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Habilitationsschrift

Evaluation nichtpharmakologischer Interventionen aus der Integrativen Medizin und Digitalen Gesundheit bei chronischen Schmerzen

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Dekan:	**Prof. Dr. med. Axel R. Pries**
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INHALTSVERZEICHNIS

ABKÜRZUNGEN

BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
DiGA	Digitale Gesundheitsanwendung
EbM	Evidenzbasierte Medizin
ePA	Elektronische Patientenakte
KI	Konfidenzintervall
SD	Standardabweichung (engl. standard deviation)

1 EINLEITUNG

"Health care, while essential, accounts for no more than 20 percent of health outcomes."

(Die Gesundheitsversorgung ist zwar von grundlegender Bedeutung, macht aber nicht mehr als 20 Prozent der gesundheitsbezogenen Ergebnisse aus.) Steven H. Woolf and Laudan Y. Aron (2021, US-amerikanische Public-Health-Experten)

Chronische Schmerzen sind ein wesentliches globales Gesundheitsproblem, welches eine hohe sozioökonomische Belastung auf der Ebene der Individuen, der Gesellschaften und der Institutionen mit sich bringt.[1-3] Schmerzen können dabei als "…unangenehme sensorische und emotionale Erfahrung, die mit einer tatsächlichen oder potenziellen Gewebeschädigung verbunden ist oder dieser ähnelt" definiert werden[4]. Die Schmerzen treten zum Beispiel bei chronischen Erkrankungen des Bewegungsapparats als Folge akuter Ereignisse, die zu chronischen Schmerzen führen können, sowie als anhaltende Nebenwirkung von Krankheiten auf. Sie können jedoch auch in einem weniger klaren Zusammenhang zu einem Gewebeschade stehen, z. B. bei Schmerzen in einem Körperteil, welches weit entfernt von der Läsion eines Schlaganfalls im zentralen Nervensystem liegt.[4] Schmerz ist immer eine persönliche Erfahrung, die in unterschiedlichem Maße von biologischen, psychologischen und sozialen Faktoren beeinflusst wird.[4] Schmerzen werden häufig bei einer Dauer von mehr als 3 Monaten als chronische Schmerzen bezeichnet.[5] Aufgrund der komplexen Natur von Schmerz, ist häufig ein multidimensionales Vorgehen zur Therapie der chronischen Schmerzen indiziert.[6] Pharmakologische Ansätze allein sind zur Linderung chronischer Schmerzen häufig nicht geeignet. Beispielsweise ist die Verwendung der sehr potenten Opioide mit dem Risiko der Toleranzentstehung, Abhängigkeit und Sucht verbunden, und ihr unkritischer Einsatz hat wesentlich die aktuelle Opioidkrise in den USA mitverursacht.[7 8]

Die Therapie chronischer Schmerzen sollte, wenn möglich, mit nichtpharmakologischen Maßnahmen beginnen und einen multidisziplinären Ansatz verfolgen[6 9 10]. Zu einer sinnvollen Kombination nichtpharmakologischer Verfahren können dabei die folgenden Verfahren gehören: Bewegungstherapie und psychoedukative Interventionen (z. B. kognitive Verhaltenstherapie, Familientherapie, Psychotherapie und Patientenschulung), Mind-Body-Verfahren (z. B. achtsamkeitsbasierte Stressreduzierung [MBSR]) und physische Interventionen (z. B. Physiotherapie, Akupunktur, chiropraktische Manipulation und Massage).[6 9] Einige dieser Verfahren eignen sich auch zur Selbstanwendung.

Die Digitalisierung kann als Digitale Gesundheit (Digital Health) möglicherweise bei der Anwendung komplexer, kombinierter Therapien hilfreich sein. So können z.B. Elemente der Verhaltenstherapie und körperliche Anwendungen, die ohne persönliche Anleitung durch einen Gesundheitsexperten auskommen und sicher sind, in digitalen Gesundheitsanwendungen bzw. -apps sinnvoll kombiniert

werden.[11] [12] Diese Digitalisierung kann für spezifische Beschwerden bzw. Krankheitsbilder oder allgemein für körperliches Wohlbefinden umgesetzt werden. Die Anwendung kann ohne Gesundheitsexperten komplett „remote" bzw. „virtuell" oder ergänzt durch klassische, stationäre Therapie als hybride Lösung erfolgen.

Auch eignen sich für die Umsetzung Verfahren wie Yoga, Akupressur oder Meditation, die der sogenannten Integrativen Medizin zugeordnet werden können. Es gibt somit eine Überlappung von Interventionen aus der Integrativen Medizin und Verfahren der Digitalen Gesundheit.

1.1 Integrative Medizin und Gesundheit

Die „'Integrative Medizin und Gesundheit' bekräftigt die Bedeutung der Beziehung zwischen Arzt und Patient, zielt auf die ganze Person ab, wird durch Evidenz informiert und bedient sich aller geeigneten therapeutischen, präventiven, gesundheitsfördernden oder Lifestyle-Ansätze, Fachkräfte und Disziplinen des Gesundheitswesens, um eine optimale Gesundheit und Heilung zu erreichen – Kunst und Wissenschaft des Heilens gleichermaßen hervorhebend. Sie basiert auf einer sozialen und demokratischen sowie natürlichen und gesunden Umwelt."[13] Damit sind auch Verfahren aus eher traditionelle Medizinsystemen, vor allem aus dem Bereich der Naturheilkunde und Komplementärmedizin, eingeschlossen.

1.2 Digitale Gesundheit (Digital Health)

Digital Health bzw. Digitale Gesundheit umfasst im Wesentlichen alle Bereiche von Gesundheit, die durch digitale Technologien unterstützt werden.[14]

Digitale Gesundheit beinhaltet dabei die Unterkategorien mobile Gesundheit (mHealth, auf die sich der Autor dieser Arbeit fokussiert), Gesundheitsinformationstechnologie (IT), tragbare Geräte, Telemedizin und personalisierte Medizin.[15] Somit sind von mobilen medizinischen Apps und Software, die Ärzte bei ihren täglichen klinischen Entscheidungen unterstützen, bis hin zu künstlicher Intelligenz und maschinellem Lernen ein breites Spektrum an Methoden eingeschlossen. Digitale Gesundheitsanwendungen haben das Potenzial die Fähigkeit zu verbessern, Krankheiten genau zu diagnostizieren und zu behandeln und die Gesundheitsversorgung für den Einzelnen zu verbessern.[15] Anwendungen können dabei dem Bereich Fitness und Wohlbefinden zugeordnet sein. Sie umfassen aber auch Technologien, die selbst als Medizinprodukt, als Bestandteil eines Medizinprodukts, als Begleitdiagnostik oder als Ergänzung zu anderen Medizinprodukten, Arzneimitteln oder Biologika verwendet werden. Sie können auch zur Entwicklung oder Untersuchung von Medizinprodukten eingesetzt werden.[15]

Eine Weiterentwicklung der Digitalen Gesundheitsanwendungen sind in Deutschland die sogenannten DiGAs (Digitale Gesundheitsanwendung oder „App auf Rezept“). Für diese wurde in Deutschland im Jahr 2019 ein Gesetz zur digitalen Versorgung (DVG) eingeführt,[16 17,] um mit DiGAs die einfache Nutzung von Online-Videosprechstunden und den Zugang zu einem sicheren Gesundheitsdatennetz für die Behandlung der deutschen Bevölkerung zu unterstützen. DiGAs sollen Teil einer digital gestützten Gesundheitsversorgung werden und z.B. in Zukunft an die elektronische Patientenakte (ePA)[18] angebunden sein. Apps dieser Art müssen besondere Anforderungen erfüllen, um in das Erstattungsverzeichnis des Bundesinstituts für Arzneimittel und Medizinprodukte (BfArM) aufgenommen zu werden[12]. So muss eine App klar definierten Kriterien entsprechen und positive Versorgungseffekte nachweisen. Positive Versorgungseffekte sind entweder ein medizinischer Nutzen oder patientenrelevante Struktur- und Verfahrensverbesserungen in der Versorgung. Eine DiGA ist ein Medizinprodukt der Risikoklassen I bis IIa entsprechend der europäischen Verordnung über Medizinprodukte[19]. Die Hauptfunktion der DiGA basiert auf digitalen Technologien. DiGAs sind „digitale Helfer“ in der Hand von Patientinnen und Patienten.[12]

Positive Auswirkungen auf die Gesundheitsversorgung müssen durch die Ergebnisse einer vergleichenden Studie nachgewiesen werden, die zeigen, dass die Anwendung einer DiGA besser ist als die Nichtanwendung einer DiGA. Hierfür wurde ein beschleunigtes Verfahren geschaffen, das es einer DiGA ermöglicht, die Bewertung des Bundesinstituts für Arzneimittel und Medizinprodukte erfolgreich zu durchlaufen und in ein Verzeichnis erstattungsfähiger digitaler Gesundheitsanwendungen (DiGA-Verzeichnis) aufgenommen zu werden.[11 12] Klinische Studien sind somit auch für den Bereich der Digitalen Gesundheit wichtig, um evidenzbasierte Medizin zu ermöglichen, auch wenn sie besondere Anforderungen erfüllen sollten.[12 20]

1.3 Evidenzbasierte Medizin

Der Begriff „Evidenzbasierte Medizin“ (EbM) leitet sich vom englischen Wort „evidence“ = Nachweis oder Beweis ab. Nach ihr basiert medizinischen Handeln auf der Trias von 1. individueller klinischer Expertise des Behandelnden, 2. der besten verfügbaren externen Evidenz basierend auf klinischer Forschung sowie 3. den individuellen Wünschen und Vorstellungen der Patienten[21], um den bestmöglichen Nutzen für den individuellen Patienten zu erzielen (Abbildung 1). Dabei bedeutet die Anwendung von EbM nicht, dass nur noch Verfahren angewendet werden dürfen, für die ein klarer Beweis der Wirksamkeit vorliegt. Um Verfahren der Integrativen Medizin und Digitalen Gesundheit evidenzbasiert anzuwenden, müssten Anwendungen somit in Studien hinsichtlich ihres Nutzens und Risikos untersucht werden. Gute Daten würden sowohl Klinikern als auch Patienten durch

transparente Informationen in die Lage versetzen, informierter individuelle Entscheidungen bezüglich der Anwendung treffen zu können.

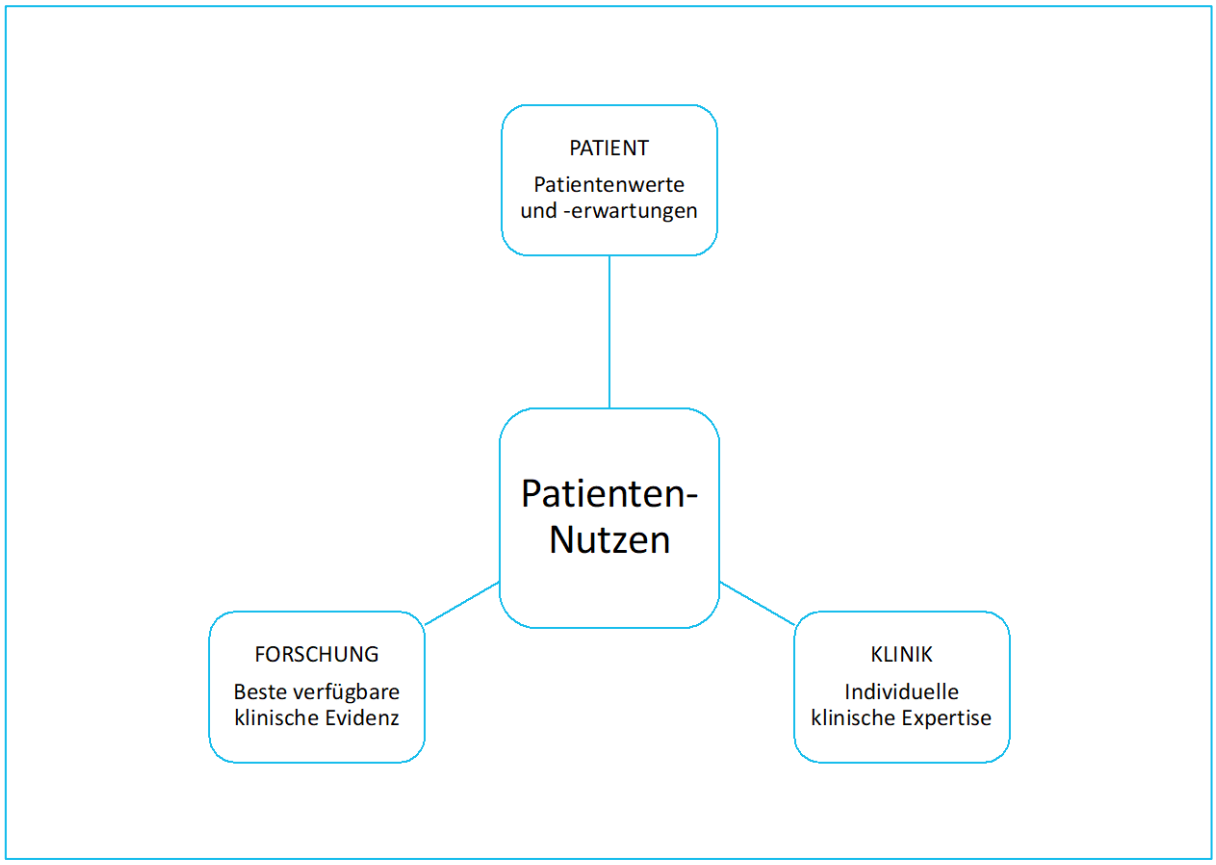

Abbildung 1. Die Trias der Evidenzbasierten Medizin nach D. L. Sacket BMJ 1996[21]

2 ZIELSTELLUNGEN DER VORLIEGENDEN ORIGINALARBEITEN

Das Ziel der ausgewählten Originalpublikationen war die Wirkung nichtpharmakologischer Interventionen aus der Integrativen Medizin und Digitalen Gesundheit bei chronischen Schmerzen zu untersuchen. Ein besonderer Fokus lag dabei auf der Untersuchung von Wirkungen, die möglichst nah an der Realität der Routineversorgung sind. Diese sogenannte „Effectiveness“[22] wurde für spezifische Interventionen in den entsprechenden Patientengruppen mittels pragmatischer randomisierter Studien untersucht.

3 EIGENE ARBEITEN

3.1 Klinische Wirkung App-basierter Akupressur bei Frauen mit Menstruationsschmerzen: eine pragmatische randomisierte Studie

Es ist sinnvoll Stakeholder in die Planung von klinischen Studien einzubinden. Dieses Stakeholder-Engagement kann jedoch auch das Design und die Fragestellung einer Studie deutlich beeinflussen.[23] Ausgehend von der Entwicklung einer klassischen klinischen Studie zur Evaluation der Wirksamkeit von Akupressur bei jungen Frauen mit Menstruationsschmerzen wurde nach Anwendung verschiedener Mixed-Methods-Forschungsverfahren und Stakeholder-Engagement die folgende dann App-basierte Interventionsstudie entwickelt und durchgeführt.[23]

Der folgende Abstrakt ist eine Übersetzung des Autors aus dem Originalartikel:

Blödt, S., D. Pach, S. V. Eisenhart-Rothe, F. Lotz, S. Roll, K. Icke, and C. M. Witt. "Effectiveness of App-Based Self-Acupressure for Women with Menstrual Pain Compared to Usual Care: A Randomized Pragmatic Trial." *American Journal of Obstetrics and Gynecology* 218, no. 2 (Feb 2018): 227 e1-27 e9. https://dx.doi.org/10.1016/j.ajog.2017.11.570.

*„**Hintergrund:** Primäre Dysmenorrhoe ist bei Frauen im gebärfähigen Alter weit verbreitet. Nichtsteroidale Antirheumatika und orale Kontrazeptiva sind wirksame Behandlungen, wirken jedoch bei etwa 20 bis 25 % der Behandelten nicht. Daher werden zusätzliche evidenzbasierte Behandlungen benötigt. In den letzten Jahren hat die Nutzung von Smartphone-Anwendungen (Apps) rasant zugenommen und kann den Einzelnen bei seinen Selbstmanagementstrategien unterstützen.*

***Fragestellung:** Ziel der Studie war die Untersuchung der Wirksamkeit App-basierten Selbstakupressur bei Frauen mit Menstruationsschmerzen.*

***Material und Methoden:** Eine zweiarmige, randomisierte, pragmatische Studie wurde von Dezember 2012 bis April 2015 mit einer Rekrutierung bis August 2014 in Berlin, Deutschland durchgeführt. Einbezogen wurden Frauen im Alter von 18 bis 34 Jahren mit selbstberichteten krampfartigen Schmerzen von 6 oder mehr Punkten auf einer numerischen Ratingskala (NRS) für die stärkste Schmerzintensität während der letzten Menstruation. Nach der Randomisierung führten die Frauen entweder eine App-basierte Selbstakupressur durch (n = 111) oder nahmen nur die alleinige Normalversorgung in Anspruch (n = 110), und zwar für 6 aufeinanderfolgende Menstruationszyklen. Der primäre Zielparameter war die durchschnittliche Schmerzintensität (NRS 0-10) an den Tagen mit*

Schmerzen während der dritten Menstruation. Zu den sekundären Zielparametern gehörten die stärkste Schmerzintensität während der Menstruation, die Dauer der Schmerzen, die 50%-Responderrate (Verringerung der mittleren Schmerzen um mindestens 50%), die Medikamenten-einnahme, die Krankheitstage und die Erwartung an die körperliche Leistungsfähigkeit, die beim ersten, zweiten, dritten und sechsten Menstruationszyklus ermittelt wurde.

Ergebnisse: *An der Studie nahmen 221 Frauen teil (Durchschnittsalter: 24,0 Jahre; Standardabweichung [SD]: 3,6 Jahre). Der mittlere Unterschied in der Schmerzintensität während der dritten Menstruation war statistisch signifikant zugunsten der Akupressur (Akupressur: 4,4 Punkte; 95% Konfidenzintervall [KI], 4,0-4,7; Normalversorgung: 5,0; 95% KI, 4,6-5,3; mittlerer Unterschied -0,6; 95% KI, -1,2 bis -0,1; P = .026). Beim sechsten Zyklus erreichte der mittlere Unterschied zwischen den Gruppen (-1,4 Punkte; 95% KI, -2,0 bis -0,8; P < .001) klinische Relevanz. Beim dritten und sechsten Zyklus lag die Ansprechrate in der Akupressurgruppe bei 37 % bzw. 58 % gegenüber 23 % bzw. 24 % in der Gruppe mit Normalversorgung. Außerdem waren die stärkste Schmerzintensität (Gruppenunterschied -0,6; 95% KI, -1,2 bis -0,02; und -1,4; 95% KI, -2,0 bis -0,7), die Anzahl der Tage mit Schmerzen (-0,4; 95% KI, -0,9 bis -0,01; und -1,2; 95% KI, -1,6 bis -0. 7) und der Anteil der Frauen, die beim dritten und sechsten Menstruationszyklus Schmerzmittel einnahmen, (Odds Ratio [OR], 0,5; 95% KI, 0,3-0,9] und 0,3 (95% KI, 0,2-0,5) in der Akupressurgruppe geringer. Beim dritten Zyklus war die Verwendung hormoneller Verhütungsmittel in der Gruppe mit Normalversorgung häufiger als in der Akupressurgruppe (OR, 0,5; 95% KI, 0,3-0,97), beim sechsten Zyklus jedoch nicht mehr statistisch signifikant unterschiedlich (OR, 0,6; 95% KI, 0,3-1,1]). Die Anzahl der Krankheitstage und die Erwartung an die körperliche Leistungsfähigkeit (Selbstwirksamkeitsskala) unterschieden sich nicht zwischen den Gruppen. Auf einer Skala von 0 bis 6 lag die durchschnittliche Zufriedenheit mit der Intervention beim dritten Zyklus bei 3,7 (SD 1,3), die Weiterempfehlung der Intervention bei 4,3 (1,5), die Angemessenheit der Akupressur bei Menstruationsschmerzen bei 3,9 (1,4) und die Anwendung der Akupressur bei anderen Schmerzen bei 4,3 (1,5). Die Intervention war sicher, und nach dem sechsten Zyklus wandten zwei Drittel der Frauen (67,6 %) die Akupressur immer noch an allen Tagen mit Schmerzen an.*

Schlussfolgerung: *Die per Smartphone-App durchgeführte Selbstakupressur führte zu einer Verringerung der Menstruationsschmerzen im Vergleich zur Normalversorgung. Die Wirkung nahm mit der Zeit zu, und die Therapieadhärenz war gut. Künftige Studien sollten Vergleiche mit anderen aktiven Behandlungsoptionen beinhalten."*

GYNECOLOGY

Effectiveness of app-based self-acupressure for women with menstrual pain compared to usual care: a randomized pragmatic trial

Susanne Blödt, PhD[1]; Daniel Pach, MD[1]; Sanna von Eisenhart-Rothe; Fabian Lotz; Stephanie Roll, PhD; Katja Icke; Claudia M. Witt, MD, MBA

BACKGROUND: Primary dysmenorrhea is common among women of reproductive age. Nonsteroidal anti-inflammatory drugs and oral contraceptives are effective treatments, although the failure rate is around 20% to 25%. Therefore additional evidence-based treatments are needed. In recent years, the use of smartphone applications (apps) has increased rapidly and may support individuals in self-management strategies.

OBJECTIVE: We aimed to investigate the effectiveness of app-based self-acupressure in women with menstrual pain.

MATERIALS AND METHODS: A 2-armed, randomized, pragmatic trial was conducted from December 2012 to April 2015 with recruitment until August 2014 in Berlin, Germany, among women aged 18 to 34 years with self-reported cramping pain of 6 or more on a numeric rating scale (NRS) for the worst pain intensity during the previous menstruation. After randomization, women performed either app-based self-acupressure (n = 111) or followed usual care only (n = 110) for 6 consecutive menstruation cycles. The primary outcome was the mean pain intensity (NRS 0−10) on the days with pain during the third menstruation. Secondary outcomes included worst pain intensity during menstruation, duration of pain, 50% responder rates (reduction of mean pain by at least 50%), medication intake, sick leave days, and body efficacy expectation assessed at the first, second, third, and sixth menstruation cycles.

RESULTS: We included 221 women (mean age, 24.0 years; standard deviation [SD], 3.6 years). The mean pain intensity difference during the third menstruation was statistically significant in favor of acupressure (acupressure: 4.4; 95% confidence interval [CI], 4.0−4.7; usual care 5.0; 95% CI, 4.6−5.3; mean difference −0.6; 95% CI, − 1.2 to −0.1; $P = .026$). At the sixth cycle, the mean difference between the groups (−1.4; 95% CI, −2.0 to −0.8; $P < .001$) reached clinical relevance. At the third and sixth menstruation cycles, responder rates were 37% and 58%, respectively, in the acupressure group, in contrast to 23% and 24% in the usual care group. Moreover, the worst pain intensity (group difference −0.6; 95% CI, −1.2 to −0.02; and −1.4; 95% CI, −2.0 to −0.7), the number of days with pain (−0.4; 95% CI, −0.9 to −0.01; and −1.2; 95% CI, −1.6 to −0.7) and the proportion of women with pain medication at the third and sixth menstruation cycles (odds ratio [OR], 0.5; 95% CI, 0.3−0.9] and 0.3 (95% CI, 0.2−0.5) were lower in the acupressure group. At the third cycle, hormonal contraceptive use was more common in the usual care group than in the acupressure group (OR, 0.5; 95% CI, 0.3−0.97) but not statistically significantly different at the sixth cycle (OR, 0.6; 95% CI, 0.3−1.1]). The number of sick leave days and body efficacy expectation (self-efficacy scale) did not differ between groups.

On a scale of 0 to 6, mean satisfaction with the intervention at the third cycle was 3.7 (SD 1.3), recommendation of the intervention to others 4.3 (1.5), appropriateness of acupressure for menstrual pain 3.9 (1.4), and application of acupressure for other pain 4.3 (1.5). The intervention was safe, and after the sixth cycle, two-thirds of the women (67.6%) still applied acupressure on all days with pain.

CONCLUSION: Smartphone app−delivered self-acupressure resulted in a reduction of menstrual pain compared to usual care only. Effects were increasing over time, and adherence was good. Future trials should include comparisons with other active treatment options.

Key words: acupressure, dysmenorrhea, mHealth, pain

Primary dysmenorrhea[1] affects up to 81% of women of reproductive age,[2,3] with approximately 15% experiencing severe pain.[2] Menstrual pain has a relevant impact on quality of life[4] and results in a substantial economic loss.[5,6]

Nonsteroidal anti-inflammatory drugs and oral contraceptives are effective treatments,[7] although the failure rate is around 20% to 25%[5,8,9] because of side effects[7,10] and lack of effectiveness in some cases.[10-12] Additional evidence-based treatments are needed.[13] Of women with menstrual pain, 70% are reported to practice self-management.[10] A few studies have investigated the effect of self-acupressure for dysmenorrhea, mostly as an add-on to therapist-administered acupressure.[13-16] Although results showed a beneficial effect for self-acupressure,[17-21] the evidence is unclear due to risk of bias (mostly due to performance and attrition bias).[13]

In recent years, the use of smartphone applications (apps)[22] has increased rapidly. Mobile and electronic health solutions are already widely used in the general public and are seen as a valuable tool for various health problems[22-25] and self-management.[26] Mobile health (mHealth) solutions might have improved the autonomy and participation of users already,[26] for example by facilitating the search for information and health services, as well as by structuring of information and data. Health data is increasingly being collected via smartphones and portable devices (so-called wearables) and can be shared with doctors and other service

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providers. Individual behavior can be positively influenced with the help of behavioral change techniques and used, for example, for smoking cessation or weight control.[27,28] Only a few mHealth solutions have been investigated in randomized controlled trials to date, and the majority of available apps do not report any health care professional involvement in their development[22,25] Nevertheless, a strong increase in mHealth solutions and increasing integration into usual care is expected. App-based self-acupressure might be innovative to support women with menstrual pain; however, its effectiveness in a usual care setting remains unclear.

In this study, we aimed to investigate whether app-based self-acupressure is more effective in reducing pain than usual care for women with menstrual pain.

Materials and Methods

Study design

We performed a 2-armed, randomized, pragmatic trial with a treatment duration and observation time of 6 menstruation cycles per woman. The design of the trial and the development of the smartphone app "AKUD" were shaped by stakeholder engagement (see previous publication[29]). A statistician not involved in the study used "ranuni" random number generator of the SAS/STAT software version 9.2 (SAS Institute, Cary, NC) to generate the randomization list (1:1 ratio). The list was transferred into a secured database (Microsoft Office Access 2010; Microsoft Corporation, Redmond, WA) and hidden behind the interface so that it was not accessible to anyone involved in the random allocation or treatment. Eligible women were randomized by clicking a button of the database interface. The result could not be changed, which ensured allocation concealment.

This study followed the standards of the Declaration of Helsinki[30] and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use good clinical practice (ICH-GCP) guidelines, and were approved by the respective Ethics Committee (Charité–Universitätsmedizin Berlin EA1/027/12). All patients gave oral and written informed consent. The trial was registered at clinicaltrials.gov (NCT01582724), and the study protocol was published.[29]

Participants and setting

Women were recruited in Berlin, Germany, from December 2012 to August 2014, using information materials (posters, flyers, and leaflets), the intranet platforms of Charité–Universitätsmedizin Berlin, and students' e-mail lists. In adition, the study was advertised on 2 Berlin subway lines for 5 months. Telephone interviews were used for participant prescreening. To facilitate recruitment, a financial compensation of 30 EUR was introduced after 8 months.

