Title

Digitally-delivered Cognitive Behavioral Therapy for Overweight and Obese Primary Care Patients with Anxiety or Stress: Sub-Group Analysis of a Non-Randomized Trial

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Digitally-delivered Cognitive Behavioral Therapy for Overweight and Obese Primary Care Patients with Anxiety or Stress: Sub-Group Analysis of a Non-Randomized Trial

By

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PART ONE: Review of the Literature

The growing societal burden of chronic diseases has been identified as a major problem for the U.S. healthcare system. In 2010, costs for the management of chronic diseases represented 86% of total U.S. healthcare spending. Approximately, half of all adults in the U.S. have at least one chronic disease[1,2] which are associated with physiological, psychological, and social consequences[3]. Among these chronic conditions, coronary heart disease (CHD) is the second leading cause of death and disability in the U.S., following mental health disorders[4]. In the last several decades, the identification of clinical risk factors and comorbidities and the development of advanced interventions have substantially improved the prognosis of CHD. However, coordinated care for comorbid mental health disorders, a key driver of disability and poorer health outcomes in cardiovascular patients, remains notably absent from routine practice. Mental health issues such as depression, anxiety, and stress are highly prevalent among patients with CHD. A large, multi-state population analysis of cardiovascular disease patients in the U.S. revealed that the lifetime diagnosis of depression and anxiety among CHD patients are 21.2% and 15.6%, respectively[5].These common mental health disorders (CMHD) have also been associated with poorer cardiovascular disease outcomes[6–10]. According to a meta-analysis that aimed to assess the link between anxiety after an MI with long-term prognosis, post-MI anxiety was associated with a 36% increased risk of all-cause mortality, cardiac mortality, and additional cardiac events[11].

Compelling data demonstrate that CMHDs lead to reduced adherence to medication and life-style change recommendations[12], further illustrating the importance of integrating mental health treatment in cardiovascular disease treatment programs. Furthermore, anxiety diagnosed at young age has been shown to independently predict CHD events in adulthood, which has implications for primary prevention of CHD[13,14]. The INTERHEART study, a large global case-control study aimed at identifying risk factors for acute myocardial infarction (MI), also found that psychosocial stress was associated with a higher risk for an acute MI, suggesting that targeting anxiety and stress could reduce risk for CHD[15]. Although depression has been the main focus in clinical cardiac practice to date[16], research examining stress and anxiety suggests that screening and treating these CMHDs should also be at the forefront of cardiovascular disease management.

Despite the results of these studies, accessibility of mental health services remains an issue[17]. Recently, digital health has shown great promise for

improving chronic disease prevention and management, while simultaneously reducing the cost of care delivery and improving treatment accessibility[18]. Digital health intervention (DHI) is an umbrella term that includes telemedicine, web-based treatment/management, email, mobile, text-messaging, or monitoring sensors. Often times, several of these strategies are integrated into a DHI product. The efficacy of digitally-delivered psychological interventions have been deeply explored for a variety of conditions- eating disorders[19–21], stress management[22], anxiety[12,23,24], depression[25], and somatic disorders[26]. Several of these studies have demonstrated that the results of technology-based therapies are comparable to that of face-to-face, therapist-assisted treatments.

In this review, I will examine the literature on psychotherapy research in patients with cardiovascular disease (CVD). I will pay additional attention to psychotherapy aimed at reducing risk factors (e.g. physical activity, treatment adherence, smoking cessation, etc.) for CVD. Lastly, I will review the current state of knowledge of digital health research within this field.

Treatments and Interventions for Anxiety and Stress

Behavioral Therapy

Several studies have been performed to evaluate the potential of psychological interventions as a supplement to traditional cardiac rehabilitation programs for secondary prevention and risk factor reduction. Research to date has evaluated Cognitive Behavioral Therapy (CBT), the gold standard for anxiety and stress management[27], and stress management with the aim of preventing myocardial infarction recurrence and/or reducing depressive symptoms, anxiety symptoms, managing stress and improving quality of life[28]. Both the ENHANCD and SUPRIM trials found that a cardiac rehabilitation program that included CBT for stress management improved cardiac outcomes when compared to traditional care[29,30]. Cossette et al. found that a psychosocial intervention program involving multiple home-based visits by nurses reduced psychological distress and potentially improved long-term prognosis post-MI[31]**.** In the Recurrent Coronary Prevention Project, behavioral counseling was shown to decrease recurrent cardiac events from 21.2% to 12.9% over the 4.5 year study period, suggesting that integrating psychological intervention with cardiac rehabilitation can improve overall cardiac outcomes in patients with cardiovascular disease[32].

Despite the promising results of these studies, a handful of studies identified that psychotherapy and stress management provided little to no

psychological or cardiac benefit to patients who previously had an MI. The ENRICHD study assessed the effects of CBT on mortality and cardiac events in patients with depression and/or low perceived social support after an acute MI. The study found that CBT provided a slight improvement in depressive symptoms, but did not significantly impact non-fatal infarction or mortality[33]. Merswolken et al. showed that anxiety scores were reduced in both psychotherapy intervention and traditional treatment groups over time, but found no statistically significant effect between the two treatment strategies[34]. Jones and West found no significant differences in anxiety or clinical complications between post-MI patients who received psychological rehabilitation and those who received the standard of care. Though this study boasts a large, multicenter RCT design, it does not integrate mental health care into traditional cardiac rehabilitation strategies such as exercise and nutrition counseling. Nonetheless, the authors reported that mental health services may have a role in cardiac rehabilitation[35].

