The Development, Feasibility, Acceptability, and Efficacy of a 12-Week Online Mind-Body Intervention for People with Primary Biliary Cholangitis

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

Department of Medicine

University of Alberta

ABSTRACT

Introduction: Persons with primary biliary cholangitis (PBC) experience significantly higher rates of mental distress, impaired health related quality of life (HrQoL), and fatigue than the general population. While mind-body interventions have been shown to improve mental health and HrQoL, and reduce fatigue in other chronic disease populations, there is limited evidence in PBC.

Objectives: The purpose of these studies were to determine the feasibility, acceptability and efficacy of a 12-week online mind-body intervention for people with PBC.

Methods: For the pilot study, the intervention was assessed through a single group sequential mixed-methods pre-post feasibility study (Chap 4). It included a core program of follow-along movement, meditation and breathwork videos, and supplementary content including tips from PBC physicians and cognitive behavioral therapy informed activities. Feasibility was assessed by recruitment, adherence and retention and acceptability was assessed through a survey at the end of the program. A pre-post exploratory efficacy assessment included surveys for anxiety, depression, stress, resilience, HrQoL, and fatigue. A qualitative descriptive approach with semi-structured interviews was used to evaluate study experiences. The intervention was revised using feedback from the pilot study and the efficacy of the intervention was assessed through a sequential mixed-methods randomized controlled trial (RCT) (Chap 5). The primary outcome was changes in the Hospital Anxiety and Depression Scale (HADS). Secondary outcomes evaluated fatigue, perceived stress, resilience and HrQoL. ANCOVA was used to determine between group differences. A qualitative descriptive approach with semi-structured interviews evaluated study experiences.

Results: For the pilot study, 32 participants were recruited within 30 days and 29 (91%) were retained to end-of-study. Of these, 25 (86%) adhered to carrying out the mind-body practice at least 2-3 days per week. Feedback supported acceptability (satisfaction score 90%). The exploratory efficacy assessment revealed significant improvements in fatigue (13%, p=0.004), anxiety (30%, p=0.005), depression (28%, p=0.022) and five PBC-40 domains (itch, fatigue, cognitive, emotional, general symptoms). Qualitative interviews supported improved stress management, better coping, and a more positive mindset. Fatigue and self-sabotaging thoughts were cited as barriers to participation. For the RCT, 123 patients were screened and 87 were randomized (control group: n=44, intervention group: n=43). The between-group HADS total score improved by 20.0% (95% CI 4.7, 35.2, p=0.011) and the HADS depression score improved by 25.8% (95% CI 4.8, 46.8, p=0.017). Significant improvements were seen in perceived stress (15.2%), and two PBC-40 domains (emotional symptoms (16.3%), and social symptoms (11.8%)) with a mean satisfaction of 82/100. While no significant improvements were observed in fatigue, interviews revealed improved coping with fatigue. Of the 36/43 participants who completed the intervention, 20 (56%) completed the program at least 3x per week.

Conclusion: The 12-week virtually-supported home exercise program was feasible and acceptable and demonstrated positive impacts on measures of mental health and quality of life. Future studies could explore strategies to optimize adherence and increase scalability of the intervention and could increase the physical activity intervention, which may result in a greater impact on fatigue.

PREFACE

This thesis is an original work by Makayla Elizabeth Watt. The research projects, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board. Project names "Assessing the feasibility and acceptability of a 12-week online stress reduction/wellness intervention for chronic disease populations: a series of pre-post single-arm interventional studies", Pro00106526, January 14th, 2021, and "A randomized control trial evaluating the impact of a 12-week mind-body wellness intervention in patients with primary biliary cholangitis (PBC)", Pro00112622, August 5th, 2021.

Chapter 3 has been published as M. Watt, J. C. Spence, and P. Tandon, "Development of a Theoretically Informed Web-Based Mind-Body Wellness Intervention for Patients with Primary Biliary Cholangitis: Formative Study," JMIR Formative Research, vol. 5, issue 10, 229064. I was responsible for the manuscript composition. J. C. Spence and P. Tandon were the co-senior authors and were involved with concept formation and manuscript edits.

Chapter 4 has been submitted for publication as M. Watt, A. Hyde, J. C. Spence, G. M. Wright, S. Vander Well, A. Mason, M. McLeod, E. Johnson, and P. Tandon, "The feasibility and acceptability of an online mind-body wellness program for patients with primary biliary cholangitis." Co-authors listed have contributed to either: i) conception or design of work [MW, PT, GW, SV], ii) acquisition, analysis, or interpretation of data for the work [MW, PT, AH, EJ, JCS], or iii) drafting the work or revising it critically for important intellectual content [MW, AH, JCS, GMW, SV, AM, MM, EJ, PT]. All persons listed have read and approved the final version of the manuscript.

Chapter 5 is in the process of being submitted for publication as M. Watt, C. Sadasivan, A. Hyde, G. M. Wright, S. Vander Well, E. Johnson, J. C. Spence, A. Mason, H. Ko, E. Tam, and P.

Tandon, “A randomized control trial evaluating the impact of a 12-week mind-body wellness intervention in patients with primary biliary cholangitis (PBC).”Co-authors listed have contributed to either: i) conception or design of work [MW, PT, GW, SV], ii) acquisition, analysis, or interpretation of data for the work [MW, PT, EJ, AH], or iii) drafting the work or revising it critically for important intellectual content [MW, PT, CS, AH, GMW, SV, EJ, JCS, AM, HC, ED].

DEDICATION

This thesis is dedicated to the PBC community. Thank you for volunteering your time to take part in the studies that make up this thesis, and for welcoming me into your journey with PBC. The relationships I've built with you will continue to inspire and motivate me as I enter the medical community.

ACKNOWLEDGEMENTS

I'd like to start by thanking the members of my supervisory committee. To my primary supervisor, Dr. Puneeta Tandon: Thank you for introducing me to the world of research and for supporting me through my dream master's project. The endless encouragement, and opportunities that you have provided me with have helped me grow into the person that I am today, and will continue to influence how I approach the next steps of my career. To Dr. Ashley Hyde: thank you for generously sharing your academic knowledge, and for the personal guidance that you have provided during this thesis. You've continuously gone above and beyond to support me, and I'm very grateful for your mentorship. To Dr. John Spence: your wisdom and support have been key to the success of this thesis. I hope we get the opportunity to work together again in the near future. To Dr. Andrew Mason: thank you for lending your time, clinical perspectives, and enthusiasm to this work. I hope to cross paths with you during the next steps of my academic journey.

