Internet-Based Cognitive Behavioral Therapy for Depression and Anxiety Symptoms in Cancer: A Meta-Analysis

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Background: Depression and anxiety affect up to 20% of patients with cancer. Physical treatment and side effects are usually the only factors given attention to during treatment and recovery. Psychological distress can have deleterious effects in their quality of life, and may even affect healing. Treatment options for depression and anxiety are limited. One well-studied treatment is cognitive behavioral therapy (CBT). However, face-to-face treatment has been a challenge for the oncology team during this pandemic. Internet-based cognitive behavioral therapy (iCBT) can be a new means of dealing with cancer patients' psychological health.

Objective: To evaluate iCBT in alleviating depression and anxiety symptoms in patients with cancer.
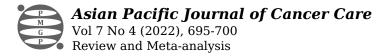
Methods: A systematic search of Pubmed, Embase, Cochrane, Clinical trials databases and hand search were utilized to identify randomized controlled trials (RCTs) investigating the role of iCBT in addressing psychological distress in cancer patients. Meta-analysis was conducted on 4 randomized controlled trials (N=548). All 4 studies were included for analysis. Psychological distress was measured as depression and anxiety based on the Hospital Anxiety and Depression Scale (HADS) total scores.

Results: There was a trend in improvement of anxiety and depression in the iCBT treatment group, however, it was not significant (p = 0.06). Due to substantial heterogeneity, subgroup analyses was done and showed improvement of anxiety and depression in patients with different cancer types and baseline psychological distress (p < 0.00001).

Conclusion: The results indicate that iCBT can be a potential treatment option in cancer patients who exhibit baseline depression and anxiety, especially during this pandemic. More studies are needed to determine the efficacy of iCBT in cancer patients who are not clinically diagnosed with psychological disorders.

Introduction

Cancer treatment has been drastically evolving and progressing during the past decade. Novel treatment options have been emerging due to new information on the biology of different cancers. This gave way to more treatment options other than intravenous cytotoxic systemic chemotherapy. Majority of cancer patients now have a wide array of treatment choices. Targeted therapies, such as monoclonal antibodies and tyrosine kinase inhibitors, are now emerging as first line treatment. Other routes of delivery, such as oral, are also now available. The most common side effects of chemotherapy are then avoided. The development of imaging tests and molecular markers have also improved the diagnosis and detection of cancers. Due to these advances, cancer patients are living longer. Some cancers are now considered long term conditions [1]. However, these patients do not only deal with their cancers' biology, but also the psychological burden that it comes with. It is important to note that the goal of cancer care is not only to prolong lives, but also to give the
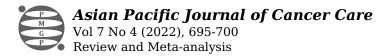
best quality of life.

In a systematic review, the mental health needs of cancer patients are given the least concern. Attention of the primary physician is more on the physical health, cancer treatment, and the side effects of treatment [2]. Psychological health should also be assessed during and after treatment of the patient. In 2018, depression and anxiety affected up to 20% and 10% of cancer patients, respectively, regardless of treatment goal. Poor recognition of these psychological issues is associated with poor quality of life and reduced survival [1]. A meta-analysis showed that depression (both minor and major) may increase mortality rates up to 39%. Patients who manifest few depressive symptoms may have increased risk of mortality to up to 25% [3]. A local study in 2013 showed that among Filipino adult cancer patients aged 18 years old and above, 22% was categorized as depressed (N=53/247). These patients scored lower on cognitive, emotional, role, physical, and social functioning as compared to those who were not categorized as depressed [4].

Depression and anxiety screening are measured using several methods, but no single standardized test is preferred over the other [2]. There are at least 19 different tools for screening. One simple tool is the Hospital Anxiety and Depression Scale (HADS) (Appendix 1). It is a self-rating scale that screens patients for anxiety and depression, and assesses the severity of symptoms. Patients score each question from 1 to 3. A score of 8 or more shows borderline symptoms of anxiety or depression, depending on the subscale. Other tests include the Patient Health Questionnaire and European Organization for Research and Treatment of Cancer Quality of Life Questionnare Core 30.

Currently, there is no standard of care treatment for depression and anxiety in cancer patients. Both pharmacological and psychosocial treatments are available. Antidepressants used in psychiatric patients, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic anti-depressants (TCAs), are also used in cancer patients. Antidepressants are widely used in non-cancer patients, but drug-to-drug interactions in cancer may occur. A well-studied interaction is between tamoxifen in breast cancer patients and SSRIs. Tamoxifen is converted into its active metabolite by CYP2D6. SSRIs which inhibit CYP2D6 at varying degrees may decrease the efficacy of tamoxifen in these group of patients. Hence, the benefit of tamoxifen is decreased [5]. Physicians must weight the benefits and risks of adding anti-depressants to chemotherapy and endocrine therapy. Moreover, due to the emergence of novel drugs with different mechanisms of action, more studies are warranted. A meta-analysis comparing SSRIs and TCAs vs placebo found no difference on effects on symptoms of depression. Furthermore, the studies included in this meta-analysis on the optimal treatment for depression and anxiety in cancer patients are limited and of poor quality [6].

Another treatment option for depression and anxiety in cancer patients is cognitive behavioral therapy (CBT). Several studies have assessed this treatment option. A meta-analysis on the efficacy of cognitive behavior therapy on quality of life and psychological health of breast cancer survivors showed that CBT is an effective therapy for psychological symptoms of cancer patients and survivors. Ten studies were included with the following outcomes: quality of life, depression, stress, anxiety, and hyperarousal cluster of symptoms. All outcomes were deemed significant [7]. CBT was also studied to alleviate distress and pain for breast cancer patients with 20 studies included. The treatment groups reported less distress and less pain. No differences in effects were observed between non-metastatic and metastatic disease in breast cancer, showing benefit in early and advanced stage disease [8]. A meta-analysis in 2019 by Sun H., et al. reviewed CBT to treat depression and anxiety and improve quality of life in early stage breast cancer patients. Eight studies were included and the benefit was observed in anxiety [9]. Another meta-analysis compared CBT and patient education on depression, anxiety, pain, physical functioning, and quality of life in adult cancer survivors. Fifteen studies were included with 1,492 patients in total. CBT was shown to improve depression, anxiety, and quality of life. In addition, this study recommended an individual format when delivering CBT [10]. Given the results of these studies, cognitive behavioral therapy is a valid option for depression and anxiety in cancer patients. It avoids the risk of drug-to-

drug interactions that may compromise the treatment outcome, increase the toxicity and adverse effects, and decrease survival of patients who receive anti-depressant medications. In contrast with taking anti-depressant medications, cognitive behavioral therapy requires regular and more frequent hospital visits. Since the emergence of the Novel Coronavirus 2019 (2019-nCoV), face-to-face hospital and clinic follow-ups have greatly declined. This is a major limitation for those giving and undergoing CBT. Internet- based cognitive behavioral therapy (iCBT) was previously developed for those who have difficulty in accessing face- to-face consults. iCBT has potential in solving the gaps of CBT during this pandemic. Several randomized controlled trials were done using iCBT in patients with cancer. In a study be Beatty, L. et al in 2015, web-based CBT was assessed for reducing cancer distress, quality of life, and maladaptive coping. Cancer types included were breast, bowel, lymphoma, ovarian, uterine, and thyroid. Significant effects for time were seen in cancer distress, global quality of like, physical function, role function, social function, and anxious preoccupation. The result of this study show potential efficacy in improving the mentioned outcome measures [11]. In the iCanADAPT Early study in 2019, internet delivered CBT for clinical depression and/or anxiety in cancer survivors was assessed. One-hundred fourteen were randomized to receive either iCBT or treatment- as-usual (TAU). Cancers included were breast, prostate, gynecologic, lymphoma, bowel, and melanoma. Results showed that iCBT was superior on all outcome measures posttreatment which included: anxiety, depression, fear of cancer recurrence, and quality of life. Adherence and satisfaction were also higher in the iCBT group [12]. Given the results of these studies, we hypothesize that iCBT can be a potential novel treatment for depression and anxiety in cancer patients during this current time.

Materials and Mehods

Literature search strategy and study identification

Studies included and collected were reviewed by a systematic literature search of Pubmed, Embase, and Cochrane Library without date limits were used (Figure 1).

Figure 1. Forest Plot of Mean Difference in Change of HADS Score from Baseline of Cancer Patients who Underwent iCBT vs Care as Usual. SD, standard difference; IV, inverse variance; CI, confidence interval.
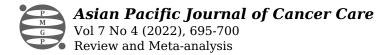
There were no language restrictions. Duplocates were removed. The keywords used were 'internet-based cognitive behavioral therapy', 'cancer', 'depression, and 'anxiety'. Abstracts and full-text manuscripts were reviewed.

Resulting studies were selected and their eligibility was confirmed by three independent investigators. The systematic literature search was carried out independently by two authors (CD and JP) and any discrepancies were solved by discussion with a third author (MF).