Overall, Whalley et al. concluded in a Cochrane review that psychological interventions may reduce depression and anxiety, as well as cardiac mortality. However, there was inconclusive evidence linking reductions in recurrent heart attacks or need for cardiac surgery. The heterogeneity of psychological treatment protocols, the uncertainty about the mechanisms by which negative emotions lead to adverse cardiac outcomes, and the lack of more longitudinal studies were described as current gaps in the field[36]. Future research should aim to address these issues by evaluating the modality of treatment, as well as, a component analysis of cognitive behavioral treatment to experimentally test the theories of change in cardiac patients[37]. Furthermore, researchers should provide more information on the design of the interventions delivered so that generalizability can be assessed and results can be replicated.

Pharmacological Interventions

Anti-depressants are used to treat patients with depression and anxiety disorders, specifically generalized anxiety disorder, panic disorder and post-traumatic stress disorder. It is highly recommended that tricyclic antidepressants (TCAs) be avoided in cardiac patients with comorbid CMHDs due to the adverse cardiovascular side effects noted within this population. Instead, selective serotonin reuptake inhibitors (SSRIs) are recommend as they appear to be safer and effective and cardiac patients[12]. Epidemiological studies on TCAs have found that these medications are associated with increased rates of recurrent MI compared to patients who receive SSRIs or no treatment[38]. This is most likely due to the adverse metabolic side effects of TCAs, such as weight gain and the

development of metabolic syndrome[39]. Furthermore, secondary post hoc analysis of the ENRICHD trial found that patients who received SSRIs had over 40% reduction in cardiac mortality risk and reinfarction compared to those who did not take SSRIs over the 2-3 year follow-up[40]. The SADHART study studied the effect of sertraline, an SSRI, treatment in patients with unstable ischemic heart disease (acute MI or unstable angina) and major depression. This high impact study involving 40 outpatient cardiology centers in the U.S., Europe, Canada, and Australia found sertraline treatment to be safe and effective for the treatment of depression in cardiac patients[41]. Atypical antidepressant agents such as mirtazapine have not been shown to improve cardiovascular outcomes and are considered to be second-line treatments for CMHD for cardiac patients[42,43].

The Role of Mental Health Interventions for Reducing Risk Factors for Cardiovascular Disease

Medication Adherence

Adherence to risk-reducing lifestyle changes include healthy diet, increasing physical activity, managing stress, and adhering to treatment/medication regimens. Poor adherence to treatment and risk reduction has been associated with mental health disturbances. Studies have also identified anxiety in association with reduced adherence, although it has garnered less attention than depression [44]. More specifically, anxiety has also been associated with nonadherence in patients with CVD. Comorbid depressive symptoms have also shown to contribute to treatment nonadherence. CVD patients with comorbid anxiety are 4.4 times more likely to not adhere to medications when compared to patients without psychological symptoms [45]. Several other studies demonstrate that CMHDs lead to reduced adherence to medication and life-style change recommendations[12], further illustrating the importance of integrating mental health treatment in cardiovascular disease treatment programs. Conversely, patients with anxiety have also demonstrated a greater efforts in seeking more help from doctors to try to improve their medical condition [46]. Given the protective effect of anxiety on patient outcome, the role of anxiety in comorbidity may due to the combination of anxiety and non-protective patient behavior, perhaps due to social inhibition or poor coping strategies.

Diet and Obesity

According to a large nationally representative survey performed by the Center for Disease Control and Prevention, one-third of adults and over 16% of youth in the U.S. are obese[47]. Previous studies established that a moderate weight reduction of ~5% can lead to a significant reduction in cardiovascular

disease risk[48]. The factors that impact diet and weight fluctuations are highly complex and involve biological determinants (appetite, hunger, and taste), as well as, psychosocial components (income, availability, and psychological state). More specifically, diet and CMHDs have demonstrated a bidirectional relationship[49]. The presence of CMHDs like depression and anxiety were shown to be associated with weight gain and increased BMI percentiles in adolescents and adults. Stress-related feeding behaviors, such as increased consumption of high carbohydrate and fat-rich foods, have been postulated to play a role in this association[49–51]. Reciprocally, obesity is also associated with significantly increased risk of developing mood and anxiety orders[52]. Moreover, obesity and CMHDs act synergistically on physical and mental quality of life[53].

Considering the complex relationships between psychological factors and eating behaviors, there is an increasing push to understand and address the relationship between mood disturbances and obesity. Approximately one-third of women who sought weight loss treatment were identified with clinical depression. Several studies have identified pretreatment psychological and health behavior conditions as significant factors that negatively impact attrition to weight loss treatments[54–56]. In addition, higher levels of depression have been associated with weight regain in people who once successfully lost weight[57]. Pagoto et al. translated elements of the diabetes prevention program into a weight loss program administered through the hospital. In this study, patients with co-morbid depression and obesity lost significantly less weight compared to patients with no CMHDs (-4.0 kg vs. -6.4 kg)[58]. Another study assessed a behavioral weight loss program with a simultaneously delivered cognitive behavioral program for depression management. These researchers found that depressed patients in both the weight loss program with and without the depression management program lost a comparable amount of weight and showed improved mood[59]. The Be Active Trial tested the effects of sequential delivery of depression treatment and weight loss intervention in an effort to address the negative effects of CMHDs on weight loss. In this study, no differences in weight loss were observed between the two groups at six months or twelve months. However, patients who were treated for depression first showed significantly greater decreases in depression scores compared to the group with only the weight loss intervention. In addition, participants who were in remission from depression at six months, regardless or group, demonstrated greater weight loss than those who still had depression (-4.29% vs -2.48%)[60]. These results suggest that CMHDs may interfere with behavioral weight loss programs and patients with remission from CMHDs demonstrate clinically greater weight loss.

A Cochrane Review on digital health-based interventions for weight loss examined over one hundred studies for review. Meta-analysis of 18 of these trials showed that digital health interventions are effective for weight loss. However,

these interventions resulted in smaller weight loss compared to in-person interventions[61]. Despite the promising results of these studies, research on weight loss treatments for patients who are obese and have CMHDs is scarce, likely because patients with depression are screened out in most weight loss trials[62]. Greater efforts should be placed in studying digital health tools for the treatment of CMHDs and weight loss/management in obese patients with comorbid mental health problems.

Hypertension

Several studies have established the link between the presence of anxiety, depression and stress with the development and exacerbation of hypertension, a significant risk factor for the development of CVD later in life. A secondary analysis of the National Health and Nutrition Examination Survey found that patients with self-reported hypertension and depressive symptoms had the highest risk for all-cause mortality and ischemic heart disease across the 8-year follow-up period[63]. A meta-analysis of cross-sectional and prospective epidemiological studies on hypertension found an association between anxiety and increased risk of hypertension[64]. Furthermore, several studies highlighted that anxiety may be an important predictor of future CVD outcomes and addressed the importance of integrating psychiatric and hypertensive care[65,66].

Type 2 Diabetes

The prevalence of depression and other CMHD in the diabetic population is 24% compared with 17% in populations without type 2 diabetes (T2D). Moreover, CMHDs were found to negatively impact quality of life within this population[67]. Greater stress was associated to greater variability in patient's fasting glucose with patients will less emotional support having higher fasting glucose levels[68]. This may be due to a variety of factors, such as the secretion of stress hormones— epinephrine and cortisol— which cause increases in glucose in the bloodstream, as well as, poorer treatment adherence. To make matters worse, a majority of patients with T2D and comorbid CMHD are not adequately screened and treated for these psychological symptoms in the clinic[69]. Although antidepressants have been shown to be effective in treating depression in chronic condition populations, certain therapies have shown adverse effects on glycemic control[70]. These gaps in therapeutic strategies can potentially addressed through a more coordinated effort between clinicians, diabetes care management teams, and mental health professionals.

Digital Health Interventions for Mental Health in CVD

While online interventions for psychological interventions have demonstrated great promise, there are few studies that have assessed the

potential of digitally delivered psychological interventions for the treatment of comorbid anxiety and stress in the cardiac patient population.

The MoodCare study demonstrated that telephone-based CBT improved adherence to treatment in comparison to studies that utilized traditional face-to-face therapy, highlighting the potential of digital health for improving patient engagement to treatment[33,71]. Glozier et al. evaluated the effectiveness of internet-delivered CBT on depressive symptom severity and adherence to medical treatment and lifestyle recommendations in patients with a high risk for CVD. They found patients with mild to moderate depression experienced a modest, but robust improvement in psychological outcomes and adherence[72]. In addition, telephone counseling for psychological distress found improvements in self-rated health and the Global Improvement subscale of the Clinical Global Impressions Scale[73].

Despite the lack of evidence for DHI in CVD populations, there is significant interest in implementing DHI within the field of cardiology. An ongoing trial by Norlund and colleagues examining the effectiveness of an iCBT for depression and anxiety in patients with a recent MI will increase the evidence base in the near future[74]. A recent systematic review and meta-analysis of randomized controlled trials and cohort studies that incorporated DHI in the prevention of CVD found 39 studies that focused on primary prevention and 13 on secondary prevention. This review identified studies that utilized web-based DHI, telemedicine, and SMS texting as highly beneficial for reducing risk factors for cardiovascular disease and improving cardiovascular outcomes. In subgroup analyses, primary prevention studies did not show a strong positive preventive outcome, but secondary prevention studies showed a significant impact on CVD outcomes[75]. Despite these promising findings, few of these studies integrated behavioral health services in their DHI platform. A majority of mental health apps have been criticized due to the lack of scientific evidence to inform their design and to validate the efficacy of digital health tools. Digital health products and companies often lack the scientific rigor needed to properly evaluate their interventions[76]. In order to better understand and address the complex needs of CHD patients, additional research must be conducted to assess the feasibility and efficacy of digital mental health interventions for cardiac patients.

Implementation of Digital Health Interventions for Mental Health

DHIs have been developed and tested for a wide range of mental and physiological medical conditions. However, very few studies have discussed the implementation and integration of these mental health services into current healthcare delivery systems.

Although stand-alone DHI have been explored extensively, more and more interventions are now including a human element to the intervention. This interaction ranges from interfacing with a health coach via instant messaging or text to video calls with trained psychologists to replace in-person sessions[77]. Widespread adoption of this human element in DHIs is not surprising. Several reviews of behavioral health research consistently show that DHIs that include guidance from therapist or behavioral health specialist lead to better outcomes[78,79].

Blended DHIs aim to support the work of traditional face-to-face psychotherapy by digitizing some of the labor-intensive and resource-heavy elements of therapy, such as disseminating educational materials (via text, audio or video) or mental health exercises. In addition, blended DHIs can be utilized to re-enforce the lessons from psychotherapy into the patient's everyday life through reminders and notifications[80].

Hospital systems and clinics also seeking to adopt DHIs into primary care and speciality clinics praise the stepped care model for its ability to save healthcare resources for those who need it the most. The stepped care model is an approach to delivering healthcare and monitoring treatments that seeks to utilize the lowest tier of service necessary to achieve the satisfactory outcome. If clinically required, patients are "stepped up" to a higher tier of care involving intensive or specialist services. Building on the stepped care model, Wholly and Unutzer recommend a collaborative care intervention for cardiac patients with comorbid CMHD that involves depression screening in the primary care clinic and depression care manager who communicates frequently with the primary care physician or treating medical specialist[81]. The COPES trial examined the effectiveness of interdisciplinary stepped care interventions in patients with acute coronary syndrome (ACS) and persistent depression. The study found that patients with the interdisciplinary stepped care intervention reported greater satisfaction with their depression treatment compared to usual care. In addition, these patients responded with a significant reduction in depression symptoms and promising reduction in major adverse cardiac events, although the study was not adequately powered for the latter outcome[82].

Lastly, a step-down approach deployed after in-person psychotherapy has been explored as well. Digital health aftercare programs are designed to help patients maintain and improve self-management skills after completion of in-person therapy, maintaining the beneficial effects of treatment over a longer period of time[83,84].

Next Steps for DHI in Chronic Disease Prevention

Despite the promising research and development in DHIs for mental health, there remain significant barriers and gaps in knowledge in the research and delivery of DHIs.

In order to successfully implement DHIs, target patient populations need to be assessed for technological ownership and literacy. Fox et al. found that digital connectedness, defined as the usage of digital technologies, was highly influenced by age and education. Digitally connected people tended to be younger and more educated. In addition, they also had less cardiovascular risk factors[85]. Pew Research found that two-thirds of the U.S. population now own a smartphone with internet access. Within this population, 62% of smartphone owners reported using their phone to access health information or research a health condition. This highlights the potential widespread acceptability of using personal digital tools for the delivery of healthcare. However, Pew Research confirmed Fox et al.'s finding that smartphone ownership deviated towards young adults and people with higher income and higher education. Despite this finding, 50% of people who made less than $30k per year and 27% of adults 65+ reported ownership of a smartphone. The hopeful finding from this study was that smartphone ownership across all demographics is increasing every year[86]. Nonetheless, smartphone ownership and literacy highlights a potential barrier to access for a large proportion of CVD patients to DHIs that needs to be addressed.

Overall, DHIs for the treatment of comorbid CMHDs in patients with chronic disease are a promising step towards greater affordability and accessibility of care. Greater investments should be made in validating and improving the delivery of DHIs in the clinical setting.

PART TWO: ORIGINAL RESEARCH

Introduction

According to a large nationally representative survey performed by the Center for Disease Control and Prevention, one-third of adults and over 16% of youth in the U.S. are obese, a major risk factor for preventable cardiovascular and metabolic diseases[47]. Previous studies established that a moderate weight reduction of ~5% can lead to a significant reduction in cardiovascular disease risk (Look AHEAD Group, 2007). The factors that impact diet and weight fluctuations are highly complex and involve biological determinants (appetite, hunger, and taste), as well as, psychosocial components (income, availability, and psychological state). More specifically, diet and common mental health disorders (CMHDs) have demonstrated a bidirectional relationship[49]. The presence of CMHDs like depression and anxiety were shown to be associated with weight gain and increased BMI percentiles in adolescents and adults. Stress-related feeding behaviors, such as increased consumption of high carbohydrate and fat-rich foods, have been postulated to play a role in this association[49–51]. Reciprocally, obesity is also associated with significantly increased risk of developing mood and anxiety orders[52]. Moreover, obesity and CMHDs act synergistically on physical and mental quality of life[53].

Considering the complex relationships between psychological factors and eating behaviors, there is an increasing push to understand and address the relationship between mood disturbances and obesity. Approximately one-third of women who sought weight loss treatment were identified with clinical depression. Several studies have identified pretreatment psychological and health behavior conditions as significant factors that negatively impact attrition to weight loss treatments [54–56]. In addition, higher levels of depression have been associated with weight regain in people who once successfully lost weight[57]. Linde et al. assessed a behavioral weight loss program with a simultaneously delivered cognitive behavioral program for depression management. These researchers found that depressed patients in both the weight loss program with and without the depression management program lost a comparable amount of weight and showed improved mood[59]. The Be Active Trial tested the effects of sequential delivery of depression treatment and weight loss intervention in an effort to address the negative effects of CMHDs on weight loss. Participants who were in remission from depression at six months, regardless or group, demonstrated greater weight loss than those who still had depression (-4.29% vs -2.48%)[60]. These results suggest that CMHDs may interfere with behavioral weight loss programs and patients with remission from CMHDs demonstrate clinically greater weight loss.

A Cochrane Review on digital health-based interventions for weight loss examined over one hundred studies for review. Meta-analysis of 18 of these trials showed that digital health interventions are effective for weight loss[61]. Despite the promising results of these studies, research on digital weight loss treatments for

patients who are obese and have CMHDs is scarce, likely because patients with depression are screened out in most weight loss trials[62]. Greater efforts should be placed in studying digital health tools for the treatment of CMHDs and weight loss/management in obese patients with comorbid mental health problems.

This sub-group data analysis will examine the effects of digitally delivered cognitive behavioral therapy (CBT) in overweight and obese primary care patients with generalized anxiety disorder.

Materials and Methods

Setting and Study Participants

Study participants were enrolled in a non-randomized, two-arm parallel, clinical trial[87] aimed to assess the long-term effectiveness and implementation of a digitally-delivered mobile CBT program for anxiety in the primary care setting. Participants were recruited through four primary care clinics affiliated with the University of Pittsburgh Medical Center (UPMC). All patients receiving care at the UPMC Community Medical Inc. (CMI) are periodically assessed for overall mental and physical functioning, as well as overall health-related quality of life, through GAD-7 and SF-12 questionnaires. Patients were eligible for the trial if they were receiving or seeking medical care at UPMC CMI, were 20-65 years of age, and demonstrated GAD-7 that was greater than or equal to 5. Patients were excluded from the trial if they were pregnant or did not speak English as the CBT program was only available in English at the time of the study. Since the trial occurred at the same time as a randomized study evaluating treatments for acute back pain (IRB Protocol #015120249), patients with acute back pain were excluded.

PCPs or clinical staff explained the trial to the patients. Patients who provided consent to participate were non-randomly assigned to enhanced treatment or intervention (digitally-delivered CBT) based on convenience sampling and the treatment preference of the clinic they regularly attended.

The present study includes patients participating in the larger trial who were overweight (BMI was 25.0 to less than 30) or obese (BMI was 30.0 or greater) at baseline (268 of 359 patients participating in the larger trial).

Intervention Group

The digital CBT intervention was developed based on empirically supported CBT regimen for GAD[88,89] that was developed in conjunction with academic partnerships with the aim of treating the symptoms associated with anxiety and stress[90]. The feasibility, acceptability, and efficacy of this program was previously assessed among university students in a randomized controlled trial[24]. The core components of this digital CBT program for anxiety include:

cognitive behavioral lessons and tailored practice on anxiety and stress management; one-on-one coaching via an in-app messaging tool (Figure 1).

If a patient using the digitally delivered CBT intervention demonstrated severe or worsening symptoms, they were referred to a mental health professional for further evaluation. Under situations involving suicidal ideations, patients were provided a "crisis message" which included contact information for national crisis hotlines or recommendations to visit the nearest emergency room.

Enhanced Treatment as Usual (TAU)

The enhanced TAU at the clinics were supplemented with the National Institute of Mental Health's education brochure about GAD and its common treatments, as well as, a list of three local psychiatric practices that are available to see patients within 2 months of referral.

Data Collection

All study measures/questionnaires were completed on computer (via UPMC's electronic medical record system), within the digitally-delivered CBT mobile app (through HIPAA-compliant Qualtrics account), or via telephone from the UPMC research assistants. De-identified patient information will be maintained within the UPMC firewall.

Study Outcomes

This study is a sub-group analysis of a larger trial that was powered to examine the effectiveness of digital CBT on reducing anxiety symptom severity (GAD-7) and improving quality of life (SF-12) in primary care patients with GAD.

To assess for the presence and treatment of GAD in the study participants, the GAD-7, a brief self-reported anxiety scale, was administered during primary care clinic visits. Higher scores on the GAD-7 were strongly associated with several domains of functional impairment and is dimensional distinct from symptoms of depression. A GAD-7 score of 5-9 is categorized as mild anxiety, 10-14 is moderate anxiety, and >15 is considered severe anxiety [91]. The GAD-7 has been used extensively to assess symptoms of anxiety in patients with varying degrees of obesity[92,93].

The 12-item Short Form Health Survey (SF-12), a health-related quality of life (HRQoL) instrument. The SF-12 has a physical (physical functioning, role limitation due to physical problems, body pains, and general health) and mental (vitality, social functioning, role limitation due to emotional problems, and mental health) sub-scales, each of which has a maximum score of 50 with higher scores indicating better health-related quality of life[94,95]. Furthermore, the SF-12 demonstrated validity and sensitivity for changes in HRQoL among obese study participants[96,97].

Height and weight were assessed in the clinic and body mass index (BMI) was calculated and monitored over the course of the six-month intervention and follow-up periods.

Statistical Analysis

T-tests analyzed within-group changes in anxiety, HRQoL, and weight loss. At this early stage of the trial, data could not be released and the only analyses available were within-group. Analyses were further stratified according to BMI (overweight and obese groups). Statistical analyses were conducted using SPSS Statistics by a statistician at UPMC.

Results

Baseline characteristics and study outcome variables are listed in Table 1. Among the 359 patients who were enrolled in the trial and completed the 6-month follow-up assessments, 268 patients met the criteria for overweight or obese and were included in the present study. Among 94 overweight participants, 49 patients received enhanced TAU and 45 patients received the digitally delivered CBT. Among 174 obese participants, 62 patients received enhanced TAU and 112 received the digitally delivered CBT. The average age of participants who received enhanced treatment was higher than the age of those receiving the digitally delivered CBT intervention (48.9 vs. 43.6; $p<0.001$). The study population largely identified as female (67.3%), was predominantly Caucasian (90.9%) and over half of the study population had an additional psychiatric co-morbidity (55.7%).

Overall, the overweight intervention group demonstrated greater usage of the digitally delivered CBT program with the mean completion of 14 sessions compared to the mean completion of 11 sessions in the obese intervention group ($p=0.30$; CI: -3.9-12.6). The overweight intervention group also completed more techniques compared to the obese intervention group (18 vs 14; $p=0.32$: CI: -4.3-13.0). These differences show potential trends in digital CBT usage among overweight and obese participants; however, the differences were not statistically significant.

Participants from across all study arms showed a reduction in GAD-7 at the time of the 6-month follow-up period, though the change for overweight patients in standard care did not reach statistical significance (Table 2).

Overweight participants in both groups (-0.7 vs. -0.3) and obese participants (+0.5; $p=0.52$) who received the enhanced TAU of care showed no change in physical HRQoL, but obese participants who received digital CBT demonstrated a significant improvements in physical HRQoL (+3.7; $p=0.001$). With respect to the mental component, digital CBT users in both overweight

(+3.5; p=0.034) and obese (+4.9; p=0.001) groups and obese participants who received enhanced TAU (+3.3; p=0.002) showed a significant increase.

The only group to demonstrate a statistically significant change in BMI was the overweight enhanced TAU group, which demonstrated an increase in BMI from 27.7 to 28.2 (p=0.047).

Discussion

This is the first study, to our knowledge, that examined the effectiveness of implementing a digital CBT intervention in the primary care clinic for treatment of GAD in patients who are overweight or obese. This non-randomized trial found that the digital CBT intervention was associated with a reduction in generalized anxiety and improved mental HRQoL at 6-months among both overweight and obese patients. While the lack of between-group analyses precludes our ability to directly compare the digital CBT intervention to enhanced TAU, in all outcomes the magnitude of improvement was greater for intervention participants. Studies on other digital CBT treatments have shown mixed results on generalized anxiety reduction. Reynolds et al., found a reduction in GAD-7 over a 6-month follow-up period between both people who used Internet-delivered iCBT and control groups who used a placebo website and did not detect significant between group differences (-1.4 vs -1.7; p=0.62)[98]. Conversely, Robinson et al. found strong between-group differences between the digital CBT interventions (-5.9; CI: 4.7-7.1) and waitlist control groups (-1.7; CI: 0.6-2.8)[99]. Titov et al. found similar results between (d=1.25) the clinician-assisted computerized CBT program group (-7.4; d=1.67) and waitlist control group (-1.3; d=0.34)[100]. In both of the latter studies, the prominent between-group differences may be due to a lack of treatment or intervention in the control group. In this study, control patients received enhanced TAU, but the study did not assess if they pursued in-person psychotherapy, the frequency of attendance, or the utilization of additional mental health resources. An assessment of mental healthcare utilization and an examination of dose-response relationship between digital CBT intervention and control groups will be valuable in helping distinguish the direct effects of both interventions on reduction of generalized anxiety. Although the cited studies did not stratify according to BMI, these results, along with the results of this study, suggest that digital CBT can be used as an effective and cost-reducing mechanism for delivery of mental healthcare to patients with CMHDs like GAD[101].

The improvement in the mental component of the HRQoL measure in digital CBT groups aligns with previously published studies that examined the effects of CBT on the HRQoL in patients with GAD without stratifying for BMI[102]. In Stanley et al., mental HRQoL was improved from 42.4 to 51.2 over a 6-month follow-up period, whereas physical HRQoL scores were persistent at 44.0 to 42.4[103]. In addition, a nationally-representative survey of adults in the U.S. found negative associations in the mental HRQoL with GAD (37.9; CI: 36.8-39.0) and no association in the physical component (47.1; CI: 45.9-48.2)[104]. The baseline

mental HRQoL scores found in this study fall within the range of these survey results, but baseline physical HRQoL scores were much lower, especially in the obese groups. This may reflect a relationship between higher BMI and lower levels of physical HRQoL impairment, which have been established across several studies[105–107]. Obese patients who used digital CBT showed a significant improvement in physical HRQoL, indicating that digital CBT may be associated with improvements in physical functioning and vitality in patients with high BMIs.

Moreover, the study did not find any meaningful reduction in BMI through digital CBT, reflecting a greater persistence of physical impairments and high BMI in the face of psychotherapy alone. As this current study did not involve a direct weight loss/management component in addition to the psychotherapy, a resistance to change in physical HRQoL and BMI is congruent with the current literature.

Additional Analyses

Although these results are promising, the analyses of this study are incomplete due to lack of between-group comparisons. Further analyses should adjust for age, gender, and clinic-level median household income and education. Drop-off rates should be determined while stratifying for age and gender, which were both found to be predictors of telemedicine adoption[108]. Lastly, a dose-dependent response analyses should examine the number of sessions/techniques completed and their impact on anxiety reduction in both digital CBT and control groups.

Limitations

Additional limitations to the present study need to be considered. First, this study occurred at an academic clinic with a predominantly middle age, female, and Caucasian study population, which limits the generalizability of this study to other demographics. A largely female study population is expected because the life-time prevalence of GAD is twice as high among women compared to men and particularly prevalent in the primary care setting[109]. Women are also much more likely to seek out treatment compared to men which may lead to further self-selection in study participation[110]. In addition, the average age of the digital CBT group was markedly lower compared to the enhanced TAU group. This may be due to selection bias against older adults who have a lower level of smartphone ownership and literacy and, thus, are ineligible to participate and consent in the digital CBT arm[111]. In addition, younger users are more likely to be accepting of novel digital delivery mechanisms for health-related services[86,108]. Second, the additional treatments participants used for anxiety or other CMHDs (i.e. pharmacological, psychotherapy) during this study period were not obtained. This limits our interpretation of the results because we cannot control for the presence of outside interventions. Third, because the original trial was not

designed for examination of BMI subgroups, it is not likely powered for stratified analyses of overweight and obese patients. Lastly, this study was designed with the aim to help inform further studies on combined psychotherapy and weight loss programs. Recent reviews of literature suggest that traditional weight loss and management strategies (i.e. lifestyle modification through diet, exercise, …) may yield only short term weight reduction[112]. Further studies should also explore aspects of acceptance and commitment therapy and other weight loss/management modalities to determine the best combined therapy[113,114].

Conclusions

The aim of this trial was to assess a digital CBT intervention, as it should be administered in normal practice, so that it can help inform future clinical practice[115]. This study included patients with one or more psychiatric co-morbidities in the context of high BMI. These patients were enrolled to better emulate "real-life" situations where patients present in the clinic with complex co-morbidities[116].

Digital CBT may be an effective treatment for overweight or obese patients with GAD in the primary care setting. Randomized trials that examine the combined effects of digital CBT and different weight loss/management modalities should be further explored to address the bidirectional relationship between obesity and CMHDs. Patients with co-morbid obesity and psychiatric conditions have been shown to have difficulty adhering to weight loss treatment recommendations. Recognizing these unique challenges and barriers can allow primary care physicians and psychiatrists to promote more effective treatments for these patients. Given the low-cost and accessibility of digital health intervention, digital CBT programs can be implemented efficiently and effectively in primary care settings to address the myriad psychiatric co-morbidities and needs that exist among their patient populations.

Figure 1. Screenshots of digitally delivered CBT

Patients experience this CBT program through a journey map (a) which takes patients through different stages of the cognitive behavioral process, including education on the physiological responses of stress and anxiety (b) and coping strategies (c,d). Throughout the self-paced journey, touch-points allow the patient to interact with the app by answering questions or free-writing (c). Patients are also connected with a one-on-one health coach (e) who is able to view the patient's responses. In these sessions, the coach guides the patient and addresses any unique concerns that may come up.

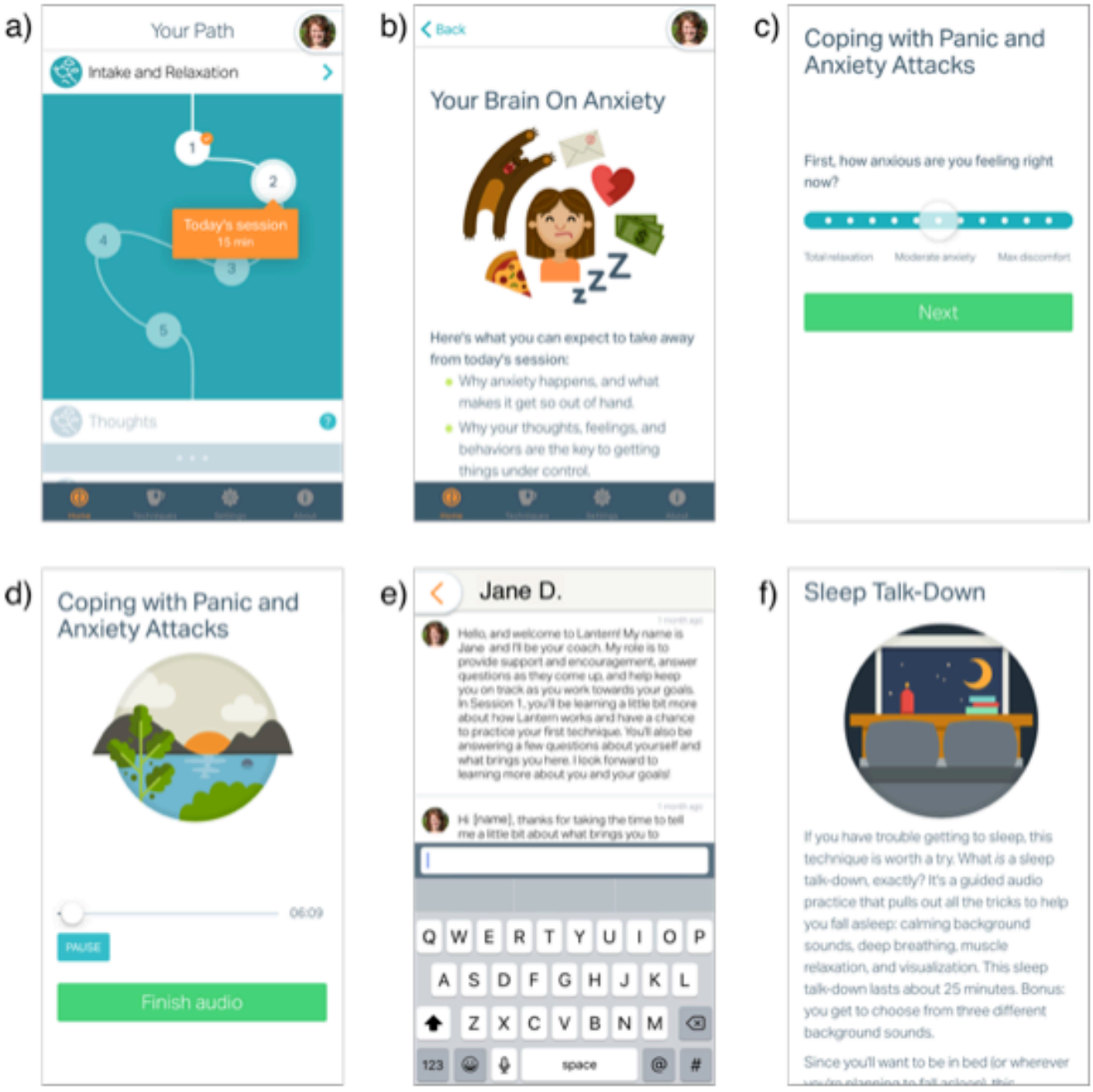

Table 1. Baseline Characteristics of Participants According to Treatment Group, Mean (SD) or Percentage of Total (%)

	Enhanced TAU (n=161)	**Digitally Delivered CBT (n=107)**	**p-value**
Age	48.89 (11.14)	43.62 (12.44)	**<0.001**
Gender			
Male	63 (37.7)	149 (31.0%)	
Female	104 (62.3)	332 (69.0%)	
Race			
Hispanic	0 (0.0%)	0 (0.0%)	
Caucasian	161 (96.4%)	428 (89.0%)	
Black/African American	4 (2.4%)	40 (8.3%)	
Asian	0 (0.0%)	2 (0.4%)	
Declined/Unspecified	2 (1.2%)	11 (2.3%)	
BMI (kg/m^2)			
Overweight	27.74 (1.58)	27.44 (1.34)	0.18
Obese	34.79 (7.15)	32.81 (6.52)	0.44
Baseline GAD-7	10.19 (4.90)	11.17 (4.92)	**0.03**
Baseline SF-12 (PHC)	36.45 (12.16)	40.92 (11.55)	**<0.001**
Baseline SF-12 (MHC)	35.38 (9.89)	35.43 (9.72)	0.96
Psychiatric Co-Morbidities			
0	69 (42.8%)	197 (44.8%)	
1	56 (34.8%)	151 (34.3%)	
2+	36 (22.4%)	92 (20.9%)	
Sessions Completed			
Overweight	-	14.27 (21.36)	0.30
Obese	-	11.18 (14.18)	
Techniques Completed			
Overweight	-	18.28 (28.33)	0.32
Obese	-	13.93 (16.62)	

Table 2. Unadjusted outcomes of digital delivered CBT for anxiety and stress on GAD-7, SF-12 (PHC and MHC), and BMI among primary care patients with obesity

		Standard Care					Lantern				
	Outcomes	Baseline	6 Months	Change	95% CI	p-value	Baseline	6 Months	Change	95% CI	p-value
Overweight (18.5 < BMI < 25.0)	**GAD-7**	10.02	8.53	-1.49	-0.21 to 3.19	0.085	10.49	8.69	-1.80	0.22 to 3.38	0.026
	SF-12 (PHC)	41.05	40.38	-0.67	-1.49 to 2.84	0.535	43.89	43.56	-0.34	-2.26 to 2.93	0.795
	SF-12 (MHC)	36.27	37.70	1.50	-4.44 to 1.45	0.311	35.96	39.46	3.50	-6.73 to -0.28	0.034
	Body Mass Index	27.74	28.15	0.41	-0.81 to -0.01	0.047	27.63	27.57	-0.06	-0.53 to 0.65	0.83
Obese (BMI>30)	**GAD-7**	10.28	7.78	-2.50	1.40 to 3.60	0.000	11.13	7.87	-3.26	1.82 to 4.69	0.000
	SF-12 (PHC)	34.35	34.87	0.52	-2.14 to 1.09	0.523	39.23	42.90	3.68	-5.72 to -1.63	0.001
	SF-12 (MHC)	34.86	38.20	3.34	-5.39 to -1.28	0.002	36.23	41.11	4.88	-7.63 to -2.12	0.001
	Body Mass Index	38.01	38.07	0.07	-0.44 to 0.30	0.726	38.83	38.44	-0.39	-0.71 to 1.48	0.469

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