Thank you to the Canadian PBC society, and namely Gail Wright and Shauna Vander Well for their invaluable partnership, perspectives, and guidance. I would also like to thank all of the patients whose feedback helped guide this work.

I would also like to extend my gratitude to all of the other community members, students, patients, movement instructors, academic professionals, and physicians who contributed to this work. It takes a village, and I feel lucky to have been supported by an incredible one.

Thank you to my wonderful and talented lab mates: Emily Johnson, Ana Teresa Limon, Ashley Hyde, Chikku Sadasivan, and Chris Cruz. The friendships we have built, and memories we have shared, have been a highlight of these last two years. I've learned so much from each of you, and look forward to watching you all continue to shine.

To my family: my mom and dad Lisa and Ted Watt, and my brothers Carter and Liam Watt, thank you for being my biggest cheerleaders through every up and down of this journey. This wouldn't have happened without your love and support. I love you all.

Lastly, I'd like to thank the MD Program at the University of Alberta for granting me a one-year deferral to complete my MSc prior to beginning medical school. I know that this opportunity will help me to be a stronger future physician.

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CHAPTER 1: INTRODUCTION

1.1 Brief Introduction

Primary biliary cholangitis (PBC) is a female predominant chronic liver disease typified by immune mediated damage to hepatic bile ducts[1]. PBC is associated with symptoms including fatigue, pruritus, social isolation, emotional dysfunction, and impaired health related quality of life (HRQOL)[2]. Moreover, individuals with PBC experience significantly higher rates of anxiety, stress, and depression as compared to the general population[3,4], all of which have been recognized as important risk factors for increased mortality and poor clinical outcomes in various autoimmune conditions[5-11]. Ursodeoxycholic acid (UDCA) is currently the only approved first line therapy for PBC in Canada[1]. While treatment with UDCA improves outcomes such as transplant free survival; this course of treatment is ineffective at improving PBC-related symptoms or mental health[12-14]. It is clear that novel therapies are needed to help patients with PBC manage their symptom burden.

When trialed in other chronic disease populations, online mind-body programming, ranging from physical activity to mindfulness interventions has positively impacted PBC-related impairments including anxiety, depression, stress, fatigue, and HRQOL[8,15-24]. Despite this, there is a lack of published research looking at mind-body interventions for people with PBC. Patients with PBC have reported that their symptom burden (i.e., pruritus and fatigue) makes it difficult to participate in self-management therapies like mind-body interventions[25]. Because of this, current interventions may not be suitable for people living with PBC. Overall, more research is required to determine whether these interventions are a feasible, acceptable, and effective way to target the symptom burden associated with PBC.

1.2 Problem Statement and Purpose of the Thesis

The proposed thesis seeks to advance the care of people with PBC by assessing (i) the feasibility and acceptability and (ii) the efficacy of a 12-week, online, mind-body wellness program designed for people with PBC. While mind-body wellness programs have been found to improve PBC-related impairments in other chronic disease populations, there is a lack of research examining interventions of this nature in PBC. The proposed thesis addresses this gap by trialing a novel mind-body wellness intervention that was refined using feedback from a team of patient partners and study participants with PBC in order to meet the needs of people with PBC. This thesis includes a formative study that describes the development process of a novel mind-body intervention for people with PBC, a single group, pre-post study evaluating the feasibility and acceptability of mind-body intervention for people with PBC, and a randomised control trial evaluating the efficacy of the intervention. The overall purpose of this thesis is to assess the feasibility, acceptability, and efficacy of a 12-week, online, mind-body intervention in patients with PBC.

1.3 Objectives

Pilot Study (Chapter 4): To use a sequential mixed-methods design to determine the feasibility and acceptability of an online mind-body wellness program in a sample of people with PBC. Feasibility was defined by:

- Recruitment rate: ≥ 30 participants consenting to the study over a 1-month recruitment period.
- Adherence: ≥ 70% of participants completing the programming 2-3x per week.
- Retention: ≥ 80% of consenting participants completing the end of study surveys.

Acceptability was defined by:

- Participants perceptions of the online program (assessed qualitatively)
- Participants satisfaction with the overall program, and with individual elements of the program
- Participants perceived likelihood of continuing with different aspects of the online program after the 12-week study period

Exploratory Objective: To determine the preliminary efficacy of the intervention by assessing changes (from baseline to 12-weeks) in: (i) anxiety and depression (Hospital Anxiety and Depression Scale), (ii) fatigue (Modified Fatigue Impact Scale), (iii) perceived stress (Perceived Stress Scale), (iv) HRQOL (PBC-40), (v) resilience (Connor Davidson Resilience Scale) and (vi) perceived capability, opportunity, and motivation to meet the adherence target (completing the program 2-3x per week) (COM-B survey).

Randomised Control Trial (Chapter 5): To assess the impact of an online mind-body wellness program, as compared to control, on the primary outcome of anxiety and depression (Hospital Anxiety and Depression Scale) and a range of secondary outcomes including fatigue (Modified Fatigue Impact Scale), perceived stress (Perceived Stress Scale), HRQOL (PBC-40), resilience (Connor Davidson Resilience Scale) and physical functioning (Lower Extremity Function Scale) as well as adherence and acceptability.

1.4 Hypothesis

Pilot Study (Chapter 4): The 12-week, mind, body wellness program will prove feasible and acceptable for people with PBC.

Randomised Control Trial (Chapter 5): As compared to control, the 12-week, mind-body wellness program will improve the primary outcome measure of anxiety and depression as

measured by the hospital anxiety and depression scale (HADS), and a range of secondary outcomes including fatigue, perceived stress, HRQOL, resilience, and physical functioning.

CHAPTER 2: LITERATURE REVIEW

2.1 Primary biliary cholangitis

2.1.1 History

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a chronic cholestatic liver disease[26]. The first case of PBC was detailed in 1851[27]. Through 2014 - 2015, the term 'primary biliary cirrhosis' was changed to 'primary biliary cholangitis' to reflect that with advancements in diagnosis and treatment, many patients with PBC do not progress to cirrhosis[27].