Participants were eligible for the trial if they fulfilled the following inclusion criteria: female sex; 18 to 25 years of age (criterion broadened to 18–34 years after 8 months of recruitment to facilitate recruitment); having dysmenorrhea, defined as self-reported cramping pain during every menstrual cycle; no prior history of a gynecologic disease that could be a reason for dysmenorrhea; having had menstruation in the last 6 weeks and a menstrual cycle duration between 3 and 6 weeks; moderate or severe pain, defined as a score equal to or greater than 6 on a numeric rating scale (NRS, 0–10) for the worst pain intensity during the last menstruation; and providing written and oral informed consent. Participants had to own a smartphone (iOS or Android) and to agree to enter study data through the app. Patients were not eligible for the trial if they fulfilled any of the following exclusion criteria: already using or planning to use acupressure, acupuncture, shiatsu, or/and tuina massage in the following 8 months; or known pregnancy or planned pregnancy in the following 8 months.

Intervention and control group

Both treatment groups received the app AKUD (Software development: Smart Mobile Factory, Berlin, Germany), which included a visualization of the menstrual cycle, questionnaires, and diaries for both groups.

Acupressure specific features were available only for the acupressure group. These included explanations of the acupressure procedure, drawings, videos, and photos of the acupressure points, as well as a timer to guide the 1-minute acupressure of each point. The acupressure intervention (points, duration, setting) resulted from a written Delphi consensus with international acupuncture experts from China, Germany, and the United States.[29] The acupuncture points SP6 (Sanyinjiao), LI4 (Hegu), and LR3 (Taichong) were used on both sides. In the acupressure group, a health care professional introduced the acupressure based on the instruction of the app at the baseline visit (Table 1). The women were reminded by the app every noon to apply acupressure starting 5 days before the anticipated menstruation. Users could switch off the reminders within the app. To keep the intervention standardized, the app received no major updates.

Women in the control group did not receive any study specific intervention. After the sixth menstruation cycle, that is, at the end of the study, the acupressure features were activated within the app and a personal face-to-face introduction to acupressure was offered.

The acupressure and the control groups could continue with usual care during the study, which was defined as all medical and nonmedical treatments with the exception of tuina, shiatsu, and acupuncture because of the use of similar pressure points.

Outcome measurements

The primary outcome measure was the mean pain intensity on the days with pain during the third menstruation on a numerical rating scale (NRS) from 0 (no pain) to 10 (worst possible pain) assessed retrospectively after the third menstruation.[31] The NRS and the time point were chosen based on the stakeholder process in preparation of the trial[29] and previous literature on acupressure on dysmenorrhea.[14] The NRS is easy to apply and well suited for implementation in a smartphone app, and 3 months seemed long enough to

TABLE 1
Instructions for applying acupressure

Carrying out acupressure
Find a comfortable sitting position. The right point will feel more sensitive than the surrounding area, and you may feel a slight soreness. When you have found the point, massage the area with the thumb using medium force (strong enough, but not so strong that you injure yourself) in small circles. Pay attention that you use circular movements and do not rub back and forth. While massaging, you should notice a distinct sensation, for example, a slight soreness, tingling, hypersensitivity, or heaviness.
Method
Concentrate on the points as you are massaging them. Massage the points on both sides consecutively for 1 minute each. Start the timer.
Application
Begin 5 days before you get your period. As a function of the app, you will receive a reminder of when you should begin the acupressure. Before your menstrual period, carry out the acupressure twice a day if possible; on days when this is not possible, carry out the acupressure at least once a day. During your period, on the painful days carry out the acupressure at least twice a day. If you like, you can repeat the acupressure up to 5 times.

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allow the development of an acupressure effect without risking recruitment or study adherence because of a relatively long study duration.

Secondary outcomes were assessed during and after the first, second, third, and sixth menstruation cycle by the app in both groups. These outcomes included worst pain intensity during menstruation (NRS), duration of pain (number of days with pain), responder rates (50% reduction of mean pain intensity on the days with pain compared to the corresponding baseline value), pain medication, sick leave (days of absence from work or school due to menstrual pain), body efficacy expectation,[32] adverse events, and suspected adverse reactions (intervention group only). Women in the acupressure group were also asked at the third cycle about satisfaction with the intervention. On the days on which acupressure was recommended, women were asked to record the number of acupressure sessions and the time that they spent for the acupressure.

At baseline, self-reported data were collected by paper and pencil. All other questionnaires and diaries were embedded into the app. Most outcomes were collected by questionnaires within the app at the end of the menstruation; however, data on pain medication and time spent for acupressure were collected by the app's diary. Women were reminded by app notifications every day at noon during the menstruation to fill in the questions of the diary. In addition, they were reminded at the respective time point to complete the questionnaires at the last day of menstruation at the first, second, third, and sixth menstruations. In the acupressure group, this notification was combined with the reminder to apply acupressure.

Statistical analysis

The study was designed to detect an effect size of 0.5 for the primary outcome measure (menstrual pain), with a power of 90% and a significance level of 5% using a 2-sided *t* test. Based on previous acupuncture studies, we assumed a mean of 5.5 in the control group and 4.0 in the intervention group, with a pooled standard deviation of 3 resulting in a total of 86 participants per group. Taking a potential drop-out rate of about 20% into account, 220 participants (110 per group) were planned. The primary analysis population was the full analysis set (FAS, with available data for the respective analysis) based on the intention-to-treat (ITT) principle of including each woman into the analysis according to her randomization group regardless of her adherence to the assigned intervention.

The primary analysis of the primary endpoint was an analysis of covariance (ANCOVA) with the treatment as a fixed effect, the baseline NRS value as fixed covariate, and a 2-sided significance level of 5%. Secondary outcomes were analyzed similarly, that is, by ANCOVA or by logistic or Poisson regression (depending on the scale and distribution of the data), adjusted for the respective baseline value (if available).

As a sensitivity analysis, multiple imputation techniques were performed using Markov Chain Monte Carlo approximation and fully conditional specification (FCS) methods.[33] The imputation model included all variables for the primary and secondary outcomes and age. Furthermore, in case of relevant differences in baseline variables between the treatment groups, those unbalanced variables were used as covariates for the analysis of the primary outcome. In addition, we evaluated the subgroups of women with hormonal contraceptive use at baseline, women with a migration background, and women with age of 26 years or more versus less than 26 years. Subgroups were evaluated using the interaction term of the respective subgroup with the treatment group in the analysis model.

As further supportive analysis, mixed models for repeated measures (MMRM) were fitted to compare the treatment groups with respect to changes in the primary outcome over time. The model included terms for treatment (acupressure vs control) and time as fixed main effects, an interaction term for treatment by time, the baseline value as covariate, and the subject as a random effect.

Analysis was done using SPSS 21.0 (SPSS Inc, Chicago, IL) and SAS 9.4 (SAS Institute, Cary, NC).

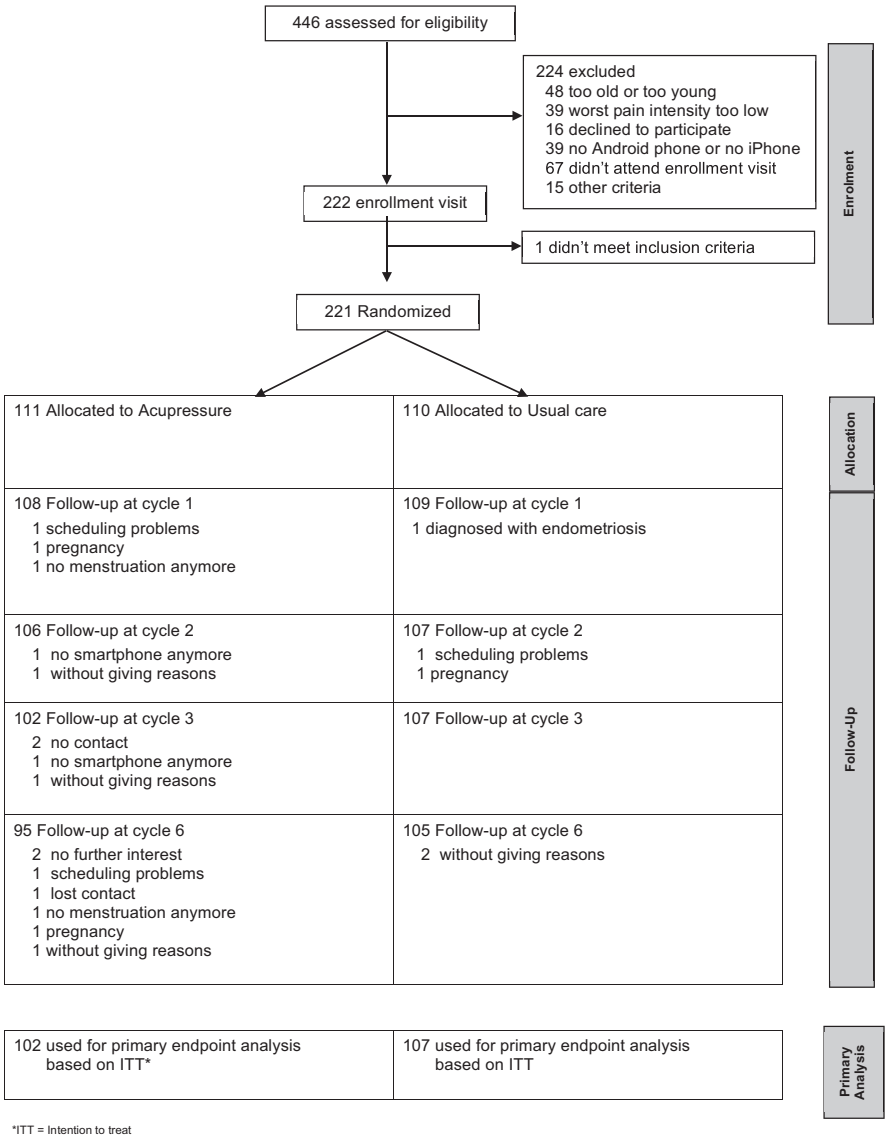
Results

Participants

The study was conducted between December 2012 and April 2015, with recruitment from December 2012 until August 2014.

Of 446 screened women, 221 were eligible for the study, gave consent, and were randomized either to

FIGURE 1
Trial flow chart.



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self-acupressure (n=111) or to usual care (n=110)(Figure 1).

The women had a mean age of 24.0 years (standard deviation [SD], 3.6 years) and were highly educated, with 89.6% having 12 or more years of school education (Table 2). A total of 37 women (16.7%) had a migration background. At baseline, the mean pain intensity on the days with pain on the NRS was 6.2 (SD, 1.6) and most women (81.0%) had taken medication during their last menstruation. The following group differences with possible relevance were seen at baseline: fewer women in the usual care group (65.1%) had a partner (acupressure group 78.4%), and more women in the usual care group used oral contraceptives (36.4% vs 23.4%).

Outcomes

Both groups showed a reduction in pain at the third and sixth menstruation cycle. The primary outcome measurement (mean pain intensity on the days of pain during the third cycle after therapy start) showed a statistically significant difference in favor of the acupressure group (acupressure: 4.4; 95% CI, 4.0−4.7; usual care: 5.0; 95% CI, 4.6−5.3; mean difference, −0.6; 95% CI, −1.2 to −0.1; $P = .026$ (Table 3 and Figure 2). At the sixth menstruation cycle, the mean difference between the groups increased (−1.4; 95% CI, −2.0 to −0.8; $P < .001$) and was considered clinically relevant.[34] The effect size (Cohen's d) for the mean pain intensity was 0.24 at the third cycle and 0.63 at the sixth cycle. Moreover, the chance to be a responder was higher for women in the acupressure group after the first, the third, and the sixth cycle with odds ratios of 2.3 (95% CI, 1.0−5.2), 2.0 (1.1−3.6), and 4.4 (2.5−7.9), respectively.

At the third and sixth menstruation cycle the worst pain intensity (group difference, −0.6, 95% CI, −1.2 to −0.02, and −1.4, 95% −2.0 to −0.7), the number of days with pain (−0.4; 95% CI, −0.9 to −0.01, and −1.2; 95% CI, −1.6 to −0.7), and the proportion of women with pain medication (odds ratio, 0.5; 95% CI, 0.3−0.9, and 0.3; 95% CI, 0.2−0.5]) was lower in the acupressure group. Hormonal contraceptive use was more common in the usual care group than in the acupressure group at the third cycle (odds ratio, 0.5; 95% CI, 0.3−0.97), but not statistically significant different at the sixth cycle (odds ratio, 0.6; 95% CI, 0.3−1.1). The number of sick leave days and body efficacy expectation (self-efficacy scale) did not differ between groups (Table 3).

On a scale from 0 to 6, the mean satisfaction with the intervention at the third cycle was 3.7 (SD, 1.3), recommendation of the intervention to others (4.3; SD, 1.5), appropriateness of acupressure for menstrual pain (3.9; SD, 1.4); and application of acupressure for other pain (4.3; SD, 1.5).

Findings were similar, and no relevant difference between results of primary, sensitivity, and subgroup analyses could be observed. The baseline characteristics of women in both groups who dropped out before the third menstruation cycle did not differ relevantly from those who did not drop out.

Safety data

In the self-acupressure group, 15 women reported having had at least 1 suspected adverse reaction (SAR). Over all cycles, the following SARs were mentioned: bruises (n = 5), deterioration (n = 3), pain in the hand (n = 1), pressure pain (n = 1), shift in menstruation cycle (n = 3), dizziness (n = 1), nausea (n = 1), pain in the legs (n = 1), and tingling in a finger (n = 2). Of those who mentioned a SAR, 10 women experienced a SAR at 1 cycle, 3 women at 2 cycles, and 2 women at 3 cycles. With the exception of 1 woman, all continued to apply self-acupressure. This woman stopped applying self-acupressure at the sixth cycle because of bruises, pressure pain, and tightness in the breast. She had already mentioned pressure pain at the first cycle, which had made it difficult to continue self-acupressure, although she did not report any SAR at the second and third cycles.

Two serious adverse events occurred in each treatment group (self-acupressure: hip surgery, hospitalization due to dizziness; usual care: surgery of the nose, appendix surgery). None was considered related to the trial or the trial intervention.

Adherence and practice time

Overall adherence was good, but declined slightly over time. At the first cycle, 108 (97.3%) of the women stated that they had practiced acupressure on at least 1 day during the menstruation cycle, and at the sixth cycle this number was 92 (82.9%). Fewer women practiced acupressure on all days with pain (first cycle 102 [91.9%]; second cycle 89 [80.1%]; third cycle 91 [82.0%]; and sixth cycle 75 [67.6%]). The mean duration of 1 practice session was similar over all cycles (first cycle: before menstruation, 5.3 minutes (mean; SD, 2.1); during menstruation, 5.4 (SD, 1.7); sixth cycle: before menstruation, 5.4 (SD, 1.5); during menstruation, 5.3 (SD, 1.5) (Table 3). Women spent about 82.5 minutes (95% CI, 73.2–91.7) for acupressure during the first cycle, and 78.8 minutes (95% CI, 68.8–88.8), 76.8 minutes (67.3–86.4), and 68.7 minutes

TABLE 2
Baseline demographic and clinical characteristics of trial groups

Characteristic	Acupressure (n = 111), mean ± SD/n (%)	Usual care (n = 110), mean ± SD/n (%)
Age (y)	24.4 ± 3.3	23.7 ± 3.9
BMI (kg/m^2)	22.0 ± 3.8	21.8 ± 3.1
≥12 Years of school	98 (88.3)	100 (90.9)
Size of household		
Single-person	17 (15.3)	20 (18.2)
Multi-person	94 (84.7)	90 (81.8)
Partnership	87 (78.4)	71 (65.1)
Migrant background [40][a]	20 (18.0)	17 (15.5)
Smartphone operating system		
iOS	45 (40.5)	38 (34.5)
Android	65 (58.6)	71 (64.5)
Duration of cycle (days)	28.7 ± 2.7	28.7 ± 2.5
Duration of menstruation (days)	5.4 ± 1.4	5.2 ± 1.0
Concomitant diseases	13 (11.7)	5 (4.5)
Complaints/pain[b]		
Abdominal cramps	98 (88.3)	88 (80.0)
Pain in lower abdomen	97 (87.4)	83 (75.5)
Back Pain	70 (63.1)	72 (65.5)
Headache	39 (35.1)	33 (30.0)
Nausea/vomiting	35 (31.5)	30 (27.3)
Other	31 (27.9)	40 (36.4)
Hormonal contraceptive	26 (23.4)	40 (36.4)
Sick leave days	0.6 ± 0.7	0.5 ± 0.7
Sport/Therapy against pain	41 (36.9)	48 (43.6)
Jogging	16 (14.4)	16 (14.5)
Fitness/gymnastics	13 (11.7)	20 (18.2)
Yoga	12 (10.8)	12 (10.9)
Meditation/relaxation	9 (8.1)	7 (6.4)
Dancing	2 (1.8)	8 (7.3)
Other	16 (14.4)	26 (23.6)
Mean pain (NRS 0–10)[c]	6.3 ± 1.6	6.1 ± 1.6
Worst pain (NRS 0–10)[c]	7.6 ± 1.1	7.5 ± 1.1
Number of days with pain	2.6 ± 1.2	2.7 ± 1.1
Pain medication intake	89 (80.2)	90 (81.8)
Body efficacy expectation	2.8 ± 0.5	2.8 ± 0.5

BMI, body mass index; *NRS*, numeric rating scale.

[a] Determination by assessment of primary language, place of birth, and place of mother's and father's birth; [b] Multiple answers possible; [c] Higher values indicate worst possible pain.

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TABLE 3
Primary and secondary outcomes at first, second, third, and sixth menstruation cycle (adjusted for baseline value)

	Acupressure, mean (95% CI)/ proportion (95% CI)	Usual care, mean (95% CI)/ proportion (95% CI)	Differences acupressure vs usual care, mean (95% CI)/OR (95% CI)	*P*
Mean pain intensity during third menstruation cycle (NRS) [primary outcome]	4.4 (4.0–4.7)	5.0 (4.6–5.3)	−0.6 (−1.2 to −0.1)	.026
Mean pain intensity (NRS)				
First cycle	4.9 (4.5–5.2)	5.2 (4.9–5.5)	−0.3 (−0.8 to 0.1)	.171
Second cycle	4.6 (4.2–5.0)	4.9 (4.5–5.3)	−0.4 (−0.9 to 0.2)	.197
Sixth cycle	3.5 (3.1–4.0)	5.0 (4.5–5.4)	−1.4 (−2.0 to −0.8)	<.001
Worst pain intensity				
First cycle	6.2 (5.9–6.6)	6.4 (6.1–6.8)	−0.2 (−0.7 to 0.3)	.383
Second cycle	5.8 (5.4–6.2)	6.1 (5.7–6.5)	−0.3 (−0.8 to 0.3)	.374
Third cycle	5.6 (5.2–6.0)	6.2 (5.8–6.6)	−0.6 (−1.2 to −0.02)	.043
Sixth cycle	4.9 (4.4–5.4)	6.3 (5.8–6.8)	−1.4 (−2.0 to −0.7)	<.001
Number of days with pain				
First cycle	2.7 (2.4–3.0)	2.8 (2.4–3.1)	−0.05 (−0.5 to 0.4)	.828
Second cycle	2.3 (2.0–2.6)	3.1 (2.8–3.4)	−0.8 (−1.2 to −0.3)	.001
Third cycle	2.3 (2.0–2.6)	2.7 (2.4–3.0)	−0.4 (−0.9 to −0.01)	.047
Sixth cycle	1.9 (1.6–2.2)	3.1 (2.7–3.4)	−1.2 (−1.6 to −0.7)	<.001
Women with pain medication intake[a,b]				
First cycle	0.5 (0.4–0.6)	0.7 (0.6–0.8)	0.4 (0.2–0.8)	.004
Second cycle	0.6 (0.5–0.7)	0.7 (0.6–0.8)	0.6 (0.3–0.1)	.051
Third cycle	0.6 (0.5–0.7)	0.7 (0.6–0.8)	0.5 (0.3–0.9)	.029
Sixth cycle	0.5 (0.4–0.6)	0.8 (0.7–0.8)	0.3 (0.2–0.5)	<.001
Number of days with pain medication				
First cycle	1.2 (1.0–1.4)	1.4 (1.2–1.6)	−0.2 (−0.6 to 0.1)	.110
Second cycle	1.1 (0.9–1.3)	1.5 (1.3–1.8)	−0.4 (−0.7 to −0.1)	.015
Third cycle	1.1 (0.9–1.3)	1.5 (1.2–1.7)	−0.4 (−0.7 to −0.1)	.021
Sixth cycle	0.9 (0.7–1.0)	1.6 (1.4–1.9)	−0.7 (−1.1 to −0.4)	<.001
Women with hormonal contraceptives[a,b]				
First cycle	0.3 (0.2–0.3)	0.3 (0.3–0.4)	0.6 (0.3–1.1)	.116
Second cycle	0.2 (0.2–0.3)	0.3 (0.3–0.4)	0.6 (0.3–1.1)	.088
Third cycle	0.2 (0.2–0.3)	0.4 (0.3–0.5)	0.5 (0.3–0.97)	.040
Sixth cycle	0.2 (0.2–0.3)	0.4 (0.3–0.5)	0.6 (0.3–1.1)	.084
General change in menstrual pain[c]				
Third cycle	2.1 (1.9–2.2)	2.8 (2.6–2.9)	–	<.001
Sixth cycle	1.8 (1.7–2.0)	2.8 (2.7–3.0)	–	<.001
Responder rate[a,b,d]				
First cycle	0.2 (0.1–0.3)	0.1 (0.05–0.2)	2.3 (1.0–5.2)	.040

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TABLE 3
Primary and secondary outcomes at first, second, third, and sixth menstruation cycle (adjusted for baseline value)
(continued)

	Acupressure, mean (95% CI)/ proportion (95% CI)	Usual care, mean (95% CI)/ proportion (95% CI)	Differences acupressure vs usual care, mean (95% CI)/OR (95% CI)	*P*
Second cycle	0.3 (0.2–0.4)	0.2 (0.2–0.3)	1.6 (0.9–3.0)	.109
Third cycle	0.4 (0.3–0.5)	0.2 (0.2–0.3)	2.0 (1.1–3.6)	.023
Sixth cycle	0.6 (0.5–0.7)	0.2 (0.2–0.3)	4.4 (2.5–7.9)	<.001
Sick leave days				
First cycle	0.3 (0.2–0.4)	0.3 (0.2–0.4)	0.04 (−0.1 to 0.2)	.497
Second cycle	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.01 (−0.1 to 0.1)	.854
Third cycle	0.3 (0.2–0.4)	0.3 (0.2–0.4)	−0.01 (−0.1 to 0.1)	.870
Sixth cycle	0.2 (0.1–0.3)	0.2 (0.2–0.3)	−0.1 (−0.2 to 0.04)	.250
Body efficacy expectation				
First cycle	2.8 (2.8–2.9)	2.9 (2.8–2.9)	−0.02 (−0.1 to 0.1)	.629
Second cycle	2.8 (2.7–2.9)	2.8 (2.7–2.9)	0.02 (−0.1 to 0.1)	.698
Third cycle	2.9 (2.8–3.0)	2.8 (2.7–2.9)	0.1 (−0.04 to 0.2)	.195
Sixth cycle	2.9 (2.8–3.0)	2.8 (2.7–2.9)	0.05 (−0.1 to 0.2)	.424

CI, confidence interval; *NRS,* numeric rating scale; *OR,* odds ratio.

[a] Proportion (95% CI); [b] Odds ratio; [c] Scale of 1–5 (menstrual pain had: 1 = improved significantly, 2 = improved slightly, 3 = no change, 4 = worsened slightly, 5 = worsened significantly); [d] Responder rate = mean pain reduced by at least 50%.

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(57.7–79.7) for the second, third, and sixth cycle, respectively.

Comment

Participating women with menstrual pain who applied self-acupressure supported by a smartphone app experienced statistically significant different pain relief after 3 menstruation cycles in comparison to women who received usual care. After 6 menstruation cycles, in the intervention group pain further decreased, resulting in a clinically relevant difference between groups.

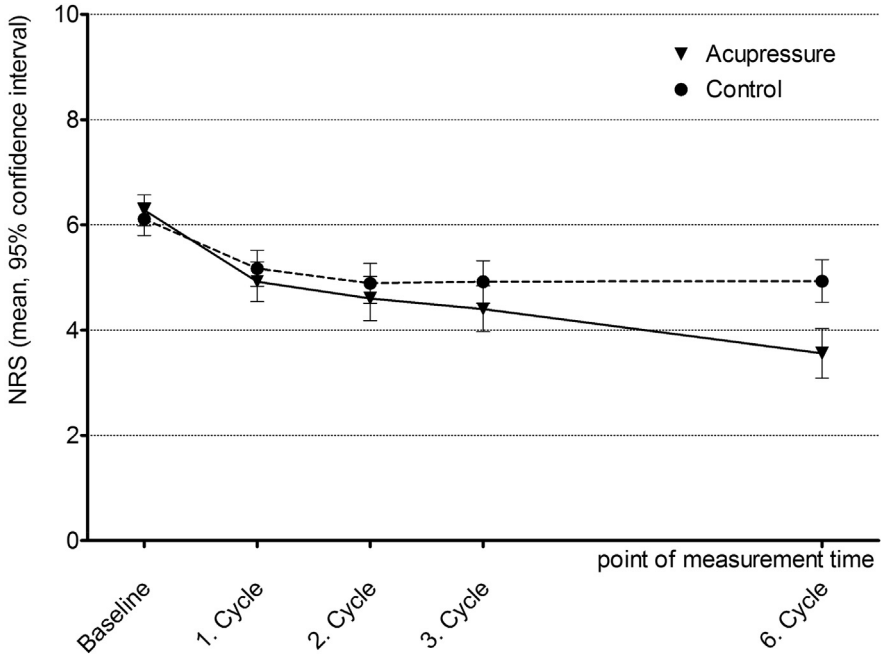
The strengths of this trial include the randomized study design, the large number of participants for an interventional randomized trial on acupressure, and the high adherence and follow-up rates. By using a smartphone app for the delivery of the intervention and for data collection, the trial used a novel study approach. Moreover, we consider the results to be transferrable to standard care settings, because this pragmatic trial resulted from an extensive stakeholder engagement process.[29]

However, the results of our trial might have been influenced by the selection of our sample. Although we aimed at a diverse sample by advertising on public transportation, almost 90% percent of participants had at least 12 years of school education, which is more than the average population. Furthermore, one-third of the screened women failed eligibility criteria. These aspects do affect the generalizability of the results. Our outcome assessment was reduced to a minimum[29] because stakeholders suggested that the outcome assessment should be short and patient-relevant, and that data should be collected by an app.

The whole trial duration, including the preparation for the app, took 4.5 years, which is a long time for a trial on consumer technology.[35] In contrast, a longer follow-up time might have provided more insight about long-term use. Based on the development of the primary outcome over time, a longer follow-up might have shown an even higher effect. However, due to the relatively short follow-up time, it is also possible that we have overestimated the impact of treatment. Recruitment for this trial was difficult, and a longer study duration might have had a further inhibiting impact on recruitment. For future studies, ways to accelerate recruitment are needed. To keep the intervention standardized, our app received no major updates. However, an advanced development of the app for future studies is already in progress.

Considering the large number of available mobile Health (mHealth) apps for smartphones, only a few have been evaluated in an randomized controlled trial setting.[27,28,36,37] To our knowledge, no randomized controlled trial evaluating a smartphone app using acupressure or targeting menstrual pain had previously been conducted. According to the updated Cochrane Review "Acupuncture for dysmenorrhoea," which included acupressure trials, evidence is insufficient to demonstrate whether or not acupuncture or acupressure is effective in treating primary dysmenorrhea because of the methodological limitations of the

FIGURE 2
Mean pain intensity (unadjusted mean, 95% confidence interval).



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included studies.[13] Although our rigorously designed trial might support the evidence base in favor of acupressure, it might also be associated with a high risk of bias because of the lack of blinding.[38] However, we think that our trial can contribute valuable data to its effectiveness in usual care.

