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Yoga, cognitive–behavioural therapy versus education to improve quality of life and reduce healthcare costs in people with endometriosis: a randomised controlled trial

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ABSTRACT

Introduction Endometriosis is a debilitating chronic inflammatory condition highly burdensome to the healthcare system. The present trial will establish the efficacy of (1) yoga and (2) cognitive–behavioural therapy (CBT), above (3) education, on quality of life, biopsychosocial outcomes and cost-effectiveness.

Methods and analysis This study is a parallel randomised controlled trial. Participants will be randomly allocated to yoga, CBT or education. Participants will be English-speaking adults, have a diagnosis of endometriosis by a qualified physician, with pain for at least 6 months, and access to internet. Participants will attend 8 weekly group CBT sessions of 120 min; or 8 weekly group yoga sessions of 60 min; or receive weekly educational handouts on endometriosis. The primary outcome measure is quality of life. The analysis will include mixed-effects analysis of variance and linear models, cost–utility analysis from a societal and health system perspective and qualitative thematic analysis.

Ethics and dissemination Enrolment in the study is voluntary and participants can withdraw at any time. Participants will be given the option to discuss the study with their next of kin/treating physician. Findings will be disseminated via publications, conferences and briefs to professional organisations. The University's media team will also be used to further disseminate via lay person articles and media releases.

Trial registration number ACTRN12620000756921p; Pre-results.

Strengths and limitations of this study

- ► Gold-standard randomised controlled trial methodology.
- ► Two mind-body interventions to be compared with education.
- ► Recruitment via clinics and from the general population to broaden access to the interventions.
- ► Longitudinal follow-up will compensate for the single-blinded design.

INTRODUCTION

Endometriosis is highly burdensome, impacting approximately 700 000 Australians and costing more than US$7.7 billion,[1] with nearly 35 000 endometriosis-related hospitalisations annually.[2] Presentation of endometriosis varies widely, with no clear association between the extent of disease and symptom severity—highlighting the role of complex drivers beyond organic disease or pathology. Pelvic pain, impaired health related quality of life (HRQoL) and fatigue are commonly reported by those affected, with >50% experiencing anxiety and depression.[3–5]

Endometriosis has been historically under-recognised and undertreated, due to the variability in symptoms, reliance on surgery for diagnosis and stigma and cultural taboos which create barriers to talking about periods.[6] Patients are often not diagnosed for 10 years or more, and even after receiving medical treatment many continue to experience pain and compromised HRQoL.[7] Usual care, mostly hormones and pain medications, has limited efficacy, can have problematic side effects and is discontinued in 10%–40% of patients.[8] Laparoscopic surgery often fails to prevent recurrence of disease and symptoms, with over half of patients receiving repeat surgery within 5 years.[9] Biomedical interventions alone are clearly inadequate in managing endometriosis symptoms.[10]

National Institute for Health and Care Excellence guidelines confirm the need for multidisciplinary pain management in treatment of endometriosis.[11] Consistent with these guidelines, several pilot studies have examined the use of non-medical and

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complementary pain management strategies for endometriosis. These pilots suggest the promise of interventions that use the mind-body nexus to impact health—pain, mental health and fatigue—but are limited by size and bias.[12] There is a need for well-designed, powered trials to establish the efficacy and cost-effectiveness of (1) a common mind-body intervention for women and for chronic pain—yoga[13] and (2) the most established psychological treatment for chronic pain—cognitive–behavioural therapy (CBT), above education to understand whether these treatments may be used to support care in endometriosis.

Yoga is purported to harness the benefits of movement, as well as breath regulation, and meditation and mindfulness, to reflect an integrated view of physical and psychological health.[14] Previous research has demonstrated that yoga can ameliorate pain[15] and improve mental health.[16] In a pilot randomised controlled trial (RCT) of yoga for endometriosis, 28 individuals randomised to 8 weeks of yoga reported reduced pain and improved well-being at 8 weeks compared with usual care.[17] No full-scale trials with a focus on efficacy, safety and cost-effectiveness are available.

The most established psychological treatment for chronic pain, CBT, is a type of psychotherapy where people are taught to challenge and restructure their maladaptive thinking styles, develop self-efficacy and coping, and increase engagement in life tasks.[18] CBT represents best practice in psychological treatment for chronic pain.[19] However, no full-scale RCTs on CBT for endometriosis have been conducted to date.

Establishing the efficacy and cost-effectiveness of these treatments is reliant on well-designed and suitably powered trials. It is similarly of interest to examine the relative efficacy and cost-effectiveness of such treatments as compared with education. Yoga and CBT vary along the lines of costs and accessibility. As such, the efficacy and cost-effectiveness of (1) yoga and (2) CBT, each compared with (3) education, will be evaluated. Consistent with the National Action Plan for Endometriosis focus on improving HRQoL[1] and noting that HRQoL is an outcome of priority to those with endometriosis[10]—the impact of these treatments on HRQoL and biopsychosocial well-being will be examined. These outcomes are also consistent with the recent identification of an endometriosis core outcome set.[20]

It is hypothesised that, compared with education (n=86), both yoga (n=86) and CBT (n=86) interventions will have the following outcomes at 8 weeks, and 6 and 12 months postrandomisation inpatients with endometriosis:

Primary outcome: Improvement in HRQoL.

Secondary outcomes: Improvement in pain, mental health, fatigue, self-efficacy, central sensitisation, pain catastrophising, sleep, satisfaction and improvement in the most troublesome symptom and cost-effectiveness, from both health system and societal perspectives based on the QoL measure.

METHODS AND ANALYSIS

Ethical approval

This protocol has been approved by Deakin University Human Research Ethics Committee (Ref. 2020-394), Barwon Health Human Research Ethics Committee (Ref. 20/136) and Monash Health Human Research Ethics Committee (Ref. RES-20-0000-838X) in November 2020. Written informed consent will be obtained before patients are randomised to the groups.

Design

This study is a parallel RCT. Participants will be randomly allocated to one of three groups: yoga, CBT or education, with a ratio of 1:1:1. Randomisation will occur after participants sign the consent form and before completion of the baseline questionnaires. Allocation concealment will be ensured by the person randomising not having patient contact. Block randomisation will be conducted, using a table of computer-generated random numbers. The randomisation schedule will be created using computer software by the study statistician who has no direct patient contact. Participants will be enrolled and assigned to groups by the study coordinator. Blinding the treatment groups is not possible as is often the case in psychotherapy and mind-body trials. However, outcome measures will be collected via on-line self-report questionnaires, and as such, there are no researchers collecting patient data that need to be blinded, making it a single-blinded study. The statisticians and health economist performing the analyses will be blinded to group status. The study will be advertised as a trial comparing 'mind-body interventions' to reduce bias and reduce the likelihood of control withdrawal, as they will receive education. Participants in all groups will continue their usual medical care.

Participants

Inclusion criteria

1. Diagnosis of endometriosis by a qualified physician, with pain for at least 6 months, and supported by an ultrasound, histology, operation report or letter from treating physician confirming the above. Pain can include dysmenorrhoea, dyschezia, dysuria with periods or mid cycle pain.
2. At least 18 years of age.
3. Capacity to provide informed consent.
4. English speaking, or sufficient level of English to understand the trial intervention, answer relevant questionnaires and participate in a group context.
5. Access to internet.

Exclusion criteria

1. High risk of harming self or others, as confirmed during psychological screening by clinical psychology team or treating physician.
2. Severe mental illness (eg, schizophrenia, severe depression), as confirmed during psychological screening by clinical psychology team or treating physician.

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3. Significant cognitive impairment, as confirmed during psychological screening by clinical psychology team or treating physician.
4. Major physical issues/injuries as one of the mind-body interventions involves physical movement.
5. Inability to read or write.
6. Inability to speak or understand English (as explained above).
7. Currently pregnant.
8. Recent therapist-led course of yoga (within the past 6 months).
9. Recent therapist-led course of CBT (within the past 6 months).

Participants will not be excluded if they require surgery, since surgery may make the pain worse, better or no different. However, we will record surgical findings (eg, surgeon level using the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) scale, surgical technique used, complete versus incomplete treatment at the discretion of surgeon) and will control for it in our analysis, if required.

Recruitment

Potential participants will be identified from the databases of major Victorian metropolitan and regional hospitals by the clinical team, with the support of recruitment nurses and a trial manager. Individuals who meet the inclusion criteria will be provided with a flyer, which includes the study contact details, to contact the research team to discuss the study further.

The study will also be advertised at all participating services, and endometriosis support groups. Interested individuals will be instructed to contact the trial manager to express their interest in participating in the study. For individuals outside the participating hospitals, they will be required to provide a letter from their treating physician confirming their diagnosis. After participants have completed the online consent form, the psychology team will then assess for relevant psychological exclusions. Participants may be reimbursed for large travel times or parking requirements. Otherwise, no monetary incentives are included.

Power calculations

In a recent meta-analysis, only one RCT was identified specifically examining yoga for endometriosis, reporting a large intervention effect of yoga, relative to a standard care control, for pain (Cohen's d=−1.17; 95% CI −1.97 to −0.37, n=40).[17] We identified other studies examining yoga for chronic pelvic pain.[21–23] All found extremely large effect sizes compared with a no-intervention control (Cohen's d range 1.17–1.99) for improvement in pain. As pain was examined more consistently than QOL, we used pain as a proxy. In our previous pilot studies of yoga and CBT for chronic health conditions, improvements in QoL had larger effect sizes than pain[24–27] suggesting that our power analyses based on changes in pain are conservative. Other meta-analyses examining yoga for generalised chronic back pain have found more modest effects (d=0.62). We performed a meta-analysis on the included studies and have identified a pooled effect size of d=1.06. CBT has demonstrated comparatively small but robust effects for reductions in chronic pain and improvements to QoL (f=0.2 to 0.3 compared with treatment as usual control).[28] Given the disparity in expected effect sizes between interventions, we powered for the median of the two expected effects. This conservative approach minimises the expected effect size and anticipates overestimated effect sizes from small, open-label studies.

Sample size

Using R statistical software and the 'WebPower' package, we estimate an effect size for a repeated-measure analysis of variance (ANOVA), with three groups and four time points. With an alpha of .01, 80% power and an effect size of f=0.25, the minimum sample size for the entire sample is N=228 or n=76 per group. Comparable studies with similar designs have reported attrition rates of approximately 15% over the duration of the intervention, and the minimum sample size should, therefore, be increased by this amount. As such, the minimum total sample size for this study was set at N=258 (86 per group).

Intervention and control condition

CBT for chronic pain

In addition to their usual medical care provided by their treating physicians (mostly hormones and pain medications), participants randomised to CBT will attend 8 weekly group CBT sessions of 120 min (10–13 participants/group). The programme draws on Beverly Thorn's widely available CBT protocol for pain.[29] The programme aims to assist individuals to: gain an understanding of pain including education about chronic pain; learn practical strategies for managing pain and mood; practice the techniques both in and outside of the group setting, and; learn how to maintain the gains they have made during therapy and prevent relapse. The programme will be conducted by psychologists under the supervision of a senior clinical psychologist.

Participants will be encouraged to complete 20 min home practice (at least 3 days/week)—involving simple CBT activities. Patient's home practice fidelity and adherence will be measured with a weekly online questionnaire.

The intervention can be delivered either face to face or online (with face to face preferred if allowed, depending on the COVID-19 pandemic-related regulations). If the latter, participants will attend 8 weekly group online CBT session via Zoom for 120 min. Prior to beginning online CBT, participants will be encouraged to attend an online test meeting to ensure they are able to access Zoom. The programme will be conducted in the same way as a face-to-face CBT session.

Yoga programme

In addition to their usual medical care provided by their treating physicians, participants randomised to yoga will

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attend 8 weekly group yoga sessions of 60 min (10–13 participants/group). Classes include physical postures (suitable for all levels of experience); breath awareness and techniques; and relaxation and meditation. The yoga sequence will be based on the therapeutic yoga approach of T. Krishnamacharya, which emphasises adaptations for individual needs and capacities (see online supplemental appendix 1).

Classes will be led by experienced yoga instructors under the supervision of the yoga therapist responsible for the programme development. Before beginning classes, participants will attend a 60 min session with the yoga therapist to develop their home practice, accounting for any injuries or health issues. This information will be documented on a Yoga Therapy Consultation form. Participants will be encouraged to complete 20 min home practice (at least 3 days/week) involving simple movement and breathing techniques, and sustainable once the study concludes. Patient's home practice fidelity and adherence will be measured with a weekly online questionnaire.

The intervention can be delivered either face to face or online (with face to face preferred if allowed, depending on the COVID-19 pandemic-related regulations). If the latter, participants will attend 8 weekly online group yoga sessions for 60 min via Zoom. Like in-person yoga, participants will attend a 60 min online session with the yoga instructor and a yoga home practice. The yoga programme will be developed and conducted with the yoga therapist in the same way as face-to-face yoga sessions.

Education (control)

In addition to standard medical care provided by their treating physicians (mostly hormones and pain medications), the control group will receive education via weekly emails, consisting of educational handouts on endometriosis adapted from the Jean Hailes educational website. Eight weekly topics align with the eight website topics: symptoms and causes; diagnosis; management and treatment; fertility and pregnancy; emotions, complications and risks; relationships and sex; and further resources. In the case of COVID-19 restrictions, there will be no change to the provision of education. At 12 months, patients will be offered their choice of yoga or CBT.

Intervention fidelity

Treatment fidelity to CBT will be maintained by using the same therapy protocol for psychologists experienced in CBT. Training in using the programme and regular supervision will be provided to the psychologists by a senior clinical psychologist. For yoga, the same yoga sequence will be used across classes, and delivered by trained and qualified yoga teachers. Training in using the sequence and regular supervision will be provided by the study's yoga therapist. In addition, 10% of CBT/yoga sessions will be voicerecorded and monitored, with additional training given, if required.

Outcome measures

Primary outcome measures

Endometriosis-related QoL will be measured by the 30-item Endometriosis Health Profile: The scale was derived from interviews of patients and consists of two parts: a 30-item core questionnaire relating to pain, control and powerlessness, emotions, social support and self-image, and a 23-item questionnaire examining work life, relationships with children, sexual intercourse, the medical profession, treatment and infertility. It exhibits good reliability and validity.[30]

Generic QoL will be measured by the European Quality of Life Five Dimension (EQ-5D-5L), which encompasses mobility, self-care, usual activities, pain/discomfort and mental health, with good reliability and validity.[31] The generic QoL EQ-5D-5L can be converted to a single utility score using Australian weights[32] to determine an incremental cost–utility ratio.

Secondary outcome measures

Sleep Quality with the Jenkins Sleep Scale, which is a 4-item self-report patient-reported outcome measure recommended for use with chronic pain patients.[33] Psychological symptoms with the Depression Anxiety Stress Scale—21 items, a self-report measure designed to assess depression, anxiety and stress with high internal consistency and retest reliability.[34] Fatigue with the Fatigue Symptom Inventory, which has 14 items to assess the severity, frequency and daily pattern of fatigue as well as its perceived interference with QoL. The item has good reliability and validity.[35] Menstrual symptoms with the Menstrual Symptoms Questionnaire, an instrument to assess symptoms of menstruation.[36] Pain questions using the pain Numerical Rating Scale to assess period pain, mid-cycle pain, bowel pain, bladder pain and sexual discomfort/pain on a scale from 0 ('no pain') to 10 ('worst pain possible'). Pain and functioning with the Brief Pain Inventory, an 11-item instrument to assess the severity of pain and extent of pain interference, with good validity and reliability.[37] Pain Catastrophising using the Pain Catastrophising Scale which assesses rumination, magnification and feeling helpless about pain.[38] Self-efficacy with the Pain Self-Efficacy Questionnaire, a 10-item self-report to assess the confidence people with ongoing pain have in performing daily activities while in pain.[39] Central sensitisation with the Fibromyalgia Criteria-2016, which includes six items related to symptoms, and a question on pain sites,[40] and is considered to be the gold standard of central sensitisation self-report measures.[41] Health utilisation and cost data will be collected via a patient health service utilisation and employment questionnaire administered at baseline, 8 weeks, 6 and 12 months. The questionnaire will be developed for the trial and will include questions on hospital same day and overnight admissions, including procedures, length of stay, hospital attendance with no admission and community allied health visits

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related to pelvic pain and other symptoms associated with endometriosis. The questionnaire will include questions on: time lost to work and/or personal care needs related to either the intervention or endometriosis. Medicare Australia records will be retrieved with patient consent to determine medical services, investigations and pharmaceutical use over 12 months.

Other outcomes

Treatment satisfaction will be measured with a 4-point satisfaction scale from 1 = 'not at all satisfied' to 4 = 'very satisfied' and most troublesome symptom improvement will be measured with a 4-point improvement scale from 1 = 'not improved' to 4 = 'very much improved'. Skill adoption will include patient yes/no response to the question: 'Have you been using the skills taught in the mind-body intervention?' as well as to describe why or why not. *Adverse events* will be monitored by the trial manger. Participants will be contacted at the end of weeks 1, 4 and 8 of the intervention programme to discuss any event(s) that may have occurred during the intervention period or in the context of the intervention; please see the attached ethical protocol for our step-by-step guide to monitoring, reporting and addressing adverse events. Qualitative measures will involve postintervention semi-structured interviews questions, including questions regarding most significant change and barriers and enablers that impacted intervention involvement.

Analysis

Analysis of quantitative data

Quantitative data analyses will be conducted in STATA SE V.16 for all outcome measures using mixed-effects ANOVA and linear mixed effects models to identify change over time within and between groups, followed by post hoc analyses to identify statistically significant differences. Analyses will be carried out on intention-to-treat basis. Adjustments will be made if necessary (eg, for type of treatment as usual (TAU)).

Economic data evaluation will involve a cost–utility analysis from a societal perspective, with outcomes based on the primary outcome (EQ-5D-5L). Total costs from a societal perspective for each participant will be determined from the costs of the intervention, health service utilisation, productivity change and informal healthcare needs over 12 months in both intervention and control groups. Intervention costs will include the costs of delivering CBT or yoga to the study population (based on time for consultation, preparation and wage rate).

Hospital admissions and non-admitted hospital episodes will be costed from the self-reported data on utilisation. A diagnosis-related group (DRG) for each endometriosis-related hospital visit will be assumed based on whether a procedure occurred, and the type of procedure. Our Australian Refined Diagnosis Related Groups (ARDRGs) will include non-procedural management, laparoscopy and laparotomy. A DRG cost will be determined from costing information from the Activity Based Funding guidelines of the Independent Hospital Pricing Authority, an independent government agency of the Commonwealth of Australia.[42] The cost of primary care health service and pharmaceuticals will be derived from participant-level Medicare data.

The incremental cost-effectiveness ratio around the primary outcome (EQ-5D-5L) will be calculated as the difference in total programme, health service use, productivity loss and informal care costs, and the difference in the QoL utility index between the preintervention and 12-month postintervention periods for each intervention compared with the control group. One-way sensitivity analyses will investigate the robustness of the cost-effectiveness ratio to a range of cost and effect estimates.

Analysis of qualitative data

Qualitative data collected during semistructured interviews with participants will be transcribed and analysed thematically, following the main procedural steps of Template Thematic Analysis.[43]

Ethics and dissemination

All participants will be reassured that participation in the study is voluntary and that they can withdraw at any stage of the study. Participants will be informed of their ability to access standard medical care during the study. Patient information documents will provide details on the degree of participant commitment and include contact details of the clinical team, should any queries or concerns arise. Patient data will be stored securely on a password-protected drive at Deakin University, with access limited to the investigators only.

In the service of optimising safety for participants, all potential subjects with physical disabilities or cognitive disabilities severe enough to compromise safety or ability to participate in the interventions, will be excluded. Adverse events will be assessed at weeks 1, 4 and 8. Participants with deteriorating mental health will be referred to certified mental health providers.

Findings will be disseminated to clinicians via publications, conferences and briefs to the RANZCOG, which is responsible for Australian endometriosis guidelines. Our programme will also be included in RANZCOG dissemination initiatives. Thanks to the leadership roles of our team members within the International Pelvic Pain Society, the Australasian Gynaecological Endoscopy and Surgery Society and Endometriosis Care Centre of Australia we will actively promote awareness of our findings via these organisations. The public will be reached via The Conversation articles and media releases led by Deakin University.

Patient and public involvement

Endometriosis support group leaders and members were consulted in the initial stages of planning the study to understand whether people with endometriosis would be interested in CBT and yoga as interventions to

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improve well-being. Patient data have also been used in the selection of outcome measures, with well-being and QOL emerging as important to people with endometriosis.[1] We intend to work with peak bodies, to integrate yoga and CBT into national dissemination initiatives, including across websites and social media. Our strategy to include support groups and individuals with endometriosis in the translation conversation is important since knowledge translation is more successful when informed by consumer views of barriers and facilitators.[44] We have achieved this from study conception—by including early consultation with stakeholders to ensure that our interventions are tailored to their needs—to dissemination, where patients will be asked for their feedback on our planned strategies via poststudy interviews, and work with our partners to disseminate research findings through websites that patients seek out.

DISCUSSION

This clinical trial meets the need for innovative, high-quality research to improve treatment of endometriosis, a debilitating chronic condition. Poor psychological prognosis associated with endometriosis symptoms has led to urgent calls for integrated approaches that address both symptoms of endometriosis and mental health to prevent further degradations in QoL.[45] It is likely that CBT and yoga would have benefits for people with endometriosis in terms of improving overall well-being. Although CBT is a standard treatment for other conditions characterised by chronic pain, no large scale RCTs have been conducted to date. Similarly, only small pilot trials are available for yoga,[12] and a well-designed RCT comparing treatment to standard care/waitlist is needed.

By undertaking an RCT, using gold-standard methodology, the trial has the potential to impact the lives of many individuals living with endometriosis through the rapid translation of findings into clinical guidelines and practice. The primary outcome of the trial is to improve the HRQoL of Australians living with endometriosis. Secondary outcomes hold promise in improving pain, psychological symptoms and patient satisfaction in treatment of endometriosis. As a well-designed, powered RCT, the results will establish the efficacy of (1) yoga and (2) CBT, above education, to understand how to best improve QoL. Health economic analysis will aim to evaluate the cost-effectiveness of each intervention compared with usual care from perspectives of the healthcare system and society.

Importantly, in designing this trial, best practice was considered, including selection of outcome measures that are important to patients, randomisation methods and close monitoring of the study intervention (ie, monitoring for treatment fidelity, adherence and adverse events). However, since psychotherapy trials cannot be easily blinded, employing a longitudinal follow-up has been recommended to address this design limitation.[46] The present trial will, therefore, be single blinded. Importantly, treatment effects of CBT and yoga (if the participants continue with yoga practice) might persist longer than placebo effects and thus a 12-month follow-up proposed in this trial may increase confidence in the efficacy of yoga and CBT. Finally, placebo and nocebo effects need to be acknowledged in this context, with recent research showing that prior encounters with a specific intervention can generate these effects.[47 48]

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Contributors AM-W contributed to the trial design, drafted the protocol paper, approved its final version and is the guarantor of the submission. MD, MO'S, DS, JJW, AE, JT, SK, JH, CD and EP contributed to the trial design, commented on drafts of the protocol paper, and approved the final version. SE designed the trial, contributed to drafts of the protocol paper and approved the final version.

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Competing interests AM-W has served as an educational speaker for Janssen and Ferring. SK has served as an educational speaker for Janssen, Ferring and Takeda.

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