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ORIGINAL ARTICLE

Feasibility and Impact of a Guided Symptom Exposure Augmented Cognitive Behavior Therapy Protocol to Prevent Symptoms of Pharmacologically Induced Depression: A Pilot Study

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Abstract
Depression is the leading cause of disability and a major cause of morbidity worldwide, with societal costs now upwards of 1 trillion dollars across the globe. Hence, extending current efforts to augment prevention outcomes is consistent with global public health interests. Although many prevention programs have been developed and have demonstrated efficacy, studies have yet to demonstrate that CBT is effective in preventing symptoms in populations at risk for developing depression induced by pharmacological substances. Using a randomized, controlled design, this pilot study reports on the feasibility and preliminary effects of a novel, guided symptom exposure augmented cognitive behavioral prevention intervention (GSE-CBT) in a sample diagnosed with Hepatitis C at risk for developing medication induced depression. Results demonstrated that the guided symptom exposure augmented CBT (GSE-CBT) was feasible in this population and was delivered with high integrity. Although not statistically different, we observed a pattern of lower depression levels in the GSE-CBT group versus those in the control group throughout. This pilot study demonstrates that a psychosocial prevention intervention is feasible for use in patients at risk for developing pharmacologically induced depression and that a guided symptom exposure augmented CBT protocol has the potential to prevent symptoms of depression that develop as a side effect to taking these medications. Results are preliminary and future studies should use larger samples and test the intervention in other populations.

Keywords Depression · Prevention · Adulthood · CBT · Exposure · Interoceptive exposure · Mood induction · Hepatitis · Interferon

Introduction

Depression is one of the most common illnesses across the globe, and is the leading cause of disability as well as a major cause of morbidity worldwide (Greden 2001; Kessler et al. 2005; World Health Organization 2017). Approximately 4.3% of the global population (322 million people) meet criteria for depression annually and 6.7% meet criteria over their lifetime (Kessler et al. 2007; Hasin et al. 2005, 2018; World Health Organization 2017). Suicide rates among mood disordered outpatient populations range between 2–10% and can be as high as 15% among inpatient individuals suffering from major depression (Welton 2007). Depression is associated with comorbid disorders (e.g., anxiety, substance abuse, personality disorders), cognitive deficits (e.g., decision-making difficulty, poor short-term memory), and poorer physical wellbeing. Social and occupational impairments tend to endure well beyond remission

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and individuals with depression are at a heightened risk for recurrence, and have an increased likelihood and frequency of relapse with each successive episode. Depression also has deleterious effects on family members. For example, studies show that children of depressed individuals are at an increased risk for negative psychological and physical outcomes (Weissman et al. 2006). Societal costs associated with depression are also significant. Although costs associated with treating and preventing depression are considerable, costs associated with decreased production, sick leaves, increased healthcare utilization, premature death, and other factors that are affected by the experience of an untreated mood disorder are far greater by comparison, and are now upwards of 1 trillion dollars across the world (Kessler et al. 2008; World Health Organization 2017). Costs to the individual, family, and society are even higher when accounting for the unmet potential of sufferers.

The efficacy of cognitive and behavioral therapies (CBT) for the treatment of depression has been well demonstrated in patients presenting with primary depression (Beltman et al. 2010; Cuijpers et al. 2010, 2011; Di Giulio 2010; Dimidjian et al. 2006; Hofmann et al. 2012; Jorm et al. 2008; Hollon et al. 2005; Tolin 2010; van Straten et al. 2010), and in those suffering from comorbid depression associated with medical illnesses such as AIDS, diabetes, M.S. TMJ, chronic pain, and cancer (Church 1998; Edelman et al. 1999; Hopko et al. 2008; Li et al. 2017; Safren et al. 2009, 2012; Soroudi et al. 2008; Tovote et al. 2017; van Straten et al. 2010; Ye et al. 2018). However, even under the most optimal circumstances, existing treatments succeed in reducing the burden of depression disorders by only 35% (Cuijpers et al. 2008), suggesting that more needs to be done to alleviate the burden of illness.

Targeting depression before it begins is another way to minimize its impact. Efforts to prevent depression are especially critical given that having a first episode of depression increases the likelihood of suffering additional episodes of depression in the future, and given that each episode leads to mounting disability and costs to the individual, family, and society. Many studies have demonstrated the efficacy of CBT in preventing depression (Cuijpers et al. 2011; Munoz et al. 2010). CBT has been used to help prevent depression in the general population without known risk factors (i.e., universal programs; Horowitz et al. 2007; Pössel et al. 2011; Shochet et al. 2001; Wahl et al. 2011), in people with several known risk factors for the illness (i.e., selective programs; Beardslee et al. 2013; Garber et al. 2009; Munoz et al. 1995; Seligman et al. 2007), and in those with sub-clinical symptoms of depression (i.e., indicated programs; Allartvan Dam et al. 2007; Clarke et al. 1995, 2001; Gillham et al. 1995; Seligman et al. 1999; Stice et al. 2010; Vázquez et al. 2016). A few studies have shown that CBT is also effective in preventing depression in individuals with medical illnesses (Kohn et al. 2000; Pitceathly et al. 2009; Sharpe et al. 2001; Silberbogen et al. 2012).

However, research has yet to target or demonstrate that a psychosocial intervention is effective in preventing symptoms of depression induced by pharmacological substances. Up to 40% of individuals who receive a course of Interferon (IFN), a medication used to treat a variety of medical illnesses such as multiple sclerosis and HCV, develop symptoms of depression in addition to other side effects (e.g., Dieperink et al. 2000; Mohr et al. 1997; Pariante et al. 1999; Robaeys et al. 2007) and consequently either discontinue or are withdrawn from medical treatment, and may have mortality secondary to non-completion of medical treatment. Most develop symptoms of depression between one to three months of IFN treatment (e.g. Horikawa et al. 2003; Lucaciu and Dumitrascu 2015; Robaeys et al. 2007; Schäfer et al. 2007) and suicidal symptoms occur in up to one-quarter of individuals (Lucaciu and Dumitrascu 2015; Sockalingam et al. 2011). Hence, extending current efforts to prevent depression in these populations is imperative.

Furthermore, although research shows that preventive CBT programs can help to reduce the occurrence of new mood episodes (Cuijpers et al. 2011), the observed effect sizes (e.g Hedges $g = .22$ in Jane-Llopis et al. 2003) of prevention programs in general are lower compared to those observed in treatment studies of MDD (Cohen's $d = .73$; Robinson et al. 1990), with universal programs showing the smallest effect sizes in comparison to selective or indicated programs (Challen et al. 2014; Calear and Christiansen 2010; Cuijpers et al. 2008; Garber et al. 2009; Horowitz and Garber 2007; Merry et al. 2004; Spence et al. 2005; Tak et al. 2016). Hence, extending current prevention efforts to further augment outcomes is a global priority given that the disease burden of depression continues to increase each year (Cuijpers 2011, 2017; Cuijpers et al. 2012).

The comparably smaller effects observed in prevention studies could be due to several reasons; for example, individuals with no symptoms or subclinical symptoms, by definition, are not ill or as ill and, consequently, results may be limited by a floor effect. Relatedly, because CBT relies on a skills-based approach, teaching skills to counteract symptoms that are not yet present (or impairing) may be one possible reason such programs have lower effect sizes. One way to enhance effects in the absence of symptoms may be to artificially induce symptoms of a psychological illness in order to help individuals without current symptoms understand and tolerate symptoms of depression when they arise in the future, and to facilitate their acquisition and practice of cognitive and behavioral skills. Although induction of moods has been used routinely to assess vulnerability to depression (Gotlib and Joormann 2010; Ingram and Ritter 2000; Newman and Sears 2015), inducing moods or other symptoms of an illness have not been used as an intervention

to inoculate people against depression or other psychological conditions. However, principles of medical vaccination have demonstrated that receiving low levels of a physical illness are successful in inoculating individuals against a variety of medical illnesses. Although the mechanism to inoculate against psychological illnesses are quite different from those of medical illnesses, the strategy of inducing symptoms has been successfully used in the psychosocial treatment of anxiety disorders (Barlow 2014; Clark and Beck 2010) and may be worth investigating to see if it is successful in preventing psychological illnesses. In other words, the use of interoceptive exposure to treat anxiety offers a model for its use as an attempt to inoculate individuals against the development of a future psychological illness. Further, confronting emotional experiences without distraction, suppression, escape, avoidance, or judgment is a key feature of cognitive and behavioral treatments in general (Allen et al. 2008; Clark and Beck 2010; Hayes et al. 1996; Linehan 1993) and is believed to help individuals confront and overcome emotional avoidance strategies that exacerbate negative emotions (Allen et al. 2008). Although strategies to induce interoceptive symptoms and to tolerate negative emotions and overcome emotional avoidance have been used successfully to treat anxiety disorders (Barlow 2014; Clark and Beck 2010) and depression (Farchione et al. 2012; Hayes et al. 2004), inducing a mood and other symptoms of a psychological illness and then teaching people to allow themselves to experience emotional states and symptoms in order to prevent the future impact of depression, anxiety, or other psychological illnesses has not yet been tested.

Using principles of medical vaccination, prior work in CBT treatments of anxiety and other conditions, and methods to study depression vulnerability as guides, the present study incorporated a novel psychological vaccination protocol with the goal of preventing future symptoms of depression in individuals at risk for developing depression induced by pharmacological substances. We incorporated a novel guided symptom exposure (GSE) protocol to better educate participants on symptoms of depression and to facilitate their learning of CBT skills - with the goal of preventing future episodes of sadness from developing or becoming prolonged, distressing, and impairing (Guided Symptom Exposure Augmented CBT – GSE-CBT; McGinn et al. 2008). The hypothesis was that by inducing and guiding participants to experience symptoms triggered during a depressive episode, participants might be better able to understand symptoms of depression and how they fluctuate, to better grasp the purpose of the CBT intervention, and to tolerate symptoms and practice and generalize the skills when—and if—they later experienced symptoms of depression. Specifically, the guided symptom exposure was developed as a psychological "vaccination" against future depression, whereby non-depressed individuals were asked to undergo symptom induction exercises and then guided to (1) understand and tolerate induced symptoms of depression without distraction, suppression, escape, avoidance, or judgment, (2) learn through experience that emotions such as sadness and other symptoms of depression are normal and can be transient, and (3) understand and modify maladaptive thoughts and behavioral urges associated with negative emotions and symptoms.

Given that psychosocial prevention efforts have not yet targeted individuals at risk for developing pharmacologically induced depression, this study represents the first attempt to prevent depression induced by pharmacological substances using a psychosocial intervention. The intervention was tested in a group of individuals with Hepatitis C (HCV) for whom the imminent risk of depression was high because they would soon receive a medication known to lead to depressive symptoms—interferon-α (IFN). The added benefit of testing the intervention in this population was that we had an estimate of imminent rates of conversion to depression absent any intervention. Typically, one of the challenges faced by prevention researchers is that it is difficult to predict who will ultimately get depressed and when.

HCV-infected populations have significant challenges, including a high rate of drug use and poor utilization of health care resources that could limit the efficacy of CBT. Given these factors, it was important to assess if a structured psychotherapeutic intervention could be feasibly conducted on this complicated, medical sample at risk for pharmacologically induced depression. If the treatment proved to be feasible and showed preliminary effects in this population, it could also be useful to evaluate it in a fully powered trial with this and other populations of individuals at risk for depression.

The primary aim of the pilot study was to examine the feasibility of a guided symptom exposure enhanced CBT protocol (GSE-CBT) to prevent symptoms of depression in a sample at risk for pharmacologically induced depression. We also assessed the preliminary efficacy of the GSE-CBT intervention at mitigating pharmacologically induced depressive symptoms. We hypothesized that our intervention, including the novel guided symptom exposure paradigm, would be feasible in this sample, and would result in smaller increases in depressive symptoms over the course of follow-up, relative to individuals in the control group.

Method

Participants

18 participants (Intervention = 12; Control = 6) were enrolled in the study. The sample was composed of 16% Caucasians (n = 3), 33% Hispanics (n = 6), and 50% Blacks

(n = 9). Due to recruitment challenges related to meeting medical eligibility criteria outlined in detail below, we were able to recruit only half the proposed number of participants. The majority of participants were recruited from the primary care and liver specialty clinics of an academic hospital in an extremely low income, under-represented minority neighborhood in New York City and had a diagnosis of HCV and prior substance abuse. Additional recruitment was done via advertisements in local newspapers and in community settings. All study procedures were approved by the Mount Sinai Medical Center Institutional Review Board (IRB) and the Albert Einstein College of Medicine IRB. The study was funded by the National Institute of Health.

Procedure

All participants completed the informed consent process and were administered a demographic questionnaire, the Patient Health Questionnaire 9-item form (PHQ-9; Kroenke et al. 2001), and the Beck Depression Inventory II (BDI-II; Beck et al. 1996). Although both were used as outcome measures, the PHQ-9 was primarily added as a means to exclude those with existing depression while the BDI was used as the primary outcome measure. Participants inclusion criteria were: English speaker; sixth grade reading level; treating physician determination that participant was ready to begin treatment with IFN and ribavirin for HCV. Exclusion criteria included: actively abusing illicit drugs or alcohol (methadone use was acceptable); medical contraindications to a standard course of IFN/ribavirin therapy; less than 1 year of life expectancy given the long, arduous course of the medical regimen; current participation in CBT or in any structured psychotherapy; antidepressant medication initiated less than 6 months before enrollment; severe comorbid psychopathology including bipolar disorder, personality disorder, psychotic disorder, or active suicidal ideation. Participants were also excluded if current depression as assessed by the Patient Health Questionaire-9 (PHQ-9); determined by five of nine items answered positively for "more than half the days" *and* endorsing feeling depressed *or* little interest or pleasure in doing things). Measures were administered by study personnel to all participants to determine eligibility.

The study used a randomized, controlled design. Patients were informed that they would be receiving information and support sessions to help facilitate their treatment with interferon therapy but were blinded to whether they were in the intervention or the control arm. Patients who met eligibility were randomized in blocks of six at a time (four participants' assigned to the GSE-CBT group and two participants assigned to the control group) (see Fig. 1), using a computer-generated random number. The random assignment was conducted by an independent person not involved in the study. Unbalanced randomization is indicated in early phase trials, where the aim of investigation is to explore critical treatment dimensions (e.g., feasibility, dose, schedule, compliance etc.) that are needed to determine clinical utility and plan for future larger RCTs (Hey and Kimmelman 2014). This justification is particularly compelling when there are grounds for believing, as was the case in this study, that intervention dimensions such as feasibility or compliance are vital even in the absence of efficacy. Additionally, a larger sample size in the active treatment group (compared to 1:1 randomization) confers a gain in statistical power for monitoring feasibility issues, response rates, or certain adverse events. Uneven allocation is also recommended when study treatments are especially costly, or in this case extensive in terms of assessment, or when there is a mall sample size with a group therapy that recruits in a rolling fashion. Finally, unbalanced randomization improves accrual given that potential participants perceive that they have a higher chance of receiving active treatment and when therapy is deemed to be effective, thus allowing for minimization of the control group (Hey and Kimmelman 2014).

Participants, in both groups, received baseline measures *(CBT week 1)*, at the visit when IFN was initiated *(CBT week 4, IFN week 0)* and when they received future injections. IFN injections for individuals with HCV Genotypes 2 and 3 were scheduled on IFN weeks 0, 2, 4, 8, 12, 18, 24 given that a shorter course of IFN is indicated for these two Genotypes. HCV Genotypes 1 and 4 have a longer course of IFN and hence these participants received injections on IFN weeks 2, 4, 8, 12, 18, 24, 30, 36, & 42. Participants received $20 for each visit, and a pass for public transportation to get to the session. The assessments were handed out, collected, and de-identified by personnel who were blinded to whether patients were in the intervention or the control arm.

Participants in the intervention group received three group GSE-CBT sessions three weeks prior to initiation of IFN, one group session when IFN was initiated, and four sessions following IFN initiation (see Fig. 2). A licensed clinical psychologist specializing in CBT conducted intervention sessions. Participants in the control arm of the study received eight support group sessions to coincide with the eight GSE-CBT group sessions attended by the active group (see Fig. 2). The frequency of sessions was front-loaded because the risk for developing IFN-induced depression is greatest during the first 3 months (Horikawa et al. 2003). Both groups received a reminder call prior to each group session, Additionally, all participants were assigned a "buddy" within the group who was responsible for calling to remind them of upcoming sessions and to generally be available to talk. Comparable efforts were made to retain subjects in both groups; both the active and control groups received incentives and reminder calls for attending.

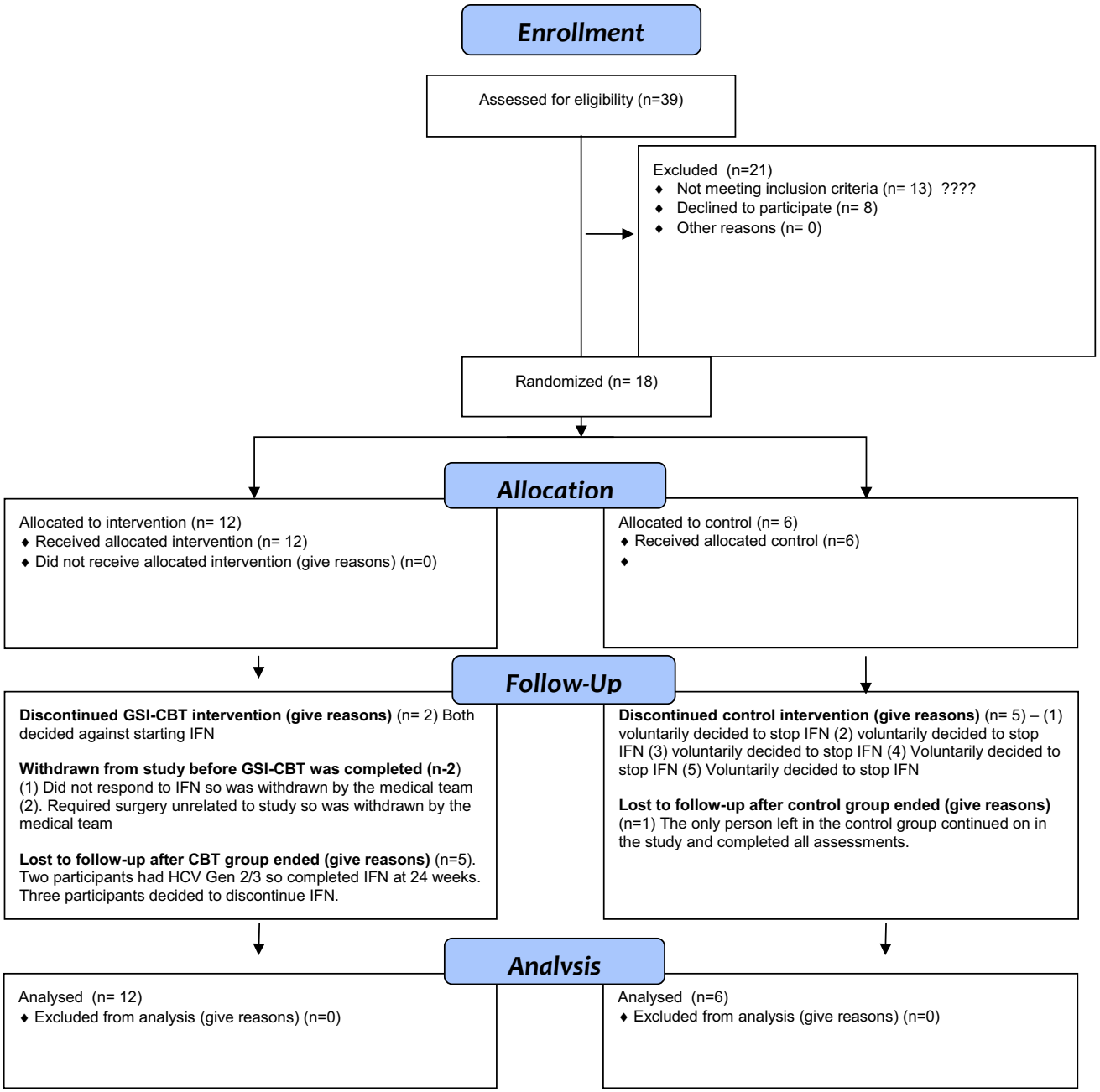

Fig. 1 Study flow diagram

Guided Symptom Exposure Augmented CBT (GSE-CBT)

The intervention (McGinn et al. 2008) was comprised of a prevention program using a series of eight, 90-min, face-to-face group GSE-CBT sessions. Each GSE-CBT session included a brief didactic component in which participants were given specific information on a particular CBT skill (e.g., cognitive restructuring). The didactic components were followed by group discussion focused on mastering the skill to target the cognitive, behavioral, and somatic symptoms of depression. Culturally relevant examples were used and issues specific to HCV were discussed based on prior studies examining the nature of symptoms in patients with HCV undergoing IFN (Krauskopf et al. 2010; McGinn et al. 2005; McGinn 2016). For example, HCV is a stigmatized disease and many people do not discuss their diagnosis with loved ones. Thus, how to discuss their illness was a topic in one session, as was the importance of seeking out social support.

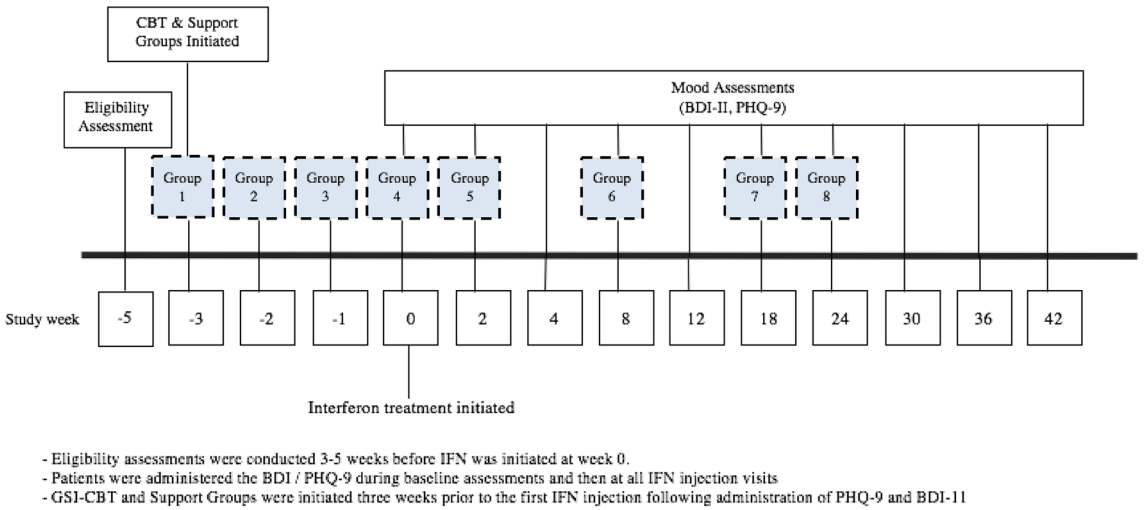

Fig. 2 Study procedure program

Participants were encouraged to regularly practice skills learned in each session for homework. This was facilitated by a client workbook, which included information on the topics covered in each session, including basic information on HCV and its treatment, depression, and CBT. Sessions included psychoeducation, behavioral activation, social support, guided symptom exposure, cognitive restructuring, and relaxation and mindfulness exercises. The focus of the first six sessions was to learn and practice techniques so that participants would have the necessary skills to utilize these strategies if they developed symptoms of IFN-induced depression. Sessions seven through eight were designed to help participants consolidate skills and practice skills in between sessions.

The third session included the novel guided symptom exposure paradigm that was intended to teach participants how to fully experience symptoms triggered such as a sad emotions, so that they would better understand how to use the cognitive behavioral therapy skills, should they later start feeling depressed. The symptom exposure consisted of a guided protocol that triggered emotions and symptoms that were likely to be triggered upon receipt of IFN. Based on stimuli successfully used in induction studies (Gotlib and Joormann 2010; Ingram and Ritter 2000; Newman and Sears 2015), symptoms were induced in the present study by guiding participants to pair stimuli such as sounds and songs while imagining a personally relevant memory. Patients were educated on symptoms of depression and then guided to tolerate and accept symptoms rather than avoiding them or retreating from them, and to understand that the emotions and symptoms were temporary and would eventually pass on their own. Patients were also guided not to uncritically accept or believe depressogenic cognitions that could arise during the mood induction or to act upon depressogenic behavioral urges. A positive mood was induced at the end of the session to demonstrate the contrasting effects of a positive mood on thoughts and behaviors, and to reinforce their learning that emotions vary and fluctuate over time. Patients were asked to practice the taped guided symptom exposure in-between sessions, and were assigned to use the same skills during naturally occurring moments of depression. For example, patients were asked to allow themselves to accept rather than retreat from naturally occurring moments of sadness, irritability, and fatigue in-between visits, to accept depressogenic thoughts as symptoms of depression but not to believe them as if they were true, and to act in opposition to depressogenic behavioral urges.

Support Group

Participants randomized to the control group also met for a series of eight, 90-min, face-to-face group support group sessions and were given standardized patient information developed from recommendations by the Centers for Disease Control and Prevention and National Institutes for Health during these sessions. The groups reviewed the basics of IFN, and what to expect during medical treatment in terms of side effects. Participants were taught how to monitor for certain side effects such as depression and anemia. Session time was then spent in informal discussions between members aimed at offering one other with socialization and support.

Measures

Patient Characteristics

Using a structured demographic questionnaire, study personnel assessed patient medical history including substance

use (intravenous drug use, alcohol and other) and other relevant comorbid medical disorders. Psychiatric history was also assessed, including whether or not the participant had a past diagnosis of depression, current psychopharmacological interventions, and current psychotherapeutic interventions. Additionally, study personnel administered the Mini-Mental Status Exam to determine whether their cognitive function was sufficient to participate.

Intervention Integrity: Intervention Adherence and Intervention Competence

The study evaluated intervention integrity by conducting adherence and competence assessments.

Observer Rated Adherence Adherence to the manual for the GSE-CBT group was assessed by a review of videotapes of random selected sessions to determine whether the therapist adequately addressed each component of the intervention. Using a random number generator, tapes were selected for adherence rating from three groups of session data: tapes from early, middle, and late in treatment. This stratified selection process is in line with recommendations advising representative samples (Waltz et al. 1993), and renders a total of 33% of data reviewed. A three-item (yes/no) adherence rating scale was developed for each session, itemizing the topics and CB techniques that were supposed to be covered. Adherence raters were doctoral candidates in clinical psychology. Three raters were bachelors level raters and two of the five raters were advanced, masters-level students with training in delivering CBT. Ten hours of training was provided, which encompassed a review of the treatment manual and principles of adherence rating. Raters also practiced coding sessions after which discrepancies were discussed and consensus achieved. Each sampled tape was reviewed by two raters. These ratings were used to establish overall levels of adherence and competence for the study, with interrater reliability calculated for the adherence scale ratings using observed percentage agreement (Mowbray et al. 2003); raters agreed on between 72% and 95% of items across sessions.

Observer Rated Competence Intervention competence was assessed by an experienced licensed clinical psychologist with an expertise in delivering and supervising CBT, as well as prior experience in serving as a therapist and conducting competence ratings in clinical studies. 20% of sessions were randomly selected for review of competence. Intervention competence was represented as the mean score for all 12 items of the CTS-R, a revised version of Young and Beck's Cognitive Therapy Scale (1980), which is scored on a 0–6-point Likert scale for each session (Blackburn et al. 2001). This version has good psychometrics, with high internal consistency indicated by an average Cronbach's alpha of .95 across raters. Interrater reliability is reflected in a Pearson correlation of .87 for total scores, and product moment correlations ranging from .42–.67 for individual items (Blackburn et al. 2001). The CTS-R has 12 items, rated on a seven-point Likert scale from "incompetent" to "expert" and includes excellent anchors for each item to facilitate raters' discrimination between different levels of competence on each skill. The items on the CTS-R also lend themselves well to a group intervention, making it an appropriate measure for the current inquiry.

All raters were unaware of subjects' depression ratings, were not involved in administering the protocol, and did not have a vested interest in the outcome.

Intervention Feasibility

Consistent with established criteria for assessing feasibility (Orsmond and Cohen 2015), the present study evaluated the acceptability and suitability of the intervention, as well as participant response to the intervention. Towards assessing acceptability and suitability of the intervention, the study assessed participants' attendance, comprehension, engagement, completion of therapy assignments, and satisfaction. Participants were asked to complete brief quizzes following each session in order to assess their engagement and comprehension of the session content. This was also seen as an indirect way of assessing therapist adherence to the manual and was reported as the mean percentage of correctly answered items on session review questionnaires. The therapist was also asked to indicate the percentage of the assigned homework completed by each patient at the end of each session. The mean percentage of completion of in-between therapy assignments was also used as a measure of intervention feasibility. Finally, patients were asked to indicate their satisfaction with the intervention and to indicate which of the intervention components were most useful to them.

Depressive Symptoms

Depressive symptoms were assessed at baseline (CBT week 0), at Interferon initiation (CBT week 4, IFN week 0), and at each subsequent IFN infusion (weeks 2, 4, 8, 12, 18, 24, 30, 36, & 42). Depression was assessed using two measures: the BDI-II (Beck et al. 1996) and the PHQ-9 (Kroenke et al. 2001). The PHQ-9 is a nine item self-report measure designed to screen for and diagnose depression. It has strong psychometric properties (Kroenke et al. 2001; Wittkampf et al. 2009) and good test–retest reliability (Kroenke et al. 2001). For this study, a score of ten or higher indicated a moderate level of depression (Kroenke et al. 2001). Cronbach's alpha varied across administrations in our sample,

α = . 62–.83. The BDI-II is a 21-item self-report scale that assesses the severity of a variety of depressive symptoms. A score of 20 or greater is considered clinically significant depression, and a score of 13–19 is considered mild depression (Beck et al. 1996). In our study, a score of 13 or higher was considered to indicate clinically significant depression. This measure has been found to be reliable and valid in assessing current depressive symptomatology in clinical populations and nonclinical populations (Beck et al. 1996) and in populations with medically related depression (Williams et al. 2002). The test–retest reliability is .93 (Beck et al. 1996). This measure has good internal consistency; in our study Cronbach's alpha ranged from .80 to .88.

Analytic Plan

Intervention integrity was established by conducting observer rates adherence and competence assessments of the delivered intervention. The outcomes for assessing feasibility were patient attendance, engagement/comprehension, completion of between session therapy assignments, and patient satisfaction reports. Efficacy was assessed by comparing symptoms of depression between the GSE-CBT and control groups using the PHQ-9 and the BDI-II. Repeated measures ANCOVA, controlling for depression scores on the PHQ-9 and BDI, as well as antidepressant use (at the eligibility assessment) evaluated differences in depressive symptoms on both the PHQ-9 and the BDI-II over the course of the follow-up period. Analyses were conducted according to the intention-to-treat principle. Due to the longitudinal nature of this study, missing data were anticipated; missing data points were filled using last observation carried forward.

Results

Participant Characteristics

The intervention and control groups did not differ on any of the demographic or baseline clinical characteristics (see Table 1). Baseline depression scores on both the BDI-II ($t(16) = 0.41$, $p = 0.68$) and the PHQ-9 ($t(16) = 0.48$, $p = 0.64$) were not statistically different between the intervention and control groups.

Intervention Integrity

Overall, the study therapists delivered 83% of the intended content, with adherence rates ranging from 67 to 97% across sessions, suggesting good fidelity to the protocol. Mean total CTS-R scores for the rated sessions were 59.5 and mean item scores were 4.75, indicating that the intervention was delivered skillfully.

Table 1 Demographic and clinical characteristics of sample at baseline

	Treatment	Control
N	12	6
N (%)		
Female	5 (42)	4 (67)
Age	55	53
Asian	0 (0)	0 (0)
Hispanic	3 (16)	3 (16)
White	2 (11)	1 (5)
Black	7 (38)	2 (11)
Employed	3 (25)	3 (50)
High school graduate	9 (75)	4 (67)
Suicidal ideation	0	0
Taking an anti-depressant	6 (50)	1 (17)
Engaged in psychotherapy	7 (58)	3 (50)
M (SD)		
BDI baseline	9.75(7.)	8.17 (7.8)
PHQ-9 baseline	3.58(3.4)	2.83 (2.6)

Intervention Feasibility

Intervention Attendance

On average, 64% (8/12) of participants attended each session of the GSE-CBT group. 78% of people (on average) attended the first three sessions, and 55% (on average) attended the last three sessions of GSE-CBT. By comparison, 50% on average (3/6) attended each session of the support group. Although 89% percent attended the first three sessions of the support group, only 28% attended the last three sessions of the support group.

Finally, eight of the 12 participants (66%) in the GSE-CBT group versus only one of the six participants in the control group (16%) remained on IFN until the end, and hence completed all group sessions (week 24) (Relative risk = 4.00; 95% CI: 0.64 ~ 25,02). Four people in the GSE-CBT group were withdrawn from IFN early by the medical team and hence couldn't remain in the GSE-CBT group - one person didn't respond to IFN and the other required emergent surgery unrelated to depression, HCV, or IFN. And, although two people in the GSE-CBT group voluntarily discontinued IFN (and hence had to drop out of GSE-CBT), their reasons for discontinuation were because they did not want to continue receiving IFN, not a wish to stop attending GSE-CBT therapy—no participant stopped attending GSE-CBT therapy, but continued with IFN.

Attrition rates from IFN were higher once therapy group sessions ended. Only three patients in the intervention arm and one patient from the control group completed the final follow-up assessment at week 42. However, of the remaining 8 intervention group patients in the study, the medical team discontinued two because they achieved a sustained viral response (successful removal of the virus) at week 24 and did not voluntarily drop out.

Comprehension and Engagement

On average, participants were able to correctly answer 89.2% of post-session questions (SD = 8.9%), indicating that the intervention was adequately delivered and understood.

Homework Completion

Patients in the GSE-CBT group completed 73% of the assigned homework, indicating good engagement.

Patient Satisfaction

Seven out of the eight patients who completed the GSE-CBT group reported in a survey that they were satisfied with the intervention, and of all the strategies learned, found the psychoeducation and the guided symptom induction components to be the most useful in dealing with the onset of depressive symptoms. Six out of the eight participants reported that the relaxation exercises were the least useful.

Intervention Efficacy

Results did not show a significant difference between the groups at post-test. There was no main effect of group on depression scores, as measured by the BDI, $F(1) = 2.60$, $p = .129$; partial $eta^2 = .16$ (see Fig. 3). There was no main effect of group on PHQ-9 scores, $F(1) = 2.05$, $p = .174$; partial $eta^2 = .13$ (see Fig. 4). Unfortunately, given that this was a feasibility study, the samples size was small. As a result, these analyses are underpowered for efficacy so the results must be interpreted with caution. It is notable that the average change in BDI-II score from eligibility to week 4 for the GSE-CBT group was .17, and for the control group it was 4.0. Similarly, the average change in PHQ-9 score was 1.58 for the GSE-CBT group and was 2.83 for the control group. These differences were maintained through the end of the study, see Fig. 5.

Discussion

The present pilot study demonstrated the feasibility of a CBT protocol augmented with a unique guided symptom exposure component (McGinn et al. 2008) to prevent pharmacologically induced depression in a medically compromised,

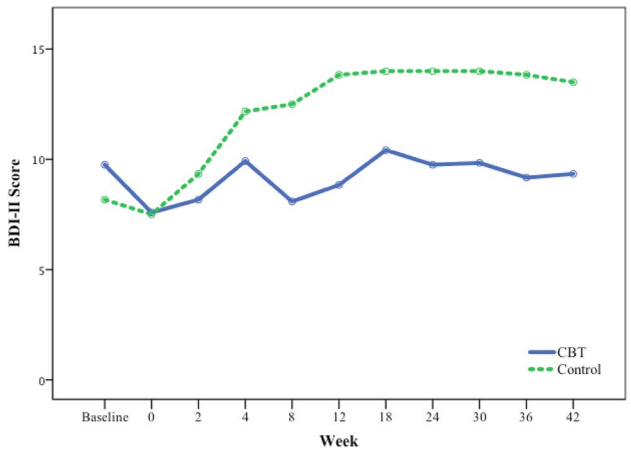

Fig. 3 BDI-II scores at each time point

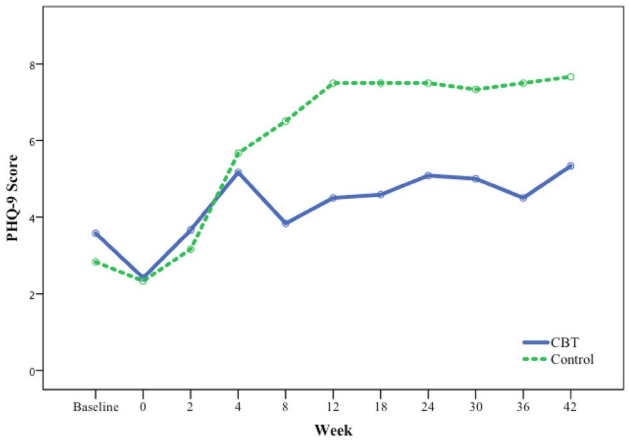

Fig. 4 PHQ-9 scores at each time point

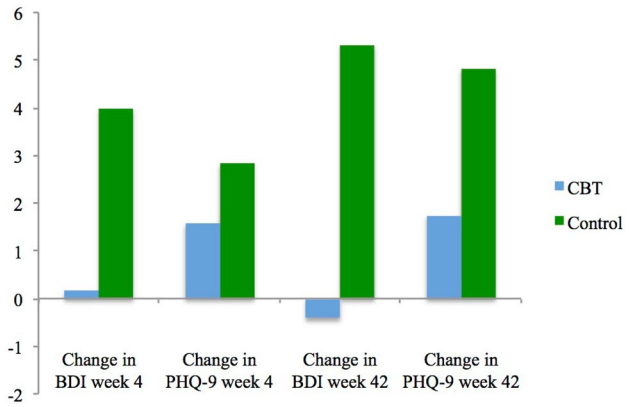

Fig. 5 Differences in change in depression scores from baseline to Week 4 and Week 42 (16 weeks following therapy end)

economically disadvantaged, urban, predominantly ethnic minority sample. Results also showed that patients in the GSE-CBT group were engaged, compliant with therapy assignments, demonstrated good comprehension of the material, and reported a high degree of satisfaction with the CB intervention. Although this was a small, pilot study underpowered for demonstrating efficacy, the study also suggested a pattern of lower depression scores as measured by the BDI-II and the PHQ-9 in the intervention group as compared to the control group, which was present across the course of the intervention. However, given the small sample size and given that results did not reach statistical significance, these results may very well have been caused by chance and must be considered extremely preliminary.

Of note, the individuals in the control group received more psychological support than individuals who normally get IFN. Hence, the finding that the depression trajectory was more promising in the GSE-CBT group even with an active control is encouraging. Our pilot results suggest that a non-pharmacological intervention is feasible and has the potential to be efficacious in reducing pharmacologically induced depression in a medically compromised population. Using a non-pharmacological intervention such as CBT to prevent pharmacologically induced depression in a medically ill sample is unique. The present study is the first study to examine effects of a non-pharmacological intervention to prevent symptoms of pharmacologically induced depression. Furthermore, only one other small feasibility *treatment* study—to our knowledge—has examined the impact of a non-pharmacological intervention on the *treatment* of pharmacologically induced depression (Silberbogen et al. 2012).

Results showed that GSE-CBT was delivered with good integrity; fidelity to the intervention was high and the intervention was delivered with a high degree of skill. Although more patients completed the GSE-CBT group versus the control group (8:1) and more people who had attended the GSE-CBT group versus the control stayed on their medical regimen and completed all follow-up assessments (3:1), the number was too small to make meaningful comparisons and attrition rates were high in both groups, particularly once therapy groups ended. We did not anticipate the degree of financial and other barriers (e.g., incarceration, eviction). Specifically, challenges associated with housing and poverty were a factor in participants' ability to attend visits and continue with IFN, and to receive the full preventive intervention in some cases. Although none of the participants chose to discontinue GSE-CBT, few people completed IFN whether voluntarily or involuntarily, resulting in small numbers of participants in both the GSE-CBT and control groups. Although under ideal circumstances, a retention rate of 66% would be disappointing, our sample was unique in the level of burden participants were under, as we have elaborated above. Additionally, a 34% dropout rate (20% if those who were involuntarily withdrawn are excluded) is not inconsistent with rates of dropout reported for CBT outcome studies in general (Fernandez et al. 2015). Because the ultimate goal of the GSE-CBT intervention is to prevent depression in people at risk for depression—not merely to prevent depression in a group receiving a medical intervention—we anticipate that in a population with fewer complications, GSE-CBT would be even more feasible.

The study has many limitations such as the use of self-report measures, and the lack of measures of the unique mechanism (guided symptom exposure). Additionally, given that this was a small, pilot study designed to examine feasibility, it was underpowered for efficacy. We also faced recruitment challenges largely related to participants needing to meet medical eligibility criteria, and relatedly, being able to begin group CBT at the same time given the complicated medical tests that they needed to undergo in order to determine eligibility (e.g., liver biopsies). Hence, we were able to recruit only half the proposed number of participants. Still, the small sample size is a notable limitation as is the rate of attendance and attrition. Further, randomization, although a critical design element of efficacy studies, may be unreliable in small samples. Hence, designing future studies with larger samples is of vital importance. However, although IFN treatment differed across condition given that more patients attended the intervention group and fewer patients dropped out of the intervention group, the fact that we still saw greater decreases in depression in the intervention group despite this is notable.

Notwithstanding the limitations, this is the first study to evaluate the effects of a psychotherapeutic intervention on preventing the future occurrence of pharmacologically induced depression symptoms, as well as the first study to evaluate the impact of an innovative, guided symptom exposure augmented CBT intervention to prevent future onset of negative symptoms and illnesses. Mood induction has been used to examine vulnerability to depression in prior studies (Gotlib and Joormann 2010; Ingram and Ritter 2000; Newman and Sears 2015), but has not been studied as an intervention to treat or prevent depression. Although strategies to induce interoceptive symptoms and tolerate negative emotions and overcome emotional avoidance have been used successfully to treat anxiety disorders (Barlow 2014; Clark and Beck 2010) and depression (Allen et al. 2008; Farchione et al. 2012; Hayes et al. 1996; Linehan 1993), they have not been used to prevent emotional illnesses. However, these studies offer a reasonable justification to study the induction of symptoms of an illness as a means to prevent an illness. GSE-CBT is unique in that it induces symptoms in asymptomatic individuals and then guides them to understand, experience, and tolerate aroused emotions and symptoms in order to minimize the future impact of negative moods and symptoms.

Although future studies will need to assess if the guided symptom exposure component adds benefit beyond traditional CBT components, it was notable that seven out of the eight patients who completed the GSE-CBT group reported in a survey that they were satisfied with the intervention, and of all the strategies learned, found the psychoeducation and the guided symptom exposure components to be the most useful in dealing with the onset of depressive symptoms. Six out of the eight participants reported that the relaxation exercises were the least useful.

Because the results were promising, but not conclusive, it is important that this preventive intervention be tested on larger samples. Given that prevention studies typically have smaller effect sizes than treatment studies, testing this model with larger sample sizes based on power analyses and numbers recruited in prior prevention studies as a guide, is particularly critical. Future studies should examine the effects of GSE-CBT on individuals in universal samples, and in other at-risk and indicated populations. For future studies involving HCV or other at-risk populations with complicated psychosocial situations, it will be important to incorporate services to address poverty, housing, and other factors that are likely to interfere with participation.

In summary, our study suggests that a psychosocial intervention (GSE-CBT) maybe a feasible intervention for patients who develop pharmacologically induced depression and has the potential to mitigate or prevent the onset of depressive symptoms. Although a small sample size, and high attrition and dropout rates for IFN limited our ability make inferences from the results of this study, our results found that individuals who received GSE-CBT exhibited a non-significant pattern toward lower dropout and lower symptoms of depression following initiation of IFN. In contrast, those in the control group had more dropouts and showed a pattern of increasing depressive symptomatology—consistent with the expected depressogenic effects of IFN—over the course of the study. Because depression may actually prevent an individual from starting or completing IFN, which is a potentially life-saving medical treatment for many medical conditions even beyond Hepatitis C, it is worth conducting future studies to examine the effects of GSE-CBT in a larger sample receiving IFN or other medical regimens. Furthermore, future studies examining the effects of GSE-CBT might demonstrate better retention and efficacy for preventing depression in non-medical samples; we recommend that future studies also examine the effects of GSE-CBT in preventing anxiety and depressive disorders in other at-risk or universal populations.

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Compliance with Ethical Standards

Conflict of interest Lata K. McGinn, Anna Van Meter, Ian Kronish, Jessica Gashin, Karen Burns, Natalie Kil and Thomas G. McGinn declare that they have no competing interests to report.

Informed consent and Animal Rights All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. No animal studies were carried out by the authors for this paper.

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