2.1.2 Epidemiology

Recent reports have estimated that the global incidence and prevalence of PBC ranges from 0.33 to 5.8 per 100,000 and 1.91 to 33.8 per 100,000 respectively[28]. While this is low in comparison to other liver diseases, these rates are increasing globally[1,26,28]. Incidence and prevalence of PBC is asymmetrical across regions, with North America displaying the highest, and the Asia-Pacific region demonstrating the lowest incidence and prevalence[26,29]. It has been hypothesized that this could be because of true epidemiological differences, or differences in PBC awareness and diagnosis among regions[s]. PBC is a female predominant condition. While studies of different hospital sites have estimated up to a 13:1 female:male ratio[30], more recent studies of population wide registers have estimated female:male ratios ranging from 4.8:1 to 1.6:1[31]. Although more research is needed to determine why we see female predominance in PBC, studies have explored the potential role of sex hormones, genetic factors, the microbiome, and epigenetics[32]. PBC is also asymmetrical across age, with studies estimating a median age of diagnosis of 65 years old and increasing incidence rates beginning through ages 20-29[29,33]. PBC has never been diagnosed in women pre-menarche[33].

2.1.3 Etiology

PBC is initiated through immune mediated damage to epithelial cells in the small and intermediate intrahepatic bile ducts. This leads to biliary damage, cholestasis, and progressive fibrosis[34-36]. It is still unclear what triggers this immune attack, but accumulating evidence suggests that PBC occurs in a genetically susceptible host in the presence of environmental triggers[37]. Genetics are thought to play a role, as genome wide association studies have identified alleles that contribute to PBC susceptibility[37]. Moreover, a study looking at a genealogical database in Iceland found that first, second, and third-degree relatives of people with PBC had a significantly higher risk ratio of getting PBC as compared to controls[37]. As only ⅔ of monozygotic twins share PBC, it is clear that other factors contribute to the development of PBC[38,39]. More research is needed to discern specific environmental triggers related to PBC onset, but an association has been shown with cigarette smoking and urinary tract infections[26].

2.1.4 Diagnosis

Recent clinical practice guidelines have outlined diagnostic criteria for PBC, which include any two of the following[1]:

1. Elevated levels of serum alkaline phosphatase (ALP).
2. Presence of antimitochondrial antibodies (AMA), which can be detected in 95% of PBC patients with a titre of >1 in 40 regarded as positive.
3. Histological evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts.

Notably, histological examination of the liver is only required to confirm a diagnosis of PBC in AMA negative patients[26,33].

2.1.5 Natural History

PBC begins with a "preclinical phase," during which AMA alone is present in the serum. This is followed by gradual elevation of serum ALP[40]. The majority of patients are asymptomatic at diagnosis, with some patients remaining asymptomatic through the course of their disease, and others developing symptoms throughout their disease course[40]. Four histological stages have been defined for PBC: 1) inflammation and/or abnormal connective tissue is confined to portal triads, 2) number of normal bile ducts is reduced; the inflammation and/or fibrosis is confined to portal and periportal areas, 3) fibrous septa link adjacent portal triads, 4) cirrhosis with regenerative nodules[1,40]. Patients who are asymptomatic at diagnosis are typically at an earlier histological phase[18]. Without treatment, it has been estimated that on average patients will progress one histological stage every 1.5 years however, histological progression is highly variable[18]. Due to this variability, the Mayo Natural History model was developed to predict survival probability in an untreated patient with PBC[41].

2.1.6 Symptoms

Fatigue is acknowledged as the most common and debilitating symptom of PBC, with up to 80% of patients with PBC experiencing fatigue[42]. Fatigue is a poorly understood symptom, and more research is required to determine the cause of fatigue in PBC. Fatigue is thought to be independent of the stage and severity of PBC[26]. Fatigue has been correlated with gender and age at disease onset, with worse fatigue observed in women and patients who presented at a young age[43]. Studies have also associated fatigue with depression, autonomic dysfunction, and sleep disturbances[26].

Pruritus (itching) is a common symptom in patients with cholestatic liver disease, and up to 80% of patients with PBC experience pruritus during the course of their disease[44]. In patients

with cholestasis, itching primarily occurs on the palms and soles, and is worse at night[41]. While more research is required to determine the cause of cholestatic pruritus, accumulation of bile acids, increased endogenous opioids, and elevated lysophosphatidic acid levels may play a role[44]. Pruritus is thought to be independent of biochemical abnormalities, histological progression, and duration of disease[41].

Patients with PBC also report high rates of mental health comorbidities, and impaired quality of life[25]. One study of over 2000 patients with PBC found that 35% of individuals with PBC report impaired health related quality of life (HrQoL) as compared to 6% of healthy controls. In this study, fatigue was the strongest predictor of impaired HrQoL[12]. Patients with PBC are also several times more likely to report depressive symptoms and anxiety as compared to the general population, with studies estimating that 30-45% of patients with PBC experience depressive symptoms[3,25,45]. Across a range of chronic disease populations, these psychiatric comorbidities have been associated with impaired coping, poor prognosis, and increased mortality[25,46].

2.2. Primary biliary cholangitis treatment

2.2.1 First-line treatment with UDCA

Ursodeoxycholic acid (UDCA) is the only approved first-line treatment for PBC. As a naturally occurring bile acid, UDCA displaces endogenous bile acids, reducing their toxicity[41]. Because UDCA is hydrophilic, it does not cause cell lysis like other bile acids[41]. A dose of 13-15mg/kg per day has been shown to improve liver biochemistry, delay histological progression of PBC[41], and improve transplant-free survival[47]. Studies have estimated that 30-40% of PBC patients do not exhibit a complete biochemical response to UDCA, as defined by ALP>1.67x the upper limit of normal, and/or bilirubin>2x the upper limit of normal after one year of treatment

with UDCA[47]. These patients display more rapid disease progression[48], and worse transplant free survival[49] than complete responders, however a 2019 study reported that transplant free survival was still significantly improved as compared to control in patients with an incomplete response to UDCA[50]. An additional 10% of patients are unable to tolerate UDCA, with reasons for discontinuation including weight gain, diarrhea, alopecia, dizziness, flu-like symptoms, and worsening of pruritus and fatigue[1].