Our results might have practical implications, because they could add a self-care option to the recommended treatment options of oral contraceptives and nonsteroidal anti-inflammatory drugs, which are effective but have limitations because of associated side effects[7,10] and failure rates.[5] Moreover, self-care treatments such as rest, medication, heating pads, tea, exercise, and herbs are already used by women with menstrual pain.[10] Therefore an additional nondrug and self-care treatment option might fit well into women's perceptions of how to treat menstrual pain[39] and might further support self-empowerment of affected women.

In our trial, for self-care acupressure, the effect increased over time, showing clinical relevance on the pain scale after 6 cycles[34] and a responder rate of about 60%. A similar increase was also shown by a trial from Chen et al.[19] However, most trials on acupressure and dysmenorrhea have had shorter follow-ups.[14] The findings that the adherence was still high after 3 months and that the effect increased over time are encouraging. Regarding the high prevalence of menstrual pain, a treatment option with a modest-to-moderate effect and a good safety profile might have a considerable public health impact and should be further evaluated. It would be interesting to compare app-based self-acupressure with other active treatment in future research.

To conclude, self-acupressure supported and evaluated by a smartphone app was able to achieve a sustainable reduction in pain and medication in comparison to usual care. This self-care intervention showed a high retention rate and was safe. We suggest that future trials should provide long-term data and compare acupressure with other active treatments options among a more diverse target group. ■

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3.2 Klinische Wirkung App-basierter Entspannung für chronische Nackenschmerzen: eine pragmatische randomisierte kontrollierte klinische Studie

Ausgehend von den Erfahrungen mit der klinischen Studie zu App-basierter Akupressur bei Frauen mit Menstruationsschmerzen (siehe oben) wurden 2 weitere digitale Gesundheitsanwendungen für chronische Nackenschmerzen und für chronische Kreuzschmerzen entwickelt, die Interventionen aus dem Bereich der Integrativen Medizin und Gesundheit integrierten. Diese wurden im Rahmen von randomisierten kontrollierten Studien evaluiert.[24] Die Studie zu chronischen Nackenschmerzen ist inzwischen publiziert und wird im Folgenden dargestellt.

Der folgende Abstrakt ist eine Übersetzung des Autors aus dem Originalartikel:

Pach, D., S. Blödt, J. Wang, T. Keller, B. Bergmann, A. A. Rogge, J. Barth, K. Icke, S. Roll, and C. M. Witt. "App-Based Relaxation Exercises for Patients with Chronic Neck Pain: Pragmatic Randomized Trial." *JMIR Mhealth Uhealth* 10, no. 1 (Jan 7 2022): e31482. https://dx.doi.org/10.2196/31482.

*„**Hintergrund:** Chronische Nackenschmerzen sind eine weit verbreitete Erkrankung. Das Erlernen einer Entspannungstechnik wird in zahlreichen Leitlinien für chronische Nackenschmerzen empfohlen. Smartphone-Apps können Entspannungsübungen anbieten; ihre Wirksamkeit, insbesondere im Rahmen der Selbstbehandlung, ist jedoch unklar.*

***Fragestellung:** Ziel dieser pragmatischen, randomisierten Studie war es zu untersuchen, ob App-basierte Entspannungsübungen, einschließlich audiobasiertem autogenem Training, Achtsamkeitsmeditation oder Guided-Imagery (geführte Bilder), bei der Verringerung chronischer Nackenschmerzen wirksamer sind als die alleinige Normalversorgung.*

***Methoden:** Smartphone-Besitzer im Alter von 18 bis 65 Jahren mit chronischen (>12 Wochen) Nackenschmerzen und einer durchschnittlichen Nackenschmerzintensität von ≥4 auf der numerischen Ratingskala (0 = überhaupt kein Schmerz bis 10 = maximal vorstellbarer Schmerz) wurden randomisiert entweder einer Interventionsgruppe zugeteilt, die App-basierte Entspannungsübungen praktizierte, oder einer Kontrollgruppe (übliche Versorgung und App nur zur Dateneingabe). Für beide Gruppen wurden die Follow-up-Daten mithilfe von App-basierten Tagebüchern und Fragebögen erhoben. Der primäre Zielparameter war die durchschnittliche Intensität der Nackenschmerzen während der ersten drei Monate auf der Grundlage täglicher Messungen. Zu den sekundären Zielparametern gehörten Nackenschmerzen auf der Grundlage wöchentlicher Messungen, Schmerzakzeptanz, Nackenschmerz-bezogener Stress, Krankentage, Einnahme von Schmerzmitteln*

und Adhärenz. Diese wurde alle bis zur 6-monatigen Nachuntersuchung gemessen. Für die primäre Analyse wurde eine Kovarianzanalyse, adjustiert für die Nackenschmerzintensität zu Baseline, durchgeführt.

Ergebnisse: *Es wurden 748 Teilnehmer gescreent und 220 Teilnehmer in die Studie aufgenommen (Durchschnittsalter 38,9 Jahre, SD 11,3 Jahre; mittlerer Ausgangswert für Nackenschmerzen 5,7 Punkte, SD 1,3). Die mittlere Intensität der Nackenschmerzen nahm in beiden Gruppen innerhalb von 3 Monaten ab; es wurde jedoch kein statistisch signifikanter Unterschied zwischen den Gruppen festgestellt (Intervention: 4,1, 95% KI 3,8-4,4 Punkte; Kontrolle: 3,8, 95% KI 3,5-4,1 Punkte; Gruppenunterschied: 0,3, 95% KI -0,2 bis 0,7 Punkte; P=.23). Darüber hinaus wurden keine statistisch signifikanten Unterschiede zwischen den Gruppen in Bezug auf die Intensität der Nackenschmerzen nach 6 Monaten, die Ansprechrate, die Schmerzakzeptanz, die Einnahme von Schmerzmitteln oder die Krankentage festgestellt. Es gab keine schwerwiegenden unerwünschten Ereignisse, die als mit der Studienintervention in Zusammenhang stehend angesehen wurden. In Woche 12 führten nur 40 % (44/110) der Teilnehmer in der Interventionsgruppe die Übungen mit der App weiter durch.*

Schlussfolgerungen: *Die Studien-App konnte chronische Nackenschmerzen nicht wirksam reduzieren und die Teilnehmer nicht dazu gewonnen werden, die Übungen im Rahmen der Selbstbehandlung durchzuführen. Zukünftige Studien zu App-basierten Entspannungsinterventionen sollten die neuesten wissenschaftlichen Erkenntnisse zu Verhaltensänderungstechniken berücksichtigen.“*

Original Paper

App-Based Relaxation Exercises for Patients With Chronic Neck Pain: Pragmatic Randomized Trial

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Abstract

Background: Chronic neck pain is a highly prevalent condition. Learning a relaxation technique is recommended by numerous guidelines for chronic neck pain. Smartphone apps can provide relaxation exercises; however, their effectiveness, especially in a self-care setting, is unclear.

Objective: The aim of this pragmatic randomized trial is to evaluate whether app-based relaxation exercises, including audio-based autogenic training, mindfulness meditation, or guided imagery, are more effective in reducing chronic neck pain than usual care alone.

Methods: Smartphone owners aged 18 to 65 years with chronic (>12 weeks) neck pain and the previous week's average neck pain intensity ≥4 on the Numeric Rating Scale (0=no pain to 10=worst possible pain) were randomized into either an intervention group to practice app-based relaxation exercises or a control group (usual care and app for data entry only). For both groups, the follow-up data were collected using app-based diaries and questionnaires. The primary outcome was the mean neck pain intensity during the first 3 months based on daily measurements. Secondary outcomes included neck pain based on weekly measurements, pain acceptance, neck pain–related stress, sick-leave days, pain medication intake, and adherence, which were all measured until the 6-month follow-up. For the primary analysis, analysis of covariance adjusted for baseline neck pain intensity was used.

Results: We screened 748 participants and enrolled 220 participants (mean age 38.9, SD 11.3 years; mean baseline neck pain 5.7, SD 1.3 points). The mean neck pain intensity in both groups decreased over 3 months; however, no statistically significant difference between the groups was found (intervention: 4.1 points, 95% CI 3.8-4.4; control: 3.8 points, 95% CI 3.5-4.1; group difference: 0.3 points, 95% CI −0.2 to 0.7; *P*=.23). In addition, no statistically significant between-group differences regarding neck pain intensity after 6 months, responder rate, pain acceptance, pain medication intake, or sick-leave days were observed. There were no serious adverse events that were considered related to the trial intervention. In week 12, only 40% (44/110) of the participants in the intervention group continued to practice the exercises with the app.

Conclusions: The study app did not effectively reduce chronic neck pain or keep the participants engaged in exercising in a self-care setting. Future studies on app-based relaxation interventions should take into account the most recent scientific findings for behavior change techniques.

Trial Registration: ClinicalTrials.gov NCT02019134; https://clinicaltrials.gov/ct2/show/NCT02019134

International Registered Report Identifier (IRRID): RR2-10.1186/1745-6215-15-490

(JMIR Mhealth Uhealth 2022;10(1):e31482) doi: 10.2196/31482

KEYWORDS

neck pain; relaxation; RCT; mHealth; smartphone app; mobile phone

Introduction

Neck pain is a global public health issue entailing a high socioeconomic burden [1,2]; moreover, it is one of the top 5 global chronic pain conditions in terms of prevalence and cause of disability [3,4]. According to the data from the European Social Survey 2014 [5], approximately 40% of all respondents reported back or neck pain. These results indicated the highest prevalence of back or neck pain in Germany (54.05%).

In most cases, neck pain is nonspecific [1]. Hence, the treatment is complex and costly. Pharmacological approaches are often used to alleviate chronic pain; however, these approaches include possible risks of tolerance, dependence, and addiction when using opioids [6,7]. Moreover, previous research showed that exercise treatment might also be beneficial in patients with neck pain [3].

Mind–body therapies focus on the interactions among the brain, mind, body, and behavior and their effects on health and disease [8]. As components of mind–body medicine, relaxation techniques have gained wide acceptance within conventional medicine [9]. The relaxation response leads to a variety of physiological benefits that may enhance pain relief through reduced sympathetic activity, decreased muscular tension, modulated pain awareness, and increased release of endogenous opioids [10,11]. Studies directly comparing the effects of self-administered versus therapist-administered interventions found similar effects on pain reduction [12]. Moreover, according to the recent *Neck Pain Guideline* of the German Society of General Practice and Family Medicine [13], learning a relaxation technique is recommended for patients with nonspecific chronic neck pain that lasts for >12 weeks. Thus, relaxation techniques alone or in addition to conventional medical care can influence the treatment and rehabilitation of chronic neck pain. However, the accessibility of cognitive and mind–body therapies for chronic low back pain and neck pain remains a major challenge [14].

Medical smartphone apps or other mobile digital health solutions can allow easy access to self-care activities [15] and support behavior changes by incorporating features such as the provision of information, tracking of activity, or providing feedback. A review [16] identified 606 mindfulness apps; however, only 3.8% (23/606) of those apps actually provided mindfulness training, and only 1 app [17] was evaluated in a randomized controlled trial (RCT). Another review [8] on apps with self-management support functions for people with persistent pain identified only 2 evidence-based apps; however, none of them were for chronic pain.

In this study, we aim to conduct a pragmatic app-based RCT to evaluate whether app-based audio relaxation exercises are more effective in reducing chronic neck pain than usual care.

Methods

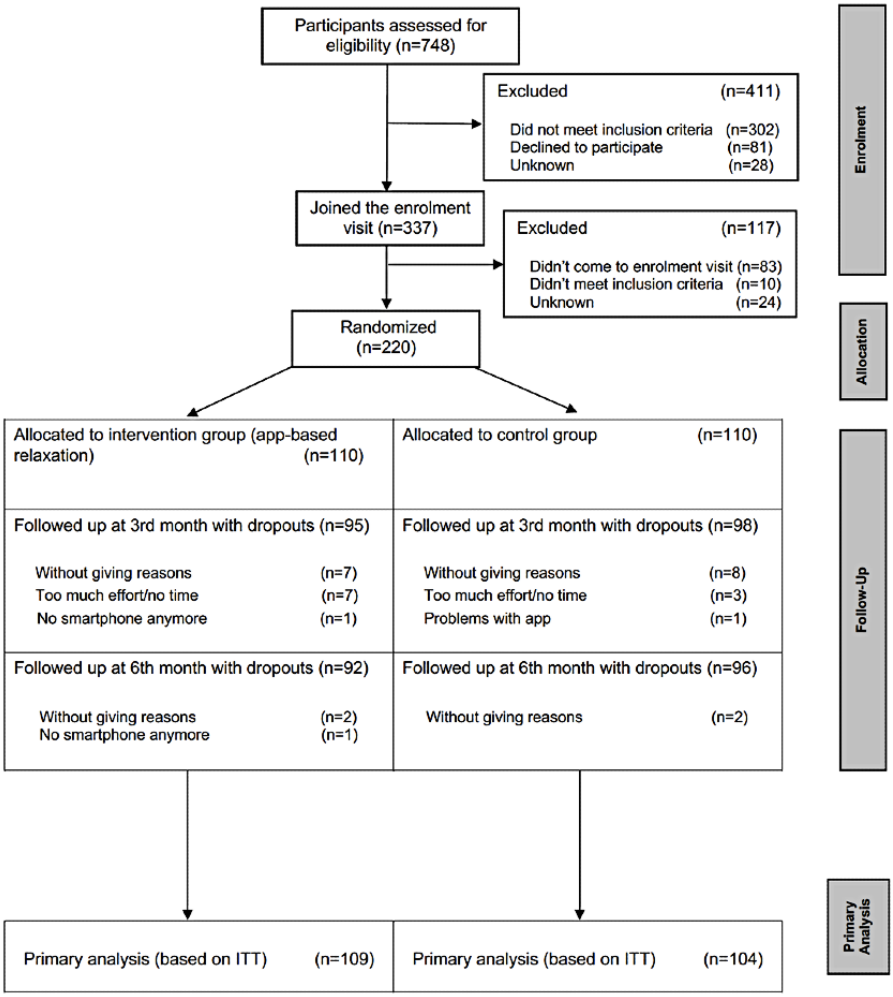
Study Design

The trial design and methods have been published elsewhere [18] and have not been changed afterward. The study app remained *frozen* without any updates during the trial.

We conducted a 2-armed, randomized, parallel-group, single-center pragmatic trial to investigate the effectiveness of additional relaxation exercises delivered by a smartphone app compared with usual care alone. Participants were randomized in a 1:1 ratio to either the app-based relaxation intervention group or the control group. The trial flow is presented in Figure 1.

The intervention duration was 6 months, with the primary outcome summarizing the effect of the first 3 months.

Figure 1. Trial flow chart. ITT: intention-to-treat.



Participants and Setting

The first participant was randomized on March 31, 2014, and the final data recording was on January 11, 2017, in Berlin, Germany. Information on the study was posted with brochures and posters in universities, gyms, and general practitioners' offices. Moreover, the study was advertised in local subways from December 2014 to July 2015. Eligibility was checked by a study nurse at the study site. Eligible participants completed the paper-and-pencil baseline questionnaires. Then, the study nurse helped the participants install the app on their own smartphones and provided a randomly allocated code to activate the study app and the respective app features according to the group allocation. Participants received compensation of €20 (US $ 22.60) after participating in the study.

The inclusion criteria were as follows: aged 18-65 years, chronic neck pain within at least the past 12 weeks, average neck pain intensity ≥4 on the Numeric Rating Scale (NRS; 0=no pain to 10=worst possible pain) in the previous week, possession of a smartphone (iOS or Android), willingness to be randomized and follow the app-delivered interventions, and willingness to enter data through the study app.

Participants were excluded if their neck pain was caused by a known malignant disease, trauma, the presence of a known rheumatic disorder, a history or planned surgery of the spinal column of the lower neck in the next 6 months, known neurological symptoms (eg, radicular symptoms because of a prolapsed disk), regular intake of analgesics (more than once per week) because of additional disease, intake of centrally acting analgesics, or a history of severe acute or chronic disorders that did not allow participation in the study.

Further exclusion criteria were known alcohol or substance abuse, insufficient German language skills, current application for a pension claim, participation in another clinical trial during the 6 months before the study and parallel to the study, applying regular relaxation techniques, mindfulness meditation, or any other *mindfulness-based* therapy 6 weeks before the study or planned in the next 6 months.

Participants in both groups were allowed to continue with their usual care (medical and nonmedical); however, the regular application of any other relaxation techniques, including mindfulness meditation or mindfulness-based training, was not permitted.

The follow-up data (daily, weekly, and at the third and sixth month) were collected through the app-based questionnaires and by in-app tracking of the length of the practiced exercises. Serious adverse events were documented during the study period to evaluate safety.

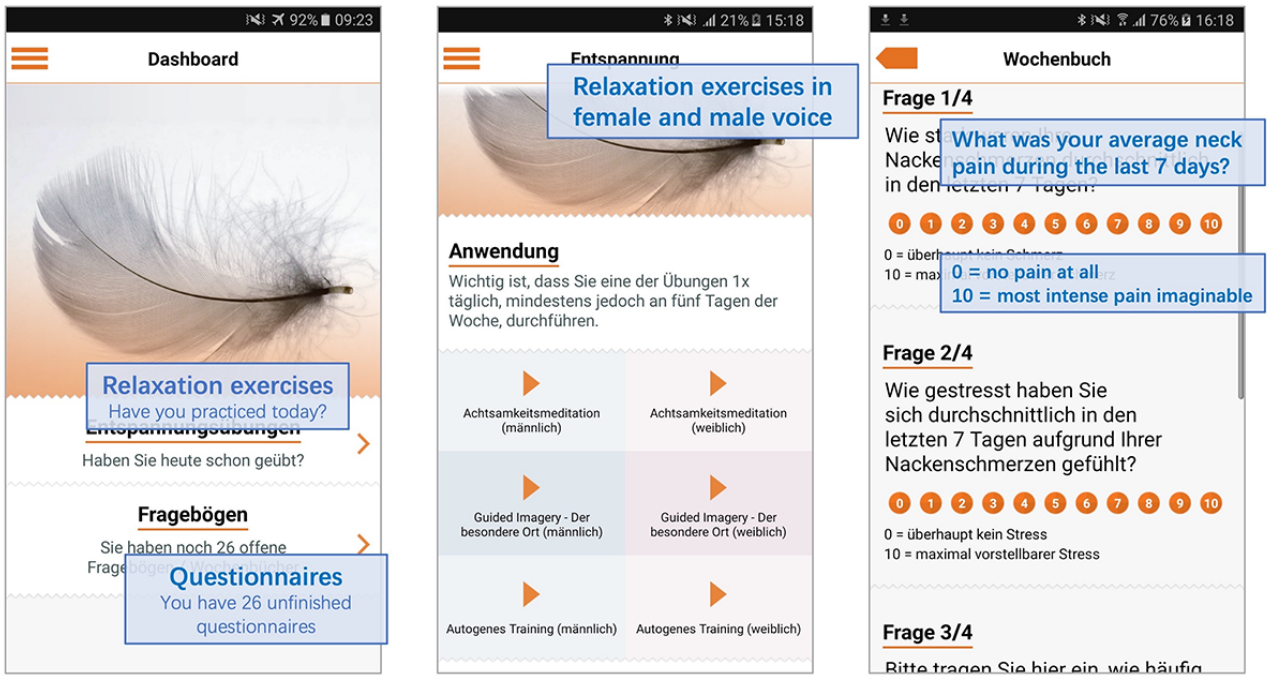
The Relaxneck App

Overview

The study app *Relaxneck* was developed by the Institute of Social Medicine, Epidemiology and Health Economics, Charité–Universitätsmedizin Berlin, Germany, together with Smart Mobile Factory, Berlin, Germany, which is an agency focused on mobile solutions [18]. The app supported iOS and Android systems and was available in the German Apple Appstore and the Google Play Store free of charge. However, the app could only be activated by entering an individual code assigned to each study participant by the study nurse.

The app supported notification features, a diary, and questionnaire options for all participants, whereas it provided audio relaxation exercises only for those in the intervention group. The app's user interface and content were available in the German language (Figure 2). The app concept was approved by the data protection officer of the Charité–Universitätsmedizin Berlin.

Figure 2. Screenshots of the study app (dashboard, relaxation exercises, and questionnaires).



App-Based Relaxation Interventions

Overview

The duration of the audios for the relaxation interventions, as well as their intensity and dosage; the use of push notifications; the diary content: and the German translation of guided imagery instructions resulted from stakeholder engagement during the planning phase of the study [18].

There were 3 types of exercises (autogenic training, mindfulness meditation, and guided imagery), with a length of 15 minutes each, that were available in 2 versions (female and male voices) in the study app for the intervention group. They were accompanied by a short instructional text (Figure 2). Relaxation exercises could be applied in different positions (sitting, walking, and lying) according to the participants' needs. It was recommended to apply a relaxation exercise daily or at least 5 days per week for 6 months.

Autogenic Training

Autogenic training is a form of self-relaxation technique that is commonly used to treat stress disorders, pain, and anxiety [19-21]. Autogenic training was developed by the German psychiatrist Johannes Schultz in 1932. It focuses on the physical sensation of the breath or heartbeat and visualizes the body as warm, heavy, or relaxed [21]. Participants learn to react to 6 verbal commands, such as "my arms are very heavy," "my heart beats regularly and calm," and "my belly is warm," to make the body feel relaxed [18].

Mindfulness Meditation

Mindfulness is a practice based on Vipassana (ie, insight) meditation, which has Buddhist roots. It is defined as "paying attention in a particular way: on purpose, in the present moment and in a nonjudgmental way" [22]. It focuses on the breath and uses it as an anchor when the mind starts to wander [18]. This concept is also used in mindfulness-based stress reduction developed by Kabat-Zinn [22-24].

Guided Imagery

In guided imagery, the mind is directed to intentionally create images to produce positive changes [25]. The audio guides the participants to visualize or conjure a place that is associated with positive feelings such as safety, security, and well-being. The guided imagery audio is accompanied by soft background music and directs visualization and imagination to a pleasant and peaceful place that has meaning for the participant to replace negative or stressful feelings [26].

Behavior Change Techniques in the App

To enhance changes in participants' behavior, behavior change techniques (BCTs) can be implemented in intervention settings [27]. As this was not a common feature in app development in 2013, we retrospectively analyzed the Relaxneck app using the BCT taxonomy (version 1) by Michie et al [27] to identify BCTs that were represented in the app, although not formally preplanned.

App for the Control Group

Participants in the control group downloaded the same app as the intervention group. All study data after baseline measurements were collected by means of app-based diaries and questionnaires. The participants were able to activate reminders for the questionnaire notifications. However, no intervention features, that is, relaxation exercises, were accessible in their version of the app. The relaxation exercises were activated after 6 months after all the survey data were collected. In addition, participants could continue using usual care, defined as all medical and nonmedical treatments, while using the app; however, relaxation techniques, mindfulness meditation, or any other mindfulness-based trainings were not permitted to be practiced during the study.

Outcome Measurements

The primary outcome measure was the mean neck pain intensity during the first 3 months of intervention based on daily measurements of pain intensity on the NRS (0=no pain to 10=worst possible pain) [18].

The secondary outcome parameters included the mean pain intensity during the first 6 months after randomization based on daily measurements, the mean pain intensity measured weekly (using NRS) as the average pain intensity of the previous 7 days over 3 and 6 months, pain acceptance (German version of Chronic Pain Acceptance Questionnaire [28]), *neck pain–related stress*, sick-leave days, and pain medication intake. Data on adherence, self-reported general changes in neck pain, suspected adverse reactions, and serious adverse events were additionally collected [18].

If a weekly survey had not been completed, the patient received an SMS text message as a reminder; if 2 consecutive weekly surveys had not been completed, the patient was contacted by telephone call; if there was no response after 2 calls, the patient received a reminder letter.

The number of participants who practiced the exercises was recorded to reflect exercise adherence over time. Practice of the exercise was defined by (1) tracking the number (and duration) of applied types of intervention with the app and (2) asking the participants weekly about the number of applied types of intervention without using the app. The complete stop of filling in any data with the study app was defined as participant dropout. Adverse events and suspected adverse reactions (only in the intervention group) were assessed after 3 and 6 months.

Sample Size

According to previous literature [29], an effect size of 0.62 has been described for mind–body therapies compared with no intervention in a group setting. We assumed a smaller effect size of 0.4 (Cohen *d*, baseline adjusted) for individual self-care relaxation exercise compared with usual care alone, as individuals might be less focused and consequently less adherent in a self-care setting [18]. To obtain a power of 80% using a 2-sided *t* test with a significance level of .05, 100 participants for each treatment group were needed (a total of 200 participants). Thus, a final sample size of 110 participants per group (220 in total), allowing a dropout rate of 9.1%, was required.

Randomization, Allocation, and Implementation

Eligible participants were randomized to either the intervention (app-based relaxation and usual care) or the control (usual care only) group using blocked randomization with variable block lengths and an allocation ratio of 1:1, that is, 110:110 participants. The randomization sequence was generated by a data manager who was not involved in the analysis of the data or the enrollment of the patients; SAS (version 9.3, SAS Inc) was used for this process. The randomization list was included in a safe Microsoft Access database to ensure that it was not accessible during the randomization process of individual participants and that the screened patients were strictly consecutively enrolled. The randomization process was conducted by the study office at the Institute of Social Medicine, Epidemiology and Health Economics. To ensure allocation concealment, first, the study team added the participants' information into the database, and then, random allocation of the participants into the intervention or control group was performed.

Statistical Analysis

For the primary analysis of the primary outcome (mean pain intensity over 3 months measured as the daily pain intensity), an analysis of covariance with a fixed factor of *treatment group*, adjusted for the baseline NRS value (fixed covariate), was performed. The analysis was based on the full analysis set (all available data without imputation of missing values, as only a small number of missing values was expected based on experiences with a previous app-based study conducted by our study team in a similar study setting [30]) based on the intention-to-treat principle with a 2-sided significance level of .05.

All the secondary analyses were explorative, and *P* values were interpreted as such. The secondary outcomes were analyzed for the full analysis set, similar to the primary analysis, depending on the scale and distribution of the outcome, that is, analysis of covariance or logistic regression, adjusted for the respective baseline value. For sensitivity analysis, the primary analysis of the primary outcome was repeated based on the per-protocol population.

Subgroup analyses were performed on the primary outcome by including an interaction term (subgroup variable by treatment) in the main model and performing separate analyses for each subgroup. Subgroups were specified with covariates in age, education (>10 years of school education or ≤10 years of school education), sex (male or female), and duration of disease. Kaplan–Meier survival analysis was conducted to investigate

whether the app features (with or without app-based intervention content) predicted the dropout of app use.

SAS version 9.4 (SAS Inc) was used for data analysis, except for the Kaplan–Meier survival analysis for adherence, which was conducted using SPSS version 22.0 (SPSS Inc).

Ethics

The study was approved by the local ethics review board at the Charité–Universitätsmedizin, Berlin (approval number Relaxneck EA 1/259/13). The study was conducted according to the common standard guidelines for clinical trials (Declaration of Helsinki and, where applicable, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice revised version, Somerset West, Republic of South Africa, 1996).

All study participants provided oral and written informed consent. The trial was registered at ClinicalTrials.gov (NCT02019134), and the study protocol has been published elsewhere [18].

Results

Baseline Characteristics

Of the 748 screened participants, 220 (29.4%) were eligible for the study and gave informed consent. They were randomized either to the app-based intervention group (110/220, 50%) or to the usual care group (110/220, 50%).

The sociodemographic and clinical characteristics of the participants at baseline are presented in Table 1. The participants had a mean age of 38.9 (SD 11.3) years and an average education, with 70% (154/220) having ≥10 years of school education. Of the 220 participants, 35 (15.9%) participants had a migration background. In the previous 7 days, the average neck pain on the NRS was 5.7 (SD 1.3) points, and 26.8% (59/220) of participants had taken medication for neck pain.

Although both groups were comparable at baseline, we observed small differences regarding gender (intervention vs control: female 74/110, 67.3% vs 79/110, 71.8%), partnership status (56/110, 50.9% vs 66/110, 60%), migration background (14/110, 12.7% vs 21/110, 19.1%), duration of neck pain (mean 79.2, SD 74.8 months vs mean 86.4, SD 97.7 months), and number of sick-leave days (mean 1.7, SD 3.6 days vs mean 2.1, SD 4.5 days) after randomization.

Table 1. Baseline demographic and clinical characteristics of the trial groups (N=220).

Characteristics	App-based intervention (n=110)	Control (n=110)
Age (years), mean (SD)	37.9 (11)	39.8 (11.6)
Gender, n (%)		
Female	74 (67.3)	79 (71.8)
Male	36 (32.7)	31 (28.2)
BMI (kg/m²), mean (SD)	24.5 (4.6)	23.9 (4.1)
Graduation after ≥10 years of school, n (%)	79 (71.8)	75 (68.2)
Size of household, n (%)		
Single-person	32 (29.1)	34 (30.9)
2-person	44 (40)	42 (38.2)
Multiperson	34 (30.9)	34 (30.9)
Partnership, n (%)	56 (50.9)	66 (60)
Migration background[a], n (%)	14 (12.7)	21 (19.1)
Neck pain intensity in the previous 7 days (NRS[b,c]), mean (SD)	5.7 (1.4)	5.8 (1.3)
Neck pain–related stress intensity in the previous 7 days (NRS[c]), mean (SD)	5.4 (1.9)	5.3 (2.1)
Duration of neck pain (months), mean (SD)	79.2 (74.8)	86.4 (97.7)
Sick-leave days, mean (SD)	1.7 (3.6)	2.1 (4.5)
Medication intake against neck pain, n (%)	28 (25.5)	31 (28.2)
Pain acceptance, mean (SD)	73.3 (16.7)	73.6 (15.9)
Subscale pain willingness, mean (SD)	30.1 (10.1)	31.1 (8.2)
Subscale activity engagement, mean (SD)	43.2 (8.8)	42.4 (9)
Expected effectiveness of relaxation exercise, n (%)		
Recovery	1 (0.9)	5 (4.5)
Distinct improvement	54 (49.1)	61 (55.5)
Light improvement	55 (50)	44 (40)
No improvement	0 (0)	0 (0)
Ineffective	0 (0)	0 (0)
Expected effectiveness of no relaxation exercise, n (%)		
Recovery	0 (0)	1 (0.9)
Distinct improvement	3 (2.7)	6 (5.5)
Light improvement	15 (13.6)	18 (16.4)
No improvement	89 (80.9)	81 (73.6)
Ineffective	3 (2.7)	4 (3.6)

[a]Based on a study by Schenk et al [31].

[b]NRS: Numeric Rating Scale.

[c]Lower values indicate better status.

Outcomes

Less intense mean neck pain was observed in both groups during the first 3 months compared with the baseline (Table 2). However, there was no significant difference in the primary outcome of the mean neck pain intensity during the first 3 months between the intervention and control groups (group difference 0.3, 95% CI –0.2 to 0.7; *P*=.23). In addition, no significant differences in the mean neck pain intensity between the 2 groups during the second 3 months (group difference −0.1, 95% CI −0.7 to 0.4; *P*=.62) or during the entire 6 months (group difference 0.1, 95% CI –0.3 to 0.6; *P*=.62) were found.

The subgroup analysis also yielded comparable primary outcomes between participants of different genders, ages, education levels, and disease durations.

Table 2. Primary and secondary outcomes (adjusted for sex and baseline value; N=220).

Outcome	App-based intervention, mean (95% CI)	Control, mean (95% CI)	Differences intervention versus control, mean (95% CI)	*P* value
Neck pain intensity during first 3 months (NRS[a,b])	4.1 (3.8 to 4.4)	3.8 (3.5 to 4.1)	0.3 (−0.2 to 0.7)	.23
Neck pain intensity (NRS[b])				
Second 3 months	3.6 (3.2 to 4)	3.7 (3.4 to 4.1)	−0.1 (−0.7 to 0.4)	.62
First 6 months	3.9 (3.6 to 4.2)	3.8 (3.5 to 4.1)	0.1 (−0.3 to 0.6)	.62
Average neck pain during previous 7 days (NRS)				
First 3 months	4.3 (4 to 4.6)	4 (3.8 to 4.3)	0.2 (−0.2 to 0.7)	.24
Second 3 months	3.8 (3.4 to 4.1)	3.9 (3.6 to 4.3)	−0.2 (−0.7 to 0.3)	.52
First 6 months	4.1 (3.8 to 4.4)	4 (3.7 to 4.3)	0.2 (−0.3 to 0.6)	.49
Pain acceptance				
After 3rd month	75.4 (73 to 77.8)	75.8 (73.4 to 78.1)	−0.4 (−3.8 to 3)	.83
After 6th month	76.1 (73.7 to 78.4)	75.8 (73.6 to 78.1)	0.2 (−3 to 3.5)	.89
Participants with medication intake against neck pain, proportion (%)[c,d]				
During 6 months	49.5 (39.8 to 59.3)	52.4 (42.4 to 62.2)	0.97 (0.5 to 1.8)	.69
Numbers of weeks with pain medication				
First 3 months	2 (1.5 to 2.5)	2 (1.4 to 2.5)	0.01 (−0.7 to 0.8)	.98
Second 3 months	2 (1.4 to 2.6)	2 (1.5 to 2.6)	−0.03 (−0.8 to 0.8)	.93
First 6 months	3.7 (2.7 to 4.7)	3.9 (2.9 to 4.9)	−0.2 (−1.7 to 1.2)	.75
Neck pain–related stress				
First 3 months	4 (3.7 to 4.3)	3.8 (3.5 to 4.1)	0.2 (−0.2 to 0.7)	.32
Second 3 months	3.6 (3.2 to 3.9)	3.6 (3.2 to 4)	0 (−0.6 to 0.5)	.88
First 6 months	3.9 (3.6 to 4.2)	3.7 (3.4 to 4)	0.2 (−0.3 to 0.6)	.46
Responder rate, proportion (%)[c,d,e]				
After third month	29.4 (21 to 38.9)	35.6 (26.4 to 45.6)	0.75 (0.4 to 1.4)	.33
After sixth month	35.9 (26.8 to 45.7)	37.5 (28.2 to 47.5)	0.93 (0.5 to 1.7)	.80
Sick-leave days				
After third month	1.2 (0.4 to 2)	1.5 (0.7 to 2.3)	−0.3 (−1.4 to 0.9)	.66
After sixth month	1.1 (0.6 to 1.6)	1 (0.5 to 1.5)	0.1 (−0.6 to 0.8)	.81
Concomitant treatment, proportion (%)[c,d]				
After third month	40 (30.8 to 49.8)	45.5 (35.9 to 55.2)	0.82 (0.5 to 1.4)	.50
After sixth month	47.3 (37.7 to 57)	43.6 (34.2 to 53.4)	1.20 (0.7 to 2.1)	.69

[a]NRS: Numeric Rating Scale.

[b]Lower values indicate better status.

[c]Between-group differences are presented as odds ratio (95% CI) instead of mean (95% CI).

[d]Proportions are not adjusted.

[e]Either at least 50% pain reduction or at least 2.5 points on the Numeric Rating Scale compared with baseline.

Furthermore, there were no significant differences between the mean average neck pain based on weekly measurements in either group during the first 3 months (group difference 0.2, 95% CI –0.2 to 0.7; *P*=.24), second 3 months (group difference –0.2, 95% CI –0.7 to 0.3; *P*=.52), or the entire 6 months (group difference 0.2, 95% CI –0.3 to 0.6; *P*=.49).

The chance of being a responder was similar for both groups after 3 months (odds ratio 0.75, 95% CI 0.4-1.4) and after 6 months (odds ratio 0.93, 95% CI 0.5-1.7).

There were also no significant differences in pain acceptance between the groups after 3 months (group difference −0.4, 95% CI −3.8 to 3; *P*=.83) and 6 months (group difference 0.2, 95% CI −3 to 3.5; *P*=.89).

There was no significant difference between the proportions of participants who took pain medication among both groups during the whole follow-up period of 6 months (odds ratio 0.97, 95% CI 0.5-1.8; *P*=.68). The number of weeks with pain medication did not differ between the groups in the first 3 months, second 3 months, and 6 months. The number of sick-leave days and pain acceptance did not differ between the groups.

The sensitivity and subgroup analyses did not change the pattern of the results, and we found no significant difference between female and male participants in a subgroup analysis of the primary outcome.

App-Based Exercise Time and Study Dropout

The overall time spent exercising declined with time. In the first week, almost all participants (109/110, 99.1%) in the intervention group practiced the exercises with the app. However, only 40% (44/110) of the participants continued to practice the exercises (for any length) in week 12, and 30% (33/110) of the participants continued to practice the exercises (for any length) in week 26. The declining trend was similar over the study phase when comparing the number of participants who practiced relaxation exercises of any length with the number of participants who practiced relaxation exercises for at least 10 minutes per week (Figure 3).

The Kaplan–Meier survival curves in Figure 4 display the study dropouts. There was no significant difference in the curves between the 2 groups according to the log-rank test (*P*=.44).

Approximately 74.5% (82/110) of participants in the intervention group and 79.1% (87/110) of participants in the control group used the study app to answer the survey questions until the end of the study (week 26).

Figure 3. Number of participants practicing the exercises over time.

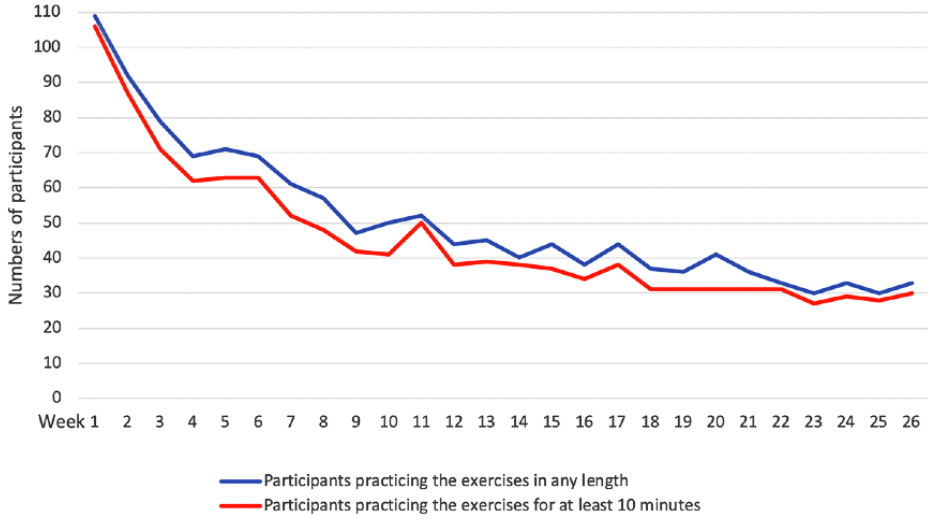
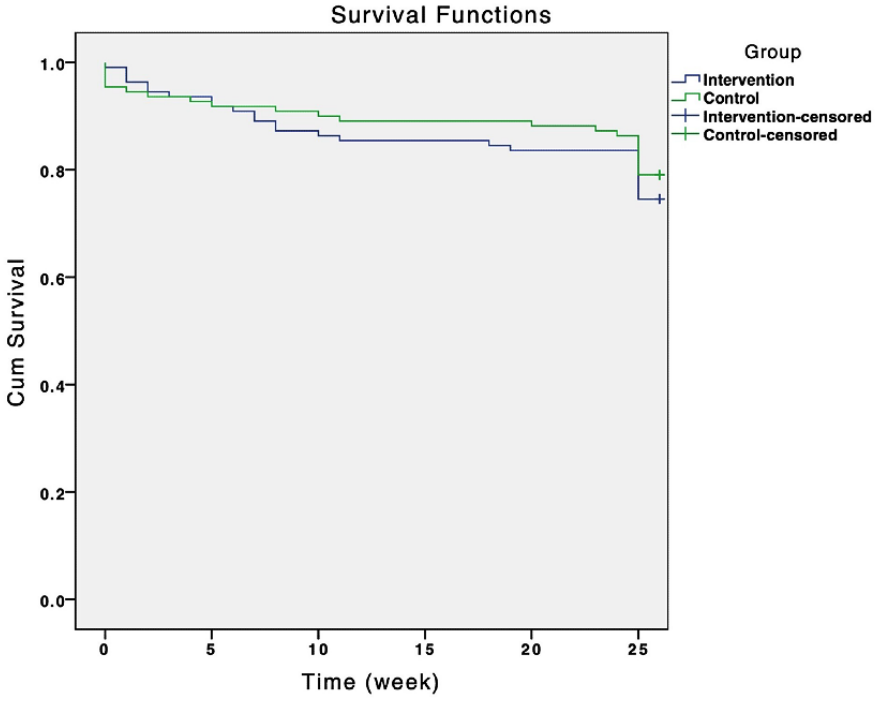


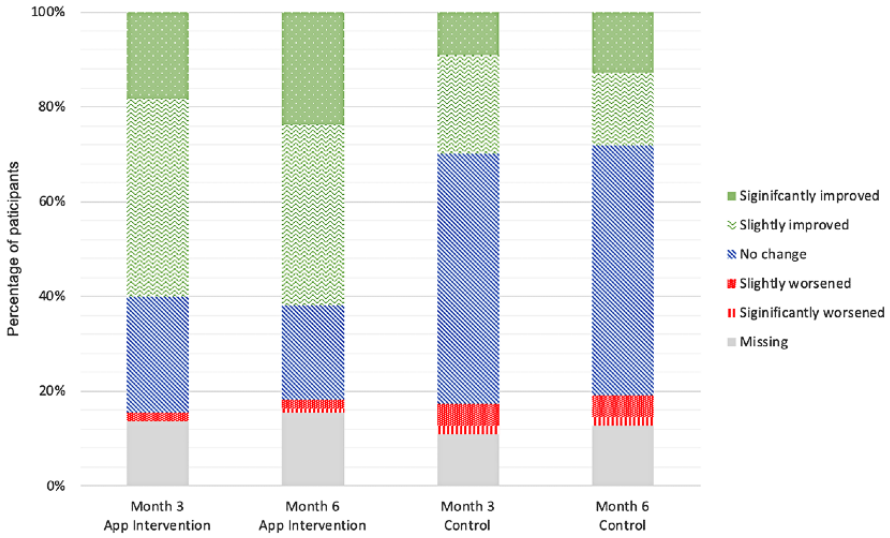
Figure 4. Probability of dropout in using the study app by group.



Self-perceived Neck Pain Change

Overall, 60% (66/110) of participants in the intervention group reported that they felt the neck pain improved significantly or slightly after 3 and 6 months, in contrast to approximately 30% (33/110) of participants in the control group who said the same (Figure 5).

Figure 5. Self-perceived improvement of neck pain.



BCTs in the App

Most parts of the app's user interface implementations can be characterized as *prompt and cues* BCT, such as the dashboard dialog showing the number of questionnaires remaining to be processed. Moreover, the *prompt and cues* BCT was combined with the *action planning* BCT to remind participants to fill out their weekly diaries. Participants could determine the time and date of the reminders (action planning and prompt and cues BCT).

To ensure proper performance of the relaxation exercises, all the exercises were explained by experienced clinicians in an audio recording (*instruction on how to perform the behavior* BCT). The Relaxneck app provided the full name, profession, professional title, and workplace of the audio recording instructors to ensure quality and safety for the participants (*credible source* BCT).

Safety Data

There were 5 serious adverse events recorded only in the control group, including cancer, sudden hearing loss, nerve injury and spinal tap, tonsillectomy, and an accident causing a fracture of the upper arm. None of them was considered related to the trial or the trial intervention.

Discussion

Principal Findings

In our trial, additional app-based self-relaxation techniques were not more effective than usual care alone for the reduction of chronic neck pain in a pragmatic setting. The results were consistent across all outcomes. The evaluated self-relaxation techniques were safe to use; however, they did not effectively relieve chronic neck pain during this app-based study.

There are a few possible reasons that helped to understand why the intervention did not improve pain. The study app's design was not updated during the study (developed in 2014) and did not include more elaborate BCTs, such as feedback about the correct application of the intervention and monitoring [27]. As the retrospective BCT analysis showed, only *prompt and cues* BCT was mainly used, whereas modern digital interventions or consumer apps widely apply BCTs [32,33]. In mobile health settings, personalized feedback from the app would be a promising virtual communication tool to enhance patient engagement and adherence [34]. Biofeedback and self-monitoring of changes are very important in relaxation- and mindfulness-based therapies for pain. Moreover, it must be considered that our study mainly measured self-reported outcomes. The study may have benefited from parameters such as step count as a measure of physical activity or sleep duration as a proxy for sleep [35]. At the time when the study was planned, wearables were not widely implemented, and it was more difficult to link these measures with an app because of interoperability issues. However, the type and duration of the audio recordings used as interventions were measured and used as measures of adherence. Although tracked outcomes may have added a more objective point of view, the implementation would have added a much larger complexity during the development of the app. In addition, mindfulness-based therapies are very often designed with progressive lengths or difficulties [36]. In our trial, the participants were required to practice 3 relaxation exercises of almost the same length repeatedly across the whole intervention period. This could have limited the participants' interest and the treatment effect. Finally, our app focused on audio relaxation alone instead of incorporating a whole theoretical framework such as mindfulness-based stress reduction or a comprehensive pain management strategy. Therefore, it is likely that the intervention of the study app was not powerful enough to improve chronic pain.

Adherence to the trial intervention was low compared with other app-based studies conducted by our research group [30,37]. The number of participants who performed the relaxation exercises

diminished during the course of the study. Potential explanations may again be the lack of an elaborate BCT concept or that chronic pain decreases motivation [38], especially to perform prescribed physical activities and exercises [39]. However, the number of practiced exercises of any length or >10 minutes remained similar over time. This might indicate that users who feel attached to the app-based relaxation exercise at the beginning finish the whole exercise process in most cases.

Although our study intervention was asynchronous, that is, contact with a health care provider and app intervention occurred at different time points, future mobile health studies may also include synchronous interventions in which health care providers could offer real-time interventions to the users. This approach might be helpful to improve the app and study adherence. However, this approach might also increase the complexity of the intervention and increase the costs.

In our trial, stopping the app-based intervention did not necessarily predict stopping the answering of the app-based survey questions. Only 30% (33/110) of the participants continued to practice the app-based relaxation exercises until the end of the follow-up; however, 74.5% (82/110) of participants used the app to answer survey questions until the end of the trial. Meanwhile, adherence to app use for answering survey questions was not affected by whether the app contained intervention features. The proportion of participants who used the app regularly to answer surveys until the end of the study was rather similar in both groups. A possible explanation for the good response rate in both groups could be our reminder system for the questionnaires or the paid compensation for the efforts.

Although all other outcomes did not show statistically significant group differences, most participants in the intervention group reported self-perceived improvement of neck pain, whereas most participants in the control group reported no change or worsening of neck pain. This result might be attributed to a digital placebo effect. The concept of the digital placebo effect has already been discussed in mental health studies [40]. A good example could be seen in a study involving a smartphone app that was designed to help patients self-monitor and record their symptoms of depression. Even without any direct therapeutic intervention, smartphone-based self-monitoring significantly reduced the symptoms [41]. Future studies should investigate the perceived changes in pain and the placebo-like effects of smartphone interventions.

Strengths and Limitations

Our app-based RCT was performed in a pragmatic setting. In addition, stakeholder engagement was implemented in the design of the trial and intervention [18]. Hence, the selection of the relaxation exercises and the length of the exercises were defined during stakeholder meetings to facilitate patient-centered therapy. Moreover, the study included a sufficient number of participants to answer our research question. Thus, our findings were considered generalizable in a real-life setting.

Some limitations have to be considered for this trial. The trial recruitment took rather long (32 months), possibly because of our conventional on-site recruitment strategy with paper-and-pencil baseline questionnaires. During that time, smartphone technologies, designs, and perceptions experienced numerous changes. For example, it is unclear whether the app's user interface was perceived as outdated by the participants. For future app-based studies, web-based recruitment and the incorporation of an app-based baseline survey could accelerate the overall trial process [15]. This acceleration of the trial process might also increase the relevance of the results.

Potential selection bias with an impact on the generalizability of the results might be another limitation of this study. The trial was conducted from 2014 to 2017. All study participants needed to own a smartphone. However, at that time, the number of smartphone owners in Germany (approximately 50%) was substantially lower than the current number (approximately 72%) [42]. It is unclear whether this affected the characteristics of our study population. To address a broader user base, we decided to build the study app for both the main platforms (iOS and Android).

Unfortunately, our sample size could not enable gender disaggregation. Gender might influence behavioral change, use patterns, and adherence to app use [43]. Some app-based studies have reported that gender is a strong predictor of the discontinuation of relaxation app use [37,44]. In this study, approximately 69.5% (153/220) of the participants were women. It would be interesting to discover the role of sex and gender in participants' adherence in future studies.

During the development of the app, we did not follow a preplanned BCT concept, and only basic BCTs were implemented, as shown in the post hoc review of the BCT techniques used. However, regarding behavioral change and intervention effects, a meta-analysis [45] concluded that implementing more (than one) theory is unlikely to improve intervention effectiveness. Future studies should be conducted to better understand the impact of BCTs on intervention outcomes for interventions for chronic pain.

Finally, the trial was single-blinded, as we could not blind the participants. However, it is common that participants cannot be blinded in nonpharmacological complex intervention trials and eHealth trials.

Comparison With Previous Work

Mind–body therapies are considered to be relatively safe [46]. However, only a few studies have been conducted on chronic neck pain. There were not enough trials for the Institute for Clinical and Economic Review (ICER) to summarize the effectiveness of cognitive and mind–body therapies for chronic neck pain [14]. According to a systematic review that investigated the effects of mindfulness- and relaxation-based interventions in an eHealth setting [47], only a few studies reported positive effects on pain, and no study reported positive effects on stress or mindfulness.

However, some eHealth studies have been conducted for chronic lower back pain. Heapy et al [48] reported that the efficacy of cognitive behavioral therapies (CBTs) delivered remotely using telephone and the internet for chronic back pain is not inferior to that of in-person CBTs. Kristjánsdóttir et al [49] reported that smartphone app–based interventions with personalized

feedback can reduce catastrophizing in women with chronic widespread pain. Instead of relaxation exercises alone, CBT, including emotion recognition, mindfulness exercises, and empathic communication, was highlighted in these studies. It seems that the evidence for only relaxation is rather low compared with systematic mind–body therapy or CBT for chronic pain. Therefore, future studies are required to investigate the effect of mind–body therapy on chronic neck pain within a comprehensive pain management strategy.

Conclusions

In conclusion, the evaluated study smartphone app, which included self-relaxation techniques such as autogenic training, mindfulness meditation, and guided imagery but without elaborate BCTs, was not more effective than usual care for chronic neck pain in a pragmatic trial. Further studies are needed to understand the potential of relaxation for neck pain and whether app-based mechanisms for relaxation and behavior change might be useful within a comprehensive pain management strategy for neck pain.

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Authors' Contributions

DP, SB, and CMW conceived and designed the study. TK performed the data analysis, and JW and the other coauthors performed the data interpretation. JW and DP wrote the first draft of the paper. All the authors discussed the results, commented on the paper, and approved the final paper.

Conflicts of Interest

This was an investigator-initiated trial. The app was developed for research purposes and is not a commercial product. The authors do not have any financial stake in the success of the app. CMW received research grants from the university for digital health projects from Krebsliga Schweiz, German Cancer Aid, The German health care Innovation Fund, and Newsenselab GmbH. Board positions related to digital health for mind and body (nonpaid) are as follows: Codirector of the Digitals Society Initiative of the University Zurich and President Schweizer Fachverband Mind Body Medicine

Multimedia Appendix 1

CONSORT-eHEALTH checklist (V 1.6.2).
[PDF File (Adobe PDF File), 91 KB-Multimedia Appendix 1]

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Abbreviations

BCT: behavior change technique
CBT: cognitive behavioral therapy
ICER: Institute for Clinical and Economic Review
NRS: Numeric Rating Scale
RCT: randomized controlled trial

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3.3 Entwicklung, Nutzung und Zugang zu einer internationalen ResearchKit-App für Frauen mit Menstruationsschmerzen

Während die vorhergehenden digitalen Studien einen hybriden Ansatz verfolgten, d.h. Gesundheitsexperten waren zumindest zu Beginn der Studien im direkten persönlichen Kontakt mit Teilnehmenden der Studie, sollten die gewonnen Erkenntnisse auch für eine rein virtuelle Studie, somit ohne Kontakt mit Gesundheitsexperten, für junge Frauen mit Menstruationsschmerzen umgesetzt werden. Die folgende Arbeit beschreibt und evaluiert den Entwicklungsprozess dieser Studie, die Inhalte auch aus dem Bereich der Integrativen Medizin und Gesundheit sowie das Initiale Nutzungsverhalten der Studienteilnehmerinnen.

Der folgende Abstrakt ist eine Übersetzung des Autors aus dem Originalartikel:

Wang, Jiani, Alizé A Rogge, Mike Armour, Caroline A Smith, Christopher R D'Adamo, Claudia R Pischke, Hung-Rong Yen, Mei-Yao Wu, Ari Ojeda Ocampo Moré, Claudia M Witt, and Daniel Pach. "International ResearchKit App for Women with Menstrual Pain: Development, Access, and Engagement." Original Paper, *JMIR Mhealth Uhealth* 8, no. 2 (2020): e14661. https://dx.doi.org/10.2196/14661.

*„**Hintergrund:** Primäre Dysmenorrhoe ist eine häufige Erkrankung bei Frauen im gebärfähigen Alter. Eine frühere, von unserer Gruppe durchgeführte App-basierte Studie hat gezeigt, dass eine Smartphone-App zur Unterstützung der Selbstakupressur, die von einer medizinischen Fachkraft eingeführt wird, Menstruationsschmerzen lindern kann.*

***Fragestellung:** In dieser Studie soll untersucht werden, ob eine spezielle Smartphone-App Menstruationsschmerzen bei 18- bis 34-jährigen Frauen mit primärer Dysmenorrhoe im Rahmen einer Selbstbehandlung wirksam reduziert. Eine Gruppe von Frauen hat Zugang zu der Studien-App mit allen Funktionen und wird mit zwei Kontrollgruppen verglichen, die Zugang zu weniger Funktionen der App haben. Hier berichten wir über das Studiendesign, die Entwicklung der App, den Zugang der Nutzerinnen und die Nutzung.*

***Methoden:** Auf der Grundlage der praktischen Auswirkungen der vorherigen App-basierten Studie haben wir die Studien-App überarbeitet sowie das ResearchKit-Framework (Apple) genutzt. Techniken zur Verhaltensänderung (BCTs) wurden in der App implementiert und durch Expertenbewertungen validiert. Der Nutzerzugang wurde durch die Bewertung des Rekrutierungsfortschritts im Laufe der Zeit geschätzt. Um die Nutzung der Nutzerinnen zu bewerten, wurden die Nutzerentwicklung und die Rücklaufquote der Umfragen zu Beginn der Studie untersucht.*

Ergebnisse: *Die Entwicklung der Studien-App für eine 3-armige randomisierte kontrollierte Studie erforderte ein multidisziplinäres Team. Die App ist für die Zielpopulation kostenlos über den Apple App Store zugänglich. In Deutschland wurde die App innerhalb von 9 Monaten 1458-mal heruntergeladen und 328 Studienteilnehmer wurden über die App ohne externe Werbung rekrutiert. Insgesamt wurden 98,27% (5157/5248) der App-basierten Baseline-Fragen beantwortet. Die korrekte Klassifizierung der in der App verwendeten BCTs erforderte psychologisches Fachwissen.*

Schlussfolgerungen: *Die Durchführung einer innovativen App-Studie erfordert multidisziplinäre Anstrengungen. Leichter Zugang und die Nutzung einer solchen App können durch die Rekrutierung über den App Store erreicht werden. Künftige Forschungsarbeiten sind erforderlich, um die Determinanten für Nutzerbindung, die optimale Anwendung der BCTs und mögliche klinische und Selbstbehandlungsszenarien für die Nutzung der App zu untersuchen. Registrierung der Studie: ClinicalTrials.gov NCT03432611; https://clinicaltrials.gov/ct2/show/NCT03432611 (Archived by WebCite at http://www.webcitation.org/75LLAcnCQ)“*

Original Paper

International ResearchKit App for Women with Menstrual Pain: Development, Access, and Engagement

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Abstract

Background: Primary dysmenorrhea is a common condition in women of reproductive age. A previous app-based study undertaken by our group demonstrated that a smartphone app supporting self-acupressure introduced by a health care professional can reduce menstrual pain.

Objective: This study aims to evaluate whether a specific smartphone app is effective in reducing menstrual pain in 18- to 34-year-old women with primary dysmenorrhea in a self-care setting. One group of women has access to the full-featured study app and will be compared with 2 control groups who have access to fewer app features. Here, we report the trial design, app development, user access, and engagement.

Methods: On the basis of the practical implications of the previous app-based study, we revised and reengineered the study app and included the ResearchKit (Apple Inc) framework. Behavior change techniques (BCTs) were implemented in the app and validated by expert ratings. User access was estimated by assessing recruitment progress over time. User evolution and baseline survey respondent rate were assessed to evaluate user engagement.

Results: The development of the study app for a 3-armed randomized controlled trial required a multidisciplinary team. The app is accessible for the target population free of charge via the Apple App Store. In Germany, within 9 months, the app was downloaded 1458 times and 328 study participants were recruited using it without external advertising. A total of 98.27% (5157/5248) of the app-based baseline questions were answered. The correct classification of BCTs used in the app required psychological expertise.

Conclusions: Conducting an innovative app study requires multidisciplinary effort. Easy access and engagement with such an app can be achieved by recruitment via the App Store. Future research is needed to investigate the determinants of user engagement, optimal BCT application, and potential clinical and self-care scenarios for app use.

Trial Registration: ClinicalTrials.gov NCT03432611; https://clinicaltrials.gov/ct2/show/NCT03432611 (Archived by WebCite at http://www.webcitation.org/75LLAcnCQ).

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KEYWORDS

dysmenorrhea; mHealth; mobile applications; acupressure; pain; behavior change techniques (BCTs); ResearchKit; recruitment

Introduction

Background

In recent years, increasing smartphone access has enabled the advancement and widespread use of smartphone apps [1,2]. Apps are a promising tool for people with a wide variety of health conditions and may be particularly useful to guide and support individuals in the self-management of these conditions [3,4]. A recent systematic review on apps in pain management concluded that apps might be beneficial for patients, particularly in an outpatient setting, but that there is a need for more scientific knowledge [5]. Furthermore, in an Australian national survey on mobile health (mHealth) in women with polycystic ovary syndrome [6], current evidence-based information was considered to be the most desirable app feature. Thus, an app with evidence-based information on menstrual pain might be of great value for patients suffering from this common problem.

Menstrual disorders are highly prevalent among women of reproductive age, and especially in young women; they commonly include period pain and mood disturbances [7]. Primary dysmenorrhea is defined as menstrual pain in the absence of underlying pathology, with the pain commonly starting within 3 years of menarche (the first menstrual period) [8]. A characteristic symptom of primary dysmenorrhea is crampy, colicky spasms of pain below the belly button, occurring within 8 to 72 hours of menstruation and peaking within the first few days as menstrual flow increases [9]. Many women with dysmenorrhea also experience other menstrual-related symptoms such as back pain, headaches, bowel changes, nausea, and vomiting [9]. Primary dysmenorrhea has significant negative impacts on education [7] and productivity at work [10]. Current menstrual health literacy and understanding of effective self-care strategies for menstrual symptoms are often poor [11].

In a previous randomized pragmatic trial (trial registration: ClinicalTrials.gov NCT01582724) [12] for women with menstrual pain, a total of 221 women were randomly assigned to 1 of 2 study groups. Both groups received the study app and a short introduction by a health care professional. Although the intervention group had access to acupressure-based features, including visual and written instructions on how to apply self-acupressure before and during menstruation, the control group did not. In addition, the app could send regular reminders to start the acupressure or to fill in questions. For both groups, the app was used to collect the study-related data and support the management of the menstrual period with a simplistic period calendar. Users in the self-acupressure group reported a significant reduction in the mean pain intensity and reported less pain medication intake in comparison with the usual care control group. In addition, two-thirds of the women still used the app and continued to apply self-acupressure after 6 months [12]. Owing to the fast-developing mHealth technology, it was difficult to keep these noteworthy study results relevant for actual implementation. This was, in part, because of the user experience and because the underlying technology soon became outdated. Therefore, a complete modernization and reengineering of the app and the development of a new corresponding trial that examines its effect over a longer duration than undertaken in the initial trial were necessary.

In 2015, Apple Inc introduced ResearchKit as an open-source framework to support clinical researchers conducting structured mobile app–based health studies [1]. This free and reusable framework can simplify the integration of patient recruitment, the consent process, and the data collection in an mHealth study app. A modernization and reengineering of the previous study app using the ResearchKit framework, new software tools, and design guidelines for broader functionalities and an up-to-date interface would allow to verify the study results from our previous trial on a larger scale and in a real-life self-care setting in several different countries across the world. To our knowledge, no ResearchKit app-based interventional studies have been previously conducted targeting women with menstrual pain. By implementing this ResearchKit app, it would be possible to improve self-care for menstrual pain by encouraging users to change their behavior and regularly apply self-care activities, such as exercise, yoga, or self-acupressure.

Michie et al defined the smallest, observable, replicable intervention component with the potential to bring about change in behavior as behavior change techniques (BCTs) [13]. BCTs have been widely applied in electronic health interventions. A prior ResearchKit app-based observational study evaluated the decision making in patients with acute anterior cruciate ligament ruptures [14] and suggested that it might be possible to maintain users' motivation by providing instant feedback and relevant treatment information. In another study aimed at reducing alcohol consumption via an app [15], self-monitoring, goal setting, action planning, and feedback in relation to goals were identified as BCTs with the greatest potential to reduce alcohol use. A review on apps targeting persons with poor control of type 2 diabetes mellitus also suggests that the majority of BCTs employed are those for the promotion of self-regulatory behavior [16]. However, there is a lack of data for expert validation of BCTs implemented in apps for menstrual pain.

From the recruitment perspective, previous ResearchKit-based studies predominantly used Web-based recruitment. Web-based recruitment has the potential advantage of reaching a broader population quickly, whereas conventional recruitment is usually time consuming and costly. However, the broad reach can potentially bring in people who are not the target population of a particular mHealth study [17]. In an interventional ResearchKit

study, enrollment before eligibility screening (number of App Store visits and downloads) and after baseline questions are indicators for user engagement. However, this important measurement has not been widely reported in previous mHealth studies yet.

Objectives

To address the questions raised above and to gain a greater understanding for conducting mHealth trials, we report the development, user access, and user engagement of our ResearchKit-based study app for an ongoing pragmatic randomized controlled trial (RCT) [18] on menstrual pain.

Methods

Study App and Study Design

Technical Development of the Study App

The development of the app was started with the aim to modernize the design and technology of the study app *AKUD* (2012-2015) for a new 3-armed study in a self-recruitment self-care setting.

The study app *Luna.* (Luna, period) was developed in a collaborative project by the Institute of Complementary and Integrative Medicine of the University of Zurich, Switzerland, the Institute for Social Medicine, Epidemiology and Health Economics, Charité – Universitätsmedizin Berlin, Germany, and Smart Mobile Factory, Berlin, Germany, based on Apple's ResearchKit modular concept. The app was coded in Swift 4 with initial full support for English and German and prepared for easy deployment of other languages, such as simplified and traditional Chinese. The design followed the iOS Human Interface Guidelines (2017) and targets young women. The team involved in the development included iOS and back-end developers, designers, medical doctors, public health researchers, psychologists, and experts on integrative medicine and health.

Behavior Change Techniques in the Study App

The development of user interaction and feedback wording was based on the previous app. However, during the development of the new app, we used the BCT taxonomy (BCTTv1), according to Michie et al [19], to document BCTs employed in the app. For example, the BCT *goal setting* was implemented to promote the goal of completing certain self-care activities. In addition, bar charts that recorded change in pain and activities were set up based on the BCT *self-monitoring*. The app was developed in English. During the adaption to German and Chinese, the content of the app was always translated with care to ensure that the respective underlying BCTs were not affected.

For the scientific description of an mHealth intervention, a proper description of BCTs implemented in the app is important. For this, expert validation is essential. At a later stage after the app development was completed, 2 psychologists who were not part of the development team independently rated the individual app features to validate the proper use of BCTs according to the BCTTv1 [19]. We compared the list of BCTs (that were intended to be implemented in the app) of 1 app development team member with the rating results of these 2 psychologists. Where there was disagreement regarding which BCT was used in the app, a final agreement was reached in a consensus meeting between the 3 raters (Table 1).

Table 1. App features and corresponding behavior change techniques implemented.

App features	Wording and app content	BCTs[a] (rating)
Introduction to baseline survey	"Hello! To get to know you better, we would like to ask you some more questions. All of your data will be kept strictly confidential and anonymous."	No BCTs
Baseline survey finished	"Thank you for your patience. Now we have all the necessary baseline information. You can start with the study."	No BCTs
Notification of doing interventions/fulfilling surveys	"Time to do some activities for your period pain and record your progress."	Prompts/cues (7.1)
When a survey has been finished	"Well Done!"	Social reward (10.4)
In-app reminder of finishing survey during task days	"Missing Answers. Keep going with the questions, this can help you see your progress."	Prompts/cues (7.1)
In-app reminder for acupressure	"Apply acupressure. On days where you have pain, we recommend at least twice a day."	Prompts/cues (7.1)
When the timer for acupressure finished (for all 6 points)	"Well Done! Keep on taking care of yourself."	Social reward (10.4)
Guide for nontask days	"New questions will appear five days before your next period."	Prompts/cues (7.1)
Instructions of when to apply acupressure	When to Apply Acupressure. Instructions of when to apply acupressure (time, frequency).	Goal setting (behavior) (1.1); action planning (1.4)
Instructions of how to apply acupressure	How to Apply Acupressure. Instructions of how to apply acupressure (position, strength, and feeling).	Instructions on how to perform a behavior (4.1)
An image and location for each acupressure point	Image and description of locations of acupressure 3 points: spleen 6, liver 3, large intestine 4.	Instructions on how to perform a behavior (4.1); demonstration of behavior (6.1)
Instruction video for self-acupressure	An instruction animation for self-acupressure on 3 points: spleen 6, liver 3, large intestine 4.	Instructions on how to perform a behavior (4.1); demonstration of behavior (6.1)
Self-care recommendation	"Evidence-based information with references of 5 self-care recommendations: exercises; dietary supplementations; heating pad/hot water bottle; yoga; medication."	Information about health consequences (5.1); credible source (9.1)
Timer for self-acupressure: 1 minute for each point	A counting down timer with a picture of the corresponding acupressure point.	Goal setting (behavior) (1.1); instructions on how to perform a behavior (4.1); demonstration of behavior (6.1)
Dashboard screen	Dashboard screen, including period calendar, diagrams, and charts reviewing pain and survey questions, and a function button for period start/end.	Feedback on behavior (2.2); self-monitoring of behavior (2.3); self-monitoring of outcome(s) of behavior (2.4); feedback on outcome(s) of behavior (2.7)
Journal screen: calendar	Journal screen in calendar view, including period calendar that also displays the completion of survey questions.	Prompts/cues (7.1)
Journal screen: questions	Journal screen in questions view, including a list of survey questions with the date.	No BCTs
Self-care screen	Self-care screen, including a list and icon images for 5 self-care recommendations.	No BCTs

[a]BCT: behavior change technique.

Privacy and Data Security

Privacy and data security were considered high priorities during app development. User data collected by the app are encrypted and transferred anonymously. We adhere to the principle of data minimization [20] and collect only data that are absolutely necessary to answer the research questions. Personally identifiable information (PII), such as the name and signature collected during the informed consent procedure provided by Apple ResearchKit, is stored only on the user's iPhone and will not be sent to the back end. The individual person owning the iPhone (the study participant) will not be identifiable by the data transferred to the study server. A token will be created as an identifier to label the individual study data. Moreover, an app passcode is implemented to avoid unintended access to the app. Collection of information by the app can be stopped at any time by withdrawing from the study, using a specific button in the app's settings, and uninstalling the app. Data will be collected anonymously. In addition, the study team of the coordinating office in Germany is supervised by the data protection officer of the Charité—Universitätsmedizin Berlin. The other participating centers are supervised by their respective institutions.

Study Design

We will conduct a 3-armed, randomized pragmatic trial [18,21] to evaluate whether the smartphone app is effective in reducing menstrual pain in 18- to 34-year-old women with primary dysmenorrhea. We will compare the group of women who has access to the full-featured study app with 2 control groups who have access to fewer app features. After within-app verification of eligibility for the study, eligible women will be randomly allocated to one of the 3 groups in a 1:1:1 ratio. The potential group allocations are as follows: full-featured app version (self-care information + self-acupressure feature), control intervention I (only self-care information feature), or control intervention II (only self-acupressure feature). The app contains the interventions for all 3 groups, but the content is only unlocked and presented to the user depending on their group allocation. Study participants can use the app for the whole study duration of 12 menstruation cycles. The primary outcome of the study is the mean pain intensity measured with the in-app numerical rating scale (NRS) ranging from 0, *no pain*, to 10, *most intense pain imaginable*, on the painful days during the sixth menstruation after starting the intervention (approximately 6 months from trial start depending on cycle length). It will be calculated by adding up the daily values from the start of the menstruation until the end of bleeding and then dividing them by the number of days with available values. NRS is a common measure of pain intensity that has been utilized in many previous studies [22-24], including studies of menstrual pain [25,26]. Secondary outcome measures are described in more detail on ClinicalTrials.gov (NCT03432611).

The decisions on study design of this trial are based, in part, on decisions of the stakeholder advisory group from the corresponding previous trial and its results [12]. As no member of the study team was specialized in gynecology, this expertise was represented by a gynecologist appointed to the advisory group. Our stakeholder advisory group included a female gynecologist, a 16-year-old woman with dysmenorrhea, a female teacher, 2 acupuncture experts, and a mind-body medicine expert [27].

Intervention Components

Furthermore, 5 days before the anticipated start of the menstruation until the end of bleeding, notifications from the app will remind all the groups of participating women to complete questions and perform self-care activities, such as self-acupressure or yoga, depending on the group allocation.

The self-care feature will offer information on self-care for menstrual pain, including evidence-based information about exercise, nutrition and dietary supplementation, heating pad/hot water bottle, yoga, and when to consult a doctor and regarding how primary dysmenorrhea is treated in most cases (see Multimedia Appendix 1).

The acupressure feature will offer detailed written and multimedia descriptions of the acupressure to be used for menstrual pain (see Multimedia Appendix 2). A total of 3 acupressure points will be described that should be massaged bilaterally, if possible, twice a day, up to 5 times per day, starting from 5 days before menstruation until the end of menstruation. Each point should be massaged for 1 min (ie, altogether 6 min should be spent for 1 acupressure session). A visual timer for the acupressure will indicate desirable length of acupressure. In addition, an in-app notification on the app's dashboard will remind users to practice acupressure during painful days at least twice daily.

The acupressure intervention resulted from a written consensus process with international acupuncture experts from China, Germany, and the United States of America [27] and was already evaluated in an RCT previously conducted by our group demonstrating effectiveness of the intervention [12]. The acupuncture points SP6 (Sanyinjiao), LI4 (Hegu), and LR3 (Taichong) were chosen during this process.

Participants are allowed to continue with their own usual care (medical and nonmedical) during the study.

Participants and Group Allocation

We aim to recruit 594 young women with primary dysmenorrhea. The sample size estimation is based on the comparison of the group receiving the full-featured app (self-care information + self-acupressure) with the group receiving the app version without the self-care information (control intervention II) regarding the primary outcome (NRS after 6 menstrual cycles) that will be treated as a continuous variable. Our previous study showed a mean group difference of 1.4 on the NRS and a standard deviation of 2.15 at the sixth menstrual cycle after the onset of the trial.

Assuming that self-care information has a smaller impact on pain than acupressure, we hypothesize a difference of 0.8 on the NRS between groups. To detect a mean difference of 0.8 point on the NRS after 6 menstrual cycles between the group receiving the full-featured app (with a common standard deviation of 2.15 observed in our previous study) and control intervention II, applying a 2-sided *t* test with a power of 80% and an adjusted alpha of .025, a total of 139 participants will be needed per group (417 women for the 3 arms together). Taking into account a dropout rate of approximately 30% (based on our previous study after 6 cycles), 198 participants per group will be needed (total 594 women).

The eligibility criteria resemble the criteria of our previous study. Women owning an iPhone will be included if they have primary dysmenorrhea, are between the ages of 18 and 34 years, report moderate or severe menstrual pain ≥6 on the NRS; 0=*no pain at all*, 10=*most intense pain imaginable*), and report no existing or planned pregnancy within the next 12 months. During the app-based eligibility screening, the inclusion and exclusion criteria will be assessed by 12 compulsory eligibility questions (Table 2). After the determination of eligibility and obtaining informed consent, participants will be asked to complete the baseline survey before they receive access to the app features depending upon the respective study group allocation. We will use a server-based randomization table created by a statistician using the RANUNI random number generator of the SAS/STAT version 9.2 (SAS Inc) [28]. Participating women will be randomized in a 1:1:1 ratio by block randomization with a fixed block length.

Table 2. Eligibility questions.

Eligibility questions	Question type	Criteria
Are you a woman over 18 and below 35 years old?	Yes/no	If no, exclude
Do you suffer from period pain or menstrual cramps during every menstrual cycle?	Yes/no	If no, exclude
Do you suffer from your period pain on more than 5 days outside the period?	Yes/no	If yes, exclude
Do you think your pain started during your teenage years?	Yes/no	If no, exclude
Do you have any prior history of a gynecological disease that is known to be a reason for your period pain?	Yes/no	If yes, exclude
Did you have a period within the last 6 weeks?	Yes/no	If no, exclude
Is your cycle length between 3 and 6 weeks?	Yes/no	If no, exclude
How strong was the most severe pain without medication during your last period?	Numerical on a pain scale from 0 to 10	If <6, exclude
Are you willing to see a doctor when (1) your pain is getting worse than usual, (2) pain medication is not helping, and (3) when you have pain well before or well after the period?	Yes/no	If no, exclude
Are you pregnant?	Yes/no	If yes, exclude
Do you plan to be pregnant within the next 12 months?	Yes/no	If yes, exclude
Is this your iPhone?	Yes/no	If no, exclude and message the user because of data protection, the app should be used only on your own iPhone

Efficacy-Effectiveness Continuum

From a methodological point of view, a clinical trial provides more evidence on the effectiveness of an intervention using a pragmatic trial design or on the efficacy side using an explanatory trial design [29,30]. Pragmatic trials are usually considered to study interventions in a real-world setting, whereas explanatory trials are usually designed to investigate interventions in an ideally controlled setting. The PRECIS-2 is a wheel-format tool that helps researchers to consider trial design as more effectiveness or efficacy focused including 9 domains: eligibility criteria, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis [31]. The PRECIS-2 scoring system ranges from 1 (most explanatory) to 5 (most pragmatic).

During the design phase of the trial, PRECIS served as a tool to make better informed design decisions [32]. We used the PRECIS-2 tool to assess our app-based trial's positioning on the pragmatic-explanatory continuum. The authors independently scored the 9 dimensions.

User Enrollment

The primary recruitment strategy focuses on self-referral through the Apple App Store. On the basis of our experience from the previous trial and the associated stakeholder engagement [12,27], we anticipate that an app-based study for menstrual pain would meet wide acceptance among young women in Germany. Furthermore, we assume that no external advertising (such as posters in public transport or on campus) will be needed for recruitment. A Web-based press release on the Charité university homepage was published on February 28, 2018, (in German and English language), highlighting the results of the previous trial, while also mentioning the new study with the updated app, including a link to the App Store. The media coverage of the app is observed regularly by the study team, using Google search with keywords "selfcare + period pain + Luna," "selfcare + Luna," "app + period pain," "acupressure + period pain" (in German: "Selbsthilfe + Regelschmerzen + Luna," "Selbsthilfe + Luna," "app + Regelschmerzen," "Akupressur + Regelschmerzen").

The app use will be free of charge; no financial compensation will be provided for participating in the study.

Potential future recruitment strategies will include traditional and Web-based recruitment methods that are also adapted to the respective study sites. These will include information about the ongoing study on printed posters or information leaflets or in social media. In addition, if accepted by the Apple App Store editorial team, we will inform potential users about the study app with the *App of the day* feature option of the Apple App Store for the category *Health and Fitness*.

User Engagement

When users install and open the study app for the first time, they will be briefly introduced to the study and encouraged to participate. For potential participants who wish to continue, an app-based anonymous eligibility screening and more detailed information about the study will be provided. After the consent process, participants will finish the app-based baseline survey to unlock the intervention interface. This process is based on the onboarding process of Apple's ResearchKit framework [33]. User flow and conversion rates will be calculated based on the number of downloads, the number of eligible users, and the number of users who finish the baseline survey and enter the study.

In the baseline survey, general information relevant for menstrual pain will be assessed, such as age, education, individual exercise behavior, length of period and level of pain experienced during the period, and use of hormonal contraceptives and pain medications (Table 3). A *skip* button is available for a selection of questions and allows users to skip questions they do not want to answer. User engagement will be measured by usage of *skip* button and baseline survey respondent rate.

Table 3. Baseline questions.

Baseline questions and answer field	Skip button
Your age	X[a]
_____ years	
BMI calculated from height and weight	X
Your height: ____ cm	
Your body weight: ____ kg	
What is the highest level of education you have completed so far?	X
High school or above	
Other	
How long is your cycle usually (the time from the first day of period until the beginning of the next period)?	__[b]
_____ days	
How long is your period usually?	—
_____ days	
What kind of period pain and discomfort do you usually experience? (multi-choice possible)	X
Stomach cramps	
General pain in lower belly	
Lower back pain	
Headache	
Nausea/Vomiting	
Other symptoms, namely _____	
Do you use hormonal contraceptives (eg, birth control pills, hormone patch, vaginal ring, or hormonal IUD[c])?	X
No	
Yes	
If yes, why do you use hormonal contraceptives?	
I use hormonal contraceptives because of my period pain.	
I use hormonal contraceptives for contraception.	
I use hormonal contraceptives because of other reasons (for example, acne).	
If yes, which hormonal contraceptives are you using? _____	
If yes, how long have you been using hormonal contraceptives? for ____ months and ____ years	
Have you ever been pregnant?	X
No	
Yes	
If yes, number of pregnancies:____	
If yes, number of births:____	
How intense was the average period pain of the painful days during your last period?	—
0 1 2 3 4 5 6 7 8 9 10 (0=no pain at all, 10=most intense pain imaginable)	
During your last period, how intense was the worst period pain you experienced?	—
0 1 2 3 4 5 6 7 8 9 10 (0=no pain at all, 10=most intense pain imaginable)	
On how many days have you had period pain during your last period?	X
_____ days	
On how many days were you absent from work or education due to period pain during your last period?	X
_____ days	

Baseline questions and answer field	Skip button
Have you taken any medication for your period pain?	
No	X
Yes ->if yes, which one: _____	
Which self-care activities have you done during the previous month because of your period pain? (multi-choice possible)	**X**
No actions	
Fitness/Gymnastics	
Jogging/Running	
Acupressure	
Yoga	
Autogenic training	
Herbal medicine	
Meditation/Relaxation	
Homeopathy	
Local supply of heat	
Food supplements	
Tea	
Others: _____	
Which self-care activities have you done during the previous month because of other reasons than your period pain? (multi-choice possible)	**X**
No actions	
Fitness/gymnastics	
Jogging/running	
Acupressure	
Yoga	
Autogenic training	
Herbal medicine	
Meditation/relaxation	
Homeopathy	
Local supply of heat	
Food supplements	
Tea	
Others: _____	
When did you have your last period? Please enter the data of the first day of your last period.	—
__.__.____	

[a]X: skip button enabled.

[b]—: skip button disabled.

[c]IUD: intrauterine device.

Statistical Analysis

The PRECIS-2 score was calculated by summing up the means of each dimension based on the rating results of 11 raters; meanwhile, standard deviations were calculated to show the variability.

For the BCT ratings, the interrater reliability among BCT raters was assessed by intraclass correlations (ICCs) [34,35].

For the assessment of user access, we used the data generated by App Analytics [33] (Apple Inc) to descriptively show the source of product page views and number of downloads.

To assess user engagement, the user conversion rate and the baseline survey response data were calculated using descriptive statistics (frequencies, percentages, means, and standard deviations). The baseline survey variables were extracted from

the back-end database and only the missing values of the baseline survey (*skipped* questions) were used for the calculation of the proportion of actually skipped questions among all skippable questions to interpret the user engagement.

All collected data were analyzed with SPSS version 22.0 (SPSS Inc).

Ethics

The app is prepared for international use and can be currently (October 2019) downloaded in the German App Store and will later be made available in the App Stores of the other participating centers. The study database, the app server, and the primary study center are based in Berlin, Germany. The study was approved by the university's ethics committee (Charité—Universitätsmedizin Berlin approval Number EA1/364/16). The trial was registered at ClinicalTrials.gov (NCT03432611).

The participation of the study sites in Taichung, Taiwan (approval letter Number CMUH107-REC1-120 by Ethics Committee of China Medical University and Hospital); Sydney, Australia (approval number H13175 by Western Sydney University Human Research Ethics Committee); Florianopolis, Brazil (approval number 3.583.066 by Ethics Committee of Federal University of Santa Catarina), and Baltimore, United States is currently being processed.

Results

Study App and Study Design

The study app is a result of multidisciplinary efforts. The launch of the study app in the App Store will mark the beginning of the fully app-based study: users will be recruited via the Apple App Store, eligibility and consent will be processed by the study app, different self-care interventions will be guided by corresponding app features, and the follow-up will be recorded by app-based survey questions (Figure 1). Detailed screenshots, which depict the user flow in more detail, are listed in Multimedia Appendix 3.

The study app will display the intervention components (self-acupressure and self-care information) selectively according to the group allocation. The core features *Dashboard*, *Journal*, and *More* (Figure 2) will be accessible to all users. The *Dashboard* will display feedback according to study progress and answers of survey questions and a prediction of the next period start date. The *Journal* feature will contain a period calendar and an overview of the progress on the survey questions. With the *More* feature, users will be able to set personal identification number lock and notification time. Users' cycle information, the signed consent form, and a link to the privacy policy will also be displayed there.

Figure 1. Study design. ITT: intention to treat; PP: per protocol.

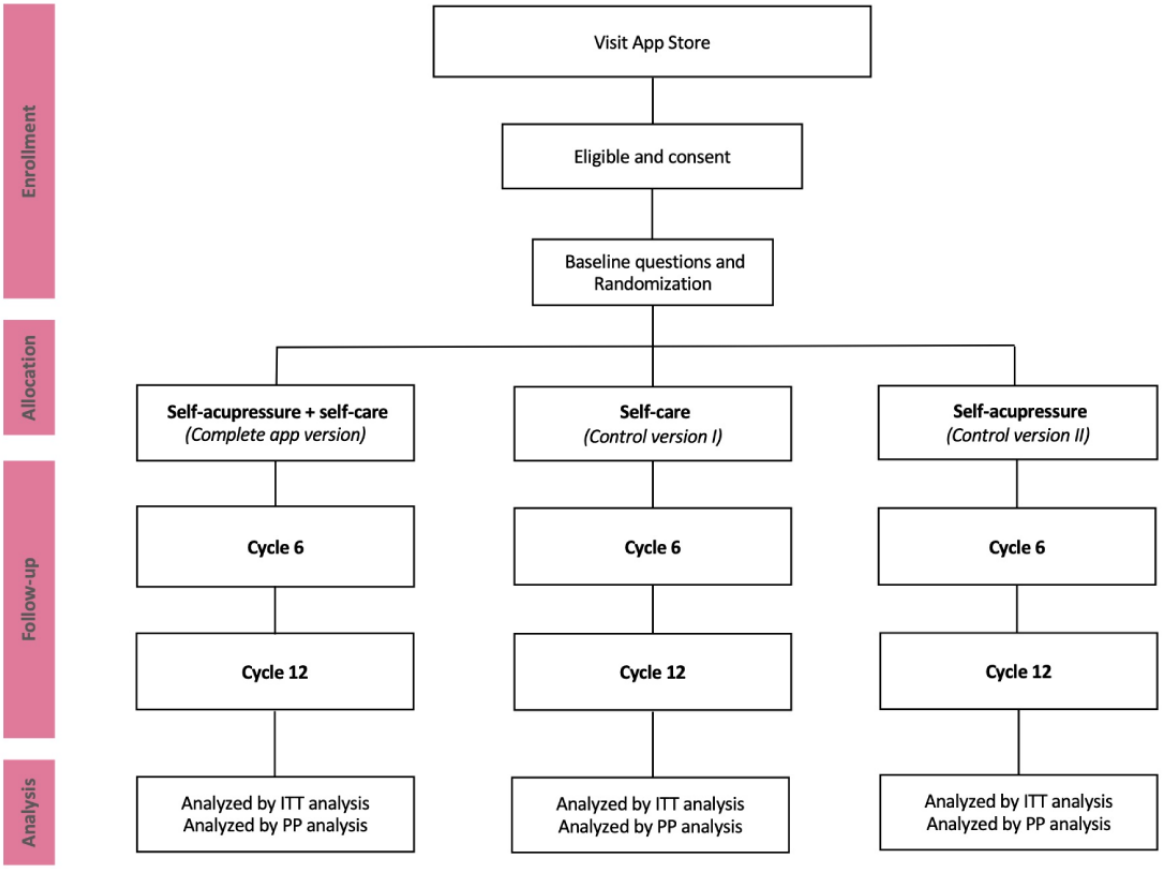
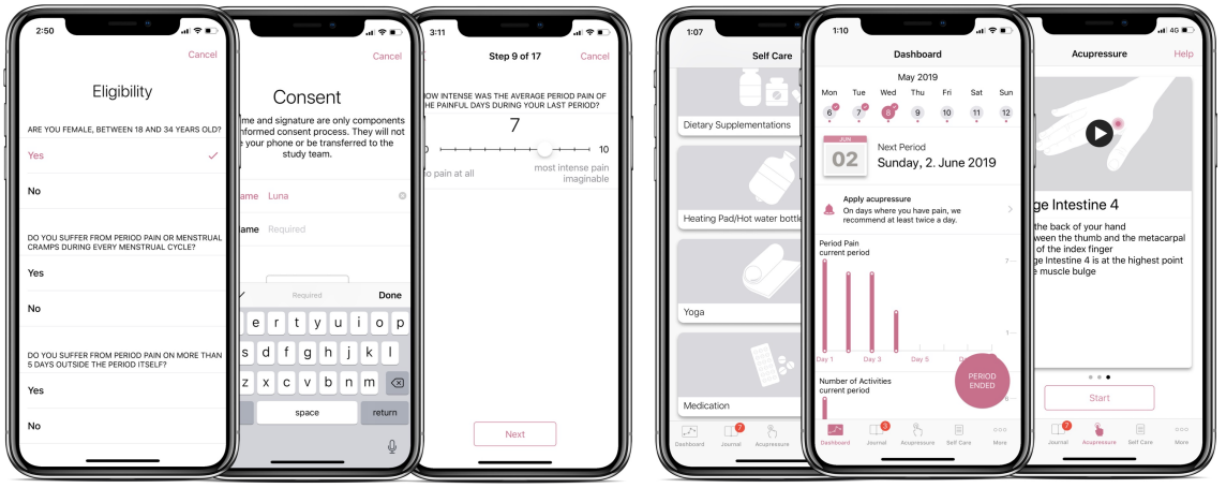


Figure 2. Screenshots of the study app.



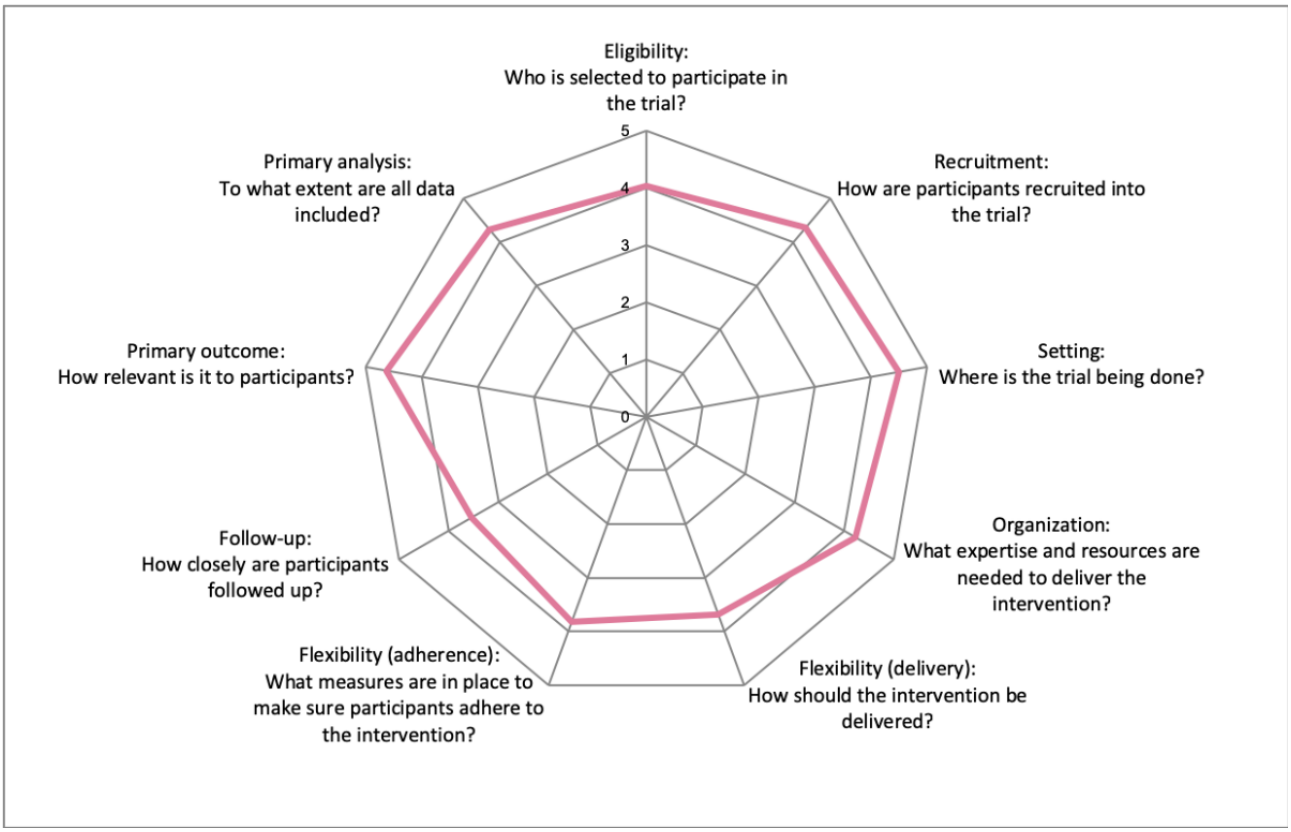
Behavior Change Technique Ratings

To validate whether the BCTs implemented in the app were properly applied, a developer rating (JW) was compared with ratings of 2 psychologists with BCT expertise (CRP and AR) who had experienced the finalized full-featured app but who had not been part of the app development process. The interrater agreement between the 2 psychologists showed an excellent ICC (ICC=0.954; 95% CI 0.87-0.98). However, the overall interrater agreement including all raters was poor (ICC=0.442; 95% CI 0.07-0.78), that is, the ratings of the BCTs used during the development by the study team, did not correspond well with the ratings of the 2 psychologists. There was no significant difference between ICCs at the item level and the cluster level based on the BCTs taxonomy (v1) [19]. The final agreement that was reached in a consensus meeting is shown in Table 2. Overall, 12 BCTs were identified in the study app. The most frequently implemented BCTs are prompts/cues (5 times), instructions on how to perform behavior (4 times), and demonstration of the behavior (3 times).

Efficacy-Effectiveness Continuum Rating

On the basis of the rating results of all authors, all 9 dimensions of the PRECIS-2 tool are defined more on the pragmatic side (Figure 3). Thus, this app-based RCT can be considered as a pragmatic trial.

Figure 3. PRECIS-2 rating results of the study design.

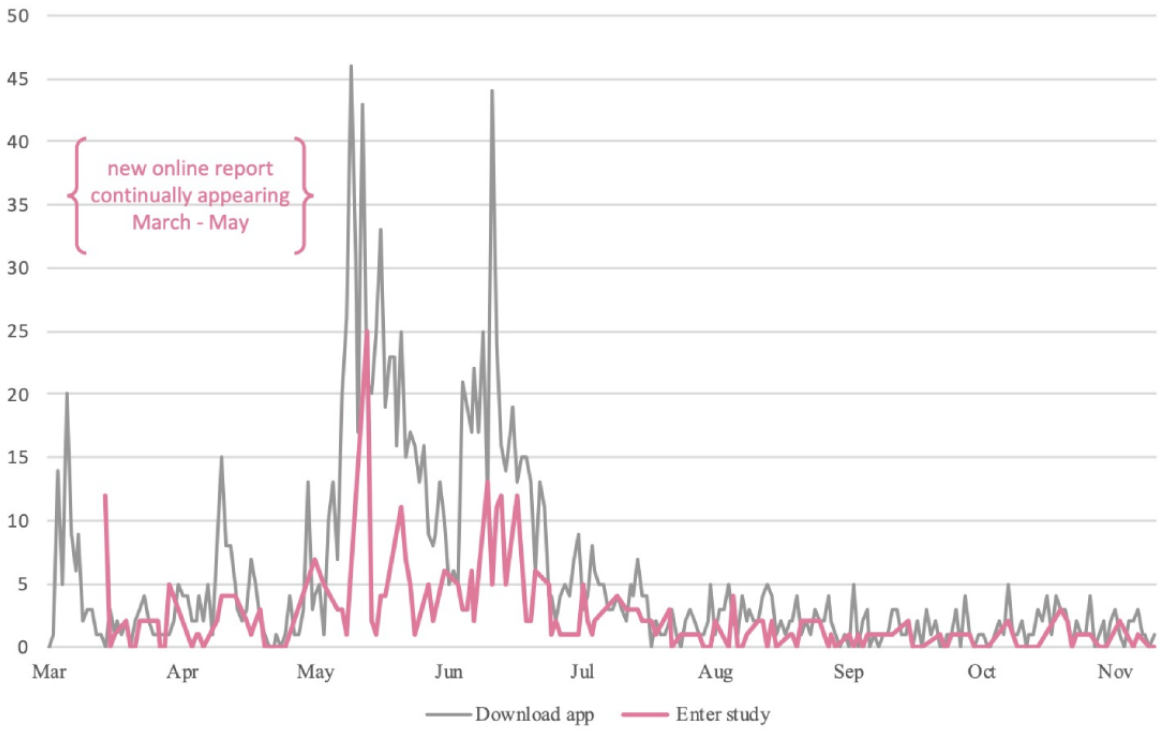


User Enrollment

Trial recruitment started in February 2018 with the launch of the ResearchKit-based study app in the German App Store. The Web-based press release was well received by the public and the media. By observation of media coverage via Google search during the following 10 weeks, 65 articles or blog entries of pharmacy or health-related websites citing the press releases in English and German could be detected. Overall, 2 printed newspapers reported about this app-based study in German. An increase of media coverage could be observed from March to May 2018. In the weeks following the press release, the app showed continuous increase in both downloads and the number of users (Figure 4).

After 38 weeks in the app store (from February 19, 2018, to November 13, 2018), there were 1458 downloads and 328 users were included into the study (22.5%). On average, we recruited around 8 study participants per week with a peak between May and June after the press release (22 new users per week). Approximately 60% (195/328) of the participants were recruited within these 2 months.

Figure 4. App downloads and new users per day.



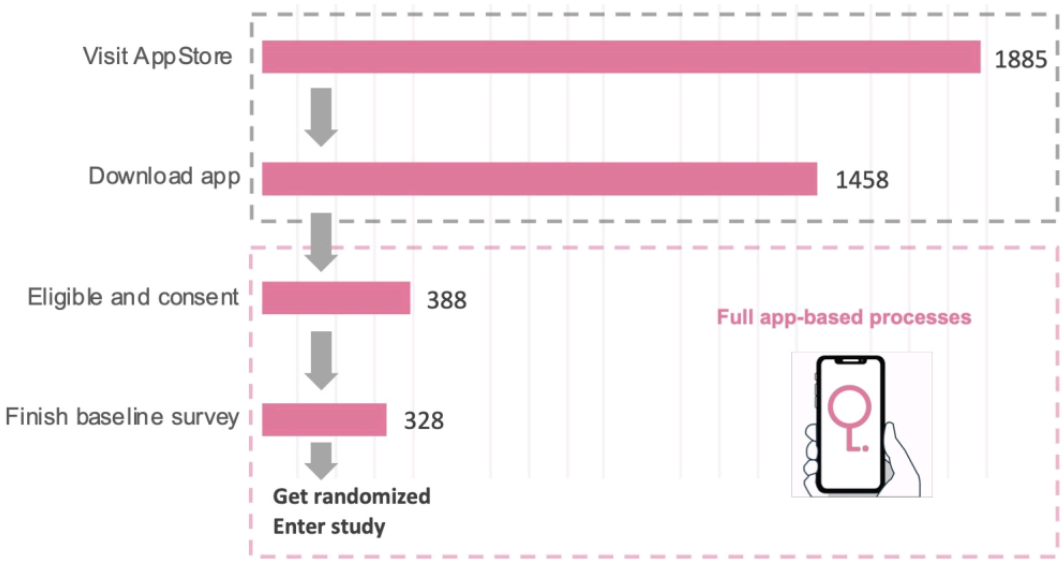
User Engagement

During the first 38 weeks of recruitment, the App Store's preview of the app was viewed 1885 times. Although 75% of the app's product page viewers found the app by searching the App Store, 25% found the app by App Store browsing, app referral, or Web referral. The app was downloaded 1458 times. A total of 388 (27%) users passed the 12-question eligibility screening and agreed to consent; 328 of the 388 users (85%) completed the 16-question baseline survey and were recruited to the study. Figure 5 displays the user evolution [14].

For 11 of 16 baseline questions, the *skip* button can be used because these questions are either not related to the primary outcome of the study or their data are not essential for the proper functioning of the app. The usage of the *skip* button of a study sample (328 users) was calculated to evaluate the user engagement in the app-based survey.

Almost all questions of the baseline survey were answered (data completeness of 98.27%; 5157/5248). A total of 276 users (276/328, 84.1%) answered all 16 baseline questions and never used the skip button. Only 3% of the data based on the skippable questions were missing. The question asking for discomfort/symptoms during the period was answered by all users (response rate 100%). For free-text fields, 105 (105/328, 32.0%) of the users provided details about their discomfort/symptoms during their period; 269 (269/328, 82.0%) users provided details about their medication for the question asking about the period pain-related medical history.

Figure 5. User evolution.



Discussion

Principal Findings

By using the ResearchKit framework, we successfully developed a study app for a fully app-based pragmatic RCT for young women with primary dysmenorrhea. The app is easily accessible via self-referral and can be used as a self-care and study tool for a highly relevant condition. The available data already indicate a high level of user engagement with the study app. We also realized that the early involvement of behavioral science experts is of great importance for the development of app-based trials.

In a young population that widely uses smartphones, a digital intervention, such as the study app, provides low entry barriers. It offers easy access to evidence-based self-care information for menstrual pain and tools to improve healthy behavior. We believe that recruitment is not only influenced by the app itself but also by the way of communicating the study. We observed a substantial increase in recruitment rates following the publication of a press release on our university's websites and corresponding media coverage. A causal relationship in the recruitment increase seems to be very probable. After 5 months without actively communicating the study with media or information material, we still could observe a basic recruitment of about 1 new study participant per day.

Almost all research or self-care apps include BCT elements, such as prompts/cues to fill in questionnaires (self-monitoring) or to engage in app- specific intervention components. Dialog boxes are also used to give feedback on behavior or to promote self-belief [19]. However, the adequate implementation and the proper description of the applied BCTs are not easy to achieve. Therefore, it is important to involve psychologists or behavioral scientists in the design and development of an app [36,37]. The review of the use of the BCT taxonomy during the development of the trial revealed some discrepancies between the study team members and the psychologists that were involved in the ratings. For future studies, the behavior change wheel framework by Michie et al [38] will be applied before the app development to improve the design and implementation of app-based interventions [39]. Moreover, the mechanisms and efficacy of BCTs implemented need to be further explored in mHealth research settings.

As in our previous mHealth studies, the app and trial simultaneously shaped each other during the trial design and app development process. In conventional RCTs, the trial intervention and outcomes are usually very standardized as they are described in the study protocol. However, during the development and coding process of the study app, we regularly made adaptations of the study protocol because of technical and design aspects. For example, during the development process, we realized that the digitally collected data can be used to give the users an overview of study progress and symptom improvement that subsequently became part of the intervention strategy. Branching within a question (the answer of an item impacts the next question choices) and combining different question types were not possible with the standard ResearchKit framework. Moreover, baseline questions had to be limited to reduce the time spent until finalization of onboarding, that is, the whole process from introduction, eligibility screening, and participant consent until completion of baseline survey and the random allocation to the respective intervention group. However, the final onboarding process in our research app was longer than what users of consumer apps might usually accept. This could have resulted in a loss of potential study participants. Some baseline questions typical for research studies, such as questions about partnership and income, were omitted because of privacy concerns. It was not necessary to collect body weight and height as PII data, as they were only used for BMI calculation on the user's iPhone and not transferred to the study backend. The study design also impacted some technical decisions. For instance, to limit recall bias, questions that required daily answers before and during the period will expire after 7 days. Moreover, the way symptoms are measured or tracked in an app is limited to validated and commonly used outcomes. NRS or Likert scales are used instead of more consumer-oriented approaches, such as individualized icons or

emojis to record mood or pain. This might limit the user experience.

Limitations

In addition to the limitation of the development process already described above, several other related limitations have to be taken into account. The decision to focus on Apple's iOS only enabled the use of Apple ResearchKit and avoided the difficulties associated with developing for 2 operating systems simultaneously, as was done in our previous trials [12,27]. Owing to this decision, only women using an iPhone can participate in the study, which consequently might introduce selection bias and therefore limit the generalizability of the study. Moreover, the impact of technical updates (ie, ResearchKit and iOS updates) or other potential adaptations of the app during the course of the study is not clear yet, but these adaptations will be thoroughly reported in the results paper of the trial.

Our study is also subject to some limitations from the access perspective. The numbers of App Store's visitors and downloads are generated by Apple's App Analytics, which we do not control. This is the only source to estimate the number of subjects interested in our study because of our anonymous study design. However, we think that it is important to also include App Analytics' data despite its nonstudy purpose. Taking advantage of these resources from the mHealth ecosystem might help future app-based studies. To be eligible to use our study app, individuals who downloaded the app had to pass our 12-question eligibility screening that is based on our relatively strict inclusion and exclusion criteria. However, for the assessment of user evolution, we could only record the number of eligible users who gave consent because of ResearchKit's design restrictions and our privacy rules. As a result, we lack knowledge about the reasons for ineligibility. In addition, although the participant's eligibility and survey data underwent comparably strict plausibility checks that we have implemented in the app, fake users and fraud registration for the study cannot be completely ruled out. However, our fully remote study allows user behavior in a real-life setting [12,21,40]. Additional plausibility checks will be developed before the analysis of the results. Another way to access the app could be on recommendation of a gynecologist and/or family physician within a therapeutic setting. Further study is required to make a definite conclusion about the extent to which the app might be of use in such a setting.

Data on user engagement in our study are limited so far. The only indicator we currently use for assessing engagement is based on the completion and response of the baseline questions. Commercial apps often use analytic tools to track user interaction with the app. These data can be used for the evaluation of engagement [41], the optimization of the app, or the addition of new features. In a study setting with strict privacy considerations, we do not use these tools. In addition, adherence would be a good measurement for user engagement. Data about adherence is not available yet but will be considered as an outcome of the study.

Comparison With Prior Studies

The study app and the app-based trial result from adaptation and amendments of our previous *AKUD* trial [12,27]. The inclusion criteria of the research population are based on the previous trial but were modified to meet the necessities of remote recruitment. In the previous *AKUD* trial, participants were recruited through onsite recruitment by 1 study center in Berlin, Germany facilitated by advertisements (posters, flyers, leaflets, students email lists, and subway advertisements). Baseline data were recorded with paper-and-pencil surveys. This way, it took 20 months to reach the recruitment target of 221 participants [12,27]. With the ResearchKit-based study app, we are now able to reach participants across Germany.

For the assessment of access of app studies, Anguera et al [40] reported the recruitment number, whereas Zens et al [14] reported the consent/download rate. The percentage of consented participants (27%) in our trial is lower than in other ResearchKit studies [14,42,43]. The mPower study [42] reported 35% consent/download rate, whereas the *Back on Track* study [14] reported 58%. The differences might be explained by the observational character of these studies and the application of a comparably strict eligibility process in our study with 12 eligibility questions.

User adherence and survey response rate are usually considered to be the measurements for evaluating engagement in app studies [40,44,45]. However, as adherence data of the current trial are not available in the current stage of the study, the baseline survey response is used as a proxy for engagement.

The ResearchKit framework has been used for studies for many health conditions, such as asthma [43], acute anterior cruciate ligament ruptures [14], and Parkinson disease [42] since its launch in 2015 [46]. To our knowledge, no ResearchKit clinical trial for pain conditions has been conducted yet. Thurnheer et al [5] reported 15 studies without ResearchKit and their efficacy in a systematic review of app-based studies for pain management. App-based studies have been conducted both for acute pain such as acute needle stick pain [47] and acute pain before coronarography [48] and for chronic pain such as chronic cancer pain [49], neck pain [50], and low back pain [24,51]. No mHealth-based interventional trial has been conducted for examining the influence of an app promoting health behavior and the use of acupressure on menstrual pain [5,52] so far. Regarding the high prevalence of menstrual pain and the increasing ownership of smartphones [12,53,54], our trial might provide data that can have practical public health implications.

Conclusions

Conducting an evidence-based and up-to-date app study requires multidisciplinary efforts. The resulting ResearchKit-based study app for menstrual pain is accessible for the target population with positive user engagement. However, future research is necessary to investigate the determinants of user engagement, optimal BCT application, and potential clinical scenarios for app use.

Acknowledgments

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Conflicts of Interest

The app has been developed for research purposes and is not a commercial product. The authors do not have any financial stake in the success of the app.

Multimedia Appendix 1

Self care feature.
[PDF File (Adobe PDF File), 216 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Acupressure feature.
[PDF File (Adobe PDF File), 275 KB-Multimedia Appendix 2]

Multimedia Appendix 3

Screenshots and user flow to enter the study.
[PDF File (Adobe PDF File), 1343 KB-Multimedia Appendix 3]

Multimedia Appendix 4

CONSORT-EHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 577 KB-Multimedia Appendix 4]

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Abbreviations

BCT: behavior change technique
ICC: intraclass correlation
mHealth: mobile health
NICM: National Institute of Complementary Medicine
NRS: numerical rating scale
PII: personally identifiable information
RCT: randomized controlled trial

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3.4 Wirksamkeit und Kosteneffektivität von Tuina bei chronischen Nackenschmerzen

Tuina ist eine chinesische Massagetherapie, die in China oft bei Nackenschmerzen eingesetzt wird. Die Wirksamkeit im westlichen Setting ist nicht gut untersucht. Tuina ist dennoch auch im Westen zunehmend populär. Die klinische Studie „Effectiveness and Cost-Effectiveness of Tuina for Chronic Neck Pain: A Randomized Controlled Trial Comparing Tuina with a No-Intervention Waiting List“ sollte untersuchen, ob Tuina bei Patienten mit chronischen Nackenschmerzen wirksam ist und kosten-effektiv zur Schmerzlinderung beitragen kann.

Der folgende Abstrakt ist eine Übersetzung des Autors aus dem Originalartikel:

Pach, D., M. Piper, F. Lotz, T. Reinhold, M. Dombrowski, Y. Chang, B. Liu, S. Blödt, G. Rotter, K. Icke, and C. M. Witt. "Effectiveness and Cost-Effectiveness of Tuina for Chronic Neck Pain: A Randomized Controlled Trial Comparing Tuina with a No-Intervention Waiting List." *Journal of Alternative and Complementary Medicine* (Oct 26 2017). https://dx.doi.org/10.1089/acm.2017.0209.

*„**Fragestellung:** Es sollte untersucht werden, ob Tuina bei Patienten mit chronischen Nackenschmerzen wirksamer und kosteneffektiver zur Schmerzlinderung beiträgt als keine Intervention.*

***Design:** Monozentrische randomisierte zweiarmige kontrollierte Studie.*

***Setting:** Universitätsambulanz, spezialisiert auf Integrative Medizin.*

***Probanden:** Ambulante Patienten mit chronischen Nackenschmerzen wurden zufällig entweder einer Tuina-Behandlung oder der Gruppe ohne Intervention zugeteilt.*

***Intervention:** Sechs Tuina-Behandlungen innerhalb von 3 Wochen.*

***Zielparameter:** Der primäre Zielparameter war die durchschnittliche Nackenschmerzintensität während der letzten 7 Tage auf einer visuellen Analogskala nach 4 Wochen (VAS, 0-100 mm, 0 = überhaupt kein Schmerz, 100 = maximal vorstellbarer Schmerz). Zu den sekundären Zielparametern gehörten die Neck Pain and Disability Scale (NPDS), der Neck Disability Index (NDI), die gesundheitsbezogene Lebensqualität (12-teiliger Fragebogen zur Lebensqualität [SF-12]), die Medikamenteneinnahme und die Kosteneffektivität nach 4 und 12 Wochen. Die statistische Analyse umfasste eine für den Baseline-Wert adjustierte Kovarianzanalyse und eine ökonomische Analyse aus gesamtgesellschaftlicher Perspektive.*

***Ergebnisse:** Insgesamt wurden 92 ambulante Patienten eingeschlossen (46 in beiden Gruppen, 87 % weiblich, Durchschnittsalter 45,4 Jahre [Standardabweichung ±9,7 Jahre] und durchschnittliche VAS 57,7 ±11,5 mm). Die Tuina-Behandlung führte zu einer klinisch bedeutsamen Verringerung der Nackenschmerzintensität (Gruppenunterschiede, 4 Wochen: -22,8 mm [95% Konfidenzintervall, -31,7 bis -13,8 mm]; $p < 0,001$ und 12 Wochen: -17,9 mm [-27,1 bis -8,8 mm], $p < 0,001$). Es wurden keine*

schwerwiegenden unerwünschten Ereignisse beobachtet. Sowohl die Gesamtkosten als auch die qualitätskorrigierten Lebensjahre (QALYs) unterschieden sich nicht signifikant zwischen den Gruppen. Berücksichtigt man die Gruppenunterschiede unabhängig von ihrer statistischen Signifikanz, so würden die Kosten pro gewonnenem QALY (inkrementelles Kosten-Effektivitäts-Verhältnis) in einem kosteneffektiven Bereich zwischen 7.566 EUR (bei Kosten von 10,28 EUR pro Sitzung) und 39.414 EUR (Kosten von 35 EUR pro Sitzung) liegen.

***Schlussfolgerung:** Eine zusätzliche Behandlung mit sechs Tuina-Sitzungen über drei Wochen war für Patienten mit chronischen Nackenschmerzen wirksam, sicher und relativ kosteneffektiv. In einer künftigen Studie sollte Tuina mit anderen optimalen Behandlungsmethoden verglichen werden."*

3.5 Standardisierte versus individualisierte Akupunktur bei chronischen Kreuzschmerzen: eine randomisierte, kontrollierte Studie

Akupunktur wird inzwischen als Bestandteil der Integrativen Medizin evidenzbasiert zur Behandlung von Schmerzerkrankungen eingesetzt und in Deutschland für chronische Kreuzschmerzen und chronische Schmerzen bei Kniegelenksarthrose auch von den gesetzlichen Krankenkassen regulär erstattet. Sie ist sowohl bezüglich der klinischen Wirkung[25] als auch hinsichtlich der zugrundeliegenden Mechanismen[26 27] gut untersucht, auch wenn noch viele Fragen offen bleiben[28-30]. Die Akupunktur kann dabei individualisiert durch individuelle Auswahl und Nadelung von Akupunkturpunkten auf Basis einer chinesischen Syndromdiagnostik erfolgen, oder sie folgt z.B. einem fest vorgegebenen Punkteschema mit entsprechender Nadelung auf Basis von in klinischen Studien erfolgreich eingesetzten Akupunkturpunkten. Es ist unklar, ob der individualisierte Ansatz einem standardisierten bei Schmerzerkrankungen überlegen ist. Ziel der folgenden Studie war es, die Wirksamkeit einer standardisierten und einer individualisierten Akupunkturbehandlung bei Patienten mit chronischen Kreuzschmerzen zu vergleichen.

Der folgende Abstrakt ist eine Übersetzung des Autors aus dem Originalartikel:

Pach, D., X. Yang-Strobel, R. Lüdtke, S. Roll, K. Icke, B. Brinkhaus, and C. M. Witt. "Standardized Versus Individualized Acupuncture for Chronic Low Back Pain: A Randomized Controlled Trial." *Evidence-Based Complementary and Alternative Medicine* 2013 (2013): 8. http://dx.doi.org/10.1155/2013/125937.

„Unser Ziel war es, die Wirksamkeit einer standardisierten und einer individualisierten Akupunkturbehandlung bei Patienten mit chronischen Kreuzschmerzen zu vergleichen. Eine randomisierte, kontrollierte einfach verblindete Studie wurde in einer Allgemeinarztpraxis in Deutschland durchgeführt, die von einer aus China stammenden Ärztin geleitet wurde, die sowohl in westlicher und als auch chinesischer Medizin ausgebildet ist. Es wurden 150 ambulante Patienten mit chronischen Kreuzschmerzen nach dem Zufallsprinzip zwei Gruppen zugeteilt (78 standardisierte und 72 individualisierte Akupunktur). Die Patienten erhielten entweder standardisierte Akupunktur oder individualisierte Akupunktur. Die Behandlung umfasste je nach den individuellen Symptomen zwischen 10 und 15 Behandlungen mit zwei Behandlungen pro Woche. Das Hauptergebnis war die Fläche unter der Kurve (AUC), die die täglich bewertete Schmerzstärke über 8 Woche zusammenfasste. Diese wurde mit einer visuellen Analogskala (0 mm = kein Schmerz, 100 mm = maximal vorstellbarer Schmerz). Es wurden keine signifikanten Unterschiede zwischen den Gruppen bei der AUC festgestellt (Mittelwert der individualisierten Akupunktur: 1768,7 (95% KI, 1460,4; 2077,1); standardisierte Akupunktur 1482,9 (1177,2; 1788,7); Gruppenunterschied, 285,8 (-33,9; 605,5) $P = 0,080$). In dieser unizentrischen Studie

war die individualisierte Akupunktur der standardisierten Akupunktur bei Patienten mit chronischen Schmerzen nicht überlegen. In einem nächsten Schritt sollte eine multizentrische Nichtunterlegenheitsstudie durchgeführt werden, um zu untersuchen, ob die standardisierte Akupunkturbehandlung bei chronischen Kreuzschmerzen in einem breiteren Rahmen der Normalversorgung anwendbar ist. Diese Studie ist bei ClinicalTrials.gov NCT00758017 registriert."

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Research Article

Standardized versus Individualized Acupuncture for Chronic Low Back Pain: A Randomized Controlled Trial

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We aimed to compare the effectiveness of standardized and individualized acupuncture treatment in patients with chronic low back pain. A single-center randomized controlled single-blind trial was performed in a general medical practice in Germany run by a Chinese-born medical doctor trained in western and Chinese medicine. One hundred and fifty outpatients with chronic low back pain were randomly allocated to two groups (78 standardized and 72 individualized acupuncture). Patients received either standardized acupuncture or individualized acupuncture. Treatment encompassed between 10 and 15 treatments based on individual symptoms with two treatments per week. The main outcome measure was the area under the curve (AUC) summarizing eight weeks of daily rated pain severity measured with a visual analogue scale (0 mm = no pain, 100 mm = worst imaginable pain). No significant differences between groups were observed for the AUC (individualized acupuncture mean: 1768.7 (95% CI, 1460.4; 2077.1); standardized acupuncture 1482.9 (1177.2; 1788.7); group difference, 285.8 (−33.9; 605.5) $P = 0.080$). In this single-center trial, individualized acupuncture was not superior to standardized acupuncture for patients suffering from chronic pain. As a next step, a multicenter noninferiority study should be performed to investigate whether standardised acupuncture treatment for chronic low back pain might be applicable in a broader usual care setting. This trial is registered with ClinicalTrials.gov NCT00758017.

1. Introduction

In Western countries, chronic low back pain is a major health concern affecting the quality of life and productivity. Low back pain has a high economic impact. More than 70% of the population in industrialised countries is affected by low back pain [1]. In the United Kingdom, low back pain accounts for 13% of absences due to illness. The annual incidence in adults is up to 45%, with those aged 35–55 years affected most often. Although 90% of the episodes of acute low back pain settle within six weeks, up to 7% of patients develop chronic pain [1]. For chronic low back pain, a wide range of treatment options are available [2] although their efficacy is not always clear. A multimodal approach is recommended including providing information and counseling, exercise, pain therapy, behavioral therapy, and physiotherapy [2–4]. However, long-term effects are difficult to achieve [4].

Complementary and alternative medicine (CAM) therapies are widely used [5–10], and acupuncture was shown to be useful for chronic low back pain [11–14]. The acupuncture treatment costs are reimbursed by the German statutory health insurance companies [15]. However, the question remains whether individualized acupuncture, which needs more training and experience, is necessary to improve pain compared to a standardized acupuncture.

The practice of acupuncture has traditionally been based on the Chinese medical system of diagnosing "patterns of disharmony" where identifying the pattern determines the appropriate treatment principle [16]. Treatment principle, in turn, purportedly influences the treatment given, including the specific modalities used and acupoints stimulated. From the perspective of the Chinese medicine, patients with a single condition as defined by the western biomedicine may have one of several Chinese medical patterns, each of which

requires a different treatment [17]. According to a study by Hogeboom et al., Chinese medical diagnoses and treatment recommendations for specific patients with chronic low back pain vary widely across practitioners [17]. They conclude that a comparison of individualized treatment with a thoughtfully developed standardized approach is warranted to determine which, if either, is superior [17]. A more standardized formulaic approach with a fixed set of points based on the best evidence might have the potential of improving the quality and efficiency of treatment and can support the integration of acupuncture into conventional care. At present, in China, standardization of acupuncture is strongly encouraged. For diagnoses such as stroke formulaic approaches are already well established [18].

The aim of our randomized controlled trial is to compare a standardized acupuncture that is based on evidence from previous acupuncture studies with individualized acupuncture based on the theory of Chinese medicine in patients with chronic low back pain.

2. Methods

2.1. Design. We performed a randomized controlled single-blind trial with treatment duration of eight weeks and a total observation time of 26 weeks per patient to compare the effectiveness of standardized with individualized acupuncture. Participants were blinded to group allocation.

This study followed the standards of the Declaration of Helsinki (revised version, Somerset West (SA), 1996 [19]) and the ICH-GCP guideline and was approved by the Ethics Committee Charité—Universitätsmedizin Berlin (Approval no. EA1/098/08). All patients gave oral and written informed consent.

2.2. Participants and Setting. Patients were recruited from the regular patients of a general medicine practice in Berlin, Germany, run by a Chinese-born medical doctor trained in western and Chinese medicine. The MD usually provides both conventional care and acupuncture to her patients. The acupuncture is usually individualized based on the Chinese medicine syndrome diagnosis. Patients with chronic low back pain suitable for acupuncture therapy (which is reimbursed by the German health insurances) were invited to participate in the study. No additional allowance was paid for the study. Participants were informed about the study using the following descriptions for both interventions: one group receives acupuncture according to individually selected points on the basis of diagnostics of Chinese medicine and the other group receives acupuncture consisting of acupuncture points that have shown their effectiveness in several studies.

The randomization sequence was generated by a data manager, who was not involved in the analysis of the data and enrolment of the patients, with Microsoft Office Excel 2003 in a 1 : 1 ratio stratified for gender. The list was integrated into a secured database (Microsoft Office Access 2003) and was not accessible to the other staff members or the study physician. Randomization took place in the practice using the secured database. The patient's allocation to the different treatment groups and the patient identification number for each single patient were assigned and accessible for the enrolling physician after patient data such as name and date of birth was entered and saved in the secured database. With that approach, the randomization list was hidden in the database and not accessible for anyone participating in the enrolment.

Patients were eligible for the trial if they fulfilled the following inclusion criteria: age of at least 18 years, male or female, low back pain for at least 3 months (clinical diagnosis of chronic low back pain confirmed by a medical specialist) and indication for treatment of low back pain with acupuncture confirmed by a medical specialist, average pain intensity of the last 7 days more or equal to 40 mm measured by a visual analogue scale (VAS 0–100 mm), intellectual and physical ability to participate in the study, and informed consent.

Main exclusion criteria were acupuncture during the last 6 months, start of a new therapy for low back pain within the last 4 weeks, pregnancy, substance or drug abuse, and participation in another clinical trial.

2.3. Intervention. All patients received Chinese medicine diagnostics including examination of pulse and tongue to avoid a bias due to a possible placebo effect caused by this kind of examination. Both acupuncture interventions were applied by the same medical doctor specialized in western general medicine (25 years of clinical practice) and trained in Chinese medicine with 20 years' experience in treating low back pain with acupuncture. According to the current statutory health insurance benefit catalogue, 10 to 15 treatment sessions per year are usually reimbursed. In our study, two treatment sessions per week had to be applied, with a maximum number of 10 to 15 sessions depending on the patient's individual needs. The standardized acupuncture was based on the acupuncture intervention from a large multicenter trial previously performed by our group [13, 20], developed by a large and systematic expert consensus [21]. From this trial's database, we determined the most frequently used points. Two Chinese medicine experts (BB and XYS) with more than 15 years of experience in acupuncture finalized the standardized treatment protocol used for the present study. Only body-needle acupuncture without electrical stimulation was allowed. Standardized acupuncture used the following points: (1) local points Bl 23, 24, and 25 and (2) distant points Bl 40, Bl 60, Gb 34, and K 3 in each session on both sides of the body. Individualized acupuncture was based on syndrome diagnosis, which was done before each treatment session. However, not more than 14 needles were applied to be comparable with the group with standardized acupuncture. For this study, we purchased Viva Sterile Acupuncture Needles, for single use only, pyrogen free, from Oxford Medical Supplies Ltd., Fairford, Gloucestershire, England. They had a needle length of 20 to 40 mm and a diameter of 0.2 to 0.3 mm. They were vertically inserted 1-2 cm deep into the skin depending on the size of the respective muscle. The needles were manually stimulated by rotation and lift-thrusting until a deqi sensation was reached. The needle retention time was about 25 min in both groups.

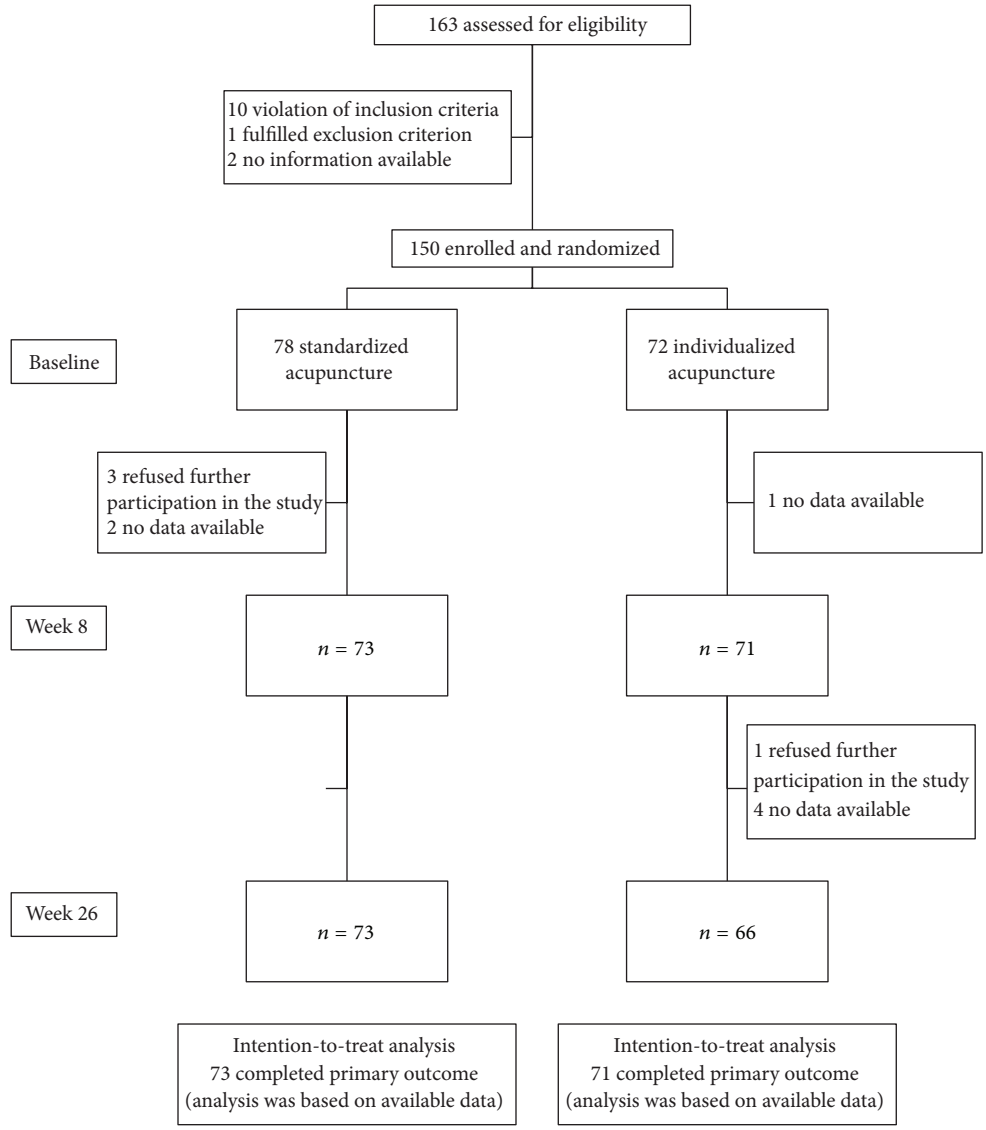

Figure 1: Recruitment, treatment, and follow-up of patients with chronic low back pain.

Because it was a trial in a real-life setting, comedication was allowed in both groups, and their intake was documented using diaries.

2.4. Outcome Measurements. The primary outcome measure was the area under the curve (AUC) summarizing the average low back pain intensity over eight weeks. For this, the back pain intensity of the last 24 hours was rated daily in a diary using a visual analogue scale [22] (VAS, 0–100 mm, 0 = no pain, 100 = worst imaginable pain) and then summed up over 56 days.

Secondary outcome measures included the VAS for pain during the previous 7 days at eight and 26 weeks and the following outcomes at eight and 26 weeks: back function (Hannover Functional Ability Questionnaire, HFAQ; in German, Funktionsfragebogen Hannover Rücken) [23], general health related quality of life (SF-36) [24], days absent from work, mean number of treatment sessions, mean duration of treatment, and days with physical therapy because of back pain. The patient diary (baseline to week 8) was also used to calculate the number of days with pain medication between weeks one and eight. In addition, we evaluated the safety of the interventions (recording of adverse events at each visit through the treatment physician) and blinding (patient guess of intervention group at 8 weeks). Except for safety data and data in the diary, outcome data was obtained by a study nurse, who was not blinded to the treatment arm.

To assess the patients' and doctor's expectation for improvement due to the treatment before randomization, patients and doctors had to document their expectation of the therapy on categorical scales: "recovery," "distinct improvement," "slight improvement," and "no improvement" as well as their assessment of the presumed therapy's effectiveness: "very effective," "effective," "small effect," and "no effect."

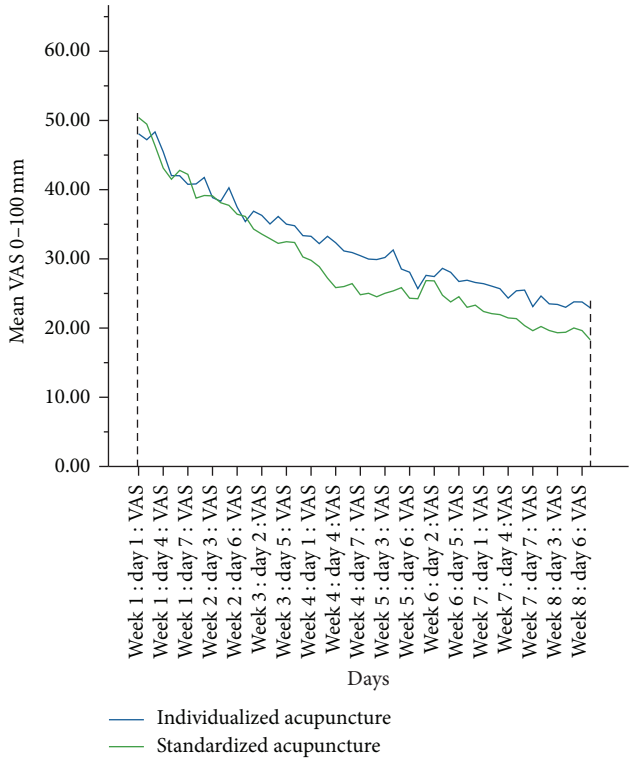

Figure 2: Mean symptom severity VAS of daily data over 8 weeks, nonadjusted data. Dashed lines represent the borders of the area under the curve.

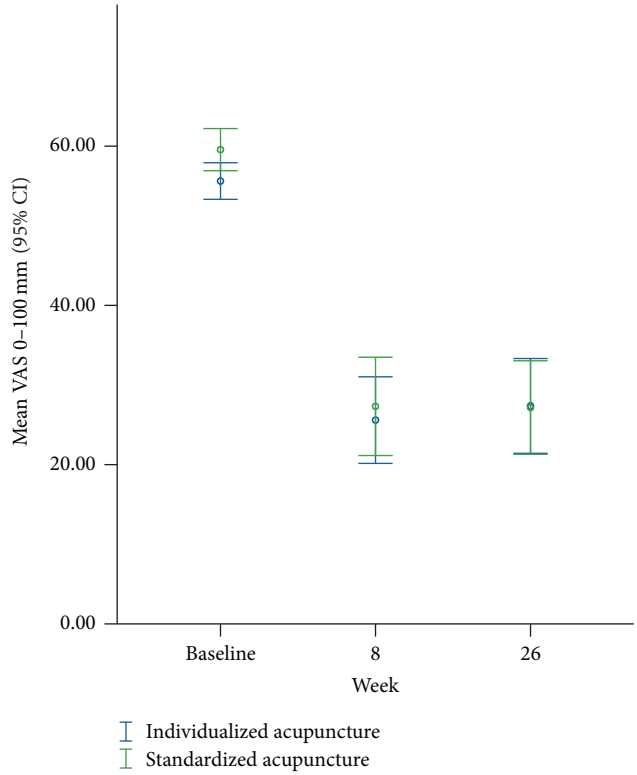

Figure 3: Mean (with 95% confidence interval) pain intensity over the last 7 days (VAS) at week 8 and at week 26, nonadjusted data. At baseline, VAS was different between both groups (0.014), but not for the latter time points.

2.5. Statistical Analysis. The study was designed to detect a clinically relevant effect (standard mean difference of 0.5) for the primary outcome measure with a power of 80% and a significance level of 5% using a two-sided t-test. Based on that calculation, a total of 128 participants were needed. Taking about 20% potential drop-outs into account, 150 participants (75 per group) were planned to be included into the study. The primary analysis population was the intention to treat (ITT) population, based on the available data. Each randomized participant was included into the analysis regardless of the adherence to the assigned treatment.

The primary outcome (daily low back pain intensity summed over 8 weeks) was evaluated using analysis of covariance (ANCOVA) including treatment group, with baseline value and participants' initial expectation from treatment as covariates. This resulted in adjusted mean severity scores per treatment group, 95% confidence intervals and P value for treatment group comparison. Secondary outcome parameters were analysed by similar ANCOVA or generalized estimating equation (GEE) models in a similar fashion. Missing data were not imputed. All tests were two-sided; the significance level for the primary outcome was set at 0.05, and all other P values were considered explorative. Analyses were performed in SAS Version 9.1 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Participants and Treatment. From 163 possible participants screened, 150 were enrolled between January 2009 and January 2011 (Figure 1) and randomized into the two groups (standardized group $n = 78$, individualized group $n = 72$). The mean age was 57.8 ± 12.5 (mean ± sd) years, 58% were female and the mean duration of symptoms was 16.3 ± 12.3 years. At baseline, the average pain intensity on the VAS was 58.5 ± 11.3 mm (for other baseline characteristics see Table 1).

The mean number of treatments was 10.4 ± 2.8 in the standardized group and 11.0 ± 2.5 in the individualized group (median 10.0 and 10.0, resp.). Six patients were lost to follow-up at week eight but were included in the ITT analysis. Follow-up data after 26 weeks was available for 139 patients (standardized group $n = 73$, individualized group $n = 66$). The reasons for missing follow-up data are shown in Figure 1.

3.2. Outcomes. Both groups showed a clinically meaningful improvement [25] after 8 weeks regarding pain severity (Figure 2). The primary endpoint, the area under the curve (AUC) for the pain severity from baseline to end of week 8, was comparable between both groups (Table 2, Figure 2 for unadjusted data) and showed no statistically significant differences (adjusted group difference, 285.8 (95% CI −33.9; 605.5); $P = 0.080$, Table 2).

Secondary outcomes showed consistent results. The average pain severity after 8 weeks and 26 weeks did not differ significantly between both groups (Table 2, Figure 3 for unadjusted data). Accompanying therapy including concurrent

Table 1: Baseline demographic and clinical characteristics of trial groups.

Characteristics	Standardized acupuncture (n = 78)	Individualized acupuncture (n = 72)
Age (years; mean ± sd)	59.3 ± 12.0	56.1 ± 12.9
Gender (n (%))		
Female	42 (53.8)	45 (62.5)
Male	36 (46.2)	27 (37.5)
BMI (kg/m^2; mean ± sd)	27.2 ± 4.6	27.0 ± 5.0
>10 years of school (n (%))	10 (12.8)	24 (33.3)
Size of household (n (%))		
Single person	22 (28.2)	16 (22.2)
Multiperson	55 (70.5)	56 (77.7)
Average low back pain during the previous 7 days (VAS[$]; mean ± sd)	60.7 ± 12.0	56.2 ± 10.0
Duration of low back pain (years; mean ± sd)	16.8 ± 12.8	14.9 ± 11.8
Concomitant diseases (n (%))		
Diseases of the nervous system	0 (0)	2 (2.7)
Endocrine, nutritional, and metabolic diseases	1 (1.2)	3 (4.1)
Diseases of musculoskeletal system	12 (15.3)	4 (5.5)
Sick leave days of previous 8 weeks (days; mean ± sd)	8.9 ± 14.8	8.2 ± 13.5
Prior consultation because of low back pain (n (%))	78 (100)	69 (95.8)
Low back pain/disability (HFAQ[#]; mean ± sd)	36.0 ± 19.1	37.4 ± 20.4
SF-36 quality of life (SF-36[#]; mean ± sd)		
Physical health	34.7 ± 7.7	35.7 ± 9.3
Mental health	49.7 ± 11.1	46.2 ± 12.5
Experiences with acupuncture (n (%))	60 (76.9)	56 (77.7)
Expected effectiveness of acupuncture (n (%))		
Very effective	32 (41.0)	24 (33.3)
Effective	41 (52.5)	48 (66.6)
Less effective	4 (5.1)	0 (0)
Ineffective	0 (0)	0 (0)
Preference (n (%))[$]		
Standardized acupuncture	30 (38.4)	35 (48.6)
Individualized acupuncture	46 (58.9)	37 (51.3)

BMI: body mass index; VAS: visual analogue scale for assessing the average low back pain intensity; HFAQ: Hannover Functional Ability Questionnaire; SF-36: 36-item quality-of-life questionnaire.
[$]Lower values indicate better status.
[#]Higher values indicate better status.
[$]Missing answers add to 100%.

therapies was not significantly different between both groups regarding days with medication intake (week 1 to end of week 8), days with physical therapy because of back pain (week 1 to end of week 8), and number of therapy sessions and duration of therapy (baseline to end of therapy). Furthermore, for the secondary outcomes HFAQ, QoL, and sick leave days at week 8 and week 26, no significant group differences were observed (Table 2).

Of the 150 patients in both intervention groups, none reported acupuncture-related side effects. However, adverse events reported by the patients included breast cancer, herpes zoster, and common cold (individualized group: 7 events, standardized group: 8 events), but none had a causal relation to the acupuncture treatment.

After the end of treatment, patients were asked to guess what treatment intervention had been administered to them. In the standardized group, 78.1% guessed they were in the standardized group while, in the individualized group, 55.7% guessed they were in the individualized group (Table 3).

4. Discussion

In our study, we could not show a statistically significant difference between standardized and individualized acupuncture in the treatment of chronic low back pain. Results were consistent over all outcomes.

Table 2: Primary and secondary outcomes at 8 and 26 weeks (adjusted for baseline value and participant's expectation)*.

	Standardized acupuncture mean (95% CI)	Individualized acupuncture mean (95% CI)	Differences individualized versus standardized acupuncture (95% CI)	*P* value
Overall low back pain—area under the curve** (sum of daily VAS§): week 1 to 8μ	1,482.9 (1,177.2; 1,788.7)	1,768.7 (1,460.4; 2,077.1)	285.8 (−33.9; 605.5)	0.080
Mean overall low back pain: (mean daily VAS§): weeks 1 to 8μ	26.5 (21.0; 31.9)	31.6 (26.1; 37.1)	5.1 (−0.6; 10.8)	0.080
Days with pain medication: weeks 1 to 8μ	4.9 (0.4; 9.3)	5.6 (1.2; 10.0)	0.7 (−3.9; 5.4)	0.752
Days with physiotherapy: weeks 1 to 8μ	2.1 (0.1; 4.0)	1.9 (0.01; 3.8)	−0.2 (−2.2; 1.8)	0.867
Number of acupuncture therapy sessions	9.8 (8.4; 11.2)	10.3 (8.9; 11.7)	0.5 (−0.3; 1.3)	0.226
Duration of therapy (minutes per week)	41.1 (30.7; 51.5)	44.4 (34.4; 54.4)	3.3 (−2.6; 9.3)	0.272
Average low back pain during the previous 7 days (VAS§)				
8 weeks	27.4 (21.2; 33.7)	28.7 (23.4; 34.0)	1.3 (−5.8; 8.4)	0.723
26 weeks	27.3 (21.0; 33.7)	30.5 (24.6; 36.3)	3.1 (−4.5; 10.8)	0.424
Low back pain/disability (HFAQ#)				
8 weeks	25.8 (21.9; 29.6)	27.5 (22.8; 32.1)	1.7 (−3.4; 6.8)	0.513
26 weeks	24.3 (20.4; 28.3)	25.9 (21.0; 30.8)	1.5 (−3.7; 6.8)	0.569
SF-36 quality of life (SF-36#)				
Physical health at 8 weeks	42.7 (40.3; 45.1)	42.1 (40.1; 44.1)	−0.5 (−3.5; 2.4)	0.714
Physical health at 26 weeks	43.1 (40.7; 45.5)	41.7 (39.5; 43.8)	−1.5 (−4.5; 1.6)	0.343
Mental health at 8 weeks	49.5 (47.0; 52.1)	50.0 (47.4; 52.6)	0.4 (−2.7; 3.6)	0.788
Mental health at 26 weeks	48.8 (46.1; 51.6)	50.7 (47.9; 53.5)	1.9 (−1.6; 5.4)	0.287
Sick leave days				
8 weeks	4.8 (1.8; 7.8)	4.5 (1.5; 7.4)	−0.3 (−3.4; 2.8)	0.843
26 weeks (previous 4 months)	9.0 (3.6; 14.4)	9.7 (4.1; 15.2)	0.6 (−4.8; 6.0)	0.817

VAS: visual analogue scale for assessing the average low back pain intensity; HFAQ: Hannover Functional Ability Questionnaire; SF-36: 36-item quality-of-life questionnaire.
*The area under the curve was evaluated using analysis of covariance (ANCOVA) including treatment group, with baseline value and participants' initial expectation from treatment as covariates. Secondary outcome parameters were analysed by similar ANCOVA or generalized estimating equation (GEE) models in a similar fashion.
μBased on daily data from a diary.
§Lower values indicate better status.
#Higher values indicate better status.
**The area under the curve (AUC) represents the sum of daily VAS scores (0–100) over 8 weeks.

Table 3: Guesses of group allocation.

Patients' guesses	Group assignment	
	Standardized	Individualized
Standardized	57 (78.1%)	39 (55.7%)
Individualized	16 (21.9%)	31 (44.3%)

*Chi-square test.

The main strengths of this trial are the randomized single-blinded study design, the relatively large sample size for a single-center trial on CAM, and the high compliance and follow-up rates. We aimed to answer a research question that has relevance for usual care practice. Therefore, the chosen setting in a general medical practice reflects a real-world setting. This routine care setting is a reason for the broad inclusion and exclusion criteria in our trial and the decision to leave the decision on the number of visits to the physician. The physician who performed the acupuncture usually treats her patients with individualized acupuncture. However, to evaluate the quality of care in her practice, she was highly motivated to compare it with a standardized acupuncture approach, which was comprised of those acupuncture points that were most frequently used by the participating physicians in a large randomized multicenter trial of acupuncture in patients with low back pain [20]. We think the fact that this was a single-center trial carried out by a single practitioner is both strength (reducing implementation variability) and a weakness (limiting generalizability).

The outcome measure VAS is a validated and sensitive tool, which is widely used to measure pain. By using the area under the curve summarizing the VAS of week 1 to week 8 as our primary outcome, we were able to include different time points into one primary outcome measure. However, this might have caused an underestimation of the treatment effect, because the measure averages the pain intensity of the whole treatment course. Using only week 5 to week 8 data would have been another option; however, secondary

outcomes such as the pain measured after eight weeks and after 26 weeks showed also no significant differences between groups. The secondary outcome measures we included in our study such as medication intake, back function, and quality of life also confirmed the results.

We tested sustained blinding in both treatment groups. The standardized group guessed the right treatment more often than one could expect by chance. One reason might be that more than half of the study patients were experienced with acupuncture. We do not think that this affected our results because both groups were informed to get an effective treatment and improved similarly. Furthermore, assessing blinding is a controversial discussion and was deleted from the current version of the CONSORT checklist [26].

The aim of this study was not to assess the efficacy of acupuncture for chronic low back pain. Berman et al. discussed its clinical relevance, [11] and a very recent patient-level data meta-analysis came to the conclusion that acupuncture is statistically significant superior to sham-acupuncture for chronic low back pain, [14] although the effect between groups was of small size.

Another option for a research question would have been noninferiority trial to evaluate whether standardized acupuncture for chronic low back pain is noninferior to individualized acupuncture. However, we decided to follow a superiority hypothesis, because individualized acupuncture requires more time resources, both from a training and application perspective. A multicenter trial would have produced more generalizable results and reduced possible bias of the participating physicians regarding their favored therapy.

Our study results suggest that there is no relevant difference in the outcome of standardized and individualized acupuncture in the treatment of chronic low back pain. For week 1 to week 8, one could even observe a trend toward superiority of the standardized acupuncture. However, this lack of statistical significance has to be interpreted with caution. Because of our statistical superiority approach, our study does not prove that standardized acupuncture is non inferior or equivalent to individualized acupuncture.

Our study might be compared with a study conducted in the United States that directly compared individualized acupuncture with standardized acupuncture [27]. They showed that performing a Chinese medicine diagnosis did not change the result that patients in all acupuncture groups (individualized, standardized, or sham) improved significantly more than patients receiving usual medical care, but the acupuncture groups did not differ significantly from one another [11]. Standardized acupuncture points in Cherkin's study were based on an expert consensus and comprised of eight points (individualized 11 points). Our standardized acupuncture was based on data from a large trial on low back pain and comprised 14 points.

In conclusion, in this single-center trial, individualized acupuncture was not superior to standardized acupuncture for patients suffering from chronic low back pain. If a fixed set of points can be well established for a specific condition, this might have wide implications. Without the necessity for a diagnosis according to Chinese medicine, it might reduce time and knowledge necessary for the treatment. These can extend the availability of acupuncture toward conventional care. A next step multicenter noninferiority study to investigate whether standardized acupuncture treatment for chronic low back pain might be applicable in a broader usual care setting and is more cost-effective could have clinical and health policy implications.

Authors' Contribution

Claudia M. Witt, Daniel Pach, and Benno Brinkhaus conceived and designed the experiments. Claudia M. Witt, Daniel Pach, and Xiaoli Yang-Strobel performed the trial. Claudia M. Witt, Daniel Pach, Katja Icke, Rainer Lüdtke, and Stephanie Roll analyzed and discussed the data. Daniel Pach wrote the first draft of the paper. BennoBrinkhaus, Claudia M. Witt, Daniel Pach, Katja Icke, Rainer Lüdtke, Stephanie Roll, and Xiaoli Yang-Strobel revised the paper and approved the final version.

Disclosure

Daniel Pach and Claudia Witt had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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4 DISKUSSION

Die vorliegende Arbeit untersuchte nichtpharmakologische Interventionen zur Schmerztherapie aus der Integrativen Medizin und Digitalen Gesundheit mittels randomisierter kontrollierter Studien bezüglich ihrer klinisch relevanten Wirkung und bot damit Daten, um die Anwendung Evidenzbasierter Medizin in der Integrativen Medizin und Digitalen Gesundheit zu erleichtern.

Die per Smartphone-App durchgeführte Selbstakupressur führte bei jungen Frauen zu einer Verringerung der Menstruationsschmerzen im Vergleich zur Normalversorgung. Die Wirkung nahm mit der Zeit zu, und die Therapieadhärenz war gut.

Im Gegensatz dazu konnte die Studien-App, die Verfahren aus dem Bereich der Mind-Body-Medizin integrierte, chronische Nackenschmerzen nicht wirksam reduzieren. Die Adhärenz zur Intervention war weniger gut.

Unsere neuere Studie zu Menstruationsschmerzen zeigte, dass Betroffene auch ohne direkten Kontakt zu Gesundheitsexperten und allein über einen App-Store erreicht werden können und die App dann auch nutzen. Bei dieser Studie steht die Bewertung des medizinischen Nutzens jedoch noch aus.

Im Setting einer Hochschulambulanz zeigte sich eine zusätzliche Behandlung mit sechs Tuina-Sitzungen über drei Wochen bei Patienten mit chronischen Nackenschmerzen als wirksam, sicher und relativ kosteneffektiv im Vergleich zu einer Patientengruppe mit chronischen Nackenschmerzen ohne zusätzliche Intervention.

Eine im ambulanten Setting einer Allgemeinarztpraxis durchgeführte individualisierte Akupunktur zeigte sich einer standardisierten Akupunktur bei chronischen Kreuzschmerzen nicht überlegen. Die Studie weist darauf hin, dass eine Vereinfachung der Akupunkturbehandlung und ein möglicherweise breiterer Einsatz möglich wären.

Sowohl aus den Einzelstudien als auch aus den Studien in ihrer Zusammenschau lassen sich wichtige Erkenntnisse für den Bereich Integrative Medizin und Digitale Gesundheit ableiten. Neben den üblichen Qualitätskriterien wie Fallzahl, Randomisierung, Verblindung bei der Interpretation dieser Studien sollten dabei auch weitere Punkte beachtet werden. So ist u.a. wichtig, ob die Interventionen entweder 1. klassisch im direkten Patientenkontakt, 2. in einem hybriden Setting, d.h. in einer Kombination aus digitalem Angebot und direktem Kontakt mit Gesundheitsexperten oder 3. rein digital (virtuell) implementiert und untersucht wurden. Auch ist wichtig, ob die einzelnen Studien unter sehr kontrollierten Bedingungen als Efficacy-Studie oder eher unter Alltagsbedingungen als Effectiveness-Studie durchgeführt wurden.[31]

Unsere erste Studie zu Menstruationsschmerzen wurde in einem hybriden Setting durchgeführt. Die Rekrutierung erfolgte klassisch über ein Studienzentrum und sowohl in die App und als auch in die Akupressur wurde durch eine Gesundheitsexpertin eingeführt.[32]

Die Studie zu den App-basierten Entspannungsverfahren bei chronischen Nackenschmerzen[33] erfolgte auch als hybride Studie, die verschiedenen implementierten Interventionen wurden jedoch nicht ausführlich durch einen Gesundheitsexperten erklärt. Dies könnte eine der Ursachen sein, warum diese Intervention keine Effektivität zeigte.

Unsere digitalen Studien wurden in einer relativ frühen Phase der Entwicklung von Digital Health als randomisierte kontrollierte Studien durchgeführt und verfügten bereits über einen konfirmatorischen statistischen Ansatz mit klar definierten patientenrelevanten Endpunkten und einer ausreichend hohen Fallzahl, um relevante Effekte, wenn sie vorhanden sind, auch nachweisen zu können. In der Vorbereitung dieser Studien kam bereits Stakeholder-Engagement[34 35] zur Anwendung. Dies sollte u.a. die externe Validität der Studienergebnisse[23 24] erhöhen.

Das finale Design einer klinischen Studie ist auch bei sorgfältiger Auswahl des Studiendesigns häufig eine Summe aus Kompromissen. Die perfekte klinische Studie, die allen Anforderungen gerecht wird, gibt es nicht. So kann eine Studie die Wirksamkeit einer Therapie unter sehr kontrollierten Bedingungen untersuchen (Efficacy) oder die Wirksamkeit unter Alltagsbedingungen (Effectiveness).[22] Auch aus diesem Grund verblieben bei diesen beiden digitalen Studien Limitationen, die bei der Beurteilung der Ergebnisse zu berücksichtigen sind. In beiden Studien waren die Teilnehmenden nicht verblindet. Die Verblindung bei komplexen Interventionen ist schwierig, u.a. weil die wirkenden und die nicht-wirkenden Komponenten oft nicht im Detail bekannt sind.[36] Um eine Verblindung der Teilnehmenden zu erreichen, wäre ein experimentelleres Studiendesign sinnvoll gewesen, welches die "Efficacy" von Einzelkomponenten untersucht. Mit beiden Studien sollte jedoch die „Effectiveness“ untersucht werden. Daher wurden pragmatische klinische Studien ohne Verblindung der Teilnehmenden geplant und durchgeführt. Die jeweiligen Teilnehmenden wussten somit, ob sie der Interventions- oder der Kontrollgruppe zugeordnet wurden. Ob dieser Faktor Einfluss auf die Ergebnisse hatte, ist offen. Auch ist das Ausmaß eines möglichen digitalen Placeboeffekts, also der Wirkung allein durch die Nutzung eines unspezifischen digitalen Tools in therapeutischer Absicht, unklar. Die Kontrollgruppen beider Studien erhielten jeweils die App zur Datenerfassung. Die Funktionen, die die eigentlichen Interventionen (Akupressur bzw. Entspannungsverfahren) darstellten, waren jedoch nicht freigeschaltet. Es ist möglich, dass bereits die aktive Erfassung bzw. das "Tracken" von Symptomen bereits einen Einfluss auf die Symptome hatte. Beide Studien benötigten mehr als zwei Jahre vom Einschluss der ersten Teilnehmenden bis zum Ende der Nachverfolgung. Diese relativ lange Studiendauer war u.a. im hybriden Design der Studien begründet,

d.h. Teilnehmende wurden in einem Studienzentrum rekrutiert und in die App eingewiesen. Ein rein digitaler Weg hätte hier Geschwindigkeitsvorteile gebracht, ist jedoch auch mit mehr finanziellem, personellem und technischem Aufwand in der Vorbereitung verbunden. Um die individuelle Studiendauer möglichst kurz zu halten und die Rekrutierung dadurch zu vereinfachen, wurde eine Nachbeobachtungszeit von 6 Monaten in beiden Studien gewählt. Der primäre Zielparameter wurde in beiden Studien bereits nach ca. 3 Monaten gemessen. Da beide Studien auf das Verhalten der Teilnehmenden wirken, dieses Verhalten verändern wollten, und die Verhaltensänderung auch einige Zeit bis zur Wirkung benötigt, ist es denkbar, dass dieser Zeitraum zu kurz gewählt war, um den wahren Effekt der Interventionen abzubilden. Auf der anderen Seite ist bekannt, dass die Adhärenz gegenüber digitalen Interventionen über die Zeit schnell abnimmt. Aufgrund der jeweils gewählten Studiendauer sind somit keine Aussagen zu Langzeiteffekten möglich, und es bleibt offen, wie valide die Aussagen zu den Kurzzeiteffekten sind. Beide Studien nutzten darüber hinaus kein elaboriertes Konzept zur Verhaltensänderung, wie zum Beispiel das Konzept der BCT[37]. Es ist somit möglich, dass dessen Anwendung zu besserer Adhärenz oder allgemein höherer Wirksamkeit der Interventionen geführt hätte.

Die untersuchten Studien-Apps waren nach Studienende aufgrund der schnellen technischen Entwicklungen im Bereich Digitale Gesundheit technologisch bereits veraltet. Auch erfüllen sie aus heutiger Sicht nicht die regulatorische Anforderungen an Software als Medizinprodukt[19 38], die bereits seit Mai 2021 die Entwicklung von Digitalen Gesundheitsanwendungen im Rahmen eines spezifischen Qualitätsmanagementsystems vorschreiben. Die Apps wären somit nicht im Alltag einsetzbar gewesen.

So wurde eine weiterer RCT zur Anwendung von Akupressur und weiteren Verfahren der Integrativen Medizin bei Menstruationsschmerzen aufbauend auf den Erkenntnissen der ersten RCTs begonnen. Dazu erfolgte die Durchführung der Studie komplett in einem virtuellen oder „remote" Studien-Setting. Die Nutzerinnen hatten dabei keinen persönlichen Kontakt mit medizinischem Fachpersonal, die Verhaltensänderungstechniken wurden systematisch implementiert und die Nachbeobachtungszeit auf 12 Menstruationszyklen verlängert. Aufgrund des virtuellen Settings war eine Einbeziehung weiterer Länder (Australien, Brasilien, Taiwan und USA) in die Studie vergleichsweise einfach möglich. Mehrsprachigkeit musste dafür jedoch bereits sehr früh in der Studienvorbereitung berücksichtigt werden. Die Rekrutierung konnte aufgrund des virtuellen Settings schneller erfolgen als in den ersten Studien. Ob die Anpassungen im Vergleich zur Vorstudie zu einem stärkeren oder geringeren Effekt geführt haben, wird sich jedoch erst nach Auswertung der Daten zeigen, die bisher nicht erfolgte. Aber auch für diese Studie sind Limitationen zu beachten. So wurden aus Ressourcengründen nicht erneut Stakeholder in die Studienplanung und -vorbereitung einbezogen

und es ist möglich, dass die Nachbeobachtungszeit ohne Kontakt mit Gesundheitspersonal zu lang gewählt worden war, um eine adäquate Adhärenz der Teilnehmenden zu erreichen.

Im Gegensatz zu den bisher beschriebenen digital gestützten Studien wurden sowohl die Studie zur Akupunktur bei chronischen Kreuzschmerzen[39] als auch die Studie zu Tuina bei chronischen Nackenschmerzen[40] als klassische Studien mit direktem Patientenkontakt durchgeführt. Beide Studien weisen auf die klinische Wirksamkeit der jeweiligen Interventionen bei chronischen Schmerzen hin. Bei beiden Studien ist jedoch die Interpretation durch das unizentrische Design der Studien eingeschränkt.

Es wäre nun spannend zu untersuchen, ob Digitalisierung diese beiden Verfahren aus einem klassischen Setting auch unterstützen könnte. Es ist sowohl für die adäquate Durchführung der Tuinamassage als auch der Akupunktur eine langjährige Ausbildung notwendig. Eine Unterstützung durch digitale Angebote ist jedoch denkbar. Die Studie zur Akupunktur weist bereits darauf hin, dass Standardisierung ggf. ein Weg sein kann, um den Zugang zur Behandlung zu vereinfachen. Eine einfache digitale Lösung, die zur Selbstbehandlung mittels Akupressur anleitet, wäre damit als ergänzende Behandlungskomponente, die zwischen einzelnen Terminen genutzt werden kann, vorstellbar.

Allen präsentierten Studien gemeinsam ist, dass jeweils Einzelinterventionen untersucht wurden. Dazu wurden randomisierte kontrollierte Studien durchgeführt. Der Evidenzgrad dieses Studientyps ist hoch. Diese Studien können in Meta-Analysen eingehen, die dann in der Zusammenschau ein noch besseres Bild zur Evidenz bieten können. Darüber hinaus sollten chronische Schmerzerkrankungen im Rahmen des biopsychosozialen Modells eher multimodal behandelt werden. Es ist jedoch methodisch nicht einfach diese komplexen Interventionen in Studien gut zu untersuchen. Hier könnte die Digitalisierung in Zukunft ggf. helfen. Digitalisierte Verfahren könnten kombiniert und als komplexe Intervention untersucht werden. Weil mit digitalisierten Anwendungen auch große Patientenzahlen rekrutiert und behandelt werden können, sind auch komplexe Studiendesigns denkbar, um komplexe Interventionen zu untersuchen.

Insgesamt reihen sich die präsentierten Studienergebnisse gut in die bestehende Literatur ein. Akupressur wird inzwischen als Option zur Behandlung von Menstruationsschmerzen angesehen[41 42], v.a. da das Risiko durch diese Intervention als niedrig eingeschätzt wird[42]. Jedoch basieren diese Empfehlungen wesentlich auf den Ergebnissen der in der vorliegenden Arbeit dargestellten Studie. Es wären noch weitere hochwertige randomisierte kontrollierte Studien mit größeren Stichproben hilfreich, um die Wirksamkeit der Akupressur besser einschätzen zu können,[43] insbesondere dann, wenn sie in einem reinen Selbstbehandlungs- oder hybriden Setting eingesetzt werden soll.

Auch Mind-Body-Verfahren gelten als relativ sicher[44] und können Teil eines multimodalen Therapieansatzes sein.[45] Die Wirksamkeit von kognitiven und achtsamkeitsbasierten Therapien bei chronischen Nackenschmerzen ist noch unklar.[3 46] Laut einer systematischen Übersichtsarbeit, die die Auswirkungen von achtsamkeits- und entspannungsbasierten Interventionen in einem eHealth-Setting untersuchte[47], berichteten nur wenige Studien über positive Auswirkungen auf Schmerzen, und keine Studie berichtete über positive Auswirkungen auf Stress oder Achtsamkeit.

Obwohl die vorliegende randomisierte kontrollierte Studie zu Tuina wichtige Erkenntnisse zur Wirksamkeit und Kosteneffektivität von Tuina bei chronischen Nackenschmerzen lieferte, bleibt die Evidenz aufgrund der geringen Studienanzahl noch immer limitiert.[48] Weitere Studien sind notwendig, um die Wirksamkeit unter Alltagsbedingungen, v.a. in einem Setting in einem westlichen Land, gut abschätzen zu können.

Für die Akupunktur bei chronischen Kreuzschmerzen ist die Studienlage gut.[3 25 49] Eine Patienten-datenmetaanalyse kam zu dem Schluss, dass Akupunktur einer Scheinakupunktur und anderen Kontrollgruppen statistisch signifikant überlegen war, wobei je nach Kontrollgruppe die Effektgrößen zwischen klein und moderat variierten.[25] Weitere Forschungsfragen bleiben offen. So ist, auch trotz der von uns durchgeführten Studie, noch immer nicht vollständig geklärt, ob eine individualisierte Akupunktur einer standardisierten Akupunktur überlegen ist und welche anderen Faktoren einen Einfluss auf das Therapieergebnis haben.[50 51]

Digitalisierte Anwendungen aus dem Bereich der Integrativen Medizin bieten potenzielle Vorteile. Sie könnten dabei helfen Studien mit großen Fallzahlen einfacher und potenziell kostengünstiger durchzuführen. Eine digitale Anwendung wird einmal entwickelt, kann dann jedoch auch ortsunabhängig sehr vielen Nutzern zur Verfügung gestellt werden. Der Aufwand für die Entwicklung sollte jedoch nicht unterschätzt werden[20], und es ist daher genau abzuwägen, für welche Studien bzw. Szenarien dieser Ansatz Sinn macht. Eine verbesserte individualisierte Therapie wäre durch Digitalisierung[52] auch denkbar, da sich digitalisierte Anwendungen auf der Basis von Nutzerverhalten und erfassten Daten individuell und zeitnah an den Nutzer anpassen können. So könnte eine Anwendung auch mit Hilfe von künstlicher Intelligenz Empfehlungen zur Selbstbehandlung oder Therapie je nach individueller Symptomschwere geben. Die Symptomschwere könnte dabei täglich über das Smartphone oder die Smartwatch erfasst werden. Die regulatorischen Anforderungen für diese Art von Anwendungen im medizinischen Kontext sind jedoch hoch, und es wären vielfältige Expertise und passende Rahmenbedingungen[20] notwendig, um Software als Medizinprodukt[38] zu entwickeln und in den Verkehr zu bringen. Darüber hinaus ist noch unklar, ob die beschriebene Individualisierbarkeit durch Digitalisierung einen klinisch relevanten Mehrwert bietet. Möglicherweise sind persönlicher Kontakt im therapeutischen Setting und die individuelle Therapieentscheidung im Austausch mit

ärztlichem Personal und auf Basis der Evidenzbasierten Medizin[21] am Ende klinisch wirksamer und unter Berücksichtigung aller anfallenden Kosten durch Digitalisierung sogar kosteneffektiver. Es gilt daher für die Zukunft die Ziele digitalisierter Anwendungen klar zu formulieren, die passenden Anwendungsbereiche zu identifizieren und die Wirksamkeit der resultierenden Anwendungen mit Hilfe klinischer Studien zu untersuchen. Insbesondere die Stärkung von Patientenautonomie und Selbstwirksamkeit[53 54] könnten lohnende Ziele sein.

Als wesentliche Schlussfolgerungen der vorliegenden Arbeit lassen sich ziehen, dass nichtpharmakologische Interventionen der Integrativen Medizin und Digitalen Gesundheit einen wichtigen Beitrag zur Behandlung chronischer Schmerzerkrankungen leisten könnten. Insbesondere die Kombination klassischer komplementärmedizinischer Verfahren und Digitaler Anwendungen scheint lohnend. Weitere Forschung zu Mechanismen, Wirksamkeit, Kosteneffektivität und optimalen Anwendungsszenarios ist notwendig. Die Grundlagen für evidenzbasiertes Arbeiten scheinen jedoch gelegt.

5 ZUSAMMENFASSUNG

Chronische Schmerzen sind ein wesentliches globales Gesundheitsproblem, welches eine hohe sozioökonomische Belastung auf der Ebene der Individuen, der Gesellschaften und der Institutionen mit sich bringt. Die vorliegende Habilitationsschrift thematisiert die Evaluation nichtpharmakologischer Interventionen aus der Integrativen Medizin und Digitalen Gesundheit bei chronischen Schmerzen.

Hierzu wurden randomisierte kontrollierte Studien zu klassischen komplementärmedizinischen Verfahren wie Tuina oder Akupunktur durchgeführt oder zu diesen Verfahren in Kombination mit modernen digitalen Technologien.

Eine Wirksamkeit konnte nur zum Teil gezeigt werden. Die per Smartphone-App durchgeführte Selbstakupressur führte bei jungen Frauen zu einer Verringerung der Menstruationsschmerzen im Vergleich zur Normalversorgung. Die Wirkung nahm mit der Zeit zu, und die Therapieadhärenz war gut. Im Gegensatz dazu konnte die Studien-App, die Verfahren aus dem Bereich der Mind-Body-Medizin integrierte, chronische Nackenschmerzen nicht wirksam reduzieren. Die Therapieadhärenz war weniger gut. Unsere aktuelle und noch laufende Studie zu Menstruationsschmerzen zeigte, dass Betroffene auch ohne direkten Kontakt zu Gesundheitsexperten und allein über einen App-Store erreicht werden können und diese die App dann auch nutzen. Im Setting einer Hochschulambulanz zeigte sich eine zusätzliche Behandlung mit sechs Tuina-Sitzungen über drei Wochen bei Patienten mit chronischen Nackenschmerzen als wirksam, sicher und relativ kosteneffektiv im Vergleich zu einer Patientengruppe mit chronischen Nackenschmerzen ohne zusätzliche Intervention. Eine im ambulanten Setting einer Allgemeinarztpraxis durchgeführte individualisierte Akupunktur zeigte sich einer standardisierten Akupunktur bei chronischen Kreuzschmerzen nicht überlegen. Die Studie weist darauf hin, dass eine Vereinfachung der Akupunkturbehandlung und dadurch ein möglicherweise breiterer Einsatz denkbar wären.

Als wesentliche Schlussfolgerungen der vorliegenden Arbeit lassen sich ziehen, dass nichtpharmakologische Interventionen der Integrativen Medizin und Digitalen Gesundheit einen wichtigen Beitrag zur Behandlung chronischer Schmerzerkrankungen leisten könnten. Insbesondere die Kombination klassischer komplementärmedizinischer Verfahren und Digitaler Anwendungen scheint lohnend. Weitere Forschung zu Mechanismen, Wirksamkeit, Kosteneffektivität und optimalen Anwendungsszenarios ist notwendig. Die Grundlagen für evidenzbasiertes Arbeiten scheinen jedoch gelegt.

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ERKLÄRUNG

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

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- mir die geltende Habilitationsordnung bekannt ist.

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