Delivery of a Mental Health Intervention for Chronic Pain Through an Artificial Intelligence–Enabled App (Wysa): Protocol for a Prospective Pilot Study

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Abstract

Background: Patients with chronic pain often experience coexisting, long-term and debilitating mental health comorbidities such as depression and anxiety. Artificial intelligence–supported cognitive behavioral therapy (AI-CBT) interventions could offer cost-effective, accessible, and potentially effective resources to address this problem. However, there is not enough research conducted about the efficacy of AI-CBT interventions for chronic pain.

Objective: This prospective cohort study aims to examine the efficacy and use of an AI-CBT intervention for chronic pain (Wysa for Chronic Pain app, Wysa Inc) using a conversational agent (with no human intervention). To the best of our knowledge, this is the first such study for chronic pain using a fully-automated, free-text–based conversational agent.

Methods: Participants with self-reported chronic pain (n=500) will be recruited online on a rolling basis from April 2022 through posts on US-based internet communities within this prospective cohort. Informed consent is received from participants within the app, and the Wysa for Chronic Pain intervention is delivered remotely for 8 weeks. Outcome measures including a numeric pain rating scale and Patient-Reported Outcomes Measurement Information System–Pain Interference, Generalized Anxiety Disorder–7, and Patient Health Questionnaire–9 questionnaires administered to test the effectiveness of the intervention on reducing levels of pain interference, depression, and anxiety. The therapeutic alliance created with the conversational agent will be assessed through the Working Alliance Inventory–Short Revised instrument. Retention and use statistics will be observed for adherence and engagement.

Results: The study will open for recruitment in April 2022, and data collection is expected to be completed by August 2022. The results for the primary outcomes are expected to be published by late 2022.

Conclusions: Mental health conversational agents driven by artificial intelligence could be effective in helping patients with chronic pain learn to self-manage their pain and common comorbidities like depression and anxiety. The Wysa for Chronic Pain app is one such digital intervention that can potentially serve as a solution to the problems of affordability and scalability associated with interventions that include a human therapist. This prospective study examines the efficacy of the app as a treatment solution for chronic pain. It aims to inform future practices and digital mental health interventions for individuals with chronic pain.

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Introduction

Background

Chronic pain is a long-term debilitating health concern that affects physical, psychological, cognitive, and social functioning [1-3] resulting in significant health care costs [4]. According to the American Academy of Pain Medicine, more than 1.5 billion people around the world have chronic pain [5]. At least 116 million US adults—more than the number affected by heart disease, diabetes, and cancer combined—live with common chronic pain conditions [6]. Research also suggests that 13% to 50% of adults in the United Kingdom are affected by chronic pain, with 10% to 14% experiencing moderate-to-severe disabling chronic pain [1,7]. The total health care cost of chronic pain ranges from $560 billion to $635 billion annually in the United States [8]. Chronic pain conditions are comorbid with depression, anxiety, sleep disturbances, fatigue, neurocognitive changes, and other symptoms [9].

Chronic Pain and Mental Health

Mental health difficulties such as depression and anxiety are among the most common comorbidities present with chronic pain [10,11]. Between 20% to 50% of patients with chronic pain have comorbid depression [1,12], and patients with severe pain are more likely to be depressed [13]. Chronic pain often leads to patients being unable to focus on normal day-to-day activities and being constantly distracted by their pain, which is associated with poor mental health [14]. Moreover, patients experiencing from pain-related depression and anxiety are also likely to have worse outcomes from chronic pain [15,16]. Numerous studies have also suggested that individuals living with chronic pain are 2 to 3 times more susceptible to suicidal ideation and suicidal behaviors [17-19].

Similarly, research suggests that anxiety and fear arising from chronic pain are likely to interfere with recovery from the pain [15]. This has been observed with the development of maladaptive behaviors including catastrophizing [20], fear avoidance, and the reduction in helpful activities [21]. Chronic pain shares a bidirectional relationship with mental health [22], and the resolution of depression and anxiety are important components in the effective management of chronic pain.

Pain Management

Chronic pain management through psychotherapeutic techniques is important since a commonly observed impact of chronic pain is the reduction in coherent behavior due to the consistent threat of pain [23]. Individuals report experiencing dissembling, with the pain moving beyond an acute experience and evolving into the prolonged state of a disabling disease [24].

Psychological treatments for chronic pain are usually cognitive or behavioral strategies aimed at reducing mental suffering and promoting active engagement with life [23]. They serve to overcome the pain perseverance paradox, which is the occurrence of self-defeating behaviors by those living with chronic pain [25]. Studies have demonstrated that treating mental health concerns such as depression can often result in better outcomes for treatment of pain [26]. Treatment strategies include behavioral techniques of relaxation, biofeedback, contingency management, exposure, and cognitive behavioral techniques that typically include programs with components of education, coping strategies training, and cognitive therapy [23].

Since depression in patients with chronic pain often goes unrecognized, it therefore remains untreated [27]. There is also a significant gap in the needs of patients with chronic pain and the care provided due to lack of therapeutic resources, acute stress on outpatient facilities [28], and worsening mental health experienced during the ongoing COVID-19 pandemic [29,30]. Several barriers to self-management of pain have been identified that include lack of support and resources, lack of time or fear of worsening the pain by engaging in physical activities, and difficulty in patient-physician interactions [31,32].

Research suggests that factors like support and encouragement from caregivers, access to a variety of self-management techniques, and treatment of depression can serve as facilitators in improving self-pain management [32]. Research also indicates the positive impact of a therapeutic alliance in improving the impact of treatment for individuals with chronic pain [33,34].

Digital Mental Health Interventions for Chronic Pain

Digital mental health interventions can potentially address the issues of accessibility, rising health care costs, low availability of therapeutic care, and other barriers [35,36] associated with standard in-person treatments for chronic pain [37] and mental health [38,39]. Studies have reported that digitally delivered mental health interventions have a positive role to play in the self-management of depression and anxiety [40,41] and have been found effective in reducing the impact of chronic pain on the quality of life [42].

Currently, one way in which these digital mental health interventions address the barriers of accessibility is by augmenting digitally delivered tools with human coaches [43-46]. However, the success of this approach is dependent on the availability and degree of involvement of therapists, which influences the cost and scalability of such interventions. Another approach that can effectively tackle the problems of scalability and cost is an artificial intelligence (AI)-enabled conversational agent that mimics human dialog with users [47]. Health care interventions involving artificial intelligence–supported cognitive behavioral therapy (AI-CBT) conversational agents, aimed at reducing symptoms or improving self-management of mental health conditions and increasing mental well-being, are increasingly being used with positive outcomes [48-50]. Many of these conversational agent–based interventions have shown significant improvements on measures of common mental health problems like depression, psychological distress, anxiety, fear of heights, and loneliness [43,51-56]. Also, these studies suggest a positive correlation between engagement level with the conversational agent and reduction in psychological distress. However, there is a need for more evidence-based studies that focus on the efficacy of the interventions driven by AI-enabled conversational agents [57,58].

Wysa for Chronic Pain

The intervention proposed in this study employs one such AI-CBT intervention, the Wysa for Chronic Pain app (Wysa Inc), that uses an AI-enabled conversational agent with a

free-text conversational interface. It listens and responds to the user's distress by recommending techniques and self-care tools based on CBT, behavioral reinforcement, and mindfulness, among other evidence-based therapies. Wysa supports the user in dealing with multiple challenges such as anxiety, sleep, low energy, motivation, loss, and pain. The app has been shown to be effective through mean improvements in symptoms of major depression (Patient Health Questionnaire–9 item [PHQ-9]) among users who were highly engaged with the app when compared to a low engagement group [59].