2.2.2 Second-line treatment with obeticholic acid

Obeticholic acid (OCA) is a farnesoid X receptor agonist that reduces the concentration of bile acids[1]. In 2016, Nevens et al. conducted a placebo-controlled trial to study the effects of OCA in PBC patients who exhibited inadequate response to UDCA or could not tolerate UDCA[14]. The study found that OCA improved liver biochemistry when taken for 12 months in conjunction with UDCA, or as a monotherapy[14]. OCA has since been approved in North America and Europe as a second line treatment for patients with an inadequate response or intolerance to UDCA[35,36]. Research is ongoing to determine whether OCA results in histological improvement and improved clinical outcomes (i.e., transplant free survival)[51]. There are a few notable limitations to OCA as a treatment for PBC. First, patients taking OCA report significantly higher rates of pruritus as compared to control[49], which has led to up to 10% of patients discontinuing OCA in trial settings[1,49]. Second, the FDA has highlighted that use of OCA in PBC patients with Child-Pugh-Turcotte group B and C cirrhosis is associated with clinical worsening or death[26].

2.2.3 Off-label second-line treatment with fibrates

Fibrates act as agonists on peroxisome proliferator-activated receptors, resulting in reduction of bile acid synthesis and upregulation of bile acid transporters[26,35]. Because of this,

fibrates, including bezafibrate and fenofibrate, have been used as an off-label second-line treatment for patients with an incomplete response to UDCA[35]. Bezafibrate as an add-on therapy to UDCA has been shown to improve biochemical outcomes, and indicators of fibrosis in patients with an incomplete response to UDCA[35,52]. More research is required to discern the long-term outcomes and safety of bezafibrate as an add-on therapy for patients with an incomplete response to UDCA[35,53]. More evidence is also required to conclude whether fenofibrates affect liver biochemistry, histological, or clinical outcomes[26].

2.2.4 Treating symptoms

To date, no pharmacological therapies have been approved to treat fatigue in PBC[54]. Fluvixamine and rituximab have been evaluated in RCTs, but no significant effect was found on fatigue as compared to control[55,56]. While 73% of patients reported perceived improvements to fatigue after a 3-day trial of modafinil, future randomized controlled trials (RCTs) are needed to assess the efficacy of modafinil in reducing PBC related fatigue[57].

A number of pharmacological treatments have been recommended for the treatment of pruritus in PBC. The AASLD and EASL recommend cholestyramine and rifampin as first line treatments for pruritus in PBC[26]. Cholestyramine alleviates itch in 90% of PBC patients. While rifampin has been shown to effectively relieve itch in patients who do not respond to or tolerate cholestyramine, it is associated with risk of liver toxicity, and professional opinions on use of rifampin are mixed[26]. Naltrexone and sertraline have also demonstrated efficacy in reducing symptoms of pruritus in PBC, with sertraline demonstrating comparable efficacy to rifampin[41,58]. Finally, improvement to pruritus with bezafibrate and fenofibrate has been reported in some patients[41,59]. The effects of bezafibrate on pruritus are being investigated in an ongoing clinical

trial[60]. Alternative approaches including plasmapheresis have been explored for patients with severe pruritus who do not respond to pharmacotherapy[61].

Pharmacological treatment has been shown to improve mental health comorbidities and quality of life in PBC[25]. Sertraline and other selective serotonin reuptake inhibitors are used to manage anxiety and depression in patients with chronic liver disease. Selective noradrenergic reuptake inhibitors are also used in patients with chronic liver disease who have anxiety and depression[3,25]. In addition to pharmacological treatments, natural therapies including meditation, breathing exercises, and yoga have been recommended to improve anxiety and depressive symptoms in PBC[25].

2.3 Online mind-body interventions

2.3.1 Introduction to mind-body interventions

Mind-body interventions have been defined as a range of procedures or techniques that focus on the connections between the mind, body and behavior and their resultant effects on one's health[62]. These interventions can include practices such as mindful movement, meditation, breathwork, and behavior therapy. Over the last two decades, there have been a growing number of studies assessing the effects of mind-body interventions in chronic disease populations[63]. Taken together, these studies suggest that mind-body interventions have the ability to positively impact mental health, quality of life, and fatigue in a variety of chronic disease populations[16,23,64-72].

2.3.2 Mindful movement interventions

Mindful movement, including yoga, tai chi, and qigong has been shown to improve mental health and quality of life in individuals with chronic disease [64,65]. Zaimin and colleagues conducted a systematic review of the effects of mind-body exercise on anxiety and depression in

patients with Chronic Obstructive Pulmonary Disease (COPD). Thirteen RCTs were included with a total of 906 participants. Of the studies analyzed, 3 included yoga, 7 included qigong, and 3 included tai chi. The duration of the interventions ranged from 8 to 48 weeks. The authors concluded that mind-body exercise has significant effects on reducing anxiety and depression in patients with COPD[64]. A second systematic review by Cramer et al. looked at the ability of yoga to improve health-related quality of life and mental health in women with breast cancer. RCTs were included if they compared yoga therapy to control or another active therapy. Twenty four studies were included with a total of 2166 participants. Moderate-quality evidence was found that yoga improved quality of life as compared to no therapy, and anxiety and depression as compared to educational interventions[65].

Studies have also demonstrated improvements in chronic disease related fatigue after participation in mind-body practices[16,66]. Oka et al. conducted a RCT (control group: n=15, intervention group: n=15) evaluating the efficacy of an isometric yoga intervention in patients with chronic fatigue syndrome who were resistant to conventional treatments. The two-month intervention consisted of biweekly 20-minute yoga sessions with an instructor, and daily at home yoga sessions. Short-term changes in fatigue were assessed through the profile of mood status questionnaire, which was administered before and after the final session with the instructor. Long term changes to fatigue were assessed through Chalder's Fatigue Scale, which was administered before and after the intervention. All participants completed the intervention. Results showed significant short-term and long-term changes to fatigue[66]. Hilfiker et al. conducted a systematic review of exercise and other non-pharmacological interventions for cancer-related fatigue. Two hundred and forty-five studies were included. The studies reported on 11 different types of interventions, including aerobic exercise, resistance training, aerobic

exercise with resistance training, psychological, relaxation, yoga, massage, healing touch, dance, music therapy, and multimodal. The interventions ranged from 3 to 52 weeks. Among the interventions analyzed, yoga had the greatest effect on fatigue after cancer treatment[16].

