Original Article

A Digital Therapeutic Application (ePAL) to Manage Pain in Patients With Advanced Cancer: A Randomized Controlled Trial

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Abstract

Background. Patients with advanced cancer often experience immense cancer pain that negatively impacts their quality of life. Interventions to address cancer-related pain are limited.

Methods. We conducted a randomized trial of a digital therapeutic app (ePAL) for patients with advanced cancer receiving care in a specialty palliative care clinic at a tertiary care hospital. Patients were randomized to ePAL or usual care. ePAL included 1) active pain monitoring; 2) artificial intelligence algorithm to triage patient symptoms; and 3) patient education to address barriers to pain management. Participants were instructed to use ePAL over eight weeks. Patient-reported pain symptoms were assessed at baseline, Week-4, and Week-8 (primary endpoint) using the Brief Pain Inventory. Secondary outcomes include pain-related hospitalizations by Week-8.

Results. We enrolled 112 patients who were randomly assigned to ePAL ($N = 56$) or usual care ($N = 56$). Patients utilized ePAL on average 2.1 times per week to report pain symptoms, and 47.6% reported their pain at least once per week over eight weeks. Patients randomized to ePAL reported lower pain scores at Week-4 (mean: 3.16 vs. 4.28, $P = 0.010$) and week-8 (mean:2.99 vs. 4.05, $P = 0.017$), compared to those receiving usual care. Participants randomized to ePAL were less likely to experience a pain-related hospitalization compared to those in the usual care group (7.1% vs. 23.2% $P = 0.018$)

Conclusions. ePAL was associated with lower patient-reported pain and fewer pain-related hospitalizations compared to usual care in patients with advanced cancer. This study demonstrates the promise of digital therapeutics for improving patients' symptoms while reducing burdensome hospitalizations. J Pain Symptom Manage 2024;68:261−271. *© 2024 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.*

Key Words

Digital therapeutic app, Advanced cancer, Cancer-related pain, Health care utilization, Pain management

Precis: A digital therapeutic app for patients with advanced cancer significantly improved pain scores by 26%, reduced patient barriers to pain management, and was associated with a 69% risk reduction in pain-related hospitalizations. This study demonstrates the promise of digital therapeutics for improving patients' symptoms while reducing burdensome hospitalizations.

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Introduction

Despite advances in oncology and pain treatments, cancer-related pain continues to be a significant clinical problem.[1–3] Cancer-related pain affects approximately 55% of patients receiving active therapy, 66% of patients with advanced disease, and 39% of cancer survivors.[2] Cancer-related pain can have devastating effects on patient and caregiver quality of life and is one of the most feared consequences of cancer.[4–6] Poorly-controlled cancer pain also results in potentially avoidable hospital admissions, substantial healthcare utilization, and increased costs of care.[7–13]

Cancer-related pain will likely become an even more prominent problem for the healthcare system in the coming decades, given the projected rising incidence of cancer between 2010 and 2030 with the aging U.S. population.[14] Integrating specialty palliative care for patients with advanced cancer has been shown to improve their quality of life and mood.[15] Yet, a growing workforce shortage of palliative care specialists hinders the scalability and dissemination of supportive care interventions to address cancer-related pain.[16,17] Thus, there is a clear imperative to develop novel care delivery models to manage cancer-related pain effectively.

One strategy to stem the impact of cancer-related pain is the use of digital therapeutics (DTx). DTx represent a rapidly growing field of diverse interventions that utilize evidence-based software to prevent, treat, or manage disease.[18] Recent advances using patient-reported outcomes (PROs) and telehealth have demonstrated significant benefits for patients with cancer.[19–21] While there have been several digital health interventions targeting musculoskeletal pain, chronic pain, burn-related pain, and patients with dementia and other serious illnesses, there have been few digital interventions targeting pain in patients with advanced cancer.[22–25] Prior studies of digital health interventions in cancer have mostly focused on cancer survivors or population-specific interventions, examined feasibility and acceptability rather than efficacy outcomes, and have shown that providing feedback to the clinical team is critical for improving pain outcomes.[26–28] However, successful DTx must carefully identify and separate meaningful clinical information from a large volume of incoming PRO data without overtaxing clinical resources.[29] Artificial intelligence (AI) provides a means to triage large amounts of PRO data and detect important and intervenable information without adding significant clinical burden to providers.

We developed a novel DTx app (ePAL) to optimize the management of cancer-related pain. The central feature of ePAL is the use of AI to triage PRO data and rapidly identify barriers to controlling pain. Real-time intervention is then provided via patient-facing education and empowerment modules delivered by the app or, when necessary, through app-triggered clinician outreach. In this randomized clinical trial, we evaluated the effects of ePAL on pain symptoms (primary outcomes) for patients with advanced cancer receiving outpatient palliative care. We also sought to assess the impact of ePAL on pain-related hospital admissions, patient-related barriers to pain management, anxiety symptoms, as well as quality of life (secondary outcomes). We hypothesized that ePAL would lead to improvement in pain, patient-related barriers to pain management, pain-related hospital admission, as well as reduction in anxiety and improvement in quality of life for patients with advanced cancer

Patients and Methods

Study Design

We conducted a nonblinded, randomized clinical trial of a DTx (ePAL) versus usual care for patients with advanced cancer receiving outpatient palliative care at Massachusetts General Hospital (MGH) (clinicaltrials.gov NCT02069743). We focused on patients receiving outpatient palliative care as the goal of ePAL was to augment clinical palliative care practice. The trial was also initially opened at the Mayo Clinic, but due to budgetary concerns, the study was closed at this site without any data collection. The Dana-Farber/Harvard Cancer Center Institutional Review Board approved the study and all patients provided informed consent.

Settings and Participants

Patient eligibility criteria included: 1) age > 18 years old; 2) a diagnosis of incurable solid tumor receiving treatment for cancer-related pain at an outpatient specialty palliative care clinic; 3) pain intensity score of at least four out of 10 on a 0–10 rating scale available in their electronic health record (EHR) within a month prior to enrollment; 4) ability to read English as ePAL was only available in English; and 5) patients must have a smart phone or be willing to download the study application. We excluded patients who were admitted to the hospital at the time of screening, had a life expectancy (as determined by their palliative care clinician) of fewer than two months, or had significant psychiatric co-morbidities that would interfere with their ability to provide informed consent based on their palliative care clinician assessment. We also excluded patients with known history of substance use as documented in the EHR, given their unique barriers to pain management that were beyond the scope of the ePAL intervention.