This is an exploratory study following a quantitative research design that aims to study the efficacy of a digital mental health intervention program for chronic pain when delivered solely by a conversational agent. The duration of the study is 8 weeks, and the efficacy will be calculated through the use of standardized statistical measures.

Chronic Pain app (a specific version of the publicly available Wysa app). This is an anonymous study where the participants enroll themselves by installing the app on their mobile phones and agree to participate in the study. We will restrict this version of the app to the Apple App Store and Google Playstore in the United States. Once enrolled in the program, participants will complete an assessment at the start of the study (comprising 4 measures), complete an 8-week program with the AI-led conversational agent during which another assessment (5 measures) will be taken halfway through the program, and complete the final set of assessments (5 measures) at the end of 8 weeks (Figure 1). Postintervention changes in pain interference will serve as the primary outcome for this study. Our secondary outcomes will include postintervention changes in depression and anxiety, as well as the therapeutic alliance between the user and conversational agent. The app will be free and available 24×7 to the participants.

Methods

Overview

In this study, 500 individuals living with chronic pain will be recruited and administered an 8-week program on the Wysa for

Figure 1. Timeline of the study. NPRS: numerical pain rating scale; PROMIS-PI: Patient-Reported Outcomes Measurement Information System Pain Inference; GAD-7: Generalized Anxiety Disorder, 7-item; PHQ-9: Patient Health Questionnaire, 9-item; WAI-SR: Working Alliance Inventory–Short Revised; CBT: cognitive behavioral therapy.
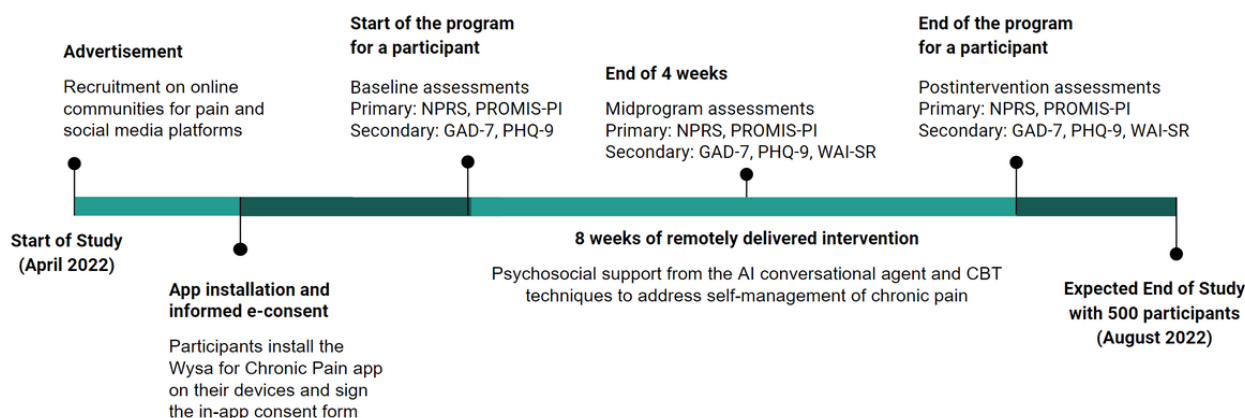
Screening

Eligibility criteria include being aged 18 years or older, experiencing chronic pain, and not receiving any form of professional mental health support. Individuals who do not self-report presenting with chronic pain will be excluded as a part of the recruitment criteria. The data of participants who score below 4 points on a 1-item numeric pain rating scale (NPRS) at the first assessment will be excluded from the analysis [60,61].

Recruitment

Participants are currently being recruited on a rolling basis from US-based internet communities centered around the experiences of living with chronic pain. We will share information about the research study by posting on social media platforms. The purpose of these posts is to introduce potential participants to the Wysa for Chronic Pain app, inform them of the aims of this research study, and subsequently invite them to download the

app on their devices. All participants will need to have an Android or iOS phone and have access to the internet while using the app. Interested participants will be screened on the basis of self-reported scores on the NPRS and their responses to a set of questions that will collect baseline demographics (age range), type of chronic pain, and the time since onset.

Ethics

Participants will remain anonymous for the duration of the study and are being recruited from a US-only population. After participants download the Wysa for Chronic Pain app and agree to the app's Terms of Service and Privacy Policy, they will opt in to the study using a consent screen following Wysa's security and compliance guidelines. The consent screen states the purpose of the trial, potential risks and benefits associated with participation in the trial study, and mechanism for opting out of the study at any time. They will also be informed of the ways in which the usage data generated from their participation in the study could potentially be used.

Intervention

A separate version of the publicly available Wysa app, Wysa for Chronic Pain, is being used for this study. This is a conversational agent–only version (ie, it does not include one-on-one human coach support, which is an option with the publicly available app). The AI-enabled free-text conversational agent offers participants a space to talk about their pain, depression, anxiety, and other issues arising from disturbances due to chronic pain. The conversational agent acts as a companion in their journey (Figure 2) of learning to live with pain and helps them build resilience by guiding them through self-care tools based on CBT and other techniques. The goal of the intervention is to improve the quality of life for the user as their ability to manage the pain improves.

The conversational agent builds an 8-week road map for the user and does daily morning and evening check-ins to encourage adherence to the program (Figure 3). Users are encouraged to set a daily goal for themselves based on what gives them joy, and ideas are suggested to help them engage in these activities, even if in a small way. Completing these activities on a regular basis gives the users a sense of joy and achievement and fosters the belief that they are capable of simultaneously managing their pain and living a normal life [62,63].

Steps included in the user's journey includes participating in activities that comprise a mix of positive psychology, acceptance and commitment therapy, and CBT techniques that will be conducted in an organized, weekly fashion to encourage the development of skills aimed at coping with pain and the reduction of depression and anxiety symptoms.

In contrast to traditional worksheets or psychoeducation materials common in digital mental health [64,65], all therapeutic interventions in this study are conducted in a conversational format via the Wysa AI-enabled agent, which guides the user through the program in order to create a sense of support similar to in-person therapy [66]. The conversational nature of the interaction is meant to engage the user more, thereby increasing adherence to the effective intervention for chronic pain. The AI-enabled conversational agent provides empathetic support to the user, answers their questions, and guides them through uncertainty and a potential lack of trust in the bot as they proceed with their journey [67]. A rapport is built between the user and Wysa by the conversational agent's ability to add personalized elements to the conversation, including welcoming messages, addressing the user by the nickname chosen by them during onboarding, and providing clarifying examples. All these are important elements of a therapeutic conversation [68].

The app provides the user an open space for conversation by giving the user the ability to converse with the conversational agent through free text (Figure 4). The free-text input enables flexibility and genuineness in the conversation, and allows the user to speak their mind. The app uses natural language processing, natural language understanding, and machine learning to interpret the user's messages, and provides the user with supportive listening and appropriate responses to unique situations using interventive techniques, thus creating an efficient interactive environment [55,69]. The conversational agent provides users with empathetic support in a nonjudgmental environment, an important aspect of health care [70]. The AI uses custom models trained by data scientists, clinicians, and conversation designers that detect different aspects of what the user is conveying [71].

Figure 2. Onboarding conversation with the conversational agent that sets the expectation for the program and administers the first assessment.
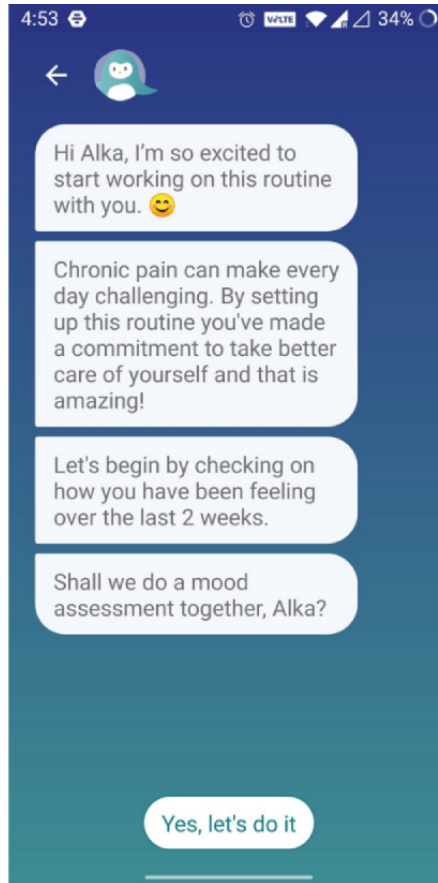

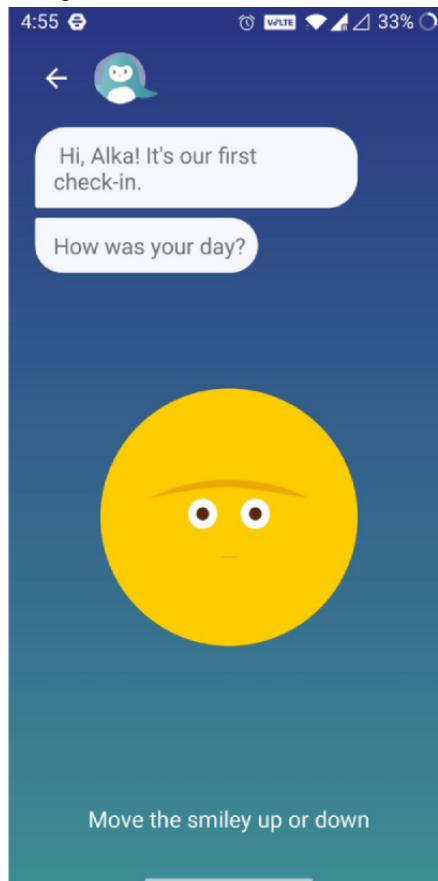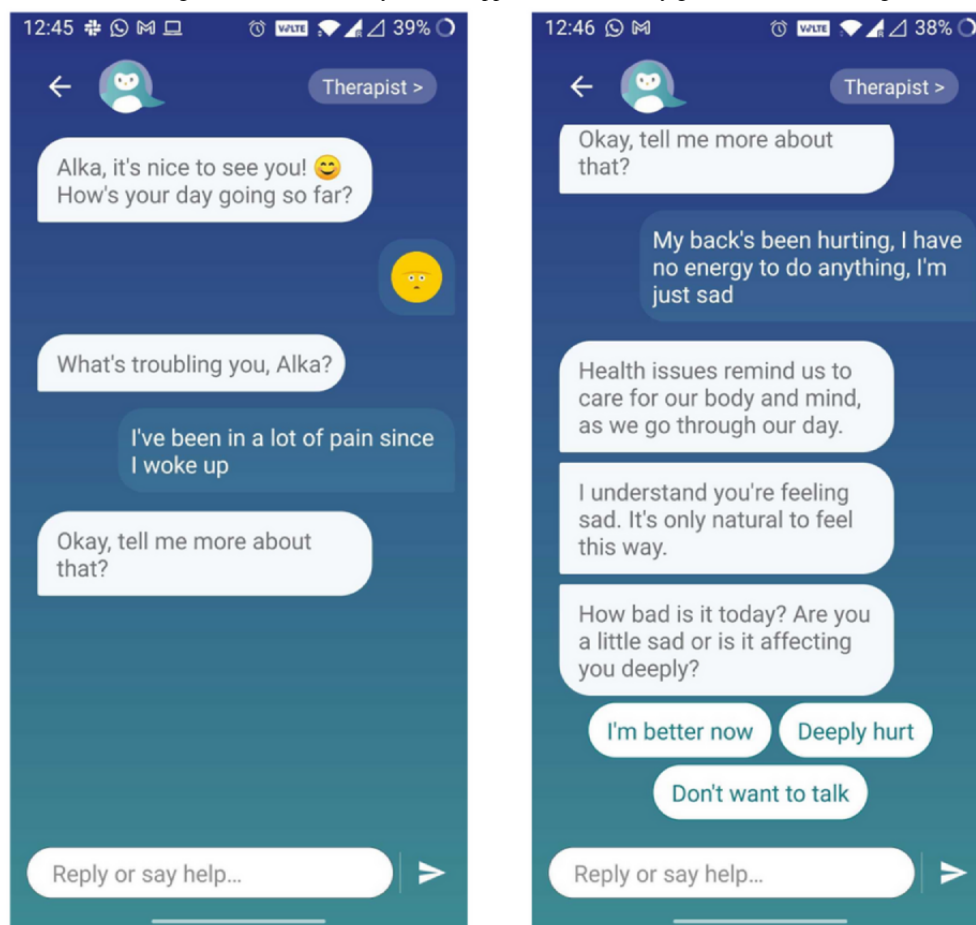**Figure 3.** First mood check-in with the conversational agent.

Figure 4. Example screenshots showing the conversational style of the app and the flexibility given to the user through free-text inputs.

Primary Outcome Measure

Study participants will complete the self-administered measures, NPRS and the Patient-Reported Outcomes Measurement Information System–Pain Inference (PROMIS-PI) short form 6b, at the baseline, midpoint, and after the completion of the study. Both measures will be administered through the Wysa app and will be completed on the participants' own devices.

Numeric Pain Rating Scale

The NPRS is a unidimensional measure of pain intensity in adults with chronic pain [72]. It is a segmented 11-point numeric scale in which the respondent rates the intensity of their pain on an integer scale of 0 (no pain) to 10 (worst pain imaginable). The minimal clinically important change score is taken to be a 2 point reduction [73,74].

Patient-Reported Outcomes Measurement Information System–Pain Interference

The 6-item PROMIS-PI was developed by the National Institutes of Health to measure the negative effects of pain on physical, mental, cognitive, emotional, social, and recreational functioning. This study uses a 6-item pain interference scale that aims to measure the extent to which pain causes a hindrance in various aspects of an individual's life, including those related to activities done for fun as well as day-to-day activities. A 5-point ordinal rating scale is used with options being 1 (not at all), 2 (a little bit), 3 (somewhat), 4 (quite a bit), and 5 (very much). The raw scores are converted to T-scores based on a

scoring manual. Although the PROMIS-PI forms are relatively new, their responsiveness has been found to be comparable to legacy pain measures [75]. A reduction in PROMIS-PI scores at the end of the study will indicate a positive impact of the intervention. Minimal clinically important change score is defined as at least 2.0 points for pain interference [76].

Secondary Outcome Measures

In order to observe ancillary impacts of the intervention, study participants will complete 2 additional self-administered measures (PHQ-9 and Generalized Anxiety Disorder, 7-item [GAD-7]) at the baseline, midpoint, and after the completion of the study. The Working Alliance Inventory–Short Revised (WAI-SR) will be administered at the midpoint and after completion of the study only. All measures will be administered through the Wysa app itself and will be completed on the participants' own devices.

Generalized Anxiety Disorder

GAD-7 is a widely adopted, standardized, and validated 7-item self-report questionnaire developed to assess symptoms of generalized anxiety disorder. This 7-item anxiety scale has been found to have good reliability as well as construct, procedural, and factorial validity [77]. This assessment asks the participants to assess themselves over the last 2 weeks with questions about whether they felt nervous or anxious, had trouble relaxing, became easily annoyed or irritated, etc. The response categories include 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The final score is calculated by

summing over the 7 questions, and scores of 5, 10, and 15 are taken as the cutoff points for mild, moderate, and severe anxiety, respectively. A reduction in the GAD-7 score at the end of the study will indicate a positive impact of the intervention. Clinically meaningful effect size is defined as at least 4.0 points for the GAD-7 [78].

Patient Health Questionnaire

PHQ-9 is a widely used, standardized, validated 9-item survey assessment tool for depression that has been shown to be valid and reliable as a longitudinal clinical tool [79]. It has demonstrated high criterion validity among populations with high rates of physical distress and has been found to be valid for diverse modalities of administration, including those via touchscreens [80]. This assessment asks the participants to assess themselves over the last 2 weeks with questions about whether they felt pleasure in doing things, felt tired or having little energy, had thoughts of hurting themselves, etc. The response categories and associated numerical scores are identical to that of GAD-7. The overall score is calculated by summing over the 9 questions and is used to monitor the severity of depression and response to treatment. A reduction in the PHQ-9 scores at the end of the study will indicate a positive impact of the intervention. Clinically meaningful effect size is defined as at least 5.0 points for the PHQ-9 [79].

Working Alliance Inventory–Short Revised

The WAI-SR is a well-established measure of therapeutic alliance, consisting of a total score and 3 subscales: bond, goal, and task [81]. This questionnaire asks the participants 12 questions related to whether the therapy gave them new ways of looking at their problem, whether their therapist cares for and respects them, and whether they agree with their therapist on the goals set for them. The response categories lie on a 5-point Likert scale and include 1 (seldom), 2 (sometime), 3 (often), 4 (very often), and 5 (always). Ratings are summed at the end, with a higher total indicating better therapeutic alliance. The WAI-SR will be administered at the end of the study via the app's conversational interface, in which the word therapist will be changed to Wysa. This measure demonstrates high internal consistency (Cronbach α>.90) [82]. Mean total scores of 3.59 (out of 5) are considered high [83].

Statistical Analysis

We will use the Wilcoxon signed-rank test to measure the efficacy of the intervention by comparing baseline and postintervention assessment scores on the NPRS, GAD-7, and PHQ-9 scales. The Wilcoxon signed-rank test is a nonparametric statistical hypothesis test used to compare the differences between 2 populations using a set of matched samples. We will also use the Wilcoxon signed-rank test for measuring the median of therapeutic alliance using the WAI-SR scale. We chose this test because we believe that our data will not be normally distributed, in which case a nonparametric test is more suitable. Finally, we will do a paired *t* test for measuring if the intervention resulted in any significant changes on the PROMIS-PI scale since its scores are mapped to T-scores. Rolling and ongoing recruitment will mediate any potential

concerns regarding the power of the study and the multiple testing problem where Type I errors may get inflated.

Results

Recruitment for this study will begin in April 2022 and continue on a rolling basis until 500 participants have been recruited. The baseline, midpoint, and postintervention assessment data for participants who have completed their 8-week intervention will be evaluated to determine if the intervention had any significant effect on their pain interference, depression, and anxiety scales. Although participants are encouraged to check in twice a day, there is no mandate for continuation in the program. Final outcomes will be based on end of program assessments, and engagement is evaluated across the cohort to evaluate efficacy in a real-world use setting. Another round of recruitment may be needed if the retention rate is low. App use, engagement, and retention will also be assessed to determine the acceptability of an AI-only conversational agent to support chronic pain management. From this pilot, we hope to learn more about what frequency and how many check-ins can be considered as sufficient use of the app so as to have desirable outcomes for the user. Data collection for all participants is expected to be completed by August 2022 and results to be published by late 2022.

Discussion

Summary

To the best of our knowledge, this is the first study to assess the efficacy of a fully automated, free-text–based conversational agent as an assistant for chronic pain patients. Prior to this, Hauser-Ulrich et al [84] evaluated the efficacy and acceptance of the Smartphone-Based Health Care Chatbot to Promote Self-Management of Chronic Pain (SELMA) in pain self-management for chronic pain patients. Some of the shortcomings of SELMA, as pointed out by its users, were the conversation being too structured, there not being enough answer options, and no ability to write free text. In addition, the notifications were sent at a fixed time and there was no way to personalize the app.

Wysa for Chronic Pain overcomes these shortcomings. Moreover, apart from using a conversational flow tailored for chronic pain, it also provides participants with a wide array of self-care tools they can use to deal with other issues like insomnia, depression, anxiety, and negative thoughts anytime they want [59,85,86]. Wysa for Chronic Pain has proven high engagement and efficacy when the intervention uses a conversational agent enhanced by a human coach [87]. This study aims to assess the efficacy of this intervention using the conversational agent alone. The quality of the therapeutic alliance built between the user and the conversational agent will also be assessed, which will further inform the utility of digital mental health interventions.

Treatment of chronic pain often requires a multidisciplinary and multidimensional approach, targeting both the physical and psychological aspects of the disease. Many techniques like behavioral activation, mindfulness exercises, CBT, interpersonal

psychotherapy, and psychoeducational tools have been tried for different kinds of pain, with each showing promise for different aspects of pain management [88]. This is one of the reasons why digital health interventions are becoming increasingly popular as they remove the barriers of experienced disrespect, distrust, and dismissal encountered while seeking care for chronic pain [89]. There have been several efforts at building digital health interventions for chronic pain and studying their efficacy for various kinds of patient groups. While many have shown promising results for different aspects of pain management, most of them involved human therapists [45,46], focused on passive consumption of psychoeducational content [45,90], or required an additional device [91,92]. Any requirement of a therapist or an additional device greatly limits the scalability and accessibility of a digital mental health intervention, and passive consumption of psychoeducational content isn't interactive, and hence, may not be very engaging [57].

To address these challenges, this study proposes to investigate the efficacy of a conversational agent–led intervention for chronic pain without the need for human coaches or special devices. The Wysa for Chronic Pain app involves no human coach in the loop, but the free-text–based AI-enabled conversational agent is capable of understanding and responding to a user's messages like a human therapist would. The advantages of using a digital mental health conversational agent like Wysa are manifold. First, therapy and self-care tools grounded in CBT, mindfulness, and other evidence-based therapies become immediately accessible to the patient via their mobile phone. Second, the strain on human resources is reduced. Third, anonymity allows patients to share their thoughts and feelings more freely, thereby increasing alliance. Fourth, especially in the context of chronic pain, when even routine activities seem overwhelming, a mobile assistant puts the resources literally in the user's hands and takes away the effort, stress, and additional challenges required to go meet a therapist. Finally, the conversational agent also acts like a companion who is always there to talk to [93].

Another facet of the treatment for chronic pain includes the therapeutic alliance between the individual and the support system. Emerging evidence for chronic musculoskeletal pain indicates that a strong therapeutic alliance may improve pain outcomes [94]. Therapeutic alliance was consistently a predictor of outcome in a study with 182 patients with lower back pain that assessed function, global perceived effect of treatment, pain, and disability [95]. Another study showed that enhanced therapeutic alliance combined with treatment led to clinically meaningful improvements in pain intensity and muscle pain sensitivity in patients with chronic low back pain [96]. This study looks at the levels of therapeutic alliance formed with the AI-enabled conversational agent and the impact on treatment outcomes for the participants.

Strengths and Limitations

A challenge associated with most digital mental health interventions is ensuring adherence and engagement [90].

Adherence is key to benefiting from a self-management program. To address this potential problem and promote adherence, the app has been built using the principles of behavioral activation, which are supported conversationally and have specific customizations for chronic pain [87].

To encourage participation, the study has intentionally been structured to be anonymous. The app does not require the creation of an account nor does it ask for personal identification data (name, age, location, etc). Any sensitive information, if provided accidentally by a participant in a conversation, is identified and redacted by an algorithm to prevent retention in the system. This kind of anonymity may promote trust in the app among the users and encourage them to feel more open and engage with the conversational agent. It is only available in English, which is a limitation of the service.

Although recruitment for this study is being done from online communities of people living with chronic pain, one challenge that remains is the inability to verify chronic pain in the cohort recruited. All participants will be self-referred, thus making it difficult to assess whether they satisfy the inclusion criteria. In addition, their presence in online communities oriented to the support of pain may indicate sampling bias toward individuals with a greater willingness to learn about pain self-management [97]. Another potential limitation of this study may be the self-reported nature of the assessments, which may indicate subjective efficaciousness due to the absence of physician-interventive metrics for change. Self-reporting also involves the risk of random answers offered by some participants. We will examine the data for outliers (any data points that lie 2 to 3 standard deviations away from the mean) and use an appropriate statistical methodology to improve data quality.

Conclusions

Chronic pain is one of the leading causes of long-term disability in the world. It is a complex problem with roots in social, economic, physical, and psychological aspects and affects more than 1.5 billion people worldwide. Treatment is difficult, and it often requires continuous pain management. Depression and anxiety are the most common comorbidities occurring with chronic pain, and psychological interventions have been shown to result in better outcomes for treatment of chronic pain. Digital mental health solutions make these interventions accessible and affordable. This study describes a novel AI-CBT intervention, the Wysa for Chronic Pain app, which is completely led by a free-text–based, AI-enabled conversational agent. The intervention takes the user through a variety of techniques and self-care tools grounded in CBT and mindfulness, which enable the user to learn how to self-manage their pain on a regular basis. The results from this study will be important in understanding the efficacy of such an intervention that can potentially serve as a scalable and cost-effective resource for chronic pain patients around the globe.

Conflicts of Interest

CS and TM report being employed by and owning equity in Wysa Inc. MG reports being employed by Wysa Inc.

References

1. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006 May;10(4):287-333 [FREE Full text] [doi: 10.1016/j.ejpain.2005.06.009] [Medline: 16095934]

2. Nicholson B, Verma S. Comorbidities in chronic neuropathic pain. Pain Med 2004 Mar 01;5 Suppl 1(suppl 1):S9-S27 [FREE Full text] [doi: 10.1111/j.1526-4637.2004.04019.x] [Medline: 14996227]

3. Demyttenaere K, Bruffaerts R, Lee S, Posada-Villa J, Kovess V, Angermeyer M, et al. Mental disorders among persons with chronic back or neck pain: results from the World Mental Health Surveys. Pain 2007 Jun;129(3):332-342 [FREE Full text] [doi: 10.1016/j.pain.2007.01.022] [Medline: 17350169]

4. Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain 2012 Aug;13(8):715-724. [doi: 10.1016/j.jpain.2012.03.009] [Medline: 22607834]

5. Gardner J, Sachdeva H. Causes of pain worldwide. In: Abd-Elsayed A, editor. Pain: A Review Guide. Cham: Springer International Publishing; 2019:1191-1192.

6. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J Pain 2008 Oct;9(10):883-891. [doi: 10.1016/j.jpain.2008.05.005] [Medline: 18602869]

7. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open 2016 Jun 20;6(6):e010364 [FREE Full text] [doi: 10.1136/bmjopen-2015-010364] [Medline: 27324708]

8. Simon LS. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. J Pain Pall Care Pharmacother 2012 Jul 05;26(2):197-198 [FREE Full text] [doi: 10.3109/15360288.2012.678473]

9. Dahan A, van Velzen M, Niesters M. Comorbidities and the complexities of chronic pain. Anesthesiology 2014 Oct;121(4):675-677 [FREE Full text] [doi: 10.1097/ALN.0000000000000402] [Medline: 25099749]

10. Fishbain DA. Approaches to treatment decisions for psychiatric comorbidity in the management of the chronic pain patient. Med Clin North Am 1999 May;83(3):737-760 [FREE Full text] [doi: 10.1016/s0025-7125(05)70132-2]

11. Romano JM, Turner JA. Chronic pain and depression: does the evidence support a relationship? Psychol Bull 1985;97(1):18-34 [FREE Full text] [doi: 10.1037/0033-2909.97.1.18]

12. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012 Jul;380(9836):37-43. [doi: 10.1016/S0140-6736(12)60240-2]

13. de Heer EW, Ten Have M, van Marwijk HW, Dekker J, de Graaf R, Beekman AT, et al. Pain as a risk factor for common mental disorders. Results from the Netherlands Mental Health Survey and Incidence Study-2: a longitudinal, population-based study. Pain 2018 Apr 15;159(4):712-718 [FREE Full text] [doi: 10.1097/j.pain.0000000000001133] [Medline: 29252911]

14. Eccleston C. Chronic pain and distraction: an experimental investigation into the role of sustained and shifting attention in the processing of chronic persistent pain. Behav Res Ther 1995 May;33(4):391-405. [doi: 10.1016/0005-7967(94)00057-q]

15. Boersma K, Linton S. Expectancy, fear and pain in the prediction of chronic pain and disability: a prospective analysis. Eur J Pain 2006 Aug;10(6):551-557 [FREE Full text] [doi: 10.1016/j.ejpain.2005.08.004] [Medline: 16199189]

16. Nijrolder I, van der Windt D, van der Horst H. Prediction of outcome in patients presenting with fatigue in primary care. Br J Gen Pract 2009 Apr 01;59(561):e101-e109 [FREE Full text] [doi: 10.3399/bjgp09X420329] [Medline: 19341545]

17. Tang NKY, Crane C. Suicidality in chronic pain: a review of the prevalence, risk factors and psychological links. Psychol Med 2006 May;36(5):575-586. [doi: 10.1017/S0033291705006859] [Medline: 16420727]

18. Racine M. Chronic pain and suicide risk: a comprehensive review. Prog Neuropsychopharmacol Biol Psych 2018 Dec 20;87(Pt B):269-280 [FREE Full text] [doi: 10.1016/j.pnpbp.2017.08.020] [Medline: 28847525]

19. Androulakis XM, Guo S, Zhang J, Sico J, Warren P, Giakas A, et al. Suicide attempts in US veterans with chronic headache disorders: a 10-year retrospective cohort study. J Pain Res 2021 Aug;14:2629-2639 [FREE Full text] [doi: 10.2147/JPR.S322432] [Medline: 34466030]

20. Peres MFP, Lucchetti G. Coping strategies in chronic pain. Curr Pain Headache Rep 2010 Oct 3;14(5):331-338 [FREE Full text] [doi: 10.1007/s11916-010-0137-3] [Medline: 20680705]

21. Wakaizumi K, Yamada K, Oka H, Kosugi S, Morisaki H, Shibata M, et al. Fear-avoidance beliefs are independently associated with the prevalence of chronic pain in Japanese workers. J Anesth 2017 Apr 3;31(2):255-262 [FREE Full text] [doi: 10.1007/s00540-016-2303-1] [Medline: 28050703]

22. Ang DC, Bair MJ, Damush TM, Wu J, Tu W, Kroenke K. Predictors of pain outcomes in patients with chronic musculoskeletal pain co-morbid with depression: results from a randomized controlled trial. Pain Med 2010 Apr;11(4):482-491. [doi: 10.1111/j.1526-4637.2009.00759.x] [Medline: 20002592]

23. Eccleston C, Morley S, Williams A. Psychological approaches to chronic pain management: evidence and challenges. Br J Anaesth 2013 Jul;111(1):59-63 [FREE Full text] [doi: 10.1093/bja/aet207] [Medline: 23794646]

24. Chapman CR, Gavrin J. Suffering: the contributions of persistent pain. Lancet 1999 Jun;353(9171):2233-2237 [FREE Full text] [doi: 10.1016/S0140-6736(99)01308-2]

25. Eccleston C. A normal psychology of everyday pain. Int J Clin Pract Suppl 2013 Jan(178):47-50 [FREE Full text] [doi: 10.1111/ijcp.12051] [Medline: 23163549]

26. Mossey JM, Gallagher RM. The longitudinal occurrence and impact of comorbid chronic pain and chronic depression over two years in continuing care retirement community residents. Pain Med 2004 Dec 01;5(4):335-348 [FREE Full text] [doi: 10.1111/j.1526-4637.2004.04041.x] [Medline: 15563319]

27. Lee H, Choi EJ, Nahm FS, Yoon IY, Lee PB. Prevalence of unrecognized depression in patients with chronic pain without a history of psychiatric diseases. Korean J Pain 2018 Apr 30;31(2):116-124 [FREE Full text] [doi: 10.3344/kjp.2018.31.2.116] [Medline: 29686810]

28. Eccleston C, Blyth FM, Dear BF, Fisher EA, Keefe FJ, Lynch ME, et al. Managing patients with chronic pain during the COVID-19 outbreak: considerations for the rapid introduction of remotely supported (eHealth) pain management services. Pain 2020 May;161(5):889-893 [FREE Full text] [doi: 10.1097/j.pain.0000000000001885] [Medline: 32251203]

29. Xiong J, Lipsitz O, Nasri F, Lui LM, Gill H, Phan L, et al. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. J Affect Disord 2020 Dec 01;277:55-64 [FREE Full text] [doi: 10.1016/j.jad.2020.08.001] [Medline: 32799105]

30. Vindegaard N, Benros ME. COVID-19 pandemic and mental health consequences: systematic review of the current evidence. Brain Behav Immun 2020 Oct;89:531-542 [FREE Full text] [doi: 10.1016/j.bbi.2020.05.048] [Medline: 32485289]

31. Al-Mahrezi A. Towards effective pain management: breaking the barriers. Oman Med J 2017 Sep;32(5):357-358 [FREE Full text] [doi: 10.5001/omj.2017.69] [Medline: 29026465]

32. Bair MJ, Matthias MS, Nyland KA, Huffman MA, Stubbs DL, Kroenke K, et al. Barriers and facilitators to chronic pain self-management: a qualitative study of primary care patients with comorbid musculoskeletal pain and depression. Pain Med 2009 Oct 01;10(7):1280-1290 [FREE Full text] [doi: 10.1111/j.1526-4637.2009.00707.x] [Medline: 19818038]

33. Hall A, Ferreira P, Maher C, Latimer J, Ferreira M. The influence of the therapist-patient relationship on treatment outcome in physical rehabilitation: a systematic review. Phys Ther 2010 Aug;90(8):1099-1110 [FREE Full text] [doi: 10.2522/ptj.20090245] [Medline: 20576715]

34. Schönberger M, Humle F, Zeeman P, Teasdale TW. Working alliance and patient compliance in brain injury rehabilitation and their relation to psychosocial outcome. Neuropsychol Rehabil 2006 Jun;16(3):298-314 [FREE Full text] [doi: 10.1080/09602010500176476] [Medline: 16835153]

35. Rosser BA, Vowles KE, Keogh E, Eccleston C, Mountain GA. Technologically-assisted behaviour change: a systematic review of studies of novel technologies for the management of chronic illness. J Telemed Telecare 2009 Oct 08;15(7):327-338 [FREE Full text] [doi: 10.1258/jtt.2009.090116] [Medline: 19815901]

36. Heapy AA, Higgins DM, Cervone D, Wandner L, Fenton BT, Kerns RD. A systematic review of technology-assisted self-management interventions for chronic pain. Clin J Pain 2015;31(6):470-492. [doi: 10.1097/ajp.0000000000000185]

37. Gardiner P, D'Amico S, Luo M, Haas N. An innovative electronic health toolkit (our whole lives for chronic pain) to reduce chronic pain in patients with health disparities: open clinical trial. JMIR Mhealth Uhealth 2020 Mar 30;8(3):e14768 [FREE Full text] [doi: 10.2196/14768] [Medline: 32224487]

38. Kretzschmar K, Tyroll H, Pavarini G, Manzini A, Singh I, NeurOx Young People's Advisory Group. Can your phone be your therapist? Young people's ethical perspectives on the use of fully automated conversational agents (chatbots) in mental health support. Biomed Inform Insights 2019 Mar 05;11:1178222619829083 [FREE Full text] [doi: 10.1177/1178222619829083] [Medline: 30858710]

39. Firth J, Torous J, Nicholas J, Carney R, Rosenbaum S, Sarris J. Can smartphone mental health interventions reduce symptoms of anxiety? A meta-analysis of randomized controlled trials. J Affect Disord 2017 Dec 15;218:15-22 [FREE Full text] [doi: 10.1016/j.jad.2017.04.046] [Medline: 28456072]

40. Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlöf E. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. Cogn Behav Ther 2018 Jan;47(1):1-18. [doi: 10.1080/16506073.2017.1401115] [Medline: 29215315]

41. Linardon J, Cuijpers P, Carlbring P, Messer M, Fuller-Tyszkiewicz M. The efficacy of app-supported smartphone interventions for mental health problems: a meta-analysis of randomized controlled trials. World Psychiatry 2019 Oct 09;18(3):325-336 [FREE Full text] [doi: 10.1002/wps.20673] [Medline: 31496095]

42. Palermo TM, Law EF, Fales J, Bromberg MH, Jessen-Fiddick T, Tai G. Internet-delivered cognitive-behavioral treatment for adolescents with chronic pain and their parents: a randomized controlled multicenter trial. Pain 2016 Jan;157(1):174-185 [FREE Full text] [doi: 10.1097/j.pain.0000000000000348] [Medline: 26335910]

43. Fitzpatrick KK, Darcy A, Vierhile M. Delivering cognitive behavior therapy to young adults with symptoms of depression and anxiety using a fully automated conversational agent (woebot): a randomized controlled trial. JMIR Ment Health 2017 Jun 06;4(2):e19 [FREE Full text] [doi: 10.2196/mental.7785] [Medline: 28588005]

44. Ly KH, Ly A, Andersson G. A fully automated conversational agent for promoting mental well-being: a pilot RCT using mixed methods. Internet Interv 2017 Dec;10:39-46 [FREE Full text] [doi: 10.1016/j.invent.2017.10.002] [Medline: 30135751]

45. Gentili C, Zetterqvist V, Rickardsson J, Holmström L, Simons LE, Wicksell RK. ACTsmart: development and feasibility of digital Acceptance and Commitment Therapy for adults with chronic pain. NPJ Digit Med 2020 Feb 13;3(1):20 [FREE Full text] [doi: 10.1038/s41746-020-0228-4] [Medline: 32128450]

46. Bailey JF, Agarwal V, Zheng P, Smuck M, Fredericson M, Kennedy DJ, et al. Digital care for chronic musculoskeletal pain: 10,000 participant longitudinal cohort study. J Med Internet Res 2020 May 11;22(5):e18250 [FREE Full text] [doi: 10.2196/18250] [Medline: 32208358]

47. Reddy S, Fox J, Purohit MP. Artificial intelligence-enabled healthcare delivery. J R Soc Med 2019 Jan;112(1):22-28. [doi: 10.1177/0141076818815510] [Medline: 30507284]

48. Fiske A, Henningsen P, Buyx A. Your robot therapist will see you now: ethical implications of embodied artificial intelligence in psychiatry, psychology, and psychotherapy. J Med Internet Res 2019 May 09;21(5):e13216 [FREE Full text] [doi: 10.2196/13216] [Medline: 31094356]

49. Boucher EM, Harake NR, Ward HE, Stoeckl SE, Vargas J, Minkel J, et al. Artificially intelligent chatbots in digital mental health interventions: a review. Expert Rev Med Devices 2021 Dec 31;18(sup1):37-49 [FREE Full text] [doi: 10.1080/17434440.2021.2013200] [Medline: 34872429]

50. Ramesh A, Kambhampati C, Monson J, Drew P. Artificial intelligence in medicine. Ann R Coll Surg Engl 2004 Sep 01;86(5):334-338 [FREE Full text] [doi: 10.1308/147870804290] [Medline: 15333167]

51. Pinto MD, Greenblatt AM, Hickman RL, Rice HM, Thomas TL, Clochesy JM. Assessing the critical parameters of eSMART-MH: a promising avatar-based digital therapeutic intervention to reduce depressive symptoms. Perspect Psychiatr Care 2016 Jul 19;52(3):157-168. [doi: 10.1111/ppc.12112] [Medline: 25800698]

52. Burton C, Szentagotai Tatar A, McKinstry B, Matheson C, Matu S, Moldovan R, et al. Pilot randomised controlled trial of Help4Mood, an embodied virtual agent-based system to support treatment of depression. J Telemed Telecare 2016 Jul 09;22(6):348-355. [doi: 10.1177/1357633x15609793]

53. Ring L, Shi L, Totzke K, Bickmore T. Social support agents for older adults: longitudinal affective computing in the home. J Multimodal User Interfaces 2014 Jun 18;9(1):79-88. [doi: 10.1007/s12193-014-0157-0]

54. Pinto MD, Hickman RL, Clochesy J, Buchner M. Avatar-based depression self-management technology: promising approach to improve depressive symptoms among young adults. Appl Nurs Res 2013 Feb;26(1):45-48 [FREE Full text] [doi: 10.1016/j.apnr.2012.08.003] [Medline: 23265918]

55. Fulmer R, Joerin A, Gentile B, Lakerink L, Rauws M. Using psychological artificial intelligence (TESS) to relieve symptoms of depression and anxiety: randomized controlled trial. JMIR Ment Health 2018 Dec 13;5(4):e64 [FREE Full text] [doi: 10.2196/mental.9782] [Medline: 30545815]

56. Freeman D, Haselton P, Freeman J, Spanlang B, Kishore S, Albery E, et al. Automated psychological therapy using immersive virtual reality for treatment of fear of heights: a single-blind, parallel-group, randomised controlled trial. Lancet Psychiatry 2018 Aug;5(8):625-632. [doi: 10.1016/s2215-0366(18)30226-8]

57. Gaffney H, Mansell W, Tai S. Conversational agents in the treatment of mental health problems: mixed-method systematic review. JMIR Ment Health 2019 Oct 18;6(10):e14166 [FREE Full text] [doi: 10.2196/14166] [Medline: 31628789]

58. Hoermann S, McCabe KL, Milne DN, Calvo RA. Application of synchronous text-based dialogue systems in mental health interventions: systematic review. J Med Internet Res 2017 Jul 21;19(8):e267 [FREE Full text] [doi: 10.2196/jmir.7023] [Medline: 28784594]

59. Inkster B, Sarda S, Subramanian V. An empathy-driven, conversational artificial intelligence agent (Wysa) for digital mental well-being: real-world data evaluation mixed-methods study. JMIR Mhealth Uhealth 2018 Nov 23;6(11):e12106 [FREE Full text] [doi: 10.2196/12106] [Medline: 30470676]

60. Krebs EE, Carey TS, Weinberger M. Accuracy of the pain numeric rating scale as a screening test in primary care. J Gen Intern Med 2007 Oct 1;22(10):1453-1458 [FREE Full text] [doi: 10.1007/s11606-007-0321-2] [Medline: 17668269]

61. Fejer R, Jordan A, Hartvigsen J. Categorising the severity of neck pain: establishment of cut-points for use in clinical and epidemiological research. Pain 2005 Dec 15;119(1-3):176-182 [FREE Full text] [doi: 10.1016/j.pain.2005.09.033] [Medline: 16298059]

62. Müller R, Gertz KJ, Molton IR, Terrill AL, Bombardier CH, Ehde DM, et al. Effects of a tailored positive psychology intervention on well-being and pain in individuals with chronic pain and a physical disability. Clin J Pain 2016;32(1):32-44. [doi: 10.1097/Ajp.0000000000000225]

63. Peters M, Smeets E, Feijge M, van Breukelen G, Andersson G, Buhrman M, et al. Happy despite pain: a randomized controlled trial of an 8-week internet-delivered positive psychology intervention for enhancing well-being in patients with chronic pain. Clin J Pain 2017 Nov;33(11):962-975 [FREE Full text] [doi: 10.1097/AJP.0000000000000494] [Medline: 28379873]

64. Baumel A, Faber K. Evaluating triple P online: a digital parent training program for child behavior problems. Cogn Behav Pract 2018 Nov;25(4):538-543 [FREE Full text] [doi: 10.1016/j.cbpra.2017.10.001]

65. Wadon ME, Winter M, Peall KJ. Internet-based cognitive behavioural therapy programme as an intervention for people diagnosed with adult-onset, focal, isolated, idiopathic cervical dystonia: a feasibility study protocol. Pilot Feasibility Stud 2020 Jul 15;6(1):100 [FREE Full text] [doi: 10.1186/s40814-020-00641-x] [Medline: 32685184]

66. Ryan RM, Deci EL. A self-determination theory approach to psychotherapy: the motivational basis for effective change. Can Psychol 2008 Aug;49(3):186-193. [doi: 10.1037/a0012753]

67. Feller C, Cottone R. The importance of empathy in the therapeutic alliance. J Humanistic Couns Educ Devel 2012;42(1):53-61 [FREE Full text] [doi: 10.1002/j.2164-490X.2003.tb00168.x]

68. Althoff T, Clark K, Leskovec J. Large-scale analysis of counseling conversations: an application of natural language processing to mental health. Transact Assoc Computational Ling 2016 Dec;4:463-476. [doi: 10.1162/tacl_a_00111]

69. Xu B, Zhuang Z. Survey on psychotherapy chatbots. Concurrency Comput 2020 Dec 28;34(7):1 [FREE Full text] [doi: 10.1002/cpe.6170]

70. Shields CG, Finley MA, Elias CM, Coker CJ, Griggs JJ, Fiscella K, et al. Pain assessment: the roles of physician certainty and curiosity. Health Commun 2013 Oct;28(7):740-746 [FREE Full text] [doi: 10.1080/10410236.2012.715380] [Medline: 23356451]

71. Kuchlous S, Kadaba M. Short text intent classification for conversational agents. 2020 IEEE 17th India Council Int Conf 2020:1-4 [FREE Full text] [doi: 10.1109/INDICON49873.2020.9342516]

72. Jensen M, McFarland C. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. Pain 1993;55:195-203 [FREE Full text] [doi: 10.1016/0304-3959(93)90148-I]

73. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94(2):149-158. [doi: 10.1016/S0304-3959(01)00349-9]

74. Michener L, Snyder A, Leggin B. Responsiveness of the numeric pain rating scale in patients with shoulder pain and the effect of surgical status. J Sport Rehabil 2011 Feb;20(1):115-128 [FREE Full text] [doi: 10.1123/jsr.20.1.115] [Medline: 21411827]

75. Chen CX, Kroenke K, Stump T, Kean J, Krebs EE, Bair MJ, et al. Comparative responsiveness of the PROMIS pain interference short forms with legacy pain measures: results from three randomized clinical trials. J Pain 2019 Jun;20(6):664-675 [FREE Full text] [doi: 10.1016/j.jpain.2018.11.010] [Medline: 30529442]

76. Chen CX, Kroenke K, Stump TE, Kean J, Carpenter JS, Krebs EE, et al. Estimating minimally important differences for the PROMIS pain interference scales: results from 3 randomized clinical trials. Pain 2018 Apr 1;159(4):775-782 [FREE Full text] [doi: 10.1097/j.pain.0000000000001121] [Medline: 29200181]

77. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006 May 22;166(10):1092-1097. [doi: 10.1001/archinte.166.10.1092] [Medline: 16717171]

78. Toussaint A, Hüsing P, Gumz A, Wingenfeld K, Härter M, Schramm E, et al. Sensitivity to change and minimal clinically important difference of the 7-item Generalized Anxiety Disorder Questionnaire (GAD-7). J Affect Disord 2020 Mar 15;265:395-401. [doi: 10.1016/j.jad.2020.01.032] [Medline: 32090765]

79. Löwe B, Unützer J, Callahan CM, Perkins AJ, Kroenke K. Monitoring depression treatment outcomes with the patient health questionnaire-9. Med Care 2004 Dec;42(12):1194-1201. [doi: 10.1097/00005650-200412000-00006] [Medline: 15550799]

80. Fann JR, Berry DL, Wolpin S, Austin-Seymour M, Bush N, Halpenny B, et al. Depression screening using the Patient Health Questionnaire-9 administered on a touch screen computer. Psychooncology 2009 Jan;18(1):14-22 [FREE Full text] [doi: 10.1002/pon.1368] [Medline: 18457335]

81. Hatcher RL, Gillaspy JA. Development and validation of a revised short version of the working alliance inventory. Psychother Res 2006 Jan;16(1):12-25. [doi: 10.1080/10503300500352500]

82. Munder T, Wilmers F, Leonhart R, Linster HW, Barth J. Working Alliance Inventory-Short Revised (WAI-SR): psychometric properties in outpatients and inpatients. Clin Psychol Psychother 2010;17(3):231-239. [doi: 10.1002/cpp.658] [Medline: 20013760]

83. Jasper K, Weise C, Conrad I, Andersson G, Hiller W, Kleinstäuber M. The working alliance in a randomized controlled trial comparing Internet-based self-help and face-to-face cognitive behavior therapy for chronic tinnitus. Internet Interv 2014 Apr;1(2):49-57. [doi: 10.1016/j.invent.2014.04.002]

84. Hauser-Ulrich S, Künzli H, Meier-Peterhans D, Kowatsch T. A smartphone-based health care chatbot to promote self-management of chronic pain (SELMA): pilot randomized controlled trial. JMIR Mhealth Uhealth 2020 Apr 3;8(4):e15806. [doi: 10.2196/15806]

85. Woolfolk RL, Carr-Kaffashan L, McNulty TF, Lehrer PM. Meditation training as a treatment for insomnia. Behav Ther 1976 May;7(3):359-365 [FREE Full text] [doi: 10.1016/S0005-7894(76)80064-0]

86. Floyd M, Scogin F. Cognitive-behavior therapy for older adults: how does it work? Psychother Theory Res Pract Train 1998;35(4):459-463 [FREE Full text] [doi: 10.1037/h0087770]

87. Leo A, Schuelke M, Hunt D, Metzler J, Miller J, Areán P, et al. A digital mental health intervention in an orthopedic setting for patients with symptoms of depression and/or anxiety: feasibility prospective cohort study. JMIR Form Res 2022 Feb 21;6(2):e34889 [FREE Full text] [doi: 10.2196/34889] [Medline: 35039278]

88.   Kohrt BA, Griffith JL, Patel V. Chronic pain and mental health: integrated solutions for global problems. Pain 2018 Sep;159 Suppl 1(1):S85-S90 [FREE Full text] [doi: 10.1097/j.pain.0000000000001296] [Medline: 30113952]

89.   Upshur CC, Bacigalupe G, Luckmann R. "They don't want anything to do with you": patient views of primary care management of chronic pain. Pain Med 2010 Dec 01;11(12):1791-1798 [FREE Full text] [doi: 10.1111/j.1526-4637.2010.00960.x] [Medline: 21029353]

90.   Palermo TM, de la Vega R, Murray C, Law E, Zhou C. A digital health psychological intervention (WebMAP Mobile) for children and adolescents with chronic pain: results of a hybrid effectiveness-implementation stepped-wedge cluster randomized trial. Pain 2020 Dec 10;161(12):2763-2774 [FREE Full text] [doi: 10.1097/j.pain.0000000000001994] [Medline: 32658147]

91.   Greenberg J, Popok PJ, Lin A, Kulich RJ, James P, Macklin EA, et al. A mind-body physical activity program for chronic pain with or without a digital monitoring device: proof-of-concept feasibility randomized controlled trial. JMIR Form Res 2020 Jun 08;4(6):e18703 [FREE Full text] [doi: 10.2196/18703] [Medline: 32348281]

92.   Rockett M. Diagnosis, mechanisms and treatment of complex regional pain syndrome. Curr Opin Anaesthesiol 2014 Oct;27(5):494-500 [FREE Full text] [doi: 10.1097/ACO.0000000000000114] [Medline: 25111604]

93.   Malik T, Ambrose A, Sinha C. User feedback analysis of an AI-enabled CBT mental health application (Wysa). JMIR Hum Factors 2022 Mar 06:1 [FREE Full text] [doi: 10.2196/35668] [Medline: 35249886]

94.   Kinney M, Seider J, Beaty AF, Coughlin K, Dyal M, Clewley D. The impact of therapeutic alliance in physical therapy for chronic musculoskeletal pain: a systematic review of the literature. Physiother Theory Pract 2020 Aug 28;36(8):886-898. [doi: 10.1080/09593985.2018.1516015] [Medline: 30265840]

95.   Ferreira P, Ferreira M, Maher C, Refshauge K, Latimer J, Adams R. The therapeutic alliance between clinicians and patients predicts outcome in chronic low back pain. Phys Ther 2013 Apr;93(4):470-478 [FREE Full text] [doi: 10.2522/ptj.20120137] [Medline: 23139428]

96.   Fuentes J, Armijo-Olivo S, Funabashi M, Miciak M, Dick B, Warren S, et al. Enhanced therapeutic alliance modulates pain intensity and muscle pain sensitivity in patients with chronic low back pain: an experimental controlled study. Phys Ther 2014 Apr;94(4):477-489 [FREE Full text] [doi: 10.2522/ptj.20130118] [Medline: 24309616]

97.   Rubinelli S, Schulz PJ, Vago F. Designing and evaluating online communities for promoting self-management of chronic low back pain. Int J Web Based Commun 2008;4(1):80 [FREE Full text] [doi: 10.1504/IJWBC.2008.016492]

Abbreviations

AI: artificial intelligence
AI-CBT: artificial intelligence–supported cognitive behavioral therapy
CBT: cognitive behavioral therapy
GAD-7: Generalized Anxiety Disorder, 7-item
NPRS: numerical pain rating scale
PHQ-9: Patient Health Questionnaire, 9-item
PROMIS PI: Patient-Reported Outcomes Measurement Information System–Pain Inference short form 6b
SELMA: Smartphone-Based Health Care Chatbot to Promote Self-Management of Chronic Pain
WAI-SR: Working Alliance Inventory–Short Revised

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