2.3.3 Meditation Interventions

Past research suggests that meditation interventions can positively impact mental health and fatigue in chronic disease[23,67]. In 2015 Chan and colleagues conducted a systematic review on meditation interventions for chronic disease populations. Authors identified 45 studies that examined the effects of meditation on a range of outcomes including anxiety and depression in chronic disease populations (including chronic pain, HIV/AIDS, chronic heart failure, COPD, diabetes, multiple sclerosis, tinnitus, organ transplant, and epilepsy). The majority of the interventions were based on mindfulness-based stress reduction and were 8-weeks long. Significant improvements in anxiety were observed in seven of the 12 studies that measured anxiety. Significant improvements to depression were observed in 15 of the 23 studies that measured depression[23]. In 2020, Izgu et al. conducted a RCT to assess the efficacy of progressive muscle relaxation meditation and mindfulness meditation in patients with type 2 diabetes. Twenty-eight participants were randomized to the progressive muscle relaxation group, 25 were randomized to the meditation group, and 24 were randomized to the control group. Both the progressive muscle relaxation and the mindfulness meditation group were instructed to practice for 20 minutes, daily for 12-weeks. Outcomes included fatigue through the FACIT Fatigue Scale. Results showed that progressive muscle relaxation had a beneficial effect on fatigue[67].

2.3.4 Breathwork Interventions

RCTs have been conducted in a range of chronic disease populations to assess the effects of online breathwork interventions on outcomes including fatigue, negative emotions, and

quality of life[68-70]. Among these is a RCT by Chakrabarti and colleagues that assessed the efficacy of breathwork to reduce cancer-related fatigue. The study included 160 patients (control n=80, intervention n=80) who had breast cancer and were undergoing radiation therapy. The intervention group performed approximately 18 minutes of breathwork practices morning and evening 5 days a week for 6 weeks. Fatigue was assessed before and after the intervention period through the Cancer Fatigue Scale. All participants completed the intervention. Between group analysis showed that the intervention group experienced significantly less fatigue after the intervention period[68]. The same research team published a separate study on the impact of the breathwork intervention on emotional disturbances. The same 160 patients were included in this analysis. Authors concluded that the intervention group experienced significantly less negative emotions as compared to the control group[69]. Prem and colleagues conducted a RCT to assess the effects of pranayama, which is a set of yogic breathing techniques, and Buteyko, which is a method of breathing that decreases respiration rate, on quality of life in patients with asthma. One hundred and twenty patients were equally allocated to the Buteyko, pranayama, or control group. Both intervention groups were instructed to practice 60 minutes/day for 3-5 days, and then 15 minutes twice daily for three months. Quality of life was assessed through the Asthma Quality of Life questionnaire. Both the Buteyko and the pranayama group showed significant improvement in quality of life as compared to control[70].

2.3.5 Behavior Therapy Interventions

Finally, growing evidence supports the use of behavior therapy, including cognitive behavior therapy (CBT) and acceptance and commitment therapy (ACT), to improve mental health and quality of life in chronic disease populations[71,72]. In 2016, Graham et al. conducted a systematic review on the use of ACT in chronic disease populations. Eighteen studies were

included, eight of which were RCTs. Studies look at a wide range of outcomes including quality of life. Researchers concluded that while a consistent post-intervention improvement in quality of life was observed, more RCTs were needed to confirm the effects of ACT on quality of life[71]. A second systematic review by Ma et al. looked at the effects of CBT in patients with COPD. Among the 16 included RCTs, significant improvements were observed in anxiety, depression, and quality of life after CBT as compared to control[72].

2.3.6 Web-based delivery of mind-body interventions

Patients with chronic disease have acknowledged barriers to taking part in mind-body programming. Frequently cited barriers include lack of time and fatigue[25,73]. Delivering these interventions through web-based platforms can help alleviate these barriers to participation. Web-based delivery is also appealing because it allows safe participation during the COVID-19 pandemic.

2.4 Summary and future directions

Overall, despite advancements in treatment, people with PBC experience a debilitating symptom burden that includes fatigue, high rates of mental health comorbidities, and impaired quality of life. Studies of mind-body interventions in other chronic disease populations show promise in influencing outcomes including anxiety, depression, stress, quality of life, and fatigue. These interventions could be made more accessible to people with chronic disease through web-based delivery. Among other several notable limitations in the current literature, I chose to focus on addressing the following. First, no RCTs have observed whether these interventions impact mental health or symptoms in PBC. Past literature has acknowledged that people with PBC find it difficult to participate in exercise because of fatigue[25,73]. Tailoring a novel mind-body intervention for PBC could allow accommodations to be made to address this

barrier to participation. Second, while delivering mind-body programming on an online platform enhances accessibility, online interventions have been associated with traditionally low adherence rates[74]. This is a problem, because adherence is recognised as an important prerequisite to intervention efficacy[74,75]. Studies have suggested that using behavior change theory to inform intervention development leads to increased adherence[76]. Past literature has also acknowledged that involving patient partners in intervention development can lead to increased engagement[77]. Finally, few studies have used qualitative methodology in their assessment of mind-body interventions. Past research has acknowledged that incorporating qualitative methods when evaluating mind-body interventions can help explain the study results, explore factors that influence engagement with complex interventions, and guide intervention refinement[78,79]. In summary, I believe that an optimal program for this population would 1) be specific to PBC, 2) target adherence by incorporating behavior theory and patient involvement during intervention development, and 3) incorporate qualitative methodology as part of the assessment.

CHAPTER 3: DEVELOPMENT OF A THEORETICALLY INFORMED WEB-BASED MIND-BODY WELLNESS INTERVENTION FOR PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC): A FORMATIVE STUDY

Authors: Makayla Watt, John C. Spence, Puneeta Tandon

3.1 Abstract

Background**:** Mind-body interventions have the potential to positively impact the symptom burden associated with primary biliary cholangitis (PBC). Interventions are more likely to be effective if they are informed by a theoretical framework. The Behaviour Change Wheel (BCW) and the behaviour change technique taxonomy version 1 (BCTv1) provide frameworks for intervention development.

Objective: This study describes how theory has guided the development of a 12-week multicomponent mind-body wellness intervention for PBC.

Methods: The steps involved in developing the BCW intervention included specifying the target behavior; explaining barriers and facilitators using the Capability, Opportunity, Motivation, and Behaviour and the theoretical domains framework; identifying intervention functions to target explanatory domains; and selecting relevant behavior change techniques to address intervention functions. Qualitative data from patients with inflammatory bowel disease using an earlier version of the program and feedback from a PBC patient advisory team were used to guide intervention development.

