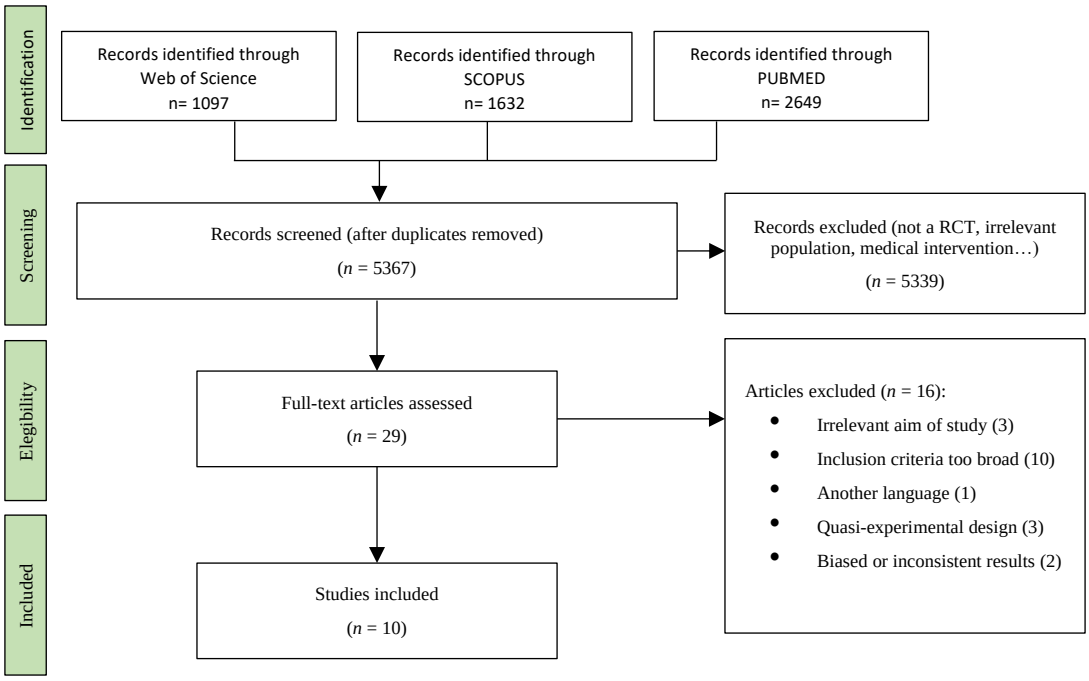

Figure 1. PRISMA-based flux diagram of the review process (Liberati et al., 2009; Moher et al., 2009).

Description of included studies

All studies used an experimental design (RCTs), where all had a control group. Studies were conducted in: the United States (3); Denmark (2), Germany (1), Iran (1), Brazil (1), Canada (1), and Cyprus (1). Three of them focused on music therapy, two on mindfulness-based cognitive therapy (MBCT), and the rest of them focused on pain coping skills training, progressive muscle relaxation + guided imagery, yoga based on mindfulness, and emotion and symptom focused engagement (EASE). The most commonly used instruments in the studies were the Brief Pain Inventory (BPI; n=5) and the Visual Analog Scale (VAS; n=2) for pain assessment. Table 1 shows and summarises the characteristics of each study.

Quality appraisal

Among the 10 studies included and assessed by the RoB 2, as can be observed in Figure 2, the highest risks of bias were in areas related to incomplete outcome data (attrition bias), blinding of participants and personnel (performance bias), and selective reporting (reporting bias). An unclear risk of bias in the studies included in this review was found for other bias and selective reporting (reporting bias). The domains with low risk were random sequence generation (selection bias), allocation concealment (selection bias), and blinding of outcome assessment (detection bias). Moreover, many studies did not specify data extraction methods and blinding process among their participants or show the complete outcomes of the investigations (including the ones which were not so suitable for the studies purposes).

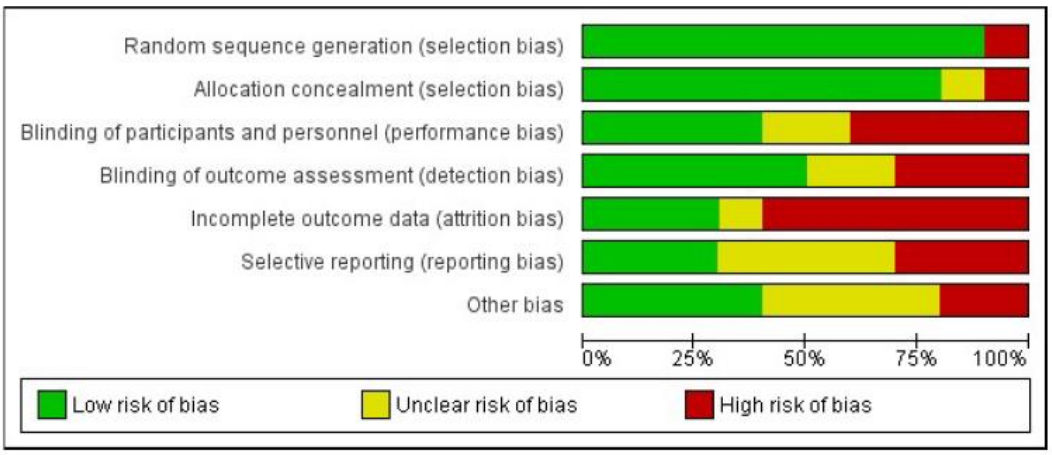

Figure 2. Risk bias assessment graphic for the studies included in the review (N=10) presented in percentages of the different domains assessed

Systematic Review

This review included treatments and therapies divided into psychological and non-pharmacological interventions or strategies. Table 1 presents the characteristics of the interventions.

Table 1

Data from the RCTs included with a risk of bias assessment summary

Citation	Relevant aim of study	Study design	Participants features	Intervention features	Relevant findings	Risk of bias assessment						
						R	AC	BP	BA	ID	SR	OB
Arruda et al. (2016)	Music therapy & poetry effects evaluation for cancer related pain relief in comparison to TAU*	Brazil August 2016- Sept. 2016 Instruments: Visual Analog Scale for pain-VAS (α=>.76), Beck Depression Inventory-BDI (α=.89) & Herth Hope Scale (α=.97)	N=65 (47W* & 18M*) Age: 18->60 years Inpatients with breast, urogenital, leukaemia, gastrointestinal and others diagnosis and treatment	Music therapy group: passive listening with headphones recorded in MP3 Poetry group: poetry listening Control group: TAU* 1 session of 30 min each 3 days, during 3 months	Statistically significant pain decreases in music therapy group in comparison to the control group (p<.001). Also, in poetry group regarding to control group (p<.001)	+	+	?	?	+	+	+
Charalambous et al. (2016)	Progressive muscular relaxation + guided imagery efficacy on pain in comparison to TAU	Cyprus December 2015-June 2016 Instruments: EORT QLQ C30 + BR 23 (α=>.70), 11 point pain numbered rating scale-NPRS (α=.70), Cancer fatigue scale (α=.88), revised Rhodes index of nausea, vomiting and retching (α =.88), Zung self-rating anxiety scale (α=.83) & BDI (α=.89)	N= 104 (52W* Y 52 M*) Age: 31->60 Patients diagnosed with breast or prostatic cancer under chemotherapy treatment.	PMR* + GI* group: breathing exercises sessions, followed by progressive muscular relaxation and finally, pleasure guided imagery Control group: TAU* for cancer symptom improvement 4 weekly sessions of 27 min during one month	PMR+GI group showed lower pain levels than control group. The treatment was statically significant over the time (p<.0001) in PMR+GI group regarding to pain level.	-	-	+	-	-	-	-

Citation	Relevant aim of study	Study design	Participants Features	Intervention features	Relevant findings	Risk of bias assessment						
						R	AC	BP	BA	ID	SR	OB
Johannsen et al. (2016)	Mindfulness based on cognitive therapy efficacy assessment on pain among other symptoms due to oncological treatments/interventions versus waiting list patients	Denmark June 2016 Instruments: Mcgill Pain Questionnaire/SF-MPQ-2 (α=.90, Hospital anxiety & depression Scale - HADS(α=.80), World health organization-5 well-being index (α=.83)	N=129 (100% women) Medium age: 56.8 years Patients with primary breast cancer who had overcame chemo/radiotherapy or surgery	MBCT group: received mindfulness breathing exercises & psychoeducation + cognitive exercises Control group: waiting list. They were just called several times to fulfil some questionnaires once the experimental group intervention finished. 8 consecutive weeks, 1 weekly session of 2 hours + 45 min exercises at home.	It was shown statically significant improvements, prolonged over time, on MBCT group pain level in comparison to control group. Both in pain intensity (*d*=0.61), as in pain perception of patients (*d*=0.26). Neuropathic pain also decreased considerably (*d*=0.24).	-	-	?	?	+	?	-
Johannsen et al. (2017)	Influence analysis of certain clinical and psychological moderators about cancer related pain reduction with a MBCT efficacy in comparison to waiting list group	Denmark September 2016- January 2017 Instruments: 11 point pain numbered rating scale-NRS (α=.70), HADS(α=.80), SF-Experiences in close relationships (α=.90) & 20 item Toronto alexithymia Scale (α=.77)	N=129 (100% women) Medium Age: 56.75 Women with primary breast cancer who already finished chemotherapy and radiotherapy or surgery	MBCT group*: mindfulness + cognitive exercises Control group: waiting list. Questionnaires filling before and after treatment by MBCT group, after 3 months and after 6 months. 8 weeks, 1 session of 2 hours	After previous MBCT efficacy evaluation on the sample, significant differences were found in those patients who had low attachment level or social support (*p*=.02) and, analysing side effect, it was observed a possible pain reduction and an efficacy increase of therapy in those who had previously received radiotherapy (*d*=0.49)	-	-	+	+	+	?	?

Citation	Relevant aim of the study	Study design	Participants features	Intervention features	Relevant findings	Risk of bias assessment						
						R	AC	BP	BA	ID	SR	OB
Kelleher et al. (2019)	Efficacy comparison between pain coping skills training (remotely) in comparison to face to face training	United States December 2018- May 2019 Instruments: BPI(α=.93), Patient Care Monitor (α=.70) & Chronic Pain Self efficacy scale (α=.87)	N=178 (128W*, 50M*) Medium age: 56.47 years Patients with diagnosis of breast, lung, colorectal and prostatic cancer	mPCST group*: cognitive behavioural sessions trough videoconference, previous symptom autoevaluation pre-session, sessions adapted to those symptoms, technological facilities for it adherence Control group: PCST* face to face in a medical center 7 sessions of 45 min, there was no time limit	There was no difference in pain intensity or interference between groups. It showed les wear (*p*=.02) and higher adherence (*p*=.03) to treatment in mPCST group. In both groups physical symptoms improved, but not pain. mPCST group showed a higher use of relaxation techniques (*p*<.001) day by day.	-	-	-	-	?	+	-
Kwekkeboom et al. (2018)	Proof the efficacy of recorded brief version of Cognitive behavioural strategies under cancer symptom cluster in comparison to psychoeducation	United States May 2018-August 2018 Instruments: 11 point pain numbered rating scale-NPRS (α=.70), Memorial symptom assessment scale(α=.85), MD Anderson symptom inventory (α=.92), Imaging ability questionnaire (α=.95), Outcome expectancy scale (α=.87), 10 item perceived stress scale (α=.87), Mood states SF(α=.92), CES*studies depression scale(α=.86)	N=164 (120 W*-44M*) Age: 29-79 years Non inpatients with metastatic cancer or recurrent (breast, gastrointestinal, lung, gynaecological, prostatic and others) who were undertreatment-	CBS group: educational block about CBS+ CBS intervention recorded on MP3 Control group: psychoeducation CBS listening on MP3 9 weeks (patients can conduct the number of sessions they want per week, but at least one). Sessions between 5-25 min	Slight punctual symptom improvement of CBS group in week 6 (*p*=.04). However, there was no significant differences regarding to symptomatology between groups.	-	-	-	-	+	?	-

Citation	Relevant aim of study	Study design	Participants features	Intervention Features	Relevant findings	Risk of bias assessment						
						R	AC	BP	BA	ID	SR	OB
Moradian et al. (2015)	Application of a type of audio/music effectiveness for vomit, nausea and other oncological symptoms reduction in comparison to TAU*	Iran November 2014 - June 2015 Instruments: revised Rhodes index of nausea, vomiting and retching (α =.88) & EORTC* QLQ C30 + BR 23 additional breast cancer questionnaire	N= 99 (100 % W*) Age: 27-70 years Breast cancer patients under chemotherapy treatment	Audio Nevasic + TAU group*: Nevasic programme listening **(Not used in this review)** Music therapy + TAU group*: music recorded in a CD listening trough headphones Control group: TAU* Sessions were self-administrated every day. Duration not indicated.	Non statistically significant differences related to pain reduction between experimental and control group (*p*=.78)	-	?	+	-	+	+	-
Porter et al. (2019)	Feasibility and efficacy of a yoga programme based on Mindfulness about pain, fatigue, insomnia, etc. In comparison to social support group	United States Sep.2018- March 2019 Instruments: Brief Pain Inventory SF-BPI (α=.93), Hospital Anxiety & Depression Scale (α=.80), Five Facet Mindfulness Questionnaire SF (α=.73)	N=63 (100% Women) Age: <50->70 Patients undertreatment for metastatic breast cancer and which do not practice yoga during the trial	Minful yoga group: postures instruction, breathing techniques and meditation, yoga principles for coping and discussion groups Control group: Social support group. Relevant issues for pain coping 1 weekly session of 2 h (completed treatment => 4 sessions)	Over time and after patients evaluation and follow up it was found certain improvement in symptoms such as anxiety, fatigue or tiredness. Related to pain non statistically significant decreases were found in none of the groups nor in interference degree (*d*=0.14) or intensity of itself (*d*=0.17).	-	-	-	-	+	?	+

Citation	Relevant aim of study	Study design	Participants features	Intervention Features	Relevant findings	Risk of bias assessment						
						R	AC	BP	BA	ID	SR	OB
Rodin et al. (2019)	Efficacy of the innovative technique "Emotion and Symptom focused Engagement" for symptoms of acute leukaemia in comparison to TAU*	Canada October 2018-April 2019 Instruments: Stanford acute stress reaction questionnaire (α=.83), Memorial symptom assessment scale(α=.85), BPI(α=.93), Illness therapy spiritual well-being scale (α=.86), BDI (α=.89), Family Satisfaction with care patient version (α=.9) & Edmonton Symptom Assessment Sytem-ESAS (α=.75)	N=42 (100% women) Medium age=52.86 years Patients with recent diagnosis of leukaemia or in relapse state who is undertreatment or waiting for chemotherapy treatment	EASE group: relational support + trauma-focused CBT (illness) along with systematic analysis of symptoms with continuous reference to early palliative care + TAU* Control group: TAU* 8 weeks, 1-2 sessions per week during hospitalization, the rest of it after discharge.	There were significant differences regarding to EASE efficacy related to application duration in EASE group, specifically, in week 12 the intensity pain level decreased (*p*=.032), and also pain interference in daily activities (*p*=.006)	-	-	+	+	-	-	?
Warth et al. (2015)	Relaxation exercise effectiveness as a part of music therapy for pain reduction in comparison to MBSR*	Germany May 2015 – August 2015 Instruments: Visual analog scale for pain-VAS (α=>.76) & EORTC* Quality Life Questionnaire PAL (α => .7)	N= 84 (60 W*-24 M*) Medium age: 63 years Patients with breast, pancreatic, ovarian, prostatic cancer located in palliative care	Relaxation+ music therapy group: Relaxation exercises + music. Control group: Mindful based on stress reduction. 30 minutes, 2 sessions	There were no significant differences in pain (*p*=.53) There was in well-being (*p*=.001) And relaxation level (*p*=.013) in experimental group	-	-	-	+	-	-	?

Note: EORTC*: European Organisation for Research and Treatment of Cancer/ TAU*: treatment as usual/ W*M*: Women and men/CES*: Center of Epidemiological Studies/ mPCST*: mobile pain coping skills training/ PMR*: progressive muscular relaxation GI*: Guided Imagery

Non-pharmacologic interventions

Music therapy

One of the studies, by Warth et al.,[30] was an investigation into the effects of relaxation as a part of music therapy in acute pain with other psychological and physiological aspects in breast, pancreatic, prostate, and ovarian cancer patients who were in palliative care. The experimental group received relaxation exercises by music therapy experts. The therapy included the exercise mentioned, as well as live music played on a monochord. The patients received breathing sessions (analysing their breath patterns, capacity used, and dynamic varying at the same time as the intensity of the instrument). The control group received a mindfulness programme based on stress reduction (MBSR) relayed, as in the experimental group, through headphones. The experimental group showed improvements in their relaxation and level of well-being, but there was no significant difference in pain.

Moradian et al.[31] performed an investigation with breast cancer patients undergoing chemotherapy with the aim of assessing the efficacy of adding music to usual medical treatment for oncological symptom reduction as pain; vomit, nausea, insomnia, emotional adaptation, cognitive, etc. The study was composed of three groups; in the first group, the treatment was music therapy + TAU, while the second (control) group received only TAU. The third group received a type of audio therapy (Nevasic) focused exclusively on other oncological symptom reduction (nausea or vomiting) + TAU. The results, regarding the music therapy + TAU group and control group, showed similar pain improvements in both groups. There were no significant differences between groups regarding the effectiveness of music therapy for pain reduction.

Subsequently, Arruda et al.[32] demonstrated the efficacy of this intervention during their investigation on people who suffered from urogenital, breast, or gastrointestinal cancer, leukaemia, and others cancer types. They included three groups: one that received

passive listening of instrumental music with headphones, one that received poetry, and one that did not receive any treatment. The results demonstrated a pain reduction in music therapy group and also in depression. The patients in the poetry group also showed a reduction in pain and depression and an increase in life expectancy. When the study was ended, at the last assessment, pain levels remained low in the music therapy and poetry patients.

Yoga

Porter et al.[33] intended to show the efficacy of mindfulness yoga on palliative pain and other symptoms in women with breast cancer. The eight mindfulness yoga sessions consisted of physical postures, breathing exercises, meditation techniques, and group discussion. They did not find significant differences in pain levels in comparison with the control group, which received support group sessions.

Psychological interventions

Mindfulness based on cognitive therapy (MBCT)

To demonstrate the efficacy of this psychological strategy for cancer-related pain reduction, Johannsen et al.[34] evaluated MBCT effectiveness on pain levels after treatment (surgery, radiotherapy, or chemotherapy) or its interference in daily life activities in a sample of women breast cancer patients. The participants were assigned to an eight-week programme in which they learnt about corporal recognition techniques, mindfulness breathing, and how to sit to focalise on their breathing, sounds, movements and current negative thoughts related to the disease versus the control group (waiting list). The results showed solid and long-lasting improvements (it remained until the therapy ended) on pain severity in the experimental group patients, as well as interference level reduction and, particularly, neuropathic pain.

Later, Johannsen et al.[35] after having demonstrated the efficacy of this technique, decided to study how the presence/absence of different psychological mediators had impact on MBCT efficacy for pain reduction. To accomplish their aim, they compared the control group (waiting list) and experimental group (MBCT). They found significant differences in those patients who presented low levels of attachment or constant avoidance of it. On the other hand, in the patients who had received radiotherapy, despite a lack of significant differences and after having analysed side effects, they found a higher impact (and long lasting) of the pain therapy. So, the mediators mentioned confirmed a possible feature that may increase the efficacy of the technique for pain reduction. In conclusion, they observe that the efficacy of this psychological intervention would be greater in patients with these clinical and psychological characteristics.

Both studies indicated the use of MBCT as a good strategy for pain treatment in patients, after having received oncological treatment.

Emotional and symptom focused engagement (EASE)

The study of this innovative technique has a cognitive-behavioural basis which consist of the combination of psychotherapy and the evaluation and screening of pain symptoms, other symptoms, and quality life. Rodin et al.[36] carried out EASE for eight weeks. Patients with leukaemia received 8-12 sessions of relational support combined with cognitive-behavioural therapy (CBT) focused on the trauma (disease) with the systematic analysis of symptoms with continue reference to early palliative care + TAU, while the control group received only TAU. The intensity and the level of interference of pain decreased in the experimental group after 4, 8, and 12 weeks and after weeks 4 and 12, respectively, while the control group showed an increase in the interference level of pain and an increasing dissatisfaction about the type of care received after the treatment ended.

Brief cognitive behavioural strategies (CBS)

Kwekkeboom et al.[37] showed the efficacy of a brief version of cognitive-behavioural strategies on, what the authors named the 'cancer clinical cluster' (pain, fatigue, and insomnia). This therapy was given to people hospitalised with metastatic/recurrent breast, gastrointestinal, lung, prostate, gynaecological and other cancers in the course of chemotherapy. They compared the application of CBS, i.e. educational block/psychoeducation on cancer causes, CBS action on symptoms, technique introduction, individualised recommendations + a CBS intervention recorded as an MP3 on symptom focalisation and imagination, imagination of pleasant exercises, relaxation exercises, and recorded nature sounds. These subjects were compared to those who received psychoeducation through an MP3 on oncological attention and control, the importance of cancer and treatment, educational sessions about cancer and recommendations to adhere patients to the listening (control group). An evaluation and follow-up were done during at weeks 3, 6, and 9 (as well as baseline measurements). The results showed that the participants who received CBS had reduced symptoms compared to those who received psychoeducation, but only at week 6. There were no significant differences between groups at the other time points or at follow-up after 9 weeks. However, the experimental group participants positively assessed the use of the recordings, pointed out the utility of the sessions, and highlighted improvements in their symptoms, such as an increase in control over them and higher levels of abstraction and relaxation.

Pain coping skills training

Kelleher et al.[38] conducted a study on pain coping skills training (PCST) efficacy through a videoconference with the mobile phone mPCST (experimental group) in comparison with the same training face-to-face PCST (control group) in patients with

breast, lung, colorectal, and prostate cancer. The videoconference sessions were based on cognitive-behavioural evidence (skills learning regarding behaviour modification, thoughts, and feelings about pain, as well as progressive muscular relaxation, activities planification, cognitive restructuring, and imagination). The aim was to distract the patient from the pain, increase pain management with other activities, and use cognitive restructuring for modify these behavioural patterns.

The results showed high accessibility, feasibility, and acceptance of the remote programme. In comparison with the control group, the participants in the experimental group presented better treatment adherence, completed sessions in the proper time, and reported more ease and motivation regarding session access Pain physical symptoms improved in both groups over time, but not immediately after the treatment. There were no differences in pain improvement between remote and face-to-face training.

Relaxation and guided imagery

An investigation carried out by Charalambous et al.[39] indicated the efficacy of these two techniques on breast and prostate cancer patients with chemotherapy and its influence on pain. Progressive muscle relaxation facilitates the action of expanding and contracting muscular groups while attending to body sensations with mental visualisation for mood improvement and physical well-being (guided imagery; GI). These authors applied these interventions on a sample compared to a control group that received the usual medical treatment for symptoms reduction derived from the disease and chemotherapy. The results showed a significant improvement in pain levels in the experimental group in contrast with the control group at the post-treatment follow-up. Both groups started with a very similar pain level at baseline, but the pain registers in the control group were even higher at the end of the study.

Meta-analysisNine studies were included to perform the meta-analysis. One study[31] was excluded for not providing pretest data. Another study[32] provided two different outcomes depending on the type of treatment (music therapy and poetry). We included these results with the labels "Arm 1" and "Arm 2," and took them into account as independent studies for the meta-analysis. Therefore, we obtained a total of 10 results to be analyzed. The results showed a significant moderate effect favorable to psychological and non-pharmacological therapies at post-treatment (k = 10, d = 0.642, 95% CI: 0.125 to 1.158), which increased at follow-up (k = 5, d = 0.826, 95% CI: 0.141 to 1.511) (see Figures 3 and 4). In both cases, the heterogeneity was high (Q = 152.060, p = .000, I^2 = 94.081 for post-treatment; Q = 39.334, p = .000, I^2 = 89.831 for follow-up).

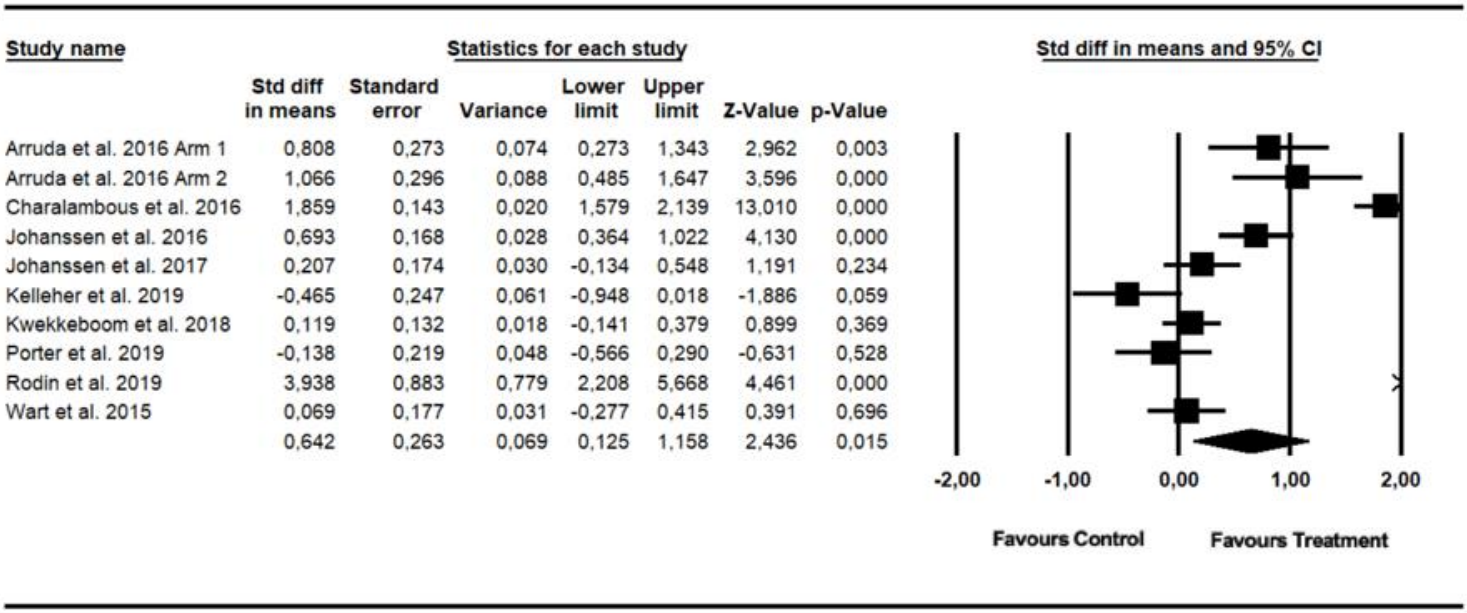

Figure 3. Forest plot of studies included at post-treatment analysis

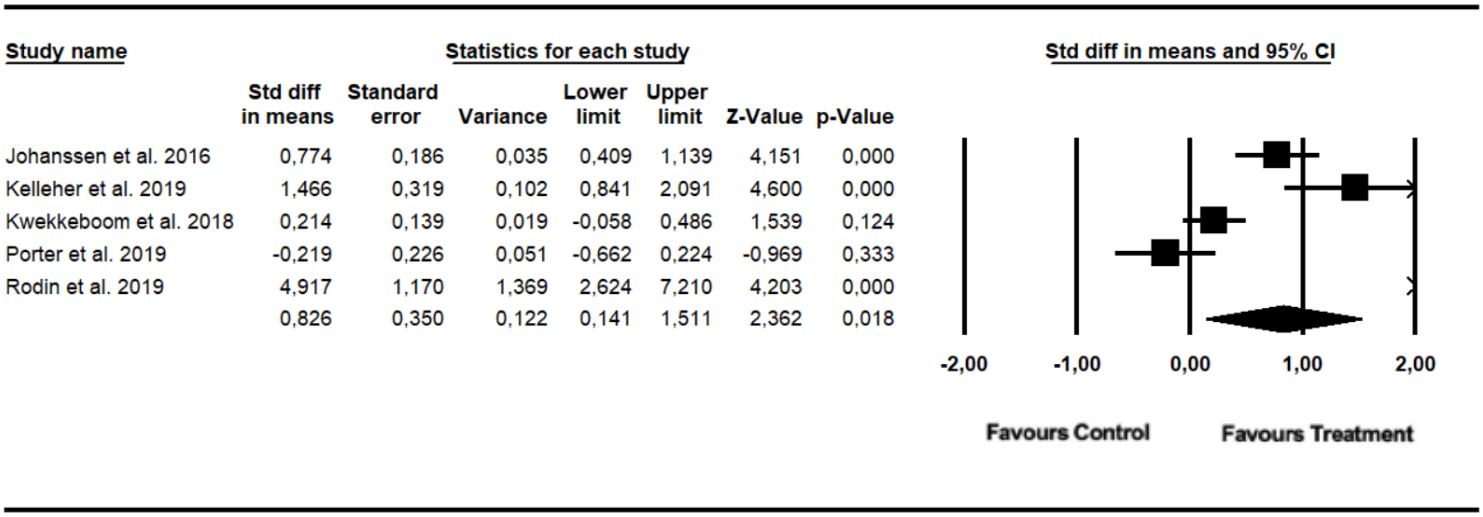

Figure 4. Forest plot of studies included at follow-up analysis

Discussion

The current review, as far as it has been bibliographically checked, is the first one to assess the efficacy both psychological and non-pharmacological interventions for cancer-related pain reduction or pain resulting from cancer treatment in adult patients. The overall result shown the efficacy of the psychological and non-pharmacological therapies to reduce pain in this population.

The findings showed that psychological strategies such as MBCT[34] are useful for pain reduction in patients who have overcome chemo/radiotherapy or oncological surgery. The improvements, apart from having effects on pain interference and intensity in daily life activities, were long-lasting and persisted until the end of therapy. In this aspect, Johannsen et al.[35] conducted an investigation to find which kind of psychological/clinical variables or characteristics facilitate MBCT efficacy related to cancer in this kind of patient; they found that low levels of attachment or social support and the avoidance of it and having received radiotherapy were considered predisposing variables to better MBCT efficacy regarding to pain. This attachment pattern reinforces what was found in a previous MBSR study,[40] in which patients who possessed insecure attachment (a pattern composed of attachment anxiety + attachment avoidance) or lack

of it showed greater stress reduction in comparison to those who had secure attachment. The greater effectiveness of MBCT in people who avoid this kind of support was due to higher pain levels at baseline than in those who had social support. Also, these people had a lack of expression or complaints related to pain.

Pain is frequently a source of stress and anxiety for these people and leads to a lack of relationships and activities that may be comforting and beneficial for pain reduction. For this reason, MBCT is important to make people aware of how they evoke these negative thoughts in others, how these are not consistent with their own expectations, and the importance of verbalising their feelings and emotions.[41]

Regarding music application as a therapy, Arruda et al.[32] applied music therapy and poetry sessions and studied if these could reduce pain in patients in comparison to TAU. The results showed a positive and long-term effect of music and poetry over pain. There was also an improvement in other psychological variables such as depression or patients' hope. Otherwise, other music therapies that were combined with breathing exercises[29] did not have an impact on pain, but there was an effect on relaxation levels and the well-being of patients. This can be attributed to the fact that the study patients were in palliative care and they were treated properly for this pain. Previous studies have demonstrated that the efficacy of this type of combined therapy is greater when symptoms are acute and they are not chronified.[31] In the same line, Moradian et al.[31] carried out the application of music therapy + TAU to assess the potential effect of this combined intervention on pain (as other oncologic symptoms) and, consequently, the possible compensation of pharmacological treatment with the simultaneous implementation of this psychological technique. In this investigation, there were no significant differences in pain levels produced by chemotherapy, nor in other symptoms in comparison to drug administration. This might be due to the patient's condition, i.e. being under hard

treatment and prone to physical and mental wear. Therefore, they may not have taken the implementation of these interventions seriously enough or had the misconception that they were not related to cancer or were useless. Patient beliefs may have an impact on their own ability to commit and adhere to treatment.[31] Patients are more likely to be involved in a treatment or intervention that is simple or that may fit easier into their daily routines (Gritz et al., 1989).[42]

Another type of psychological intervention very present in current psychological practice is PMR+GI. Accordingly, Charalambous et al.[39] evaluated the efficacy of these strategies related to pain reduction in patients, finding considerable and permanent positive results regarding the effectiveness and durability of the PMR+GI over pain reduction. These techniques provide a self-care strategy that, until a certain point, change and redirect the locus of control from the professional to the patient.[43] The most extended idea to explain GI effects on pain perception is the neuropsychological theory; according to this, image creation in the mind activates the cerebral cortex and limbic system and, consequently, the hypothalamus, which activates the nervous system[44]. A study carried out by Kwekkeboom et al.[45] was composed of 26 oncologic patients, comparing patient perception about PMR+GI in their pain scores: 11 patients confirmed PMR effectiveness in their pain levels and 5 of them described GI as a pain relief technique. In most cases, the perception of patients regarding the effect of these strategies corresponded to real changes in their pain levels. However, despite the importance of CBS (the brief version in this review) in current psychology, there were no relevant effects on pain parameters.[36] Currently, the effectiveness of many techniques based on CBT is well-supported; nevertheless, it is usually focused on other symptoms derived from anxiety, depression, or patients' quality life. Regarding pain, the evidence shows moderate effects.[45] Kwekkeboom et al.[37] used a brief version of CBS with the aim of being implemented as

soon as possible as a rapid response to symptoms, which will correspond to rescue medication for high pain levels.

The lack of significant decreases in pain after CBT application may be due to the significant short-term benefits patients experienced, which might not be captured by the assessment instrument used. Post-treatment study evaluations described a moderate/good improvement in the symptom experience of patients, despite the absence of long-term effects. On the other hand, participants could have also felt tired or bored performing the same exercises over time and, therefore, became less involved in the treatment.[37]

More recently, this was found by Porter et al.[32] in a study on mindfulness yoga. The results did not show relevant outcomes with consistent and significant effectiveness regarding pain; however, regarding anxiety or fatigue, its effectiveness was demonstrated. Furthermore, experimental group participants attended a lower number of sessions than the control group. Although they implemented a variety of techniques to increase treatment adherence, participants attended fewer sessions than recommended because many patients had problems with transportation, family, work issues, medical appointments, or holidays. Subsequently, Danhauer et al.[47] assessed the effects of yoga for a wide range of oncologic symptoms. This was based on a damping model that tries to diminish the appearance of multiple symptoms related to treatment or illness, making the technique less incisive and more powerful over certain symptoms in comparison with others, as in the case of anxiety or fatigue in contrast to pain.

In a study by Rodin et al.,[36] the results show how the technique focused on EASE favoured a reduction in pain levels and the interference of pain after the treatment and during the follow-up. This indicated the effectiveness of this new psychological strategy, and represented a breakthrough in the psycho-oncology field. Indeed, the authors intend to develop a multicentre study to assess the effectiveness of the technique. This

effectiveness can be, partly, due to participants, who were recruited quickly and who received their first EASE session within the first 5 days of randomisation, and were thus more likely to commit to the intervention. Also, they established a good therapeutic alliance which kept them motivated and involved in the study. It is important to highlight that this is the only study that used the Edmond Symptom Assessment System, a reference instrument for a symptomatic appraisal of patients with advanced cancer. This provides comprehensive control and follow-up of the patient and specific symptom evolution (it is applied two to three times per week during hospitalisation and once weekly after discharge). Thus, once a specific pain threshold is exceeded, it leads immediately to the activation of palliative care.

Finally, it is important to emphasise, taking into account the socio-sanitary moment were going through, the importance of investigating the application of remote techniques For this purpose, the investigation of mPCST by Kelleher et al.[38] intended to discover if these strategies were as effective as those applied face-to-face. They showed that, despite the influence of other variables that might be related to treatment efficacy in patients (such as motivation), the effectiveness linked to pain was not different from the demonstrated efficacy of this technique when applied face-to-face. These results were similar to those found by Somers et al.[48] when they compared both methods; they found that the benefits from mPCST were related to comfort and the ease of participation in the sessions. They found apparent positive progression of pain symptoms and a possible efficacy regarding pain management in both groups, as a long term and lasting effect. Syrjala et al.[49] likewise demonstrated the efficacy of behavioural intervention for pain management in oncologic patients. They claimed that weariness after treatment diminished the scope of the intervention. So, mPCST is more reachable, comfortable, and

improves patient motivation regarding its application. However, the authors asserted the need for more research on the subject.

Bearing in mind what has been said, these results must be taken and analysed cautiously, because the investigations included certain limitations. In the first place, some studies[32-34,36,38] did not clearly the specify sample age. This fact leads to an unclear conclusion about the effects of those interventions in the determined age range. Furthermore, the high degree of sample heterogeneity in all the trials included in this review may also complicate the generalisation of the results. Nevertheless, we can highlight that the greatest efficacy of all the techniques included in this review was found in subjects who suffered from breast cancer.

On a separate issue, there has not been a great deal of variety in investigations on this topic. It was not easy find studies which linked cancer and, particularly, pain (as the prime symptom) with psychological treatments, which is surprising due to the relevance and prevalence of this illness and its symptoms.

It is true that the outcomes obtained in some investigations (despite being positive and hopeful) are not completely consistent and reliable, because although they showed positive effects, in all of them, the authors claimed the need to perform further research due to the lack of information, previous data, resources, and time allotted to them.

This review shows certain limitations regarding to language (it only contains investigations published in English); this may have left behind some useful and relevant information. Likewise, there are some limitations linked to the exclusion and inclusion criteria. Some sociodemographic variables, such as age, that might be relevant to certain types of treatment in certain age ranges, were not correctly controlled. For this reason, in the future it is recommended that range age is taken into count with greater precision and rigour, in order to detect the strategies that are most effective at a particular age.

Investigations regarding to this topic should be encouraged in Spain, since we could not find any study performed in this country (although the prevalence of cancer in Spain is, unfortunately, alarming). It is true that, due to the current pandemic situation, attention to cancer patients have suffered from delays, however, this should be a warning call to continue the struggle against this terrible illness and the symptoms that accompany it and make the patient's life difficult. Future investigations should focus on the relevance of combined treatment, as well as analysing and discovering new medical and psychological techniques due to the importance of psychology and the role it plays in the evolution of this illness, as we have demonstrated.

Another limitation could be the short search period (the last five years), which ignores an important part of the work in this field in recent decades. However, although there are multiple systematic reviews that analyze work conducted in this area for the last 30 years,[50-53] clinical practice guidelines are usually updated every five years at most or even less.[54] Therefore, a period of five years could be appropriate to find enough articles that allow updating clinical guidelines.

Finally, the results could have been affected by some sources of bias, for example, the blinding of participants and personnel, selective reporting, or the possible existence of other bias not present or for which insufficient information is available. Related to selective reporting, according to Cochrane, if the risk of bias is unclear (?), it tends to depend on the existence of a study. Regarding this, it is convenience to point out that, although it did not occur in all the investigations included in this review, many of them[31,33,36,37] only included p-values and not size effects.

Conclusion

This review shown that psychological and non-pharmacological therapies are effective for reducing pain in cancer patients. Specifically, we found that mindfulness

based on cognitive therapy (MBCT), progressive muscle relaxation, emotion and symptom focused engagement (EASE), music therapy and poetry sessions, and pain coping skills training have long-term efficacy regarding pain reduction in cancer patients. Most of these techniques have a cognitive basis. However, due to the heterogeneity of the studies and the presence of some biases in them (particularly related to the lack of blinding and the presence of incomplete data outcomes), no solid and accurate conclusions can be reached. We can only limit ourselves to making some recommendations. Certain strategies such as yoga based on mindfulness had effects on other psychological variables, but not on pain. Other interventions, such as the brief version of cognitive behavioural strategies (CBS), reported a certain level of influence on pain levels but in an inconclusive way, only at some time points. Strategies such as MBCT, which have significant efficacy regarding pain reduction, have also showed efficacy in the presence of determined previous characteristics, reflecting an inconsistency that requires further investigation in this subject. For all of these treatments, the implementation of an effective psychological therapy or non-pharmacologic treatment against cancer-related pain cannot be fully guaranteed. It is necessary to perform trials in which blinding has been done properly and that provide clear and concise results, with a greater specification and limitation of the selected sample (reducing the range of age, sex, type of cancer, or state of it) in order to ensure the efficacy and success of psychological and non-pharmacological techniques in these patients, regardless of their circumstances, who are struggling with cancer and pain on a daily basis that prevents them from leading a full and dignified life.

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