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Authors

Zion, Sean

Taub, Chloe

Heathcote, Lauren

et al.

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Effects of a Cognitive Behavioral Digital Therapeutic on Anxiety and Depression Symptoms in Patients With Cancer: A Randomized Controlled Trial

Sean R. Zion, PhD[1]; Chloe J. Taub, PhD[1]; Lauren C. Heathcote, PhD[2]; Allison Ramiller, MPH[1]; Stacey Tinianov, MPH[1]; Michael McKinley, JD[1]; Geoff Eich, MBA[1]; Frank J. Penedo, PhD[3]; Patricia A. Ganz, MD[4]; Michael Antoni, PhD[3]; and Dianne M. Shumay, PhD[1,5]

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ABSTRACT

PURPOSE Patients with cancer often experience elevated levels of distress. This double-blind, randomized controlled trial compared the impact of an app-based version of cognitive behavioral stress management (CBSM) versus a health education sham app on anxiety and depression symptoms.

METHODS Patients with nonmetastatic (stage I-III) cancer who were receiving or recently completed (≤6 months) systemic treatment were recruited nationwide. The primary outcome of change in anxiety symptoms (PROMIS-Anxiety) over 12 weeks and the top secondary outcome of change in depression symptoms (PROMIS-Depression) over 12 weeks were analyzed using mixed-effects modeling with repeated measures (weeks 0, 4, 8, 12). Patient global impressions of change in anxiety and depression were reported at weeks 4, 8, and 12. In addition, self-reported adverse events were collected throughout the study and adjudicated by the site principal investigator.

RESULTS Four hundred forty-nine patients were enrolled in the trial (age M [standard deviation] = 52.44 [11.46]; 81% female; 76% White; 53% breast cancer). Patients randomly assigned to digitized CBSM showed significantly greater reductions in anxiety ($B = -0.03$; $P = .019$) and depression ($B = -0.02$; $P = .042$) symptoms over 12 weeks. Patients who received digitized CBSM were also significantly more likely to perceive much or very much improvement (*v* no/minimal change or much/very much worse) in their symptoms of anxiety ($\chi^2 = 31.76$; $P < .001$) and depression ($\chi^2 = 19.70$; $P < .001$) compared with the control.

CONCLUSION The use of digitized CBSM led to significant improvements in anxiety and depression outcomes compared with the sham app.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Emotional distress affects over half of patients with cancer[1] and has been endorsed by oncology organizations as the sixth vital sign.[2,3] Characterized by symptoms of both anxiety and depression, distress is associated with nonadherence to cancer treatment, greater health care utilization, poorer quality of life (QOL), and even lower survival.[4] A diagnosis of anxiety or depression subsequent to cancer is associated with an increase of $17,496 in US dollars (USD) in health care costs per patient per year.[5] Guidelines from pre-eminent organizations in psycho-oncology,[6-8] as well as The National Academy of Medicine,[9] ASCO,[10] and National Comprehensive Cancer Network,[4] dictate that standard of care include treatment of distress, and the American College of Surgeons Commission on Cancer's accreditation requires distress screening and referral for psychosocial care.[11] However, in practice, there is still a clear unmet need for addressing distress in patients with cancer.[12]

Effective interventions are available to address distress[13]; however, the supply of trained and qualified health care professionals is insufficient to meet patient demand in many high-resourced settings[14] and entirely absent from others.[15] Patients often face logistical and financial challenges with accessing in-person care, such as arranging transportation, taking time away from work or household demands, and coordinating childcare.[16] Digitizing evidence-based supportive interventions can benefit patients by enabling flexible utilization, broad access, and standardized delivery of therapeutic content, as well as allowing the limited cancer-specific mental health providers to focus on the most

CONTEXT

Key Objective
To test a digital health app against a control (sham) app to determine if it has beneficial effects on anxiety and depression symptoms in patients with cancer.

Knowledge Generated
This randomized controlled trial demonstrates that a digitized version of cognitive behavioral stress management for patients can reduce anxiety and depression for patients with early-stage cancer.

Relevance
Emotional distress, including symptoms of anxiety and depression, is common among patients with cancer, but the need for care exceeds the availability of mental health clinicians in many settings. This study suggests that a digital health app may be an accessible and scalable strategy to augment supportive care for patients with cancer to help address this unmet need.

complex cases.[17] In response to this unmet need, we developed attune (Blue Note Therapeutics, San Francisco, CA), a 10-module digitized version of cognitive behavioral stress management (CBSM). CBSM, a manualized, group-based, in-person intervention combining cognitive behavioral therapy (CBT) and relaxation training,[18] has been shown to reduce distress and symptom burden and improve QOL, physiological adaptation, and long-term health outcomes in patients with cancer.[19-23] This two-arm, double-blind, randomized controlled trial compared the relative impact of digitized CBSM (attune) with that of a digitized health education sham app (cerena [Blue Note Therapeutics]) on anxiety and depression symptoms in patients with cancer. We hypothesized that patients randomly assigned to receive attune would experience greater reductions in anxiety and depression symptoms over the 12-week study compared with those randomly assigned to receive cerena.

METHODS

This study was approved by the Western Institutional Review Board and registered on ClinicalTrials.gov identifier: NCT05227898. Funding for the study and access to the digital apps were provided by the study sponsor, Blue Note Therapeutics.

Study Design

The RESTORE study was a decentralized, two-arm, double-blind, randomized controlled clinical trial described to participants as comparing the impact of two digital applications (attune and cerena) on the physical and mental health of adult patients with nonmetastatic (stage I-III) cancer.

Participants and Procedures

Participants were recruited for this decentralized clinical trial using a nationwide online advertising campaign via social media websites, search engines, and other internet platforms. Those interested were directed to a website with information about the study and the option to complete an eligibility survey.

Eligible participants were adults (18 years and older) with a nonmetastatic (stage I-III) solid tumor or hematologic cancer who received active systemic treatment (excluding endocrine therapy alone) in the past 6 months or had a treatment plan including upcoming systemic treatment. Foundational in-person CBSM trials were conducted in nonmetastatic samples,[18,21] and the example content within the digitized version tested here was more tailored to common experiences of patients with nonmetastatic disease. Inclusion criteria also required elevated anxiety (PROMIS-Anxiety [PROMIS-A] T-score ≥60[25]), fluency in English, access to a smartphone or tablet (iOS or Android) with internet access, and willingness to download an app. Those with a PROMIS-A T-score of <60 and participants with severe depression (PROMIS-Depression [PROMIS-D] T-score ≥70[25]) or indication of suicidal risk via DART-Suicide Risk Screening (DART-SRS[26]) were excluded. Patients were also excluded if they were diagnosed with melanoma or multiple myeloma and/or if their treatment plan included stem-cell/bone marrow transplant. These criteria were introduced to reduce the heterogeneity of the experience of cancer treatment within the sample.[27] Those currently participating in an investigative psychotherapeutic or behavioral intervention trial for anxiety or depression or had taken part in any other Blue Note Therapeutics–sponsored study were not eligible. People were also excluded if they indicated cognitive deficits, severe psychiatric conditions, or other conditions that would interfere with adherence to self-directed care or the ability to complete the study. Eligibility was based on self-reported data collected during the screening process. Medical records were also obtained for ≥70% of enrolled participants to allow for independent verification of cancer diagnosis.

Eligible participants were provided with an overview of the study and asked to read and sign an electronic consent form,

schedule a 1-hour virtual onboarding visit, and complete the baseline assessment. During the onboarding visit, patients were randomly assigned 1:1 (using a dynamically generated randomized condition list created before the initiation of the study using the CFR 21 part 11 compliant software platform [Curebase version 4.61.0, San Francisco, CA]) to receive either the attune app or the cerena app. Clinical research coordinators, blind to the condition of interest and trained to conduct a standardized onboarding visit, guided participants through the app setup process but provided no further training or coaching on app session material. Participants also completed the Stanley-Brown Safety Plan[28] during the onboarding visit to identify emergency contacts and coping resources in the case of a crisis during the study. Participants completed patient-reported outcome (PRO) assessments electronically via the Curebase survey platform at baseline pre-randomization, week 4, week 8, and week 12 (end of study). Data were anonymized with a study ID to protect the identities of participants. Regardless of condition assignment, participants were compensated up to $200 (USD), $25 (USD) per assessment + a $100 (USD) end-of-study bonus for completing all assessments.

Treatment Conditions

Internal and external study documents (eg, study protocol, research coordinator training guides, etc) and patient facing materials (eg, recruitment materials, patient communications, etc) described this study as a comparative efficacy study of two cancer-specific treatment apps to blind patients and study personnel to the condition of interest. Both treatment apps were professionally designed with visually similar styling, had branded websites and informational pamphlets, and were presented as digital therapeutics specifically created for patients with cancer. Both consisted of 10 interactive self-guided sessions, and participants were instructed to progress through the program sequentially at a rate of approximately one session per week to complete their program within the 12-week treatment period. Treatment adherence, as defined by sequential session completion, was monitored throughout the study, and study staff provided reminders to participants who fell more than two sessions behind schedule. Technical support (eg, to reset a password, forgot username, etc) was available for all participants throughout the duration of the study via phone or e-mail.

Attune

Attune was developed in partnership with a panel of patient advisors under advisement of the University of Miami researchers who developed and tested in-person and live virtually delivered CBSM for oncology populations.[21,29] Attune underwent a fidelity review by two independent researchers with PhDs in clinical psychology and expertise in CBT and CBSM interventions to verify that all core clinical components of the manualized intervention were present in attune and presented in a manner consistent with the therapeutic intent. Sessions consist of a combination of videos, learning exercises, and reflection activities, which can be completed in multiple sittings. The peer-facilitated group feed feature was designed to provide a welcoming virtual setting for participants to connect with each other via text and picture posts, comments, and direct messages to discuss attune's CBSM content, personal experiences, and offer support (see Appendix Fig A1, online only for session content details and attune design).

Cerena

Cerena was based on the program HealthWatch, originally created as an online health education program.[30] Sessions contain information on a range of physical health topics (eg, maintaining bone health, risks of sun exposure, benefits of proper dental hygiene). Interactive learning exercises followed each session to ensure comprehension. HealthWatch has been used as a control in other studies of digital interventions.[31,32]

Statistical Analysis

Sample Size Determination

Sample size estimation was based on the anticipated effects of attune and cerena on PROMIS-A, accounting for anticipated loss to attrition. As there are no existing studies of a digitized CBSM intervention, we estimated an effect size of $d = 0.4$ on the basis of the existing literature on in-person studies of CBSM and non–CBSM-based digital health interventions in similar populations.[21] An effect size of $d = 0.1$ was estimated for cerena on the basis of the limited existing research on HealthWatch. However, as psychosocial interventions in patients undergoing treatment for cancer often show rates of attrition upward of 20% and studies of digital interventions frequently report rates higher than 40%, we accounted for potential loss to attrition in our a priori determination of sample size.[33-36] A sample size of 450 participants would be necessary to achieve an 80% power to detect a significant effect at the $P < .05$ level, accounting for a 25%-30% loss to attrition.

Primary End Point

The primary end point was the change in PROMIS-A over the 12-week study across treatment conditions, measured by the *PROMIS-Anxiety Short Form v1.0 8a* (*PROMIS-A*). The PROMIS-A is a validated patient-reported eight-item measure that assesses anxiety symptoms on a 5-point Likert scale ranging from never (1) to always (5) over the past 7 days. It has demonstrated strong internal validity and test-retest reliability in both healthy and clinical populations, including patients with cancer.[25] The PROMIS-A was administered at weeks 0 (baseline), 4, 8, and 12 (end of study).

Changes in PROMIS-A scores were compared across conditions using a longitudinal, repeated-measures mixed-effects model. The model set postbaseline scores (measured

at the week 4, 8, and 12 study visits) as the outcome variable. Treatment condition, time (days since random assignment), a time-by-condition interaction, and baseline PROMIS-A score were included as fixed effects. A random effect for intercept was included to account for the dependence among repeated measures. The primary hypothesis test was based on a significant time-by-treatment condition interaction term, indicating a significant difference in the trajectory of anxiety over time across conditions. Incomplete data are accommodated via the maximum likelihood estimation procedure.

To examine the effect of the treatment condition on end-of-study PROMIS-A scores within the complete case population, an analysis of covariance (ANCOVA) controlling for baseline PROMIS-A score was conducted. Effect size, measured by Cohen's *d*, was subsequently calculated to quantify the magnitude of this effect.

Secondary End Points

The first secondary end point was the change in PROMIS-D score over the 12-week study across treatment conditions. The *PROMIS-Depression Short Form v1.0 8b* (*PROMIS-D*) validated patient-reported eight-item measure assesses depression symptoms on a 5-point Likert scale ranging from never (1) to always (5) over the past 7 days. It has demonstrated strong internal validity and test-retest reliability in both healthy and clinical populations, including patients with cancer.[25] The PROMIS-D was administered at weeks 0 (baseline), 4, 8, and 12 (end of study). Analysis of this end point mirrored that of the primary end point (PROMIS-A) described above. Changes in the post-baseline scores were modeled using an identical longitudinal mixed-effects model, and the condition differences at the end of study (and corresponding effect size) were calculated using an ANCOVA.

Global impressions of change in anxiety and depression were also included as secondary end points and were assessed using The Patient Global Impression of Change Scale (PGI-C). The PGI-C is the patient report version of the clinician-reported Clinician Global Impression of Change Scale (CGI).[37] The CGI and PGI have demonstrated high agreement with each other in psychiatric symptom samples.[38] The PGI-C uses a 7-point Likert scale (very much worse [1]—very much improved [7]) to assess perceived changes in symptoms of anxiety (PGI-C Anxiety) and symptoms of depression (PGI-C Depression) since the beginning of the study. The PGI-C was administered at weeks 4, 8, and 12 (end of study). Responses were categorized into much or very much improved, no change or minimal change, or much or very much worse, as has been suggested elsewhere in the literature to simplify the 7-point Likert scale options. A chi-square test was conducted to determine whether there were significant differences in the proportions of participants within PGI-C categories across conditions at each time point.

Secondary safety, usability, and engagement outcomes were also measured. A safety management plan sought to identify any safety issues that might alter the risk-benefit of the investigational treatment in accordance with US Food and Drug Administration requirements including ICH E2A Clinical Safety Data Management, ICH E6 (R2) Good Clinical Practice, 21, and CFR §803 and §812, among other requirements. An adverse event reporting form administered at weeks 0, 4, 8, and 12 assessed the distress caused by three possible adverse effects related to the use of a digital device (headache, eye strain, and finger cramping) using an adapted version of the Rotterdam Symptom Checklist.[39] This adverse events reporting form administered at these discrete time points also included monitoring of mood and suicidality with the DART-SRS but did not otherwise include defined questions regarding psychosocial symptoms; anxiety and depression symptoms were captured in the electronic surveys as efficacy outcomes. In addition, participants had continuous access to an open-field adverse event reporting form throughout the study to report any events—physical, psychological, or otherwise—allowing for a broader capture of experiences beyond the scope of what was captured through the checklist and DART-SRS. All reported events were reviewed and adjudicated by a medically trained PI in accordance with the prespecified safety management plan.

Engagement was based on session completion meta-data recorded directly from the applications. mHealth App Usability Questionnaire[40] items "The app was easy to use" and "It was easy for me to learn to use the app," rated on a scale of 1 (strongly disagree) to 7 (strongly agree), were administered at week 12 (end of study) to assess usability.

The prespecified primary and secondary inferences (PROMIS-A and PROMIS-D analyzed using the longitudinal mixed-effects model, respectively) were hierarchically tested at the $P < .05$ level. All other statistical tests reported were not controlled for multiplicity and are reported at the nominal $P < .05$ significance level. All statistical analyses were performed using R Statistical Software (V4.1.2, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 16,641 participants completed the prescreening survey, of which 3,216 met medical and psychological (anxiety, depression, and suicidality screening) eligibilities. An additional 2,318 participants were excluded from participation for not providing informed consent (n = 1,106), opting out of participating (n = 785), or not attending an onboarding session (n = 427). The final sample size of participants who attended their onboarding visit, were enrolled, and were randomly assigned was N = 449 (attune = 226; cerena = 223; see Fig 1 for the CONSORT diagram) between March and September 2022. Of these 449 participants, 81.3% completed the study and primary outcome data were obtained from 89.9% of enrolled participants at week 12.

Participants were from 41 US states and were 80.0% female and 76.3% White, with a mean (standard deviation [SD]) age of 52.44 (11.46) years. A wide range of cancer types were represented, with breast cancer (52.8%) being the most prevalent. The sample included approximately equal proportions of patients with stage I, II, and III cancer. Demographic and clinical characteristics were comparable across conditions. See Table 1 for complete details.

Change in Anxiety (PROMIS-A)

Baseline PROMIS-A scores did not differ across conditions. The mean (SD) PROMIS-A score was 63.72 (4.49) in the attune conditions and 64.06 (4.50) in the cerena condition ($t = -7.78$; $P = .44$). Mixed-effects model analysis yielded significant differences across conditions over time in postbaseline PROMIS-A scores ($B = -0.03$, $P = .019$) such that participants in the attune condition showed a greater reduction in anxiety compared with participants in the control condition (Fig 2A).

This finding was supported by a secondary ANCOVA. Treatment condition was a significant predictor of end-of-study PROMIS-A ($F(1, 321) = 4.95$; $P = .027$), with attune reporting lower anxiety symptoms compared with cerena, controlling for baseline anxiety. This corresponded to an effect size of $d = 0.25$ (95% CI, 0.03 to 0.47).

Change in Depression (PROMIS-D)

Baseline PROMIS-D scores did not differ across conditions. The mean (SD) PROMIS-D score was 59.49 (5.65) in the attune conditions and 59.34 (5.55) in the cerena condition ($t = -2.86$; $P = .77$). The change in depression symptoms, measured by PROMIS-D, was prespecified as the first rank end point. Significant differences in PROMIS-D scores were observed over time across conditions ($B = -0.02$; $P = .042$), supporting our hypothesis and demonstrating a greater rate of reduction in depression symptoms over time in the attune condition, compared with the control (Fig 2B).

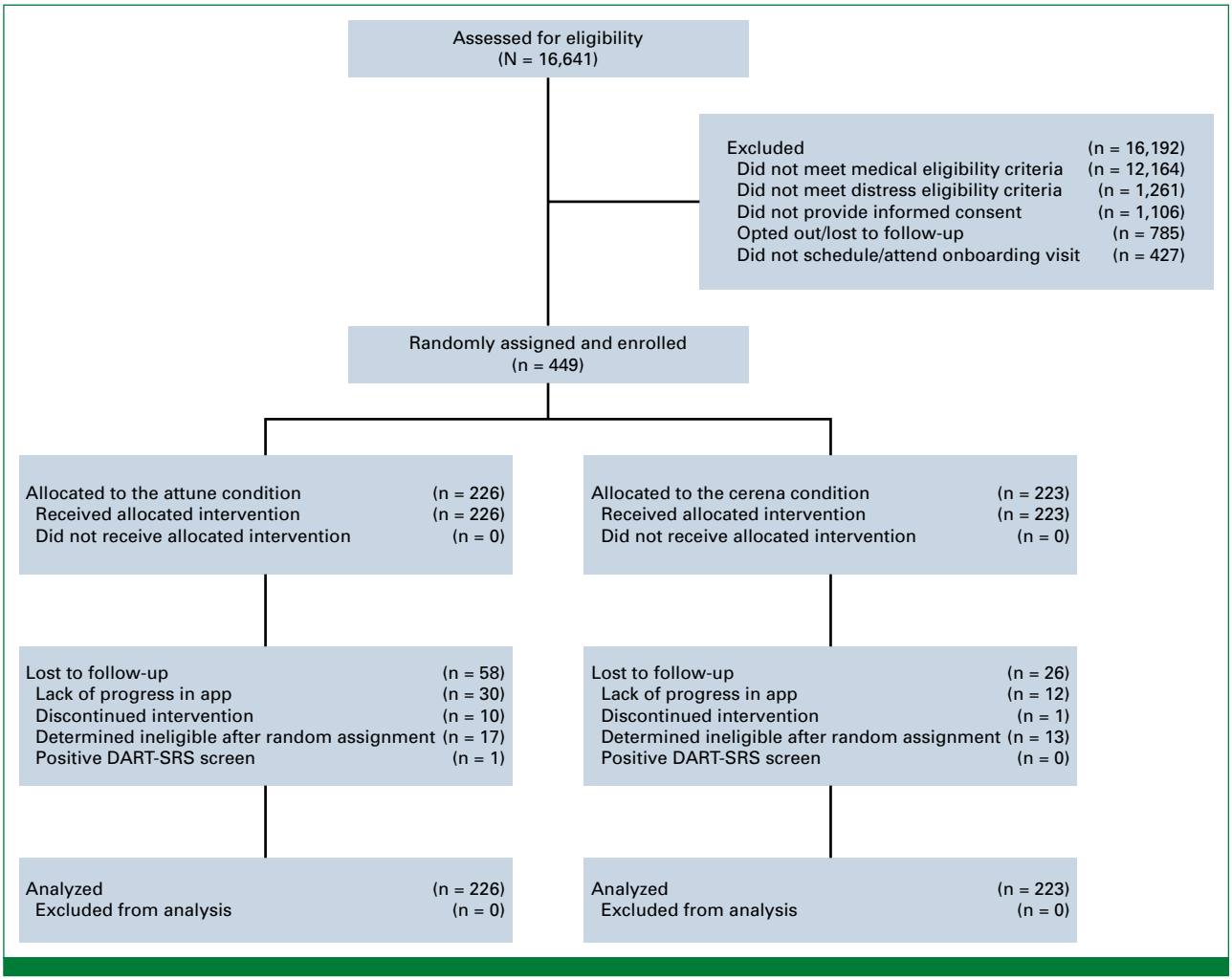

FIG 1. CONSORT diagram. DART-SRS, DART-Suicide Risk Screening.

TABLE 1. Participant Demographic and Clinical Characteristics

Demographic	Attune (n = 226)	Cerena (n = 223)	Total (N = 449)
Age, years			
Mean (SD)	52.39 (11.58)	52.49 (11.35)	52.44 (11.46)
Range	25-80	26-80	25-80
Biologic sex, No. (%)			
Female	185 (81.9)	177 (79.4)	362 (80.6)
Male	41 (18.1)	46 (20.6)	87 (19.4)
Race and/or ethnicity, No. (%)			
American Indian/Native Alaskan	2 (0.9)	2 (0.9)	4 (0.9)
Asian	5 (2.3)	4 (1.9)	9 (2.1)
Bi-/multiracial	2 (0.9)	5 (2.3)	7 (1.6)
Black	42 (19.2)	35 (16.3)	77 (17.1)
Native Hawaiian/Pacific Islander	4 (1.8)	0 (0.0)	4 (0.9)
Another race	0 (0.0)	2 (0.9)	2 (0.4)
White	164 (74.9)	167 (77.7)	331 (76.3)
Education, No. (%)			
Graduate/Professional degree	77 (34.1)	65 (29.1)	142 (31.6)
Four-year college degree	60 (26.5)	67 (30.0)	127 (28.3)
High school degree	84 (37.2)	84 (37.7)	168 (37.4)
Some high school	5 (2.2)	7 (3.1)	12 (2.7)
Marital status, No. (%)			
Married	118 (52.2)	110 (49.3)	228 (50.8)
Partnered	19 (8.4)	18 (8.1)	37 (8.2)
Single	45 (19.9)	45 (20.2)	90 (20.0)
Divorced	33 (14.6)	43 (19.3)	76 (16.9)
Widowed	11 (4.9)	7 (3.1)	18 (4.0)
Clinical characteristics, No. (%)			
Cancer type			
Brain	1 (0.5)	1 (0.5)	2 (0.5)
Breast	111 (53.1)	108 (52.4)	219 (52.8)
Colon/rectal	12 (5.7)	13 (6.3)	25 (6.0)
Endometrial	4 (1.9)	9 (4.4)	13 (3.1)
Leukemia	9 (4.3)	4 (1.9)	13 (3.1)
Lung	16 (7.7)	13 (6.3)	29 (7.0)
Lymphoma	10 (4.8)	8 (3.9)	18 (4.3)
Other Cancers	16 (7.7)	19 (9.2)	35 (8.4)
Ovarian	19 (9.1)	14 (6.8)	33 (8.0)
Pancreatic	1 (0.5)	7 (3.4)	8 (1.9)
Prostate	4 (1.9)	8 (3.9)	12 (2.9)
Thyroid	6 (2.9)	2 (1.0)	8 (1.9)
Cancer stage			
I	75 (33.2)	71 (31.8)	146 (32.5)
II	73 (32.3)	77 (34.5)	150 (33.4)
III	78 (34.5)	75 (33.6)	153 (34.1)
Baseline anxiety and depression			
Anxiety—PROMIS-A T-score (SD)			
Baseline	63.72 (4.49)	64.06 (4.49)	63.89 (4.49)
Week 4	60.13 (4.73)	60.05 (5.95)	60.09 (5.38)
Week 8	58.62 (4.59)	59.72 (6.52)	59.21 (5.73)
Week 12	57.72 (5.19)	58.83 (6.08)	58.32 (5.71)

(continued on following page)

TABLE 1. Participant Demographic and Clinical Characteristics (continued)

Demographic	Attune (n = 226)	Cerena (n = 223)	Total (N = 449)
Depression—PROMIS-D T-score (SD)			
Baseline	59.49 (5.65)	59.34 (5.55)	59.42 (5.60)
Week 4	56.25 (5.95)	56.21 (6.69)	56.23 (6.34)
Week 8	55.07 (5.90)	56.40 (7.08)	55.78 (6.58)
Week 12	53.95 (6.46)	55.18 (7.16)	54.61 (6.86)

Abbreviations: PROMIS, Patient Reported Outcomes Measurement Information System; PROMIS-A, PROMIS-Anxiety; PROMIS-D, PROMIS-Depression; SD, standard deviation.

This finding was supported by the prespecified secondary ANCOVA. Treatment condition was a significant predictor of end-of-study PROMIS-D ($F(1, 321) = 4.55$; $P = .033$), with attune reporting lower depression symptoms compared with cerena. This corresponded to an effect size of $d = 0.24$ (95% CI, 0.02 - 0.46) within the attune arm.

Global Impression of Change

For both PGI-C Anxiety and PGI-C Depression, chi-square tests of differences in proportion revealed significant differences in the proportion of participants in the different change categories between the attune and cerena conditions at the time points of week 4, week 8, and week 12. At end of study (week 12), over twice the proportion of attune participants reported their anxiety as much or very much improved compared with cerena participants (attune = 54.0%; cerena = 24.2%), whereas a greater percentage of cerena participants reported their anxiety as much or very much worse compared with attune participants (attune = 2.0%; cerena = 6.2%). Similarly, at the end of study (week 12), a greater proportion of attune participants reported their depression as much or very much improved compared with cerena participants (attune = 48.7%; cerena = 28.1%), whereas a greater percentage of cerena participants reported their depression as much or very much worse compared with attune participants (attune = 0.7%; cerena = 6.7%; Figs 2C and 2D).

Safety

Average levels of endorsements of anticipated adverse device effects (headache, eye strain, and finger cramping) were either equivalent or lower for attune (ANOVAs, sig level $P < .05$). In the attune condition, average ratings remained below 2 (a little bit) for all adverse device effects throughout the study.

A total of 44 adverse events were reported during the study, 22 in the attune condition (18.2% mild, 36.4% moderate, 45.5% severe) and 22 in the cerena condition (22.7% mild, 45.5% moderate, 31.8% severe; Tables 2 and 3). Adverse events did not differ in number or severity across conditions ($P = .650$). Ten serious adverse events (occurring in 10 patients) were recorded during the study, five in each of the two conditions. A single participant in the attune condition endorsed suicidal intent at one time point (week 8). Following the study protocol, this case was reviewed and triaged by the site PI, a licensed psychiatrist, and determined to be not device- or study-related. The participant was determined to be under the care of a treating physician and not in immediate crisis, offered additional referral and crisis resources, and was withdrawn from the study per protocol.

The study population was composed of patients who recently completed treatment or who were in active treatment and likely experiencing acute or long-term effects from cancer treatments. The majority of events were physical in nature and suggestive of cancer treatment side effects or other illness (eg, neuropathy, asthma). All adverse events that were documented during the course of the study, including in the category of mental health, were determined to be not related to the participation in the study or use of either of the devices by the site PI, a licensed medical provider.

Engagement

Both attune and cerena participants agreed that the app was easy to use and easy to learn to use (attune M [SD] = 6.02 [1.16]; cerena M [SD] = 6.40 [0.95]), demonstrating good usability of both apps.

In the ITT sample, participants in the attune arm completed a median of 8 out of 10 sessions (mean [SD] = 6.57 [3.69]). In the subset of the ITT sample that remained enrolled at the end of study (n = 365), the mean (SD) number of sessions completed by participants in the attune arm was 7.82 (3.03). Engagement on cerena was also very high; participants in the ITT sample completed an average of 8.64 (SD = 2.97) of 10 sessions. In the subset of the ITT sample enrolled at the end of study, the mean (SD) number of sessions completed was 9.31 (2.04).

DISCUSSION

In this double-blind randomized controlled trial of 449 patients with cancer across the United States, data collected demonstrated comparable safety and superior efficacy for a digitized form of CBSM (attune) compared with a visually similar health education control app (cerena). Compared

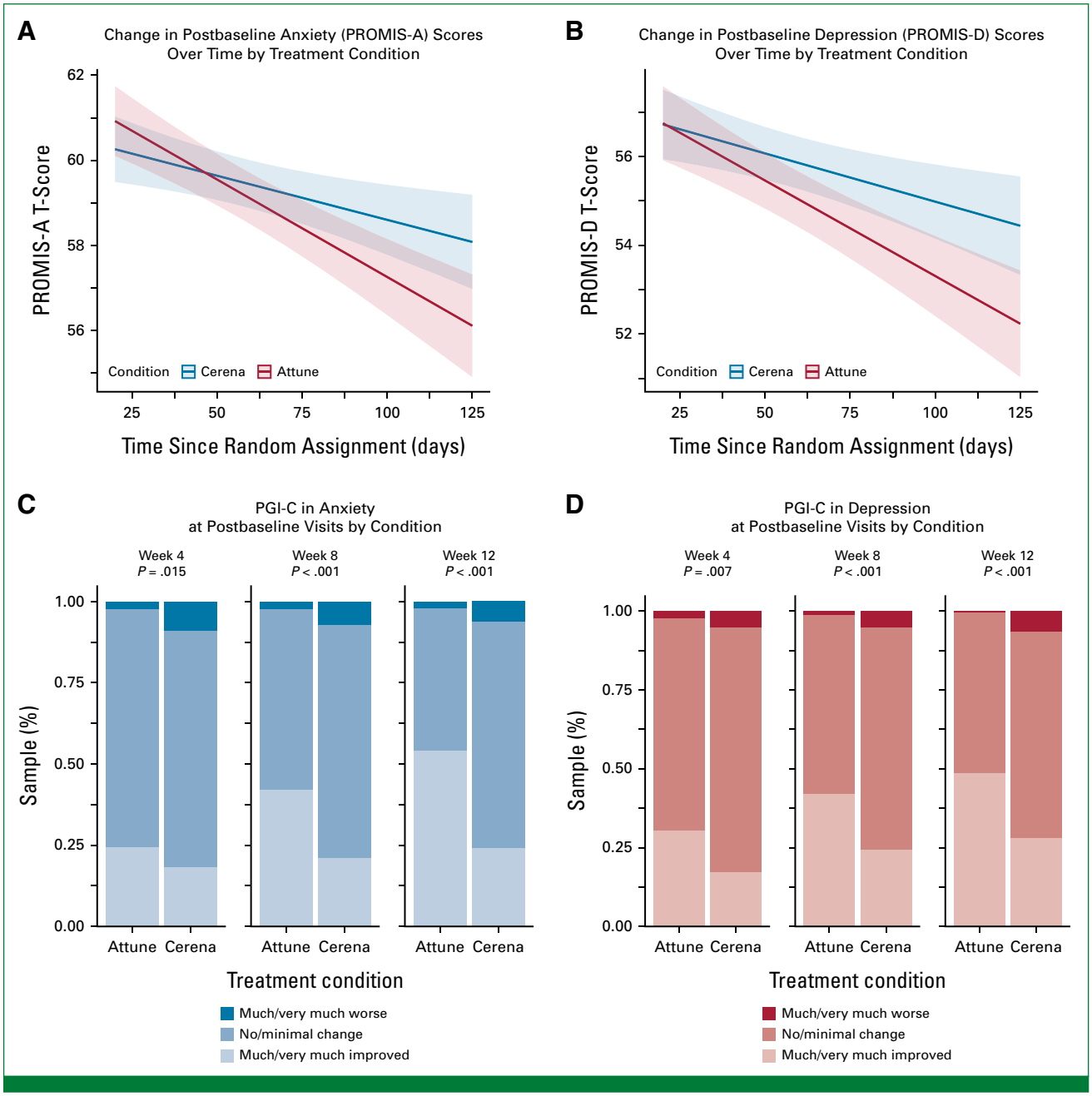

FIG 2. Anxiety and depression symptoms over time by treatment condition. PGI-C, Patient Global Impression of Change Scale; PROMIS-A, PROMIS-Anxiety; PROMIS-D, PROMIS-Depression.

with cerena, participants who used attune showed greater reductions in anxiety and depression symptoms across 12 weeks of treatment and had less anxiety and depression symptoms at the end of study, thereby meeting our prespecified primary and key secondary end points. Within the attune condition, the change in PROMIS-A and PROMIS-D scores observed over 12 weeks exceeds the minimal clinically important difference of 3.0-4.5 points.[41] More participants in the attune compared with the cerena condition self-reported that their anxiety and depression was much or very much improved and fewer felt that their anxiety and depression was much or very much worse since starting the study. Findings presented here testing digitized CBSM are consistent with studies of in-person CBSM,[18,21] indicating that this evidence-based psychological intervention can also alleviate anxiety and depression symptoms when administered as a digital therapeutic.

Strengths of this study include a rigorous, double-blind, randomized design, decentralized recruitment and enrollment, and a rigorous sham control. Using a decentralized clinical trial model allowed us to reach a substantially larger population of potential participants from across the United States; in this study, over 16,000 individuals completed

TABLE 2. Adverse Events by Condition

Event	Frequency Attune	Frequency Cerena
Second-degree burns and blisters on the right chest wall	0	1
Advancement of primary cancer	0	1
Bladder infection	1	0
Blood clot in liver	1	0
Blurred vision	0	1
Bronchitis, asthma	0	1
Burns, neuropathy	0	1
Constipation	0	1
Coughing and shortness of breath	1	0
COVID-19	1	2
Diarrhea and urinary retention	1	0
Difficulty in breathing	0	1
Extreme fatigue	0	1
Extremity swelling, UTI, and pneumonia	1	0
Hematoma, strange feelings in her legs and feet	1	0
Hernia	1	0
Hypertension and pleural effusion	1	0
Long COVID-19 symptoms	1	0
Lumpectomy and lymph node removal	0	1
Nausea and dizziness, facial dryness and breakouts, oral pain and sensitivity, stomach upset	0	1
Nausea, pain, and surgery	1	0
Nerve pain	1	0
Neuropathy	1	0
Neuropathy and dyspnea	1	0
Neuropathy, brain fog, and GI symptoms	0	1
Onycholysis	0	1
Pain and tingling of right foot	0	1
Pruritus	1	0
Rash	1	0
Restlessness	0	1
Suicidal ideation	1	0
Vomiting, diarrhea, and leg cramps	0	1
Total AE by condition	17	17

NOTE. Excludes serious adverse events, which are detailed in Table 3.
Abbreviations: AE, adverse event; UTI, urinary tract infection.

the eligibility survey. Many of those who expressed initial interest in learning more about the study were ineligible, did not provide informed consent, or were lost to follow-up prior to randomization. One benefit of this wide reach is that the sample reported somewhat more diverse sociodemographic and geographic backgrounds than is traditionally observed in oncology clinical trials.[24,42] For instance, approximately 40% of the sample reported educational attainment of a high school degree or less. While some degree of self-selection bias is present in all voluntary opt-in research studies, the increased accessibility of participation might have minimized the potential for bias and increased representativeness of findings. The use of electronically completed PROs aided in minimization of social desirability responding and increased the reliability of symptom assessment. Engagement was also quite strong. In the attune arm, engagement was comparable with session attendance levels observed in in-person CBSM trials[21] and does not reflect the concern that digital therapeutics invariably struggle with low engagement.[33]

The inclusion of a rigorous sham condition is relatively unique for this type of research. While health education is a common control condition for psychological treatments, cerena was a professionally designed, fully digitized interactive app that controlled for the novelty and engagement of the digital interface. Similar to attune, cerena showed strong engagement, which supports the notion that cerena was a robust control condition. The strength of cerena as a control condition was supported by a significant reduction in anxiety and depression symptoms in this condition. Future work may include comparison of attune with a treatment as a usual condition as it is unclear whether the effects displayed in the control condition here were driven by placebo and expectancy effects, if these reflect the natural course of the symptoms, or if there was a therapeutic effect of providing health education material. Nevertheless, the size of the effect was greater for attune than cerena, thus yielding a significant between-group difference. The use of a robust sham intervention served to match the activities and interactions of the control condition with those of the treatment condition, and doing so increased our confidence that we isolated the true effect of the therapeutic content of CBSM within the treatment condition.

This study adds to a growing body of literature demonstrating efficacy of digital delivery of CBT-based interventions. To our knowledge, as this was the first RCT trial testing attune specifically, future work for replication and expansion of this research is important. For example, this study sample did not include patients with stage IV solid tumors. While CBSM skills are broadly applicable and CBT-based approaches are intended to allow for development of lasting coping tools over a short therapy duration, unique needs of some metastatic patients (eg, end-of-life planning) and extended cancer treatment timelines may warrant additional tailoring of the intervention to maximize applicability and efficacy in this cancer subpopulation and should be a topic of future investigation. This study does not speak to durability of effects; a follow-up study is currently underway to assess intervention effects on anxiety and depression symptoms at 6 months postintervention. The current study also does not report on baseline characteristic or demographic predictors of treatment effects, nor does it examine intervention mechanisms, which are important future directions for this line of research. Differential attrition occurred in this study, as is commonly seen in behavioral trials, likely because of increased psychological effort required to engage in a CBT-based treatment compared with an education control.[43] Future directions include understanding different patterns

TABLE 3. Serious Adverse Events by Condition

Event	Frequency Attune	Frequency Cerena
Bacterial blood infection	0	1
Bowel obstruction	1	0
Chest pain and shortness of breath	0	1
Congestive heart failure	1	0
Hyperuricemia	1	0
Kidney stones	1	0
Lung inflammation and pneumonia	0	1
Mallory Weiss tear	0	1
Neutropenic fever	1	0
Renal obstruction	0	1
Total SAE by condition	5	5

Abbreviation: SAE, serious adverse event.

of user engagement with attune (eg, predictors of completion, frequency of use, etc) and assessing implementation strategies to promote efficient and equitable access to care, including examination of stepped care and integrated therapist/coach approaches.[44] Future studies will also aim to understand how use of attune—and subsequent improvements in distress—is related to objective behavioral and physiological outcomes, including increased adherence to cancer treatment, health care utilization patterns, and adaptive changes in bioinflammatory markers of stress. Finally, future work should be conducted to examine engagement and effectiveness in real-world settings outside of the context of controlled trial participation with compensation.

While professional organizations have widely agreed on the need to treat distress in patients with cancer,[10] the task at hand is to implement treatment in a way that is scalable, portable, nimble, and effective.[45] Access to appropriate aftercare for distressed patients has been cited as the most significant barrier to distress screening success.[46] Traditional therapist-delivered psychosocial interventions for patients with cancer continue to have insufficient reach because of barriers such as workforce shortages, stigma, geographic inaccessibility, and illness-related considerations—all barriers that a digital therapeutic helps address.[47] Digital therapeutics can offer a cost-effective approach to psychological care and can also contribute to health care cost savings.[48] However, the cost required for high-quality evidence generation and regulatory approval for digital therapeutics is substantial, and to prevent these costs from being passed onto the patient, it is essential that public and private insurance companies reimburse for these treatments and supporting legislation is enacted.[49] The clinical implications of the RESTORE findings are substantial as the availability of efficacious treatments for symptoms of anxiety and depression for patients with cancer remains a significant unmet need. Attune has the potential to support national guidelines for the management of emotional distress[4] by increasing the accessibility of evidence-based, efficacious care for the many patients with cancer affected by anxiety and depression symptoms.

In conclusion, attune is an efficacious treatment for symptoms of anxiety and depression in patients with cancer with a positive benefit-risk profile. Attune and similar evidence-based digital interventions may be useful tools for reducing the distress associated with cancer.

AFFILIATIONS

[1]Blue Note Therapeutics, San Francisco, CA
[2]King's College London, London, United Kingdom
[3]University of Miami, Coral Gables, FL
[4]University of California Los Angeles, Los Angeles, CA
[5]University of California San Francisco, San Francisco, CA

CORRESPONDING AUTHOR

Dianne M. Shumay, PhD, Blue Note Therapeutics Inc, 548 Market St, 55709, San Francisco, CA 94104; e-mail: dianne.shumay@gmail.com.

PRIOR PRESENTATION

Results from this study have been presented in part at the American Psychosocial Oncology Society in Portland, OR, on March 16, 2023; at the Academy of Managed Care Pharmacy Conference in San Antonio, TX, on March 23, 2023; at the American Society for Clinical Oncology, Chicago, IL, on June 3, 2023; and at the International Psycho-Oncology Society World Congress in Milan, Italy, on September 1, 2023.

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AUTHOR CONTRIBUTIONS

Conception and design: All Authors
Collection and assembly of data: Sean R. Zion, Chloe J. Taub, Lauren C. Heathcote, Allison Ramiller, Michael McKinley, Geoff Eich, Dianne M. Shumay
Data analysis and interpretation: Sean R. Zion, Chloe J. Taub, Lauren C. Heathcote, Allison Ramiller, Geoff Eich, Dianne M. Shumay
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Effects of a Cognitive Behavioral Digital Therapeutic on Anxiety and Depression Symptoms in Patients With Cancer: A Randomized Controlled Trial

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Sean R. Zion
Employment: Blue Note Therapeutics
Stock and Other Ownership Interests: Blue Note Therapeutics
Consulting or Advisory Role: Omada Health, Blue Note Therapeutics
Research Funding: Blue Note Therapeutics

Chloe J. Taub
Employment: Blue Note Therapeutics
Consulting or Advisory Role: Blue Note Therapeutics
Travel, Accommodations, Expenses: Blue Note Therapeutics

Lauren C. Heathcote
Consulting or Advisory Role: Blue Note Therapeutics

Allison Ramiller
Consulting or Advisory Role: Blue Note Therapeutics
Travel, Accommodations, Expenses: Blue Note Therapeutics

Stacey Tinianov
Employment: Citizen Corporation
Stock and Other Ownership Interests: InVitae (I)
Honoraria: Bayer
Consulting or Advisory Role: Blue Note Therapeutics, ARTIDIS, Rabble Health, InVitae, Napo Pharmaceuticals

Michael McKinley
Employment: Blue Note Therapeutics, Amgen
Leadership: Blue Note Therapeutics
Stock and Other Ownership Interests: Blue Note Therapeutics
Research Funding: Blue Note Therapeutics
Patents, Royalties, Other Intellectual Property: Patents related to Blue Note Product designs. Patent pending
Travel, Accomodations, Expenses: Blue Note Therapeutics
Other Relationship: Blue Note Therapeutics
Uncompensated Relationships: Blue Note Therapeutics

Geoff Eich
Employment: Blue Note Therapeutics
Leadership: Blue Note Therapeutics
Stock and Other Ownership Interests: Blue Note Therapeutics
Patents, Royalties, Other Intellectual Property: Blue Note Therapeutics IP
Travel, Accomodations, Expenses: Blue Note Therapeutics

Frank J. Penedo
Employment: Blue Note Therapeutics
Consulting or Advisory Role: Blue Note Therapeutics

Patricia A. Ganz
Leadership: Intrinsic LifeSciences (I)
Stock and Other Ownership Interests: Xenon Pharma (I), Intrinsic LifeSciences (I), Silarus Therapeutics (I), Teva, Novartis, Merck, Johnson & Johnson, Pfizer, GlaxoSmithKline, Abbott Laboratories, Disc Medicine (I)
Consulting or Advisory Role: InformedDNA, Global Blood Therapeutics (I), GlaxoSmithKline (I), Ionis Pharmaceuticals (I), Ionis Pharmaceuticals (I), Akebia Therapeutics (I), Rockwell Medical Technologies Inc (I), Disc Medicine (I), Blue Note Therapeutics, Grail
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Michael Antoni
Consulting or Advisory Role: Blue Note Therapeutics, Atlantis Health
Patents, Royalties, Other Intellectual Property: Coauthor of the Million Behavioral Medicine Diagnostic, patients. Inventory of Cognitive Behaviorial Stress Management, a group-based intervention registered with the Technology Transfer Office at the University of Miami (UMIP-483) and licensed to Blue Note Therapeutics

Dianne M. Shumay
Employment: Blue Note Therapeutics

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APPENDIX

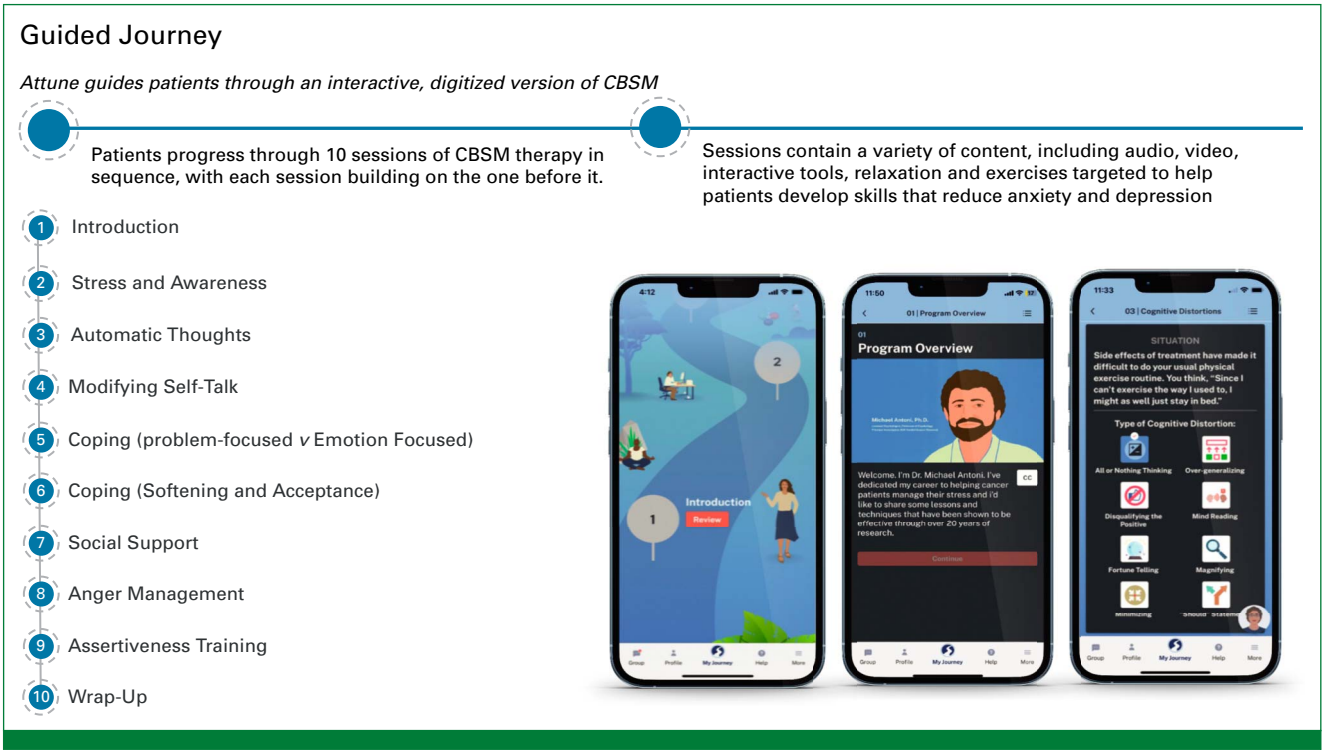

FIG A1. Attune content. CBSM, cognitive behavioral stress management.