Results: Barriers and facilitators to intervention participation associated with capability, opportunity, and motivation were identified. Intervention functions and behavior change techniques were identified to target each barrier and facilitator.

Conclusions: The Peace Power Pack PBC intervention was developed to help individuals with PBC manage their symptom burden. The theoretical frameworks employed in this intervention provide direction on targeting antecedents of behavior and allow standardized reporting of intervention components.

3.2 Introduction

Primary biliary cholangitis (PBC) is a female predominant chronic liver disease estimated to affect between 9000 and 11,000 Canadians[1]. Despite the relatively low prevalence of PBC, global incidence and prevalence rates have been reported to be on the rise[1]. PBC is associated with symptoms including pruritus and fatigue, which can lead to social isolation and emotional dysfunction [1,80,81]. Fatigue, defined as a persistent state of exhaustion, inability to perform usual routines, and a decreased capacity for physical and mental work, has been reported as the most common and debilitating among these symptoms [12,30,82,83]. Individuals with PBC also commonly experience a low health-related quality of life (HRQOL), with 1 study concluding that 35% of individuals with PBC had an impaired HRQOL compared to 6% of healthy controls[12]. Current medical therapies are ineffective at improving PBC-related symptoms or impacting quality of life [5,6,8]. Building upon the recognized need for novel interventions[12,13,83,84], our team was approached by patients and the Canadian PBC Society to develop self-care tools to manage symptom burden. Although to our knowledge, mind-body wellness interventions have never been trialed in PBC, interventions of this nature have been found to improve fatigue and HRQOL in other chronic diseases[21,67,85].

The use of a clear theoretical framework during the design of an intervention has been associated with increased adherence rates, and sustained changes to health-related behaviors[76,86,87]. The Behaviour Change Wheel (BCW), a framework synthesized from 19 individual models of behavior, has been used to guide development of several acceptable and effective theory-based interventions[88-90]. At the core of the BCW is the Capability, Opportunity, Motivation and Behaviour (COM-B) model, which describes the key antecedents to the target behavior. The BCW then outlines intervention functions that can be used to facilitate behavior change[88]. This process is further enhanced by the behavior change technique taxonomy version 1

(BCTv1), which details standardized active intervention ingredients that can be implemented to target intervention functions[91]. Optimally, theory would also extend to the evaluation of behavior change and maintenance.

This paper describes how theory has guided the development of a 12-week multicomponent mind-body wellness intervention for PBC (ClinicalTrials.gov NCT04791527) using several theoretical constructs: BCW guidelines[88], the COM-B model[88], the theoretical domains framework (TDF)[92], and the BCTv1[91]. Development of the intervention involved the following steps, which were informed by the BCW guidelines: (1) specify the target behavior; (2) explain barriers and facilitators to the target behavior by using the COM-B model and the TDF; (3) identify intervention functions to target explanatory domains; and (4) select relevant behavior change techniques to address intervention functions.

3.3 Methods

The following sections outline the processes (methods) for each of the 4 steps of intervention development. An outline of the 4 steps of intervention development can be found in Error! Reference source not found..

Figure 1. Steps involved in intervention development. BCT: behavior change technique; COM-B: Capability, Opportunity, Motivation and Behaviour; TDF: theoretical domains framework.

3.3.1 Step 1: Specify the Target Behavior

The target behavior was determined through a review of the literature on adherence to behavioral health interventions, and in consultation with the Canadian PBC Society.

3.3.2 Step 2: Explain Barriers and Facilitators to Behavior Using the COM-B and TDF

Domains from the COM-B model and the TDF were selected to explain barriers and facilitators to the target behavior. The COM-B model outlines that for a behavior to occur, an individual must have the capability, opportunity, and motivation to perform the behavior. Capability is composed of psychological capability (knowledge), and physical capability (physical skills); opportunity is composed of physical opportunity (environmental resources) and social opportunity (cultural milieu); and motivation includes reflective motivation (evaluations, plans) and automatic motivation (emotions, impulses)[88]. As the COM-B model provides a relatively general understanding of behavior, the TDF, which outlines 14 processes involved in behavior change, is often used to provide further specification of behavioral determinants[92]. To identify barriers and facilitators driving health-related behavior, we conducted qualitative interviews with individuals who had participated in the previous iteration of the intervention carried out in a separate chronic disease group (i.e., individuals with inflammatory bowel disease [IBD])[93]. Similar to PBC, individuals with IBD experience high rates of fatigue and impaired quality of life[94,95]. These interviews were coded and thematically analyzed by 2 independent coders[93]. A COM-B characteristic and a TDF domain were then identified for each barrier and facilitator of behavior mentioned by those participants.

3.3.3 Step 3: Identify Intervention Functions to Target Explanatory Domains

Intervention functions were selected to address each barrier and facilitator to behavior. The BCW specifies 9 standardized intervention functions that can be used to address barriers and facilitators to behavior change[88]. The BCW guide then outlines intervention functions that are appropriate for each TDF domain[96]. The web-based nature of the program and characteristics of

the target population (i.e., chronic fatigue) were considered when selecting intervention functions.

3.4.4 Step 4: Specify Intervention Content by Selecting Relevant BCTs

Behavior change techniques were selected to allow standardized implementation of intervention functions. Following the procedure outlined by Jennings et al[76] and Tombor et al[97], BCTs were specified for each of the intervention functions identified in step 3.

3.4 Results

The Peace Power Pack PBC (PPP_{PBC}) intervention was co-developed with a patient advisory team from the Canadian PBC society. The web-based intervention is described in Multimedia Appendix A. The intervention is 12 weeks in duration with each week featuring: (1) a video detailing a core practice of mindful movement (yoga, tai chi, and low-intensity exercise divided into a standing stream and a chair stream), energizing breathwork practices, and guided meditation (increasing in length from 20-30 minutes over the course of the program); (2) an introductory video describing a weekly positive psychology theme (3-5 minutes); and (3) an interactive positive psychology activity related to the theme for the week (3-5 minutes). All programming is hosted on the investigator's website[98]. Throughout the duration of the study, participants will receive standardized weekly motivational emails, weekly 10-minute motivational interviewing check-ins, and will be invited to participate in weekly group sessions with fellow participants. The following section outlines the outcomes (results) for each of the 4 steps of intervention development previously outlined.