Selection criteria

Most of the studies were assessed by their titles and abstracts. Eligible studies had to satisfy the following inclusion criteria: (1) randomized controlled trials (RCTs), (2) adult cancer patients, (3) patients treated with internet-based cognitive behavioral therapy, and (4) patients with psychological distress such as depression and anxiety (Figure 2).

Figure 2. Flow-chart of the Literature Search.

Data extraction

The following information was extracted from each study: Authors' names, year of publication, study type, eligibility information, the total number of patients, inclusion and exclusion criteria, measurement of depression and anxiety, and internet-based cognitive behavioral therapy given.

Quality evaluation

The collated evidence was evaluated using the Cochrane Collaboration tool. Accordingly, the quality of each study was graded as A, B or C.

Statistical analysis

The meta-analysis was conducted using Review Manager software (RevMan, version 5.4 for Mac; Cochrane Collaboration, Oxford, UK). Studies were examined for the interventions and qualitative synthesis. The data from 4 studies were then examined for meta-analysis. The effect size for the studies was summarized as mean difference. Statistical heterogeneity was tested using the Higgins I^2 index. I^2 values 0-40% mean mild or nonsignificant heterogeneity; 30-60% may represent moderate heterogeneity; 50-90% represent substantial heterogeneity; and 90-100% represent considerable heterogeneity. The random-effects model was used. P values <.05 were regarded as significant for all analyses.

Study objectives

The primary objective of this study is to evaluate the efficacy of internet cognitive behavioral therapy compared to care as usual in improving depression and anxiety symptoms in cancer patients.

Eligible studies and summary of data

A total of 67 articles were identified for evaluation. Based on the inclusion and exclusion criteria described, 4 articles with 548 patients were eligible for the meta-analysis. The characteristics of the included studies are shown in Table 1 [12-15].

Author/Year	Sample Size	Type	Population	Intervention	Outcome measures
Hummel 2017	151	RCT	Breast cancer patients	iCBT = 69	HADS
				Control = 82	SAQ
					FACT-ES
					SF-36
					QLQ-BR23
					MMQ
Compen 2018	145	RCT	Breast, gynecologic, prostate, colon, NHL, skin, thyroid, bladder, neuroendocrine cancer patients	iCBT = 75	HADS
					FCRI
				Control = 70	RRQ

					SF-12
					FFMQ
					MHC-SF
Atema 2019	155	RCT	Breast cancer patients	iCBT = 76	HADS
				Control = 79	SAQ
					FACT-ES
					HFRS
					SF-36
					GSQS
Murphy 2019	97	RCT	Breast, prostate, gynecologic, lymphoma, bowel,melanoma cancer patients	iCBT = 41	HADS
					FCRI
				Control = 56	FACT-G

Table 1. Characteristics of Eligible Studies.

RCT, randomized controlled trial; HADS, Hospital Depression and Anxiety Scale; FCRI, Fear of Cancer Recurrence Inventorys; SAQ, Sexual Activity Questionnaire; FACT-ES, Functional Assessment of Cancer Treatment-Endocrine Symptoms; SF-36, 36-Item Short Form Health Survey; QLQ-BR23, Health Related Quality of Life; MMQ, Maudsley Marital Questionnaire; RRQ, Rumination and Reflection Questionnaire; SF-12, Short Form 12; FFMQ, Five Facet Mindfulness Questionnaire; MHC-SF, Mental Health Continuum – Short Form; HFRS, Hot Flush Rating Scale; GSQS, Groningen Sleep Quality Score; FACT-G, Functional Assessment of Cancer Therapy – General.
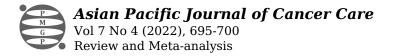
Using the Cochrane risk of bias assessment tool [7], all four studies were graded B due to the lack of blinding of the patient, personnel, and assessors in these studies (Table 2).

	Selection Bias		Performance Bias		Exclusion Bias		Detection Bias	
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Equal treatment of groups	Intention to treat	Drop out rates comparable	Blinding of oucome assessment	Outcome methods similar
Hummel 2017	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes
Compen 2018	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes
Atema 2019	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes
Murphy 2019	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes

Table 2. Risk of Bias Summary Using the Cochrane Collaboration's Tool.

Results

Four randomized controlled trials met the inclusion criteria in this meta-analysis (N=548). Two studies included only patients with breast cancer (N=306). The other 2 studies included patients with breast, prostate, gynecologic, lymphoma, colon, thyroid, bladder, skin, and neuroendocrine cancers (N=242). Outcomes of all four studies were assessed using the Hospital Anxiety and

Depression Scale (HADS) scores (Appendix 1).

The overall effect showed a trend favouring iCBT in decreasing HADS score, but was not statistically significant [MD -2.74, 95% CI (-5.68, 0.20), p = 0.06].

However, the pooled studies had significant heterogeneity (I^2 = 89%), hence sensitivity analysis was performed by excluding Hummel et al.

The pooled estimate of the remaining 3 studies confirmed the favourable effect of iCBT on HADS score. HADS score in those who underwent iCBT were significantly lower than those who underwent care as usual (MD -3.97, p = 0.001). Pooled studies still had high heterogeneity (I^2 = 80%) (Figure 3).

Figure 3. Forest Plot of Mean Difference in Change of HADS Score from Baseline with Sensitivity Analysis.

A subgroup analysis based on cancer type was performed, particularly between studies with breast cancer-only population and studies which included other types of cancers. The overall effect estimate of the two studies with breast cancer patients did not significantly favour the iCBT group (MD -0.43, 95% CI -2.52, 1.65, p = 0.68). On the other hand, the other 2 studies which included a mixed population of cancers showed the iCBT has a significant benefit in improving HADS scores (MD -5.28, 95% CI -6.49, -4.06, p < 0.00001). Pooled studies in each subgroup were homogenous (Figure 4).
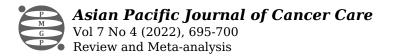
Figure 4. Forest Plot of Mean Difference in Change in HADS Score from Baseline between iCBT vs Care as Usual with Subgroup Analysis Based on Cancer Type.

Discussion

This meta-analysis integrated data from 4 studies to address anxiety and depression in cancer patients. The results showed a trend in improving both anxiety and depression in cancer patients who received iCBT, however it is not significant. This data is affected by the substantial heterogeneity of the studies included. In the study of Hummel et al., 62% of breast cancer patients were only able to complete the iCBT program. The program was longest in this group which spanned for 20 weeks. Results of this study was then based on intention-to-treat analysis.

The subgroup analysis which included breast cancer only patients did not favor iCBT. Several factors may have affected this result. The study of Hummel et al included patients who were diagnosed with sexual dysfunction based on the DSM-IV. Internet-based cognitive therapy in this study was able to improve sexual functioning, body image, and menopausal symptoms in breast cancer survivors. However, patients who had serious psychiatric comorbidity, such as depressive disorder, were excluded from this study. At baseline, few patients had clinically relevant psychological distress at 13% and 4% for anxiety and depression, respectively. The study of Atema et al also excluded overt cognitive and psychiatric comorbidity. These factors in both studies could have given less room for anxiety and depression improvement based on the HADS score.

In the subgroup analaysis of different kinds of cancers, there was a significant improvement in anxiety and depression. Both the studies of Compen et al and Murphy et al in this subgroup analysis included patients who have psychological distress at baseline. The Compen et al study included cancer patients with a baseline HADS score of 11 or more (abnormal/case). The Murphy et al study included patients with a diagnosis of 1 or more DSM-V disorder. The disorders included were major depressive disorder, generalized anxiety disorder, illness anxiety disorder, panic disorder, agoraphobia, and andjustment disorde. HADS scores showed a significant decrease after

iCBT in patients with baseline anxiety and depression based on HADS or those clinically diagnosed with DSM-V disorder. The importance of screening, especially in the local setting, is emphasized in this study since patients who have high baseline depression and anxiety scores would benefit the most in improving their psychological distress. There are a number of limitations in this meta-analysis.

One limitation of the studies included were the difficulty in blinding of patient, personnel, and assessors due to the nature of the intervention. Another limitation is the lack of a standard iCBT program. Different programs were utilized in the 4 studies and program schedules were variable from 6 to 20 weeks. This may have affected the treatment compliance of the patients.

The result of this meta-analysis is consistent with previous research on cognitive-based behavioral therapy (CBT). However, a comparison between CBT and iCBT can also be of value in assessing the value of iCBT in cancer patients.

In conclusion, Internet-based cognitive behavioral therapy can be a potential treatment option for cancer patients who have depression and anxiety at baseline. iCBT can be utilized to continue holistic care to cancer patients during the pandemic. More studies are needed to resolve the limitations such as lack of a standard iCBT program, to address patients who are not clinically diagnosed with DSM-V disorders, and to compare iCBT with CBT.

Conflict of Interest

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