A research assistant (RA) identified consecutively eligible patients by screening the EHR. Once a potentially eligible patient was identified, the RA mailed an informational letter to patients with a follow-up call to

assess their interest in study participation and obtain informed consent. Willing patients provided written informed consent and completed baseline study questionnaires. For participants without a smartphone, the study team provided them with access to a tablet to access ePAL during the study period.

Randomization

We used a computer-generated randomization schema to randomize participants 1:1, using random permuted blocks to ePAL versus usual care. Group assignments were concealed in sealed envelopes prepared by a third party and opened by study staff after the participant completed baseline assessments. Due to the nature of the intervention, neither participants nor study staff were blinded to assignment.

ePAL DTx Intervention

Patients assigned to the intervention received ePAL in addition to usual care. We developed ePAL in collaboration with software engineers at Partners Connected Health Innovation and the MGH Division of Palliative Care. We initially conducted focus groups with patients and clinicians that informed the development and content of ePAL. Study staff provided an orientation and help participants randomly assigned to ePAL download the app on their smart phone (iOS and Android supported). Study staff was also available to address any technical issues with ePAL throughout the study period, but there was no additional required contact with study participants. The ePAL intervention entailed prompting study participants to enter their average pain score on a scale of 0−10 three times weekly during an eight-week period (frequency was determined based on patient feedback in the app development phase). Participants can report symptoms without prompts at any point. If the participant reported 0−3 pain score, the participant's pain was well-controlled, and no further action was required. If the participant reported a severe pain score (i.e., 8−10) or new pain, ePAL electronically notified the palliative care triage nurse to call the participants within an hour to explore the issue. For participants with moderate pain scores (i.e., 4−7), ePAL utilized an interactive AI algorithm created by the study team which used branching logic to determine the patient's barrier to pain control based on participant responses to a series of app-prompted questions about their symptoms. If the barrier was deemed to be a patient education or empowerment issue (e.g., challenges with self-management of opioid-induced constipation), an ePAL education module was triggered to address it (e.g., evidence-based guidance on self-management of constipation). If the barrier was deemed to require clinician input (e.g., nausea preventing a participant from ingesting or retaining pain medication), the clinic's triage nurse would be notified electronically to call the participant. ePAL directed participants to call the oncology on-call services for any issues identified after business hours. Participants could also engage with ePAL at any time and input their pain scores. Additionally, participants received daily coaching tips, which were tailored through ePAL's AI platform to address recent barriers to cancer pain management. ePAL leveraged a HIPAA compliant software with all data collected from ePAL saved in a secure database, protected by the Massachusetts General Hospital firewall. ePAL also included a data capture platform to track, color-code, and log pain symptoms for the patient and the clinicians to review. Participants' palliative care clinician also received an automatically generated weekly electronic summary of the participant's pain scores and any barriers to optimal pain control. The ePAL app also contained a patient-facing educational library with content related to their pain, available external resources and support, and a video library. All ePAL educational library content was developed by the study team and included content such as basic principles of cancer pain management, the role of opioid therapy in cancer pain, and common side effects of pain medications. Additional features of ePAL included the capacity to input notes and questions to review during clinic visits, a pain-focused guided meditation, and a prescription refill request tool through which participants could notify the palliative care clinic that they were running low on pain medications. We also monitored daily participant engagement with ePAL and clinician phone calls triggered by the app by electronically tracking it through the app.

Usual Care

Patients randomized to usual care did not receive ePAL. Patients in the usual care group participated in their routine oncology and outpatient palliative care visits. At our center, patients are typically seen by their oncology clinicians during their chemotherapy infusion days. They are also typically seen by their specialty palliative care clinicians every 4-6 weeks for routine clinic visits.

Outcomes

Patients completed a baseline questionnaire which included demographics and self-report measures prior to randomization. Patients also completed the self-reported measures at four weeks (midpoint) and eight weeks (end of the intervention period). The primary outcome (BPI) was also measured at Week-2 and Week-6 in the study. Study staff administered study measures in person or by secure email via REDcap.

The primary outcome of the study was pain as measured by the Brief Pain Inventory (BPI; Cronbach Alpha = 0.85) Short Form composite severity score to assess pain.[1,30] The BPI assesses a composite of the

patient's current, average, worst, and least pain level over the past twenty-four hours (range 0−10, higher scores indicate worse pain). Secondary outcomes include patient-related barriers to pain management, anxiety symptoms, quality of life, and pain-related hospitalizations. To assess patient-related barriers to pain management, we used the Barriers Questionnaire-II (BQ-II; Cronbach Alpha = 0.92).[31] We used the Generalized Anxiety Disorder (GAD-7; Cronbach Alpha = 0.89), a seven-item measure to assess anxiety symptoms.[32] We used the functional assessment of cancer therapy (FACT-G; CronBach Alpha = 0.90) to assess quality of life.[33] All these patient-reported measures were administered at baseline, four weeks, and eight weeks. Given the potential impact of depression on pain symptoms, we also screened for depression symptoms at baseline using the Patient Health Questionnaire-8 (PHQ-8).

We also assessed overall ratings of acceptability of ePAL as a process/fidelity measure using three items focused on how easy ePAL was to understand (score range 0−10), how easy ePAL was to use (score range 0-10), and the overall usefulness of ePAL in managing pain (score range 0−10), consistent with recommendations for digital health intervention development and testing. Higher scores on a range of 0−10 indicate higher accetpabiltiy on these items.

We assessed the number of cancer pain-related hospital admissions both through the emergency department (ED) and in total at our institution. Two researchers, blinded to study assignment, independently conducted a protocolized review of the EHR to determine whether any admissions that occurred during the study were cancer pain-related. Admissions were considered to be pain related if the reason for admission was primarily due to or associated with pain from direct tumor effects or effects of cancer treatments, side effects of pain medications, or pain associated with complications of cancer (such as a pulmonary embolism, pathologic fracture, etc). The protocolized chart review resulted in a high inter-rater reliability (Kappa = 0.90).

Statistical Analyses

We performed statistical analysis using STATA (v9.3). All participants' characteristics and outcomes were summarized as frequencies and percentages for categorical variables and mean +/−SD for continuous variables. The primary endpoint of the study was a comparison of the pain severity scores (BPI) between the two groups at eight-weeks. With a sample size of 110 participants, we had 80% power to detect a 1.5-point difference (i.e., clinically meaningful difference) in BPI scores between the two groups with a 2-sided alpha of 0.05, assuming 25% missing data at week 8.

We utilized intention-to-treat principles for all study analyses. As prespecificied by the protocol, we used a two-sample T-test to compare continuous outcomes (BPI, BQ-II, GAD-7, FACT-G) between the intervention and control group at four and eight weeks. We also used a chi-square test to compare rates of clinically significant improvement in pain scores (i.e., one point improvement in BPI scores) between the two groups during the eight-week period. We then utilized mixed linear effect models, adjusting for baseline and using Maximum Likelihood to address missing data to assess the effect of the intervention on continuous outcomes longitudinally across all study time points. Longitudinal models controlled for both random intercepts and random slopes, in addition to potential imbalances between groups (baseline depression, age, and gender, see Table 1). We used a chi-square test to compare rates of hospitalizations between the two groups.

Table 1
Patient Baseline Characteristics

Baseline Characteristics	ePAL Intervention $N = 56$	Control $N = 56$
Age, mean (SD)	54.6 (10.9)	50.7 (12.4)
Female Gender, *n* (%)	25 (44.6%)	30 (53.6%)
Education, *n* (%)		
College graduate or higher	29 (51.8)	29 (51.7)
Some college	14 (25.0)	16 (28.6)
High-school or less	12 (21.4)	9 (16.07)
Missing	1 (1.8)	2 (3.57)
Marital status, *n* (%)		
Married	38 (67.9)	36 (64.3)
Living with partner	2 (3.6)	4 (7.1)
Divorced or separated	10 (17.9)	9 (16.1)
Widowed	0 (0.0)	1 (1.8)
Single	5 (8.9)	4 (7.1)
Missing	1(1.8)	2 (3.6)
Race, *n* (%)		
White	51 (91.1)	45 (80.4)
American Indian	0 (0.0)	3 (5.4)
Asian	3 (5.4)	1 (1.8)
Black	1(1.8)	4 (7.1)
Other	0 (0.0)	1 (1.8)
Missing	1(1.8)	2 (3.6)
Employment status		
Employed	21 (37.5)	20 (35.7)
Unemployed	7 (12.5)	2 (3.6)
Homemaker	2 (3.6)	5 (8.9)
Retired	12 (21.4)	11 (19.6)
Disabled	11 (19.6)	16 (28.6)
Other	1 (1.8)	0 (0.0)
Missing	2 (3.6)	2 (3.6)
Depression		
None (0−4)	17 (30.4)	17 (30.4)
Mild (5−9)	23 (41.1)	22 (39.2)
Medium (10−14)	4 (7.1)	9 (16.07)
Medium/high (15−19)	11 (19.6)	6 (10.7)
Missing	1 (1.8)	2 (3.6)
Cancer type		
Breast	8 (14.3)	7 (12.5)
Gastrointestinal	21 (37.5)	22 (39.3)
Genitourinary	3 (5.4)	2 (3.6)
Gynecologic	2 (3.6)	4 (7.1)
Head and neck	4 (7.1)	5 (8.9)
Lung	6 (10.7)	5 (8.9)
Melanoma	3 (5.4)	5 (8.9)
Sarcoma	6 (10.7)	2 (3.6)
Other	3 (5.4)	4 (7.1)

SD = standard deviation.

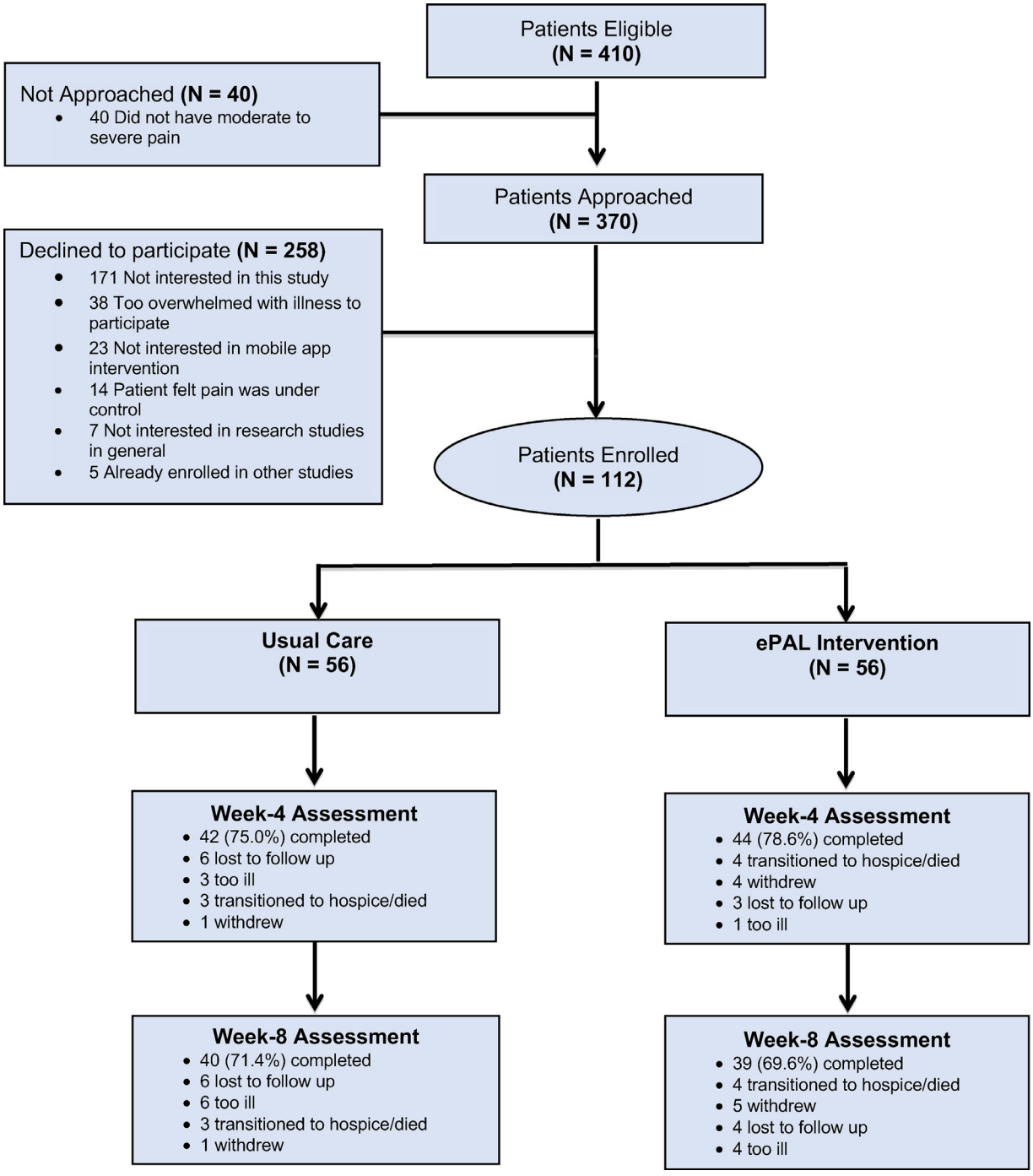

Fig. 1. Consort diagram.

Results

Baseline Characteristics

Between February 2014 and March 2018, we enrolled 30.2% (112/370) of potentially eligible participants (Figure 1). Overall, 258 patients declined to participate. The reasons for declining included: not interested in this specific study (171), feeling too overwhelmed to participate in the study (38 patients), not interested in a mobile app intervention (23 patients), feeling that pain was under control (14 patients), not interested in research studies in general (7), and already enrolled in other clinical studies (5 patients). Overall, 56 participants were randomly assigned to usual care and 56 participants were assigned to the ePAL intervention. The rate of missing data at Week 4 and Week 8 were 23.2% and 29.4%, respectively. We did not find any association between patient demographic or baseline-patient

reported outcomes with likelihood of completing the study measures. Enrolled patients were mostly White (85.7%, 96/112), and approximately half were male (50.8%, 57/112), with a mean age of 52.7 years (range 29-76) [Table 1]. Most (66.0%; 74/112) were married or partnered. Patient characteristics did not differ meaningfully between the study groups at baseline, except for age, gender, and baseline depression scores (Table 1).

ePAL Adherence and Acceptability

Throughout the eight-week intervention period, patients utilized ePAL on average 2.1 times per week to report their pain symptoms, and 47.6% of participants reported their symptoms at least once per week. Use of ePAL declined during the study, with participants using the app at least once per week falling from 86% to 48%, at least twice per week from 69% to 31%, and at least three times per week from 52% to 24% (Fig. 2A). The average per-participant frequency of app use declined from 3.5 days per week to approximately 1.5 days per week by eight weeks (Fig. 2B). Only 14.3% of patients randomized to ePAL did not engage at all with the app. Patients randomized to ePAL reported high acceptability ratings with mean scores of 8.6 (SD = 1.80) on ease of understanding, 8.63 (SD = 1.66)

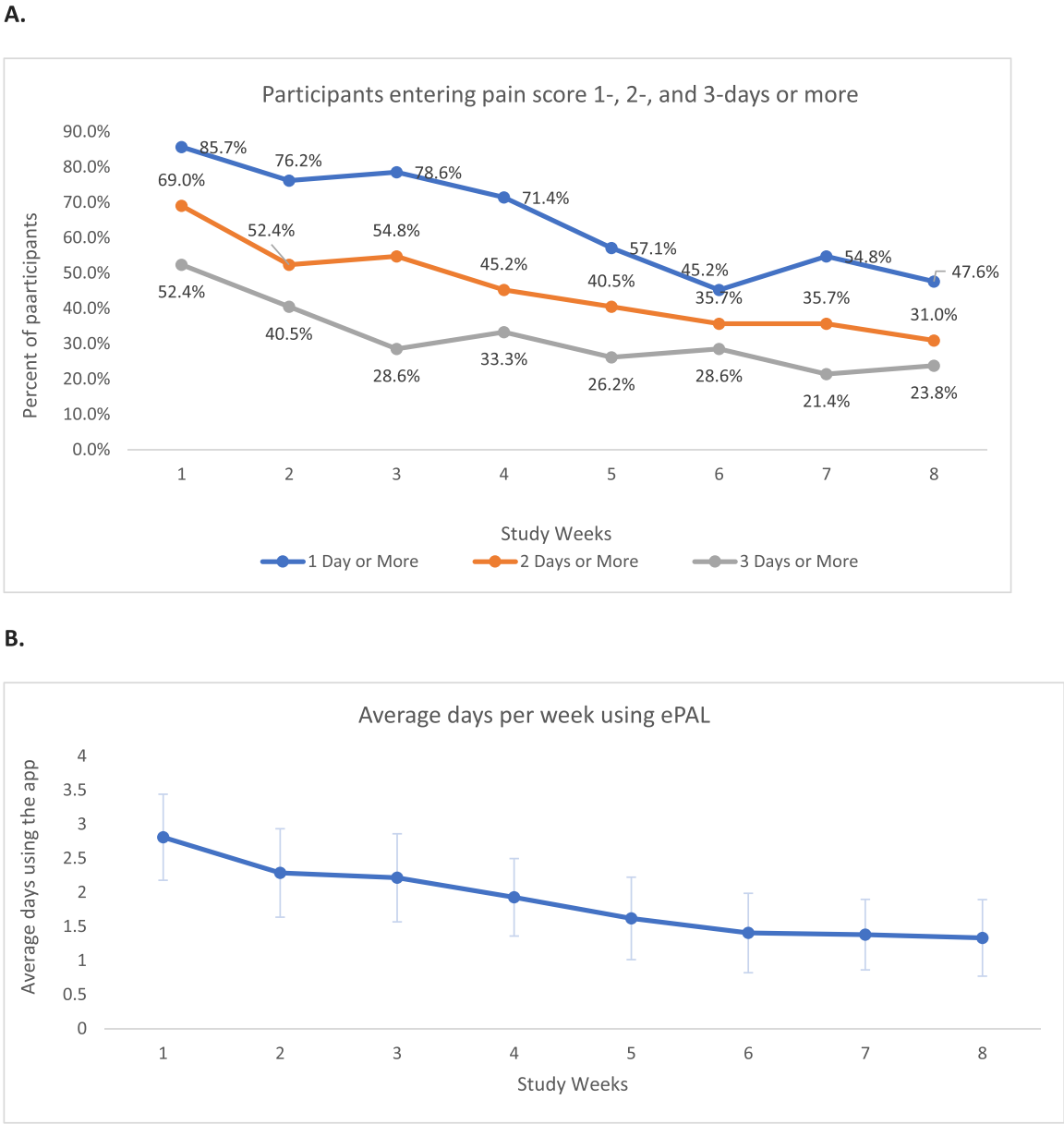

Fig. 2. ePAL intervention utilization. (A) ePAL use among participants entering pain scores 1-, 2-, or 3-days or more; (B) Average days of ePAL use per week during the eight-week intervention period.

Table 2
Effect of ePAL on Pain Symptoms

Pain Symptoms	Intervention Mean (SD)	Control Mean (SD)	*P*-value
Baseline	3.74 (1.88)	4.02 (1.67)	0.41
Four Weeks	3.16 (1.78)	4.28 (1.99)	**0.010**
Eight Weeks	2.99 (2.06)	4.05 (1.78)	**0.017**
Longitudinal model	Beta (95% CI)		*P*-value
Between Group (95% CI)	−0.09 (−0.17, −0.007)	Reference	**0.034**

Two-sample t-test to compare pain symptoms (as measured by Brief Pain Inventory) between the intervention and control group at four and eight weeks. Mixed linear effect models to examine study outcomes longitudinally across all timepoints.
SD = standard deviation; 95% CI = 95% confidence interval.
Bolded *P* values signify statistical significance.

on ease of use, and 7.8 (SD = 2.4) on the overall usefulness of ePAL.

Patient-Reported Outcomes

Baseline pain scores did not differ between the two groups (3.74 vs. 4.02, $P = 0.41$). Patients assigned to ePAL reported lower pain scores at Week 4 (mean 3.16 vs. 4.28, $P = 0.010$) and Week 8 (mean 2.99 vs. 4.05, $P = 0.017$) (Table 2). Patients assigned to ePAL were more likely to experience a clinically significant improvement in pain scores during the eight-week period (35.7% vs. 16.3%, $P = 0.041$). Anxiety symptoms did not differ between the two groups at Week 4, though patients assigned to ePAL had higher anxiety symptoms (mean 7.68 vs. 5.03, $P = 0.022$) compared to the usual care group at Week 8 (Table 3). Patient-reported quality of life or barriers to pain management (BQ-II) did not differ significantly at Week 4 and Week 8.

Using mixed linear effect models to examine data longitudinally across all time points with maximum likelihood to impute missing data and controlling for baseline imbalances between the two groups, patients assigned to ePAL reported lower pain symptoms across all time points (B = −0.09, 95% CI −0.17, −0.007, $P = 0.034$), higher anxiety symptoms (B = 0.21, 95% CI 0.04−0.37, $P = 0.015$), and lower patient-reported barriers to pain management (BQ-II) (B = −0.04, 95% CI −0.1, −0.001, $P = 0.042$) (Table 4). Patient-reported QOL did not differ between the two groups longitudinally.

Table 3
Effect of ePAL on Anxiety Symptoms

Anxiety Symptoms	Intervention Mean (SD)	Control Mean (SD)	*P*-value
Baseline	6.67 (5.88)	5.9 (4.85)	0.700
Four weeks	6.71 (5.07)	5.03 (3.67)	0.260
Eight weeks	7.68 (4.96)	5.03 (3.6)	0.022
Longitudinal model	Beta (95%CI)		*P*-value
Between group (95% CI)	0.21 (0.039, 0.37)	Reference	0.015

Two-sample t-test to compare anxiety symptoms (as measured by the Generalized Anxiety Disorder (GAD-7) between the intervention and control group at four and eight weeks. Mixed linear effect models to examine study outcomes longitudinally across all timepoints.
SD = standard deviation; 95% CI = 95% confidence interval.

Table 4
Effect of ePAL on Negative Attitudes Towards Cancer Pain Treatment

Patient-Reported Barriers to Pain Management	Intervention Mean (SD)	Control Mean (SD)	*P*-value
Baseline	1.30 (0.82)	1.18 (0.82)	0.430
Four Weeks	0.96 (0.85)	1 (0.82)	0.790
Eight Weeks	1.00 (0.84)	1.15 (0.89)	0.480
Longitudinal model	Beta (95%)		*P*-value
Between Group (95% CI)	−0.037 (−0.072, −0.001)	Reference	**0.042**

Two-sample t-test to compare patient-related barriers to pain management (as measured by the Barriers Questionnaire-II (BQ-II) between the intervention and control group at four and eight weeks. Mixed linear effect models to examine study outcomes longitudinally across all timepoints.
SD = standard deviation; 95% CI = 95% confidence interval.
Bolded *P* values signify statistical significance.

Pain-related Hospital Admissions

All-cause inpatient hospital admissions did not differ significantly between the two groups (ePAL 21.4% [12/56] vs. 26.8% [15/56], $P = 0.510$). However, the rate of cancer pain-related hospitalizations was significantly lower in the ePAL group compared to those receiving usual care (7.1% [4/56] vs. 23.2% [13/56], $P = 0.018$).

All-cause inpatient admissions through the Emergency Department also did not differ significantly between the two groups (ePAL 10.7% [6/56] vs. usual care 21.4% [12/56], $P = 0.120$). However, the rate of pain-related inpatient admissions through the Emergency Department in the ePal group was significantly lower compared to the usual care group (3.6% [2/56] vs. 19.6% [11/56], $P = 0.008$).

Phone Calls Generated by ePAL

Thirty-two app-triggered phone calls to palliative care triage nurses from 20 unique intervention participants occurred during the study period, equating to an overall ratio of 0.57 calls per enrolled intervention participant. All calls occurred within 24 hours as dictated by the study protocol for moderate pain.

Discussion

The findings of this trial demonstrate that ePAL, a DTx for patients with advanced cancer, is associated with significantly lower cancer-related pain and patient-reported barriers to pain management compared to usual care. Importantly, ePAL also led to fewer pain-related hospitalizations for patients with advanced cancer. These encouraging findings underscore the potential for ePAL to improve symptom burden and care for patients with advanced cancer, warranting further testing in a multisite randomized clinical trial.

Cancer-related pain is a highly prevalent problem that is a major cause of morbidity and health care utilization in patients with advanced cancer. ePAL resulted in lower patient-reported pain, with a 26% reduction in pain scores and a significant reduction in patient-facing barriers to optimal management of cancer pain. While barriers to achieving adequate cancer-related pain control have been delineated in the literature, studies establishing the efficacy of supportive care interventions to overcome these barriers are limited.[34] Barriers to cancer-related pain control include challenges with assessing and reporting pain, patients' misperception about pain management, opioid stigma, lack of effective patient-facing education, and difficulty with adherence to medication regimen due to confusion about side effects.[35–37] Importantly, ePAL addressed many of these barriers and there was a signal towards reduction in patient-reported barriers to optimal pain management. As many patients perceive uncontrolled pain as inevitable leading to feelings of despair and holeplessness, the mere reassurance that there are interventions that can effectively control their pain and improve their quality of life can results in improvement in perceptions of pain and distress related to pain symptoms.

Perhaps the most compelling finding from this study was the impact of ePAL on pain-related hospitalizations. This finding underscores the potential for DTx utilizing AI technology as a novel intervention to reduce pain-related hospitalization, thereby improving the overall quality of care for this vulnerable population. Over 50% of hospitalizations in patients with advanced cancer are potentially avoidable due to suboptimal symptom management.[38] Thus, ePAL has the potential to both optimize care and improve resource utilization amidst a growing workforce shortage of relevant pain and palliative care specialists.

Though there has been significant progress and interest in PROs and digital health in cancer care, challenges to harnessing their full potential exist.[29] A review of oncologic PRO interventions identified significant barriers to real-world implementation related to a lack of 1) state-of-the-art means to interpret real-time PRO data, and 2) guidance on how to use PROs to drive clinically-meaningful interventions.[39] ePAL addressed these gaps by utilizing algorithms to analyze PRO data, rapidly identify the impediment to pain control, and then deploy tailored, real-time interventions to participants. Additionally, ePAL's ability to capture, display, and integrate PRO data into clinical practice may provide an opportunity to enhance real-world clinical care and efficiency of the clinical encounters. Despite the expected reduction in adherence to ePAL over time as seen with prior digital health interventions,[40] overall engagement with ePAL was encouraging, with approximately half of patients continuing to engage with ePAL throughout the eight-week period.[41–45] This level of engagement is particularly relevant in this relatively ill population of patients with advanced cancer at high risk of disease progression and death. Nonetheless, future work should explore the sustainability of the ePAL intervention effects on study outcomes beyond the eight-week engagement period. With advances in AI and technology, future digital therapeutics could also monitor patient's facial expressions and behavior that could be indicative of escalating pain or various etiologies of pain in patients with advanced cancer. Additionally, attention must be paid with increasing AI use in the medical setting to patient's privacy and protection against security breaches to ensure confidentiality.

An unexpected finding was the small but statistically significant increase in anxiety symptoms in patients receiving ePAL compared to usual care. This increase in anxiety symptoms was still in the mild-range of anxiety and did not cross the threshold of clinically significant anxiety symptoms on the GAD-7. Interestingly, prior studies have shown an increase in patient-reported distress when actively monitoring for symptoms.[46,47] This could be theoretically due to increasing attention to pain, which can exacerbate anxiety about the illness. Future work should further explore the impact of ePAL on anxiety symptoms in patients with advanced cancer and integrate strategies to address psychological distress in the context of symptom monitoring. It is worth noting that DTx have been utilized to address anxiety and psychological distress in patients with cancer.[48] Thus, future iterations of ePAL can also incorporate cognitive-behavioral strategies to reduce psychological distress in this population.

This study has several notable limitations. First, it was conducted at a tertiary care academic center with limited sociodemographic diversity, thereby limiting the generalizability of our findings to other care settings and populations. Additionally, patients with history of substance use and those with severe psychiatric or other comorbid conditions that hinders their ability to provide informed consent were excluded from the study, and thus the study findings are not generalizable to these populations. Second, ePAL was integrated into an outpatient specialty palliative care practice with substantial expertise in symptom management. Therefore, it is possible that ePAL may have a different impact on patient outcomes in other settings, including ambulatory oncology practices without access to palliative care. Third, the study staff and participants were not blinded to randomization, which may have introduced bias. Fourth, ePAL focused exclusively on pain symptoms in this trial, which may have limited our ability to detect meaningful differences in QOL. Future iterations of ePAL will incorporate active management of other symptoms such as nausea, vomiting, constipation, diarrhea, and fatigue in patients with advanced cancer. Fifth, we were limited to information about patients'

hospitalizations that were available in their EHR, and therefore our data may not have fully captured all hospitalizations in this population. Sixth, we did not collect long-term follow-up data to assess the sustainability of the intervention effects on patient-reported outcomes. Lastly, we did not collect any qualitative data to further understand barriers to engagement with ePAL, which would help inform future iterations of ePAL.

In conclusion, ePAL is the first digital therapeutic to demonstrate improvements in cancer pain, barriers to cancer pain management, and pain-related hospitalizations in patients with advanced cancer. This work demonstrates the significant promise that digital therapeutics hold for patients with cancer-related pain. In the future, we aim to study ePAL in a multicenter study, targeting populations with limited access to palliative care. Future studies will also need to assess and address impediments to ePAL use among patients from diverse demographic backgrounds and those with limited English proficiency. A future multisite trial is critical to ensure the generalizability and reliability of ePAL for improving patients' outcomes across diverse populations, and for examining factors associated with adherence to ePAL with a more robust sample size. Interestingly, it has been posited that technology could be used to help alleviate disparities in oncology care.[49] Our hope is that ePAL will further open the door to the use of AI and DTx for symptom management in patients with cancer and other serious illnesses.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, as well as drafting and revising the final manuscript.

Disclosures and Acknowledgments

Conflict of Interest: Kamdar reports stock and employment by Tuesday Health. El Jawahri reports consulting for GSK, Incyte, Novartis, and Tuesday Health, and has stock in Tuesday Health. Jethwani reports stock and employment by Decimal Health. Rinaldi reports stock in Tuesday Health. Jackson reports consulting fees and stock in Tuesday Health. Strand reports consulting fees for Tuesday Health. Kvedar reports consulting fees for Corti, GoodRx, Chronisense, Click Therapeutics, and Roche, and stock in Piction Health, MD Revolution, b.well, Sweetch, and Gomo Health. Greer reports advising for BeiGene.

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References

1. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994;330(9):592–596. https://doi.org/10.1056/NEJM199403033300902.

2. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage 2016;51(6):1070–1090.e9. https://doi.org/10.1016/j.jpainsymman.2015.12.340.

3. Breivik H, Cherny N, Collett B, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. Ann Oncol 2009;20(8):1420–1433. https://doi.org/10.1093/annonc/mdp001.

4. Mantyh PW. Cancer pain and its impact on diagnosis, survival and quality of life. Nat Rev Neurosci 2006;7(10):797–809. https://doi.org/10.1038/nrn1914.

5. Ferrell BR, Grant M, Borneman T, Juarez G, Ter Veer A. Family caregiving in cancer pain management. J Palliat Med. 1999;2(2):185–195. https://doi.org/10.1089/jpm.1999.2.185.

6. Lemay K, Wilson KG, Buenger U, et al. Fear of pain in patients with advanced cancer or in patients with chronic noncancer pain. Clin J Pain 2011;27(2):116–124. https://doi.org/10.1097/AJP.0b013e3181f3f667.

7. Wagner-Johnston ND, Carson KA, Grossman SA. High outpatient pain intensity scores predict impending hospital admissions in patients with cancer. J Pain Symptom Manage 2010;39(2):180–185. https://doi.org/10.1016/j.jpainsymman.2009.06.012.

8. Numico G, Cristofano A, Mozzicafreddo A, et al. Hospital admission of cancer patients: avoidable practice or necessary care? PLoS One 2015;10(3):e0120827. https://doi.org/10.1371/journal.pone.0120827.

9. Ferrell BR, Griffith H. Cost issues related to pain management: report from the Cancer Pain Panel of the Agency for Health Care Policy and Research. J Pain Symptom Manage 1994;9(4):221–234. https://doi.org/10.1016/0885-3924(94)90099-x.

10. Fortner BV, Demarco G, Irving G, et al. Description and predictors of direct and indirect costs of pain reported by cancer patients. J Pain Symptom Manage 2003;25(1):9–18. https://doi.org/10.1016/s0885-3924(02)00597-3.

11. Siefert ML, Bonquist TM, Berry DL, Hong F. Symptom-related emergency department visits and hospital admissions during ambulatory cancer treatment. J Community Support Oncol 2015;13(5):188–194. https://doi.org/10.12788/jcso.0134.

12. Elsayem AF, Merriman KW, Gonzalez CE, et al. Presenting symptoms in the emergency department as predictors of intensive care unit admissions and hospital mortality in a comprehensive cancer center. J Oncol Pract 2016;12(5):e554–e563. https://doi.org/10.1200/JOP.2015.009019.

13. Rocque GB, Barnett AE, Illig LC, et al. Inpatient hospitalization of oncology patients: are we missing an opportunity for end-of-life care? J Oncol Pract 2013;9(1):51–54. https://doi.org/10.1200/JOP.2012.000698.

14. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27(17):2758–2765. https://doi.org/10.1200/JCO.2008.20.8983.

15. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363(8):733–742. https://doi.org/10.1056/NEJMoa1000678.

16. Quill TE, Abernethy AP. Generalist plus specialist palliative care—creating a more sustainable model. N Engl J Med 2013;368(13):1173–1175. https://doi.org/10.1056/NEJMp1215620.

17. Kamal AH, Maguire JM, Meier DE. Evolving the palliative care workforce to provide responsive, serious illness care. Ann Intern Med 2015;163(8):637–638. https://doi.org/10.7326/M15-0071.

18. Alliance DT. Understanding DTx. Accessed May 29, 2022, https://dtxalliance.org/understanding-dtx/

19. Gustafson DH, DuBenske LL, Atwood AK, et al. Reducing symptom distress in patients with advanced cancer using an e-alert system for caregivers: pooled analysis of two randomized clinical trials. J Med Internet Res 2017;19(11):e354. https://doi.org/10.2196/jmir.7466.

20. Denis F, Lethrosne C, Pourel N, et al. Randomized trial comparing a web-mediated follow-up with routine surveillance in lung cancer patients. J Natl Cancer Inst 2017;109(9):1–9. https://doi.org/10.1093/jnci/djx029.

21. Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA 2017;318(2):197–198. https://doi.org/10.1001/jama.2017.7156.

22. Hadjiat Y, Arendt-Nielsen L. Digital health in pain assessment, diagnosis, and management: overview and perspectives. Front Pain Res (Lausanne) 2023;4:1097379. https://doi.org/10.3389/fpain.2023.1097379.

23. Mecklenburg G, Smittenaar P, Erhart-Hledik JC, Perez DA, Hunter S. Effects of a 12-Week digital care program for chronic knee pain on pain, mobility, and surgery risk: randomized controlled trial. J Med Internet Res 2018;20(4):e156. https://doi.org/10.2196/jmir.9667.

24. Babicova I, Cross A, Forman D, Hughes J, Hoti K. Evaluation of the psychometric properties of painchek (R) in UK aged care residents with advanced dementia. BMC Geriatr 2021;21(1):337. https://doi.org/10.1186/s12877-021-02280-0.

25. Hoffman HG, Doctor JN, Patterson DR, Carrougher GJ, Furness TA. Virtual reality as an adjunctive pain control during burn wound care in adolescent patients. Pain 2000;85(1-2):305–309. https://doi.org/10.1016/s0304-3959(99)00275-4.

26. Somers TJ, Winger JG, Fisher HM, et al. Behavioral cancer pain intervention dosing: results of a sequential multiple assignment randomized trial. Pain. 2023;164(9):1935–1941. https://doi.org/10.1097/j.pain.0000000000002915.

27. Zheng C, Chen X, Weng L, et al. Benefits of mobile apps for cancer pain management: systematic review. JMIR Mhealth Uhealth 2020;8(1):e17055. https://doi.org/10.2196/17055.

28. Azizoddin DR, DeForge SM, Baltazar A, et al. Development and pre-pilot testing of STAMP + CBT: an mHealth app combining pain cognitive behavioral therapy and opioid support for patients with advanced cancer and pain. Supportive Care Cancer 2024;32(2):123. https://doi.org/10.1007/s00520-024-08307-7.

29. Aapro M, Bossi P, Dasari A, et al. Digital health for optimal supportive care in oncology: benefits, limits, and future perspectives. Supportive Care Cancer Oct 2020;28(10):4589–4612. https://doi.org/10.1007/s00520-020-05539-1.

30. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin brief pain questionnaire to assess pain in cancer and other diseases. Pain 1983;17(2):197–210. https://doi.org/10.1016/0304-3959(83)90143-4.

31. Gunnarsdottir S, Donovan HS, Serlin RC, Voge C, Ward S. Patient-related barriers to pain management: the barriers questionnaire II (BQ-II). Pain 2002;99(3):385–396. https://doi.org/10.1016/S0304-3959(02)00243-9.

32. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092–1097. https://doi.org/10.1001/archinte.166.10.1092.

33. Cella DF, Tulsky DS, Gray G, et al. The functional assessment of cancer therapy scale: development and validation of the general measure. J Clin Oncol 1993;11(3):570–579. https://doi.org/10.1200/JCO.1993.11.3.570.

34. Howell D, Molloy S, Wilkinson K, et al. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. Ann Oncol 2015;26(9):1846–1858. https://doi.org/10.1093/annonc/mdv181.

35. Kwon JH. Overcoming barriers in cancer pain management. J Clin Oncol 2014;32(16):1727–1733. https://doi.org/10.1200/JCO.2013.52.4827.

36. Bulls HW, Hamm M, Wasilko R, et al. Manifestations of opioid stigma in patients with advanced cancer: perspectives from patients and their support providers. JCO Oncol Pract 2022;18(10):e1594–e1602. https://doi.org/10.1200/OP.22.00251.

37. Bulls HW, Chu E, Goodin BR, et al. Framework for opioid stigma in cancer pain. Pain 2022;163(2):e182–e189. https://doi.org/10.1097/j.pain.0000000000002343.

38. Johnson PC, Xiao Y, Wong RL, et al. Potentially avoidable hospital readmissions in patients with advanced cancer. J Oncol Pract 2019;15(5):e420–e427. https://doi.org/10.1200/JOP.18.00595.

39. Anatchkova M, Donelson SM, Skalicky AM, McHorney CA, Jagun D, Whiteley J. Exploring the implementation of patient-reported outcome measures in cancer care: need for more real-world evidence results in the peer reviewed literature. J Patient Rep Outcomes 2018;2(1):64. https://doi.org/10.1186/s41687-018-0091-0.

40. Forbes A, Keleher MR, Venditto M, DiBiasi F. Assessing patient adherence to and engagement with digital interventions for depression in clinical trials: systematic literature review. J Med Internet Res 2023;25:e43727. https://doi.org/10.2196/43727.

41. Kamalumpundi V, Saeidzadeh S, Chi NC, Nair R, Gilbertson-White S. The efficacy of web or mobile-based interventions to alleviate emotional symptoms in people with advanced cancer: a systematic review and meta-analysis. Support Care Canc 2022;30(4):3029–3042. https://doi.org/10.1007/s00520-021-06496-z.

42. Magalhaes B, Fernandes C, Martinez-Galiano JM, Santos C. Exploring the use of mobile applications by cancer patients undergoing chemotherapy: a scoping review. Int J Med Inform 2020;144:104293. https://doi.org/10.1016/j.ijmedinf.2020.104293.

43. Marthick M, McGregor D, Alison J, Cheema B, Dhillon H, Shaw T. Supportive Care Interventions for people with cancer assisted by digital technology: systematic review. J Med Internet Res 2021;23(10):e24722. https://doi.org/10.2196/24722.

44. Escriva Boulley G, Leroy T, Bernetiere C, Paquienseguy F, Desfriches-Doria O, Preau M. Digital health interventions to help living with cancer: a systematic review of participants' engagement and psychosocial effects. Psychooncology 2018;27(12):2677–2686. https://doi.org/10.1002/pon.4867.

45. Darlow S, Wen KY. Development testing of mobile health interventions for cancer patient self-management: a review. Health Informatics J 2016;22(3):633–650. https://doi.org/10.1177/1460458215577994.

46. Rosman L, Gehi A, Lampert R. When smartwatches contribute to health anxiety in patients with atrial fibrillation. Cardiovasc Digit Health J 2020;1(1):9–10. https://doi.org/10.1016/j.cvdhj.2020.06.004.

47. Mavandadi S, Benson A, DiFilippo S, Streim JE, Oslin D. A telephone-based program to provide symptom monitoring alone vs symptom monitoring plus care management for late-life depression and anxiety: a randomized clinical trial. JAMA Psychiatry 2015;72(12):1211–1218. https://doi.org/10.1001/jamapsychiatry.2015.2157.

48. Greer JA, Jacobs J, Pensak N, et al. Randomized trial of a tailored cognitive-behavioral therapy mobile application for anxiety in patients with incurable cancer. Oncologist 2019;24(8):1111–1120. https://doi.org/10.1634/theoncologist.2018-0536.

49. Gonzalez BD. Promise of mobile health technology to reduce disparities in patients with cancer and survivors. JCO Clin Cancer Inform 2018;2:1–9. https://doi.org/10.1200/CCI.17.00141.