3.4.1 Step 1: Specify the Target Behavior

Adherence to the video-based program at least 3 days a week was selected as the primary target behavior, with a gradual increase in the video duration over the course of the 12 weeks. Based on

feedback from the Canadian PBC society, this target behavior was chosen with the intent to balance the intervention dose with likelihood of adherence. Available evidence suggests that higher levels of adherence to behavioral health interventions leads to improved outcomes in a dose-dependent manner[99]. High levels of fatigue in individuals with PBC have been associated with a decreased sense of self-efficacy for a particular behavior[100] and inability to adhere to a target could lead to further reductions in self-efficacy. To ensure participants are aware of the anticipated study commitment, the target will be advertised to participants interested in enrollment.

3.4.2 Step 2: Explain Barriers and Facilitators to Behavior Using the COM-B and TDF

A comprehensive list of barriers and facilitators, along with the associated COM-B and TDF domains is provided in **Table 1**. The most common barriers to program participation described by the individuals with IBD were difficulty fitting the program into daily routine, and finding that the movement portion of the program was not matched with the ability level[93]. Perceived facilitators to program participation included accessible presentation of content on the host website and contact with program facilitators/fellow participants. Of the 14 domains of the TDF, 9 were associated with barriers and facilitators to intervention participation: behavior regulation, physical skills, environmental context and resources, memory attention and decision processes, social influences, goals, beliefs about capabilities, beliefs about consequences, and reinforcement. The most common TDF domains were social influences (check-ins with program facilitators and other participants enhancing accountability), and behavioral regulation (fitting the program into daily routine).

Table 1. Use of behavior change techniques in developing an intervention for people living with primary biliary cholangitis.

Enabler	Barrier	COM-B[a]/TDF[b]/IF[c]	Behavior change technique	Implementation of a behavior change technique
Interactions with program facilitators enhanced accountability		· COM-B: reflective motivation · TDF: goals · IF: persuasion	· 1.5 Review behavior goal(s) · 1.6 Discrepancy between current behavior and goal · 3.1 Social support (unspecified)	· 1.5 Weekly adherence vs target adherence goal were discussed during check in · 1.6 Weekly adherence vs target adherence goal were discussed during check in · 3.1 Weekly check ins employed motivational interviewing techniques to support program adherence

Able to integrate in everyday routine	Difficulty integrating program into daily routine	· COM-B: psychological capability · TDF: behavioral regulation · IF: enablement, persuasion	· 1.4 Action planning (Future consideration · 1.6 Discrepancy between current behavior and goal · 2.2 Feedback on behavior · 15.3 Focus on past success (self-belief)	· 1.4 In week 1, participants watched an interactive video prompting them to plan their performance of the target behavior (adherence to the program at or above the set minimum adherence goal). This included committing to a personal adherence goal at or above the set minimum, and writing down (1) potential obstacles to meeting their adherence goal; and (2) actions that could be taken to avoid or overcome these obstacles. · 1.6 The host website recorded weekly participation (indicated by accessed content). At the top of the website, the user's current weekly participation was presented beside the user's adherence goal. · 2.2 The host website recorded weekly participation (indicated by accessed content). At the top of the website, the user's current weekly

				participation was presented. · 15.3 In week 1, participants watched an interactive video that prompted them to think about instances in which they successfully adhered to a goal.

Access to accommodations to physical activity program where needed	Insufficient access to accommodation to physical activity program	· COM-B: physical capability · TDF: skills · IF: enablement	· 4.1 Instruction on how to perform a behavior · 6.1 Demonstration of the behavior	· 4.1 Instruction for accommodations were provided · 6.1 Demonstration of accommodations were provided
Interaction with others in program associated with increased motivation		· COM-B: social opportunity · TDF: social influences · IF: persuasion, modeling	· 3.1 Social support (unspecified)	· 3.1 Participants were invited to weekly live group sessions in which they had the opportunity to participate in program practices with peers
Desire to feel better		· COM-B: reflective motivation · TDF: goals · IF: persuasion	· 5.1 Information about health consequences · 5.2 Information about emotional consequences	· 5.1 Introductory videos provided information about health consequences associated with participating in the program · 5.2 Introductory videos provided information about health consequences associated with participating in the program

	Difficult to participate when feeling unwell due to disease	· COM-B: physical capability, psychological capability · TDF: environmental context and resources · IF: environmental restructuring	· 12.1 Restructuring of the physical environment	· 12.1 Short meditations were provided that could be completed when individuals are not feeling as well · 12.1 All mindful movement was low intensity
Able to navigate website	Difficulty navigating website	· COM-B: psychological capability · TDF: memory attention and decision processes · IF: training	· 4.1 Instruction on how to perform a behavior · 6.1 Demonstration of the behavior (comparison of a behavior)	· 4.1 Individuals received an introduction to the online platform via zoom, in which the research assistant provided instruction on accessing the intervention. Written instructions were also forwarded to all participants in an email. · 6.1 Individuals received an introduction to the online platform via zoom in which the research assistant demonstrated accessing the intervention

Web-based format enhanced accessibility		· COM-B: psychological capability · TDF: environmental context and resources · IF: environmental restructuring	· 12.1 Restructuring the physical environment	· 12.1 Web-based format was maintained
	Physical movement was too difficult	· COM-B: physical capability · TDF: physical skills · IF: enablement, training, environmental restructuring	· 4.1 Instruction on how to perform a behavior · 6.1 Demonstration of the behavior (comparison of a behavior) · 12.1 Restructuring of the physical environment	· 4.1 Within each stream, the mindful movement videos featured description of how to perform each specific posture/exercise · 6.1 Within each stream, the mindful movement videos featured demonstration of how to perform each specific posture/exercise · 12.1 Two streams of mindful movement were implemented, which were differentiated by difficulty

	Physical movement was not difficult enough	· COM-B: reflective motivation · TDF: beliefs about capabilities · IF: environmental restructuring	· 12.1 Restructuring of the physical environment	· 12.1 Two streams of mindful movement were implemented, which were differentiated by difficulty
Feeling better/good after participating in intervention	Uncertain about benefit	· COM-B: reflective motivation · TDF: beliefs about consequences, reinforcement · IF: persuasion	· 5.1 Information about health consequences · 5.2 Information about emotional consequences · 9.1 Credible source	· 5.1 Introductory videos provided information about health consequences associated with participating in the program · 5.2 Introductory videos provided information about health consequences associated with participating in the program · 9.1 Introductory videos featured health care professionals discussing potential benefits associated with participating in the program

	Fear of getting injured during physical activity	· COM-B: reflective motivation · TDF: beliefs about consequences · IF: education, environmental restructuring	· 9.1 Credible source · 12.1 Restructuring of the physical environment	· 9.1 Welcome video featured a health care professional explaining that mindful movement was designed to be safe for PBC. · 12.1 Various streams of mindful movement were available, separated by difficulty. Adaptations were available within mindful movement.
Repetition in physical activity program helped build routine		· COM-B: psychological capability · TDF: memory, attention, and decisional processes · IF: enablement	· 8.3 habit formation	· 8.3 Routine varied but structure was conveyed through repetition of the same type of activity from week to week (eg, 1 day of each week was dedicated to a breath program, 1 day a flow day)

[a]COM-B: Capability, Opportunity, Motivation and Behaviour.
[b]TDF: theoretical domains framework.
[c]IF: intervention functions.

3.4.3 Step 3: Identify Intervention Functions to Target Explanatory Domains

The intervention functions persuasion, environmental restructuring, and education were used to target theoretical domains relating to motivation. The intervention functions persuasion,

enablement, training, and environmental restructuring were selected to target theoretical domains related to capability, and the intervention functions persuasion and modelling were selected to target theoretical domains related to opportunity. See **Table 1** for a full outline of the intervention functions selected for each domain.

3.4.4 Step 4: Specify Intervention Content by Selecting Relevant BCTs

The comprehensive list of selected BCTs along with a description of how they were operationalized can be found in **Table 1**. Examples of how selected BCTs were translated into each of the general intervention components are detailed in the following.

Implementation of BCTs Into Core Practice: To address the behavior barrier "physical movement was too difficult," the BCTs "including instructions on how to perform a behaviour," "demonstration of the behaviour," and "restructuring of the physical environment" were employed. These were operationalized by including short videos to describe and demonstrate each exercise featured in the mindful movement routines, and through restructuring the program to include participant choice between a chair versus a standing stream of mindful movement.

Implementation of BCTs Into Positive Psychology: The BCTs "action planning" and "focus on past successes" were integrated into the positive psychology portion of the program to help address the barrier "integrating the program into daily routine." Specifically, an interactive positive psychology activity at the beginning of the program was created to prompt participants to set their adherence goal, schedule their behavior, consider potential barriers and facilitators to behavior, and think about past successes with behavior change.

Implementation of BCTs Into Weekly Communications: To address the behavior facilitator "interactions with others enhances accountability," we selected the BCTs "social support (unspecified)," "review behaviour goals," and "discrepancy between current behaviour

and goal." During the weekly phone check-ins, a program facilitator will implement these BCTs by providing social support through brief weekly motivational interviewing touchpoints, revisiting the participant's initial goals, and discussing weekly adherence versus initial adherence goals.

3.5 Discussion

3.5.1 Principal Findings

The PPP_{PBC} intervention was developed to provide individuals with PBC a tool to help better manage their symptom burden. The intervention was designed to optimize participation by enhancing a participant's physical capability (ie, enable participation in a stream of mindful movement), psychological capability (ie, enable self-regulation), automatic motivation (ie, help participants build a routine), reflective motivation (ie, building intention to participate in wellness practices), and social opportunity (ie, connect with peer models). Owing to the web-based nature of this intervention, we were not able to alter the individual's physical environment and therefore did not target physical opportunity. Capability, opportunity, and motivation were targeted through the intervention functions persuasion, education, modeling, enablement, environmental restructuring (restructuring of intervention platform), and training. Additionally, 13 BCTs from the BCT taxonomy v1 were chosen to deliver the intervention content.

3.5.2 Utility of a Theoretical Framework

Informing behavioral interventions by theory not only provides a means to increase the efficacy of these interventions, but also allows researchers to standardize reporting of the active ingredients of interventions through BCTs. Current guidelines for reporting behavioral interventions are largely focused on reporting intervention delivery rather than intervention content [101,102]. Consequently, few reports detail active components of existing behavioral

interventions and often use different language to describe active components. This presents a barrier to evaluating and replicating aspects of interventions that effectively bring about behavioral change. Experts in behavioral medicine have reported a low level of confidence in their ability to replicate effective behavioral interventions, which is likely linked to poor reporting of these interventions[91]. The current intervention is among a small number of multicomponent behavioral interventions to report on theoretically informed intervention development in a standardized manner[102]. In addition, this is the first known mind-body intervention tailored to PBC. This report provides a basis for (1) better consensus to be reached around a standardized approach to employing behavior change theory to inform an intervention and (2) evidence to be synthesized around which BCTs are effective in the context of an intervention. Both of these factors will allow for replication of successful aspects of implementation and successful active components. Importantly, after study rollout is complete, subsequent qualitative and quantitative assessment of behavior change will be necessary to determine successful components of the intervention.

3.5.3 Limitations

This project is not without limitations that should be acknowledged. The qualitative feedback used to inform barriers and facilitators to participating in the intervention was provided by participants with IBD, with no large-scale data collection occurring from individuals with PBC. Given the similarity of the symptom burden experienced with IBD and PBC (eg, fatigue, depression, anxiety, stress) the barriers and facilitators provided in the interviews were deemed to be applicable to PBC. To further mitigate this limitation, we worked with an advisory team of patients with PBC to better understand how intervention design needed to be tailored to meet the

specific needs of this population (eg, providing a chair stream within the mindful movement to accommodate for potential fatigue and mobility restrictions).

3.5.4 Conclusions

To our knowledge, the PPP_{PBC} intervention is unique in that it is a mind-body wellness program designed for individuals with PBC, and in that it has taken a structured approach to considering theory in design and evaluation. Development was informed by the BCW [16] and BCTs [19]. Application of these frameworks was guided by feedback from our patient advisory team. Further standardized reporting of complex interventions conducted in different contexts, along with subsequent assessment of behavior change, is necessary to determine how contextual variables influence the effectiveness of different BCTs.

CHAPTER 4: THE FEASIBILITY AND ACCEPTABILITY OF A WEB-BASED MIND-BODY WELLNESS INTERVENTION FOR PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC)

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4.1 Abstract

Background and Aims: Persons with primary biliary cholangitis (PBC) experience significantly higher rