**Abstract.**

**Background:** Treatments for cancer-related anxiety show modest benefits but most have been trialled in patients with early stage disease or patients who are currently disease free. However, many patients with cancer have incurable disease, or their disease is slowly progressing or likely to recur. Treating anxiety in the context of realistic threat and ongoing uncertainty is particularly challenging. Based on a theoretical model of cancer-related anxiety, we developed a transdiagnostic intervention for patients with advanced or recurred disease who are experiencing clinically significant anxieties. The intervention was a novel integration of traditional and contemporary CBT.

**Aims:** To evaluate the feasibility, acceptability and preliminary efficacy of the intervention in a pilot with patients with advanced or recurred cancer.

**Method:** Twelve patients with advanced or recurred cancer, who were experiencing anxiety, participated. Feasibility and acceptability was assessed with participant’s ratings, and adherence and retention rates. Psychological outcomes (anxiety, traumatic symptoms, fear of progression, depression, death anxiety and quality of life) were assessed pre-intervention, post intervention and at 2-month follow-up.

**Results:** Eleven of the 12 participants completed at least five therapy sessions of whom eight completed all nine sessions.Participants rated the intervention as having excellent face validity. Post-intervention, statistically significant improvements were demonstrated for anxiety, traumatic symptoms, fear of progression, depression and quality of life. These improvements were maintained at follow-up for anxiety, traumatic symptoms and depression.

**Conclusions:** This pilot provides preliminary evidence for the feasibility, acceptability and effectiveness of the novel intervention for cancer-related anxiety in the context of advanced disease.

## Keywords: anxiety, psychosocial oncology, advanced cancer, cognitive behavioural intervention.

## Introduction

Anxiety is one of the most common psychological disorders diagnosed amongst cancer patients (Mehnert *et al*., 2014) and overlaps with other cancer-related clinical presentations, such as fear of cancer recurrence or progression (FCR; Simard & Savard, 2015), traumatic stress symptoms (Unseld *et al*., 2019) and fear of death (Gonen *et al*., 2012). In a large meta-analysis of studies that used clinical interview to assess for mood disorders, 10.3% of oncology and haematology patients met criteria for an anxiety disorder and 19.4% met criteria for an adjustment disorder where anxiety or post traumatic symptoms may have been a feature (Mitchell, 2011). However there was not enough power to determine prevalence by cancer stage and, to date, a meta-analysis to determine the rate of anxiety disorders in advanced disease has not been conducted. That being said, individual studies suggest that the prevalence rate of anxiety disorders amongst patients with advanced disease is around 6-8% (Kissane et al., 2004; Miovic & Block, 2007) and is higher when samples include patients with “terminal disease (12-14% (Kolva, Rosenfeld, Pessin, Breitbart, & Brescia, 2011; Miovic & Block, 2007). In addition, 24-44% of patients with advanced disease experience clinically meaningful anxiety symptoms (McFarland, 2019; Park, Chung & Lee, 2016; Park et al., 2018) and nearly half experience moderate or high symptoms of death anxiety (Lo et al., 2011; Neel, Lo, Rydall, Hales, & Rodin, 2015). Recently, research has focused on identifying subgroups of patients that experience unremitting high levels of anxiety or increasing anxiety over time. For instance, Lam et al. (2013) reported that 9% of their sample of women with advanced breast cancer had high anxiety scores across multiple assessment points over 12 months.

To date, most of the literature on interventions for patients experiencing clinically significant cancer-related anxiety is concerned with patients with early-stage disease who have completed treatment and are expected to have a good prognosis and low risk of recurrence, or patients at the end of life (Sanjida *et al*., 2018). However, about 27% of people with cancer have stage 3 or 4 disease (based on Australian Institute of Health and Welfare material, 2020) and, as medical treatments become more successful, the number of people living longer with advanced disease is increasing (Harley *et al*., 2012). These patients are often treated with palliative, but not curative, intent and experience high levels of uncertainty about whether their cancer will respond to treatment (Harley *et al*., 2012). Even if treatment is successful, there is uncertainty about whether the cancer will recur, or for those patients who are not completely disease free, whether the cancer may progress in the future (Lai-Kwon *et al*., 2019). There may also be uncertainty about the optimal frequency and duration of surveillance testing, so monitoring may occur more often than is required, despite this being especially anxiety provoking for patients (Thewes *et al*., 2017). In addition, these patients experience ongoing reminders of the cancer threat, either from external cues (e.g. doctor’s appointments and scans) or internal cues (e.g. physical symptoms; Lee-Jones *et al*., 1997). Treating anxiety in the context of a realistic and ongoing threat is a challenge for clinicians, as psychotherapy is usually provided after a threat has passed and the person’s environment is relatively safe, stable and predictable (e.g.Van der Kolk *et al*., 1995).

Further, there are few efficacious interventions to guide clinicians who work with these clients. Unfortunately, interventions for cancer-related anxiety have, on average, only demonstrated small effect sizes (Sanjidia *et al*., 2018). One possible explanation for these disappointing effect sizes is that, due to the ongoing nature of the cancer threat, people with advanced cancer may continue to experience some level of anxiety despite intervention. Unfortunately, most studies have not screened for clinically significant anxiety so the small effect sizes may reflect small reductions in anxiety within the non-clinical range. Another possibility is that most interventions have not been developed from a cancer-specific theoretical model, but are typically adapted from existing interventions for people who are experiencing anxiety in the absence of a life threat. Unfortunately, theoretically derived interventions developed for patients with advanced disease have also found small effect sizes on anxiety (e.g. meaning-centred therapies, Kang *et al*., 2019). For example, only one intervention to date (CALM; Rodin *et al*., 2018) has been shown to significantly decrease death anxiety using a valid measure (Grossman *et al*., 2018). Therefore, more extensive theoretical models from which interventions can be derived are needed.

We developed a transdiagnostic model to identify the constructs that may explain the aetiology and maintenance of cancer-related anxiety (Curran, Sharpe & Butow, 2017). The model suggests that pre-existing beliefs and coping responses become highly salient as the person draws on their knowledge and previous experience to adapt to their cancer. Anxiety is related to the degree to which the cancer is evaluated as threatening, based on previous experience or beliefs about illness, dependency or death. If the cancer impacts on role functioning, existential distress may result from disconnection with sources of life meaning. The inherent lack of control, ongoing uncertainty and awareness of mortality within the cancer context also gives rise to existential concerns, such as questioning core beliefs about the self, others and the world; and increases worries about dying. Natural cognitive processes occurring in response to the existential threat, such as intrusive thoughts, become problematic when people believe that those thoughts are uncontrollable and harmful or that worrying is helpful to prepare for future threats. People may therefore try to cope with unwanted intrusions by engaging in suppression and avoidance or worry and hyper-vigilance, thereby maintaining an anxiety cycle. Consequently, the model identifies targets for treatment, including cognitive processes(intrusions and subsequent cognitive responses such as suppression or worrying) and cognitive content (core beliefs, threat appraisals and worries about dying). This paper reports pilot testing of a novel, transdiagnostic intervention for anxiety for patients with advanced or recurrent cancer derived from the theoretical model.

**Method**

***Intervention***

In developing the intervention, we considered existing interventions that target the transdiagnostic constructs identified in the model of cancer-related anxiety. One such intervention is ConquerFear, a theoretically derived intervention for FCR (Butow et al., 2017), one of the most common forms of cancer-related anxiety. The ConquerFear intervention includes contemporary cognitive-behavioural therapy (CBT) strategies, such as meta-cognitive techniques to modify beliefs about worry, mindfulness and attention training to help people disengage from worrying, and values clarification to help people reengage with value-based goals. ConquerFear resulted in significant reductions in FCR amongst early-stage cancer survivors compared to an active control of relaxation therapy (Butow *et al*., 2017). To more explicitly address issues relevant for people with advanced disease, we added: 1) a novel strategy to explore helpful and unhelpful ways of coping when there is uncertainty and limited control (see Table 1 and Figure 1), 2) a framework to differentiate worrying from productive cognitive processing and to identify when further processing of concerns may be helpful (see Figure 2), and 3) cognitive therapy to address unhelpful appraisals, core beliefs and worries about death and dying. As such, the intervention is a novel integration of traditional and contemporary CBT (see Table 1).

In developing an integrated therapy, we reflected that some theorists consider content interventions to be incompatible with process interventions. For instance, engaging with the verbal language of thoughts is posited to underlie emotional distress and so traditional CBT techniques that attempt to modify thoughts are posited to maintain the problem (e.g. Luoma, Hayes & Walser, 2007). Also challenging thoughts with the aim of reducing distress is considered to be incompatible with the aim of living a valued life despite the experience of difficult thoughts and feelings (Luoma, Hayes & Walser, 2007). However, these views are not universally held. For example, Hofmann & Asmundson (2008) have argued that contemporary and traditional CBT strategies are compatible emotion regulation strategies that target either antecedent, cognitive responses (such as appraisals) or the resultant experiential, physiological or behavioural responses (such as suppression). Theoretically we considered that engaging with thoughts to process them in some way was problematic when this activated the cognitive attentional syndrome (Wells & Matthews, 1996). However, by disengaging from worrying, we did not consider that the person should then not process the content of their thoughts at all, but rather do so in a different way. One of the aims of the intervention was therefore to increase flexibility around *when* and *how* people engaged with their thoughts.

The intervention was delivered individually over nine 60-90 minute sessions, by the first author, a clinical psychologist with over 10 years psycho-oncology experience. The early sessions (sessions 1- 3) include assessment, development of a formulation and psycho-education about cancer related anxiety, intrusions and unhelpful coping. In addition, helpful coping skills are developed to 1) provide strategies to regulate emotions before the person moves on to process difficult thoughts and concerns and 2) practice alternative ways of responding to unwanted intrusive thoughts. The middle sessions (sessions 4-7) include cognitive strategies to process the underlying content hypothesized to be contributing to cancer related anxiety, including unhelpful beliefs, appraisals, metacognitions and schema. Mindfulness is introduced in session six to provide further practice in disengaging from thoughts and sustaining attention on a chosen activity. The final two sessions are aimed at relapse prevention by 1) addressing any remaining behavioural avoidance or over-monitoring, 2) developing plans for ongoing health surveillance, and 3) preparing for possible future triggers. Each session adheres to a general CBT format, that is, setting the agenda, reviewing between session tasks, providing clear rationale for new material and checking understanding, setting between session tasks collaboratively and allowing time for mutual feedback about the session. The manual may be available by request to the first author.

**Table 1. Session content**

|  |
| --- |
| **Session 1. Assessment and development of a formulation** |
| * Provide an opportunity for the client to relate their cancer narrative in detail. * Conduct a cancer-anxiety specific psychological assessment. * Present a brief formulation and identify targets for intervention * Psycho-education about the nature of anxiety in the cancer setting * Ban internet surfing (if relevant) |
| **Session 2. Adaptive and maladaptive coping** |
| * Discuss ways of coping in terms of primary and secondary control1 (Rothbaum, Weisz & Snyder, 1982). * Explore how each form of control can be helpful or unhelpful depending on whether it is a good fit for the current situation (see Figure 1). * Introduce an ACT metaphor to illustrate letting go of worrying or ruminating (Butow *et al*., 2013; Harris & Hayes, 2009; Vivian, 2009). * Introduce emotion regulation strategies (Linehan, 1993) as a form of secondary control. Contrast with suppression or distraction. |

1 In order to address the ongoing uncertainty and limited control inherent in the cancer context, we developed a novel intervention based on the theory of primary and secondary control (Rothbaum, Weisz & Snyder, 1982). This theory describes how people attempt to cope with a stressful situation by trying to restore a feeling of control. Primary control includes attempts to actively engage with the situation and change something about it, by gathering information, problem solving, planning ahead and/or communicating effectively to negotiate a desired outcome. In contrast, secondary control involves attempts to adjust to the unchangeable aspects of the situation, such as altering one’s attitude to the situation, shifting focus to those aspects of the situation that are still controllable, adapting one’s goals to fit in with changed circumstances, or trying to find meaning within the situation. What seems to be important is whether the coping strategy employed matches the current situation or “goodness of fit” (Weisz, Rothbaum & Blackburn, 1984). For instance, engaging cognitively with a situation (e.g. thinking through all possible scenarios in an attempt to prepare for the future) can easily become unproductive if it leads to rumination or worry. On the other hand, disengaging from further processing of thoughts may be unhelpful if this disrupts identifying practical action that could be taken which may lead to greater feelings of control and easing of anxiety. Using the concepts of primary and secondary control, we developed a unique framework to describe helpful and unhelpful coping to clients, and to introduce the strategies included in the intervention (see Figure 1). Within this framework, coping was conceptualised as servicing a function, that is, to understandably try to restore a feeling of control. Perseverative thinking about the situation (by worrying or rumination), aggressive communication, pushing oneself physically despite symptoms and over-monitoring of symptoms were conceptualised as unhelpful attempts to change an unchangeable situation (unhelpful primary control). Avoidance, distraction (including through use of alcohol), suppression and resignation were conceptualised as unhelpful attempts to cope with the emotional consequences of an unchangeable situation (unhelpful secondary control). This was contrasted with productive processing of concerns, problem solving and taking effective action, assertive communication, pacing of activities, adherence to recommended surveillance (helpful primary control), acceptance and intentional engagement in valued activities (helpful secondary control). Awareness and acceptance of current emotional states (Barlow et al, 2011; Leahy et al., 2011) and detached mindfulness (Wells, 2009) were conceptualised as strategies to “let go” of unhelpful primary control attempts.

|  |
| --- |
| **Table 1. Session Content continued** |
| **Session 3. A framework to respond to difficult thoughts and emotions** |
| * Psycho-education about the nature of intrusions * Introduce a framework to guide decisions around WHEN and HOW to engage with or disengage from cancer-related concerns (see Figure 2). * Introduce Detached Mindfulness (DT, Wells, 2005):provide rationale; practice suppression and counter-suppression exercises; practice DT for neutral and then cancer-related thoughts. * Values clarification and goal setting. Complete a card sort to identify two values and translate these into short term and medium term goals.2 |
| **Session 4. The cognitive model and Attention Training** |
| * Psycho-education about the nature of thoughts and how they interact with emotions. * Introduce thought monitoring. Illustrate with a recent example. * Introduce Attention Training(Wells, 2009) as an alternative to responding to unwanted intrusions with rumination or worry. |
| **Session 5. Cognitive reframing skills and practice** |
| * Introduce the steps of cognitive restructuring (Beck, 2011; Leahy, 2003) * Identify a belief that is contributing to cancer-related anxiety and practice modifying the belief in session. |
| **Session 6. Belief modification** |
| * Psycho-education about underlying beliefs. * Practice modifying an underlying belief through a variety of cognitive techniques including socratic questioning, validity testing, examining the consequences of the belief and behavioral experiments (Beck, 2011; Leahy, 2003) |
| **Session 7. Ongoing belief modification and introduction of mindfulness** |
| * Work on a belief that is contributing to anxiety, such as metacognitions about worry, intolerance of anxiety (Barlow *et al*, 2011; Leahy, 2016) or fears about the impact of dying on loved ones. * Introduce Mindfulness: provide rationale, contrast with distraction and suppression; practice a short exercise (Kabat-Zinn, 1990). |
| **Session 8. Address any remaining avoidance or over-monitoring** |
| * Identify any remaining maladaptive coping and associated underlying beliefs and address in session. * Distinguish between over-monitoring and reasonable surveillance. Establish plans for future medical follow-up appointments and tests and responding to new symptoms (Butow *et al*., 2013) * Brief mindfulness practice (Segal, Williams, & Teasdale, 2006). |
| **Session 9. Review and relapse prevention** |
| * Review skills learnt in the program. * Review weekly anxiety scores and discuss realistic expectations for fluctuations in the future. * Identify potential future triggers and periods of uncertainty and possible adaptive responses. * Identify signs that may indicate a need for formal psychological support in the future. |

2 We modified the card sort exercise used in ConquerFear, which lists a number of extrinsic values, such as “being wealthy” or “being ambitious and hard-working” (Ciarrochi & Bailey, 2008, page 141-143). In the context of a life limiting illness, extrinsic, outcome-focused goals may be unachievable and consequently unhelpful, especially if evaluations of self-worth are dependent on attainment of those goals. However, shifting focus to intrinsic values and goals that can be realistically expressed despite physical limitations and symptoms is adaptive (Sprangers & Schwartz, 1999). Consequently, we modified the card sort exercise to list intrinsic values (such as compassion, creativity or learning) and explored how the identified values could be translated into achievable goals despite the limits of their current circumstances.

**Primary Control-** **Changing what can be changed Secondary Control** – **changing one’s response**

**Unhelpful**

**Helpful**

|  |  |
| --- | --- |
| - Problem solving  - Planning  - Goal setting  - Assertive communication  - Realistic health behaviours  - Pacing activity  - Challenging thoughts that are untrue  ACTIVE COPING  DOING MODE | * Regulating one’s emotional response * Increasing tolerance for unwanted thoughts and emotions * Observing, acknowledging, validating and normalising * “Riding the wave” * Detached Mindfulness * Reframing thoughts that are unhelpful * Choosing one’s attitude to the situation * Being present in the moment * Choosing how to improve the next moment * Engaging in meaningful activities   ACTIVE COPING  BEING MODE |
| Take effective action  LETTING GO  - Ruminating, worrying  - Aggressive communication  - Dogged perseverance despite symptoms such as fatigue  - Over checking body for symptoms  - Rigid health behaviours  - Excessive information seeking and reassurance seeking | * Avoidance of reminders of the cancer and unwanted internal experiences * Distraction * Suppression * Withdrawing from activities * Drugs and Alcohol * Not taking possible action * Maintaining unhealthy lifestyle behaviours * Passive communication * Resignation |

## 

## Figure 1. The Control Matrix

Awareness:

If you are feeling anxious, take a moment to stop and acknowledge the thoughts, feelings, body sensations and urges that are part of your current experience.

Be flexible in your response

It would be helpful to engage with the thoughts further - by examining my thinking in this situation I am likely to learn something useful and/or deal with something that I have been avoiding.

It would not be helpful to engage with the thoughts further - they do not give me any information that will help me to move towards my desired goals.

Acknowledge and validate the thoughts and associated feelings and urges.

Disengage from processing further

Consider “what can I do to improve this moment in a helpful way?”

Process the thoughts and feelings in a contained and productive way

Even if there is a realistic worry, am I thinking in a helpful way? What is a more helpful response?

Take any realistic and practical action that would be helpful.

Bring your attention to what you are doing in the moment.

If you find your thoughts coming back to the same concern again, acknowledge and validate the thoughts and feelings and perhaps the urge to ruminate. Remind yourself of your rational response and the course of action that you have decided on rather than going over and over the problem again.

**Figure 2.** REFLECT flowchart: REsponding FLexibly and with Choice to Thoughts

***Participants***

Consecutive potentially eligible outpatients referred to a hospital psychology service were informed of the study and, if agreeable, screened.

Inclusion criteria included:

1) A diagnosis of advanced cancer, a recurrence or a second cancer primary,

2) Aged ≥ 18 years,

3) Fluent in English,

4) Clinically significant anxiety, traumatic stress or FCR as indicated by at least one of the following:

* + - * 1. Hospital Anxiety and Depression Scale –anxiety subscale (HADS-A, Zigmond & Snaith, 1983) score ≥ 8
        2. Impact of Events Scale – revised (IES-R; Weiss & Marmar, 1997) score ≥ 19
        3. Fear of Progression Questionnaire – Short Form (FOPQ-SF; Mehnert *et al*., 2006) score ≥ 34.

Exclusion criteria included:

1) A serious mental health condition requiring ongoing treatment, such as psychosis, bipolar, borderline personality disorder, or current suicidal risk. Substance dependence as indicated by a score of ≥ 6 for men and ≥ 2 for women on the Drug Use Disorders Identification Test (DUDIT, Berman *et al*, 2005).

2) Receiving concurrent psychological treatment

3) Psychotropic medication unless

1. the dose has been stable for at least 8 weeks
2. the medication was prescribed as a pre-medication before chemotherapy treatment or a medical procedure or
3. the medication was prescribed specifically to treat nausea.

4) Serious cognitive impairment as indicated by a score of ≤ 27 on the Telephone Interview for Cognitive Status – modified (Welsh, Breitner, & Magruder-Habib, 1993; Knopman *et al*., 2010).

See Figure 1 for a consort diagram of recruitment and the progress of the study. Forty-five patients were invited to participate, 16 consented to screening and 12 of 13 eligible participants commenced the intervention.

In our preregistered protocol, we used a cut-off of 19 on the IES-R, while a cut-off of 27.5 has been suggested (Schulte-van Maaren *et al*., 2013). Using this higher cut-off, one participant did not have clinically significant anxiety at study entry. We included this participant’s scores in all analyses except those that assessed clinical change.

During the intervention, one participant died, one dropped out due to feeling better and two dropped out without reason. Eight participants completed the intervention and post intervention assessments. Three participants received booster sessions during the follow-up period.

Potential participants identified from the referral information

(*N* = 45)

Did not consent to proceed to screening:

*Wanted a regular psychology appointment*

*No reason given* (*n*= 11)

*Wanted 1 or 2 sessions only* ………………….. (*n* = 3)

*Didn’t want to commit to regular appointments* (*n* = 3)

*Too much happening already to consider a study* (*n* = 2) *Presenting problem not related to anxiety* (*n* = 1)

*Not wanting a psychology appointment at all* …...…...….(*n*= 8)

*Did not respond to attempts to contact* …………………..(*n*= 1)

Screened

(*N* = 16)

Ineligible:

*Scores too low on all screening measures* (*n* = 3)

Eligible

(*N* = 13)

Withdrew *–“too much going on”* (*n* = 1)

Completed pre-intervention questionnaire and commenced intervention

(*N* = 12)

Did not complete the intervention:

*Dropped out, no reason given* (*n*= 2)

*Dropped out, improved, provided post measures* (*n*= 1)

*Deceased* (*n*= 1)

Completed intervention and

post intervention measures

(*N* = 8)

Booster session(s):

*1 booster to complete intervention content* (*n*= 1)

*2 booster sessions in preparation for transplant* (*n*= 1)

*6 booster sessions: physical symptoms impacted pace of therapy* (*n*= 1)

2 month follow-up questionnaire

(*N* = 8)

**Figure 3.** Consort diagram showing recruitment and progress of the study.

***Design***

The study was a single-group design, approved by the Hospital Research and Ethics Committee at which the research was conducted (Approval Number HREC/17/SVH/343) and registered with the Australian New Zealand Trials Registry (Registration Number ACTRN12618000406202). All procedures were in accordance with the ethical standards of the institutional research committee and informed consent was obtained for all participants in the study.

***Procedure and Measures***

Before each therapy session, participants completed the HADS-A. At the completion of each session, participants rated 1) how effective the session was in helping to manage their anxiety and 2) how essential they perceived the session to be on a 10-point scale developed from Smith and colleagues (2015). Protocol adherence was assessed with session checklists.

The following psychological outcome measures were completed pre-intervention, post-intervention and at 2 months follow-up:

**Anxiety** was assessed with the HADS-A (Zigmond & Snaith, 1983). Scores on the seven item scale range from 0 to 21, with scores ≥8 indicating probable anxiety (Bjelland *et al*., 2002).A Reliable Change Index (RCI), which indicates the likelihood that change has occurred in response to the intervention rather than as a result of fluctuations in measurement (Jacobson & Truax, 1991) was calculated using the test-retest coefficient (Spinhoven *et al*., 1997) and standard deviation (SD) from a normative population (Crawford et al., 2001). A change on the HADS-A >3.46 indicated reliable change.

**Fear of cancer recurrence or progression** was assessed with the 12-item FoPQ-SF (Mehnert *et al*., 2006). The short form correlates highly with the 43-item version (Herschbach *et al*., 2005) which received the highest rating in a review of FCR measures (Thewes *et al*., 2012). Possible scores range from 12 to 60 with a score ≥34 indicating clinically relevant fear of progression (Sarkar *et al*., 2014). A test-retest coefficient has not been published. RCI was calculated using the cronbach alpha and SD reported in a FOPQ-SF validation study (Hinz *et al*., 2015). A change on the FoPQ-SF >8.01 indicated reliable change.

**Traumatic symptomatology** was assessed with the 22-item Impact of Events Scale – Revised (IES-R; Weiss & Marmar, 1997). Items assess intrusive, avoidant and hyperarousal symptoms (range 0-88). We used a cut-off of 19 on the IES-R to screen participants into the study. However, a cut-off of 27.5 has been suggested to differentiate clinical anxiety (Schulte-van Maaren *et al*., 2013) and this higher cut-off was used to determine clinical change as reported in this study. RCIs were calculated using test-retest reliability (Weiss & Marmar, 1997) and SD from a normative population study (Schulte-van Maaren *et al*., 2013). A change on the IES-R > 11.0 indicated reliable change.

**Depression** was assessed with the abbreviated Center for Epidemiologic Studies Depression Scale (CES-D-10; Andresen *et al*., 1994).Scores range from 0-30, with scores ≥10 indicating clinically relevant depression. The abbreviated version has been validated against the 20-item CES-D (Radloff, 1997)which was reported to be the most responsive measure of depression for use with cancer patients (Wakefield *et al*., 2015). The RCI was calculated using data reported in the original validation study(Andresen *et al*., 1994).A change on the CES-D-10 > 7.48 suggested reliable change.

**Death anxiety** was assessed with the 15-item Death Anxiety Questionnaire (DAQ; Conte, Weiner & Plutchik, 1982).Items assess worries about the process of dying and death. Scores range from 0 to 30. There is no published clinical cut-off for this measure, so a criterion C score was calculated (9.91), that is, a cut-off score that determines the likelihood that the individual score is reflective of being in a "normal" population as opposed to a "clinical" population (Jacobson & Truax, 1991). The RCI was calculated using the test-retest coefficient and SD from the original validation study and SD from a normative population sample (Cella & Tross, 1987). A change on the DAQ > 5.10 indicated reliable change.

**Quality of life** was measured with the McGill Quality of Life - Revised questionnaire (MQOL-R; Cohen *et al*., 2017). The 14 item scale assesses four domains: physical, psychological, existential and social. A total score (range 0-10) is computed as the mean of the four subscale scores, with higher scores reflecting higher QOL. The measure was developed with people with life-threatening illnesses, including cancer. A test-retest coefficient has not been published. A Criterion C score (6.64) and RCI were calculated using the internal consistency (0.94)reported in the original validation study(Cohen *et al*., 2017) and the SD (1.50) as provided by S. Robin Cohen. A change >1.02 on the MQOL-R indicated reliable change.

***Analyses***

Feasibility and acceptability were assessed by uptake and retention rates. Descriptive statistics were generated. For incomplete outcome data, we assumed the last recorded value indicated treatment response (as we had weekly HADS scores which allowed us to determine whether drop-out was likely to be associated with a deterioration in symptoms). Preliminary efficacy was assessed with t-tests comparing post-intervention and follow-up scores to baseline, effect sizes (Hedges *g*), reliable change indices and the proportion of participants scoring in the clinical range. We report recovery rates, which indicate all screening anxiety scores were in the normal range.

### Results

Twelve participants, including eight males and four females, commenced the intervention (see Table 2). The sample was aged 33 to 76 years (Mean=54.3). Eleven participants had advanced disease, one participant had two, early stage cancers. The average time since diagnosis was 1.43 years (SD = 3.06). Most participants (83%) were currently receiving medical cancer treatment (see supplementary information).

**Table 2.** Sample demographics and illness characteristics (*N* = 12).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Sample range | | Mean | SD | |
| Age | 33.5 – 76.2 | | 54.3 | 13.5 | |
| Time since diagnosis (years) | 1 week – 10.0 years | | 1.42 | 3.06 | |
| Frequency (percentage) | | | | |
| Gender | |  |  | | | |
| Female | | 4 (33.3) |  | | | |
| Male | | 8 (66.7) |  | | | |
| Marital Status | |  |  | | | |
| Married / defacto | | 9 (75) |  | | | |
| Single / divorced / separated | | 3 (25) |  | | | |
| Education Level | |  |  | | | |
| Year 10 or below | | 6 (50) |  | | | |
| TAFE certificate / diploma | | 2 (16.7) |  | | | |
| University degree | | 4 (33.3) |  | | | |
| Employment Status | |  |  | | | |
| Part-time | | 4 (33.3) |  | | | |
| Full-time | | 2 (16.7) |  | | | |
| Home Duties | | 2 (16.7) |  | | | |
| Unemployed | | 2 (16.7) |  | | | |
| Paid Leave | | 1 (8.3) |  | | | |
| Retired | | 1 (8.3) |  | | | |
| Country of Birth | |  |  | | | |
| Australia | | 6 (50) |  | | | |
| Other | | 6 (50) |  | | | |
| Cancer Site / Type\* | |  |  | | | |
| Melanoma | | 3 (25) |  | | | |
| Prostate | | 3 (25) |  | | | |
| Haematological | | 3 (25) |  | | | |
| Breast | | 2 (16.7) |  | | | |
| Colorectal | | 1 (8.3) |  | | | |
| Lung | | 1 (8.3) |  | | | |
| Current treatment# | |  |  | | | |
| Hormonal therapy | | 5 (40.8) |  | | | |
| Chemotherapy | | 4 (33.3) |  | | | |
| Immunotherapy, targeted therapy or combination | | 4 (33.3) |  | | | |
| None | | 2 (16.7) |  | | | |

† One participant was diagnosed with two cancer types. ‡ Participants may have been receiving more than one treatment.

*Feasibility, acceptability and adherence:* Only 27% of those approached agreed to screening (see Consort diagram, Figure 1). Of those that declined screening (*n* = 29), over a quarter (8/29) declined because they had been referred but did not want any sort of psychological support at that time. Two-thirds (20/29) wanted a regular, free psychology appointment rather than to participate in research. Of these 3 commented that the intervention was more than they required and 3 did not want to commit to regular appointments. One person did not respond to attempts to contact. Of eligible participants, 92% (12/13) participated. The majority (92%) of participants (11/12) completed at least five therapy sessions, which we considered to be a therapeutic dose on the basis that there is evidence that 5 session interventions are efficacious amongst cancer survivors (e.g. Butow et al, 2017), and 67% (8/12) completed all nine sessions. We felt that this retention rate was acceptable in a study with patients with advanced or recurred disease where attrition rates are potentially higher than in other cancer populations. On average, HADS-A scores of non-completers (*N* = 4) was slightly but not significantly improved at drop-out (*M* = 6.5, *SD* = 6.0) compared to study entry (*M* = 8.0, SD = 2.2, *t* = .48, *p* = .66). Also, the last recorded HADS-A score from non-completers (*M* = 6.5, *SD* = 6.0) did not differ significantly from the post-treatment HADS-A score of completers (*M* = 5.0, SD = 4.7; *t* = 0.48, *p* = .64), suggesting that drop-out was not related to higher distress or deterioration in symptoms. Participants, on average, rated the sessions as effective (8.99/10) and the skills as essential (9.21/10). Adherence to the manual was acceptable (76%). Non-adherence largely related to being unable to cover all material in a single session for patients who had deteriorating physical health.

*Efficacy outcomes:* Mean scores significantly improved post-intervention on all psychological measures (all *p*s < .03), except death anxiety (p = .055) (see Table 3). Effect sizes were large for anxiety (0.88), moderate for traumatic symptoms (0.68), depression (0.56) and death anxiety (0.52), and small for FCR (0.36) and QOL (-0.40). At follow-up, improvements on mean anxiety, traumatic symptoms and depression scores were maintained or increased (all *p*s < .03), with moderate to large effect sizes.

**Table 3.**

Efficacy outcomes on psychological measures (*N* = 12)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |
| Outcome  (range) | Assessment | Mean(SD) | Change from baseline  (95% CI) | *t* | *p* | Effect size  (Hedges’ *g*) |
|  |  |  |  |  |  |  |
| Anxiety  HADS-A  (0-21) | Baseline  Post-treatment  Follow-up | 9.4 (3.5)  5.5 (4.9)  5.4 (5.0) | 3.9 (0.6 - 7.2)  4.0 (0.4 - 7.6) | 2.6  2.5 | **.03**  **.03** | 0.88  0.89 |
|  |  |  |  |  |  |  |
| Traumatic symptoms  IES-R  (0-88) | Baseline  Post-treatment  Follow-up | 32.1 (17.9)  19.8 (16.9)  18.1 (16.6) | 12.3 (4.2 - 20.3)  14.0 (4.7 - 23.3) | 3.4  3.3 | **.01**  **.01** | 0.68  0.78 |
|  |  |  |  |  |  |  |
| Fear of Progression  FOPQ-SF  (12-60) | Baseline  Post-treatment  Follow-up | 35.0 (10.2)  30.9 (11.5)  29.8 (12.6) | 4.1 (0.8 - 7.4)  5.2 (-0.5 - 10.9) | 2.7  2.0 | **.02**  .07 | 0.36  0.44 |
|  |  |  |  |  |  |  |
| Depression  CES-D-10  (0-30) | Baseline  Post-treatment  Follow-up | 11.7 (7.3)  7.5 (6.9)  7.0 (7.4) | 4.2 (1.1 to 7.2)  4.7 (1.1 to 8.2) | 3.0  2.9 | **.01**  **.01** | 0.56  0.61 |
|  |  |  |  |  |  |  |
| Death Anxiety  DAQ  (0-30) | Baseline  Post-treatment  Follow-up | 11.4 (5.5)  8.6 (5.1)  8.8 (6.9) | 2.8 (-0.1 to 5.7)  2.6 (-0.4 to 5.6) | 2.1  1.9 | .06  .08 | 0.52  0.40 |
|  |  |  |  |  |  |  |
| Quality of Life  MQOL-R  (0-10) | Baseline  Post-treatment  Follow-up | 6.4 (2.2)  7.3 (2.0)  7.1 (2.5) | -0.9 (-1.6 to -0.2)  -0.7 (-1.5 to 0.1) | -2.8  -1.8 | **.02**  .09 | 0.40  0.27 |

Abbreviations: HADS-A: Hospital Anxiety and Depression Scale – anxiety subscale; IES-R: Impact of Events Scale-Revised; FOPQ-SF: Fear of Progression questionnaire, short-form. CES-D-10: abbreviated Center for Epidemiologic Studies Depression Scale. DAQ: Death Anxiety Questionnaire. MQOL-R: McGill Quality of Life - Revised questionnaire.

Regarding reliable changes, anxiety scores (HADS-A) reliably improved for 7/10 participants post-treatment and 6/10 at follow-up (see Table 4). Of these, 6/10 demonstrated reliable *and* clinical change in anxiety post-treatment and 5/10 at follow-up. One participant reported reliable, but not clinical, deterioration in anxiety before the second session and dropped out of treatment. Regarding clinical recovery, 6/11 (55%) participants were clinically recovered at post-treatment (i.e. scored in the normal range on all three anxiety screening measures) and 7/11 (64%) at follow-up. One participant, who recovered post-treatment, showed reliable and clinical deterioration from their post-treatment outcome at follow-up on anxiety and FCR scores.

**Table 4.**

Reliable and clinical change.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Post-Intervention | | | Follow-up | | |
| Outcome  Scale Used | Number in clinical range at study entry¥ | Reliable Change | Clinical Change | Reliable and Clinical Change | Reliable Change | Clinical Change | Reliable and Clinical Change |
| Anxiety  HADS-A | 10 | 7 (70%) | 7 (70%) | 6 (60%) | 6 (60%) | 6 (60%) | 5 (50%) |
| Traumatic symptoms  IES-R |  |  |  |  |  |  |  |
| 7 | 5 (71%) | 4 (57%) | 4 (57%) | 5 (71%) | 4 (57%) | 4 (57%) |
| Fear of Progression  FOPQ-SF |  |  |  |  |  |  |  |
| 4 | 0 (0%) | 0 (0%) | 0 (0%) | 2 (50%) | 2 (50%) | 2 (50%) |
| Depression  CES-D-10 |  |  |  |  |  |  |  |
| 7 | 2 (29%) | 4 (57%) | 2 (29%) | 4 (57%) | 5 (71%) | 4 (57%) |
| Death Anxiety  DAQ |  |  |  |  |  |  |  |
| 8 | 3 (36%) | 3 (36%) | 2 (25%) | 2 (25%) | 3 (36%) | 2 (25%) |
| Quality of Life  MQOL-R |  |  |  |  |  |  |  |
| 6 | 2 (33%) | 2 (33%) | 1 (17%) | 1 (17%) | 1 (17%) | 1 (17%) |

Note: Data shows proportion of participants demonstrating reliable and/or clinical improvement.

¥Published clinical cut-offs were used when available. Criterion C was used for Death anxiety and Quality of Life, see Measures.

Abbreviations: HADS-A: Hospital Anxiety and Depression Scale – anxiety subscale; IES-R: Impact of Events Scale-Revised; FOPQ-SF: Fear of Progression questionnaire, short-form. CES-D-10: abbreviated Center for Epidemiologic Studies Depression Scale. DAQ: Death Anxiety Questionnaire. MQOL-R: McGill Quality of Life - Revised questionnaire.

### Discussion

This pilot study provides evidence for the feasibility, acceptability and preliminary efficacy of a transdiagnostic treatment for cancer-related anxiety. The majority of participants (11/12) completed at least 5 sessions and 67% (8 people) completed all nine sessions. We felt that this retention rate was acceptable in a study with patients with advanced or recurred disease where attrition rates are potentially higher than in other cancer populations. Participants rated all therapy aspects as essential and effective. Despite the small sample size, statistically significant improvements were demonstrated post-treatment for anxiety, FCR, traumatic symptomology, depression and QOL. Improvements were maintained at follow-up for anxiety, traumatic symptomology and depression.

Clinically, 55% of the participants were “recovered” post-treatment and 64% at follow-up. These results are extremely promising because the sample was predominantly patients with advanced disease experiencing ongoing uncertainty, realistic threat and poor prognosis. These results also suggest this single intervention is feasible to deliver to patients with varied anxiety-related presentations.

Clearly this is a small sample treated by a single therapist. Our inclusion criterion was broad in that we included patients with advanced disease, recurred disease and a second primary. We wanted to include these patients because they have been commonly excluded from other studies and our intervention was designed to address this gap. Also, we posited that these patients share commonalities in that the cancer threat is realistically high and the inherent features of the cancer context (uncertainty, uncontrollability and death awareness) are particularly salient to this group of patients. Many potential participants did not consent to screening as they did not want to take part in research but rather preferred to access free psychological support within the cancer service. However, in cancer settings uptake rates for participants screened for distress are typically low (on average 50%) and are significantly lower if offered face-to-face or when offered by psychologists rather than nurses (Brebach, Sharpe, Costa, Rhodes & Butow, 2016), both of which were relevant to the current study. Our low recruitment rate has implications for the feasibility of translating the study to a larger trial. One possibility is that the study design could be amended to provide greater flexibility around session length and interval so that commitment to the study is less burdensome. Also recruitment could be extended to patients from hospitals that do not provide free psychology support as part of their cancer care. Small effect sizes were demonstrated for FCR. However, only four participants scored in the clinical range for FCR at study entry, so this may have impacted the effect sizes found for FCR. Also the measure of death anxiety used in the study did not have a clinical cut-off, so future research should establish clinical cut-offs in a sample of people with advanced disease to more accurately assess the clinical effect of the intervention. Anecdotally, in this acutely unwell population, more flexibility around content delivery was needed to accommodate varying physical symptoms and capacity to cognitively engage. Therefore, we would recommend re-organising sessions into modules completed at a pace suitable to each patient.

We are unaware of any previous intervention studies that have combined elements of traditional and contemporary CBT in the cancer setting. Our model of cancer-related anxiety identified that cognitive *processes* and *content* were important targets of treatment. In the context of advanced cancer, patients do have realistic concerns that are amenable to productive processing, but describe that their attempts to work through their concerns cognitively often result in worrying and rumination. Therefore providing 1) psychoeducation around helpful and unhelpful coping in response to uncertainty and limited control and a 2) framework around *when* and *how* to process concerns and *when* and *how* to disengage from unproductive processing were important, novel, strategies included in the intervention.

The study provides preliminary evidence for the feasibility and acceptability of this transdiagnostic intervention for cancer-related anxiety in patients with advanced cancer. Clearly, we cannot make conclusions about efficacy but recovery rates in this study were encouraging, particularly given most participants had advanced disease and were living with ongoing uncertainty and, for some, clinical deterioration of their disease. While we did not have sufficient numbers to adequately assess likely prognostics factors, anecdotally, patients who were most avoidant appeared to struggle more with the content of the intervention and to have poorer outcomes. Further research is needed to evaluate the intervention in a randomised controlled trial. For instance, research should assess the underlying mechanisms of any clinical change and explore if this integrated approach is efficacious compared to a single treatment approach, such as metacognitive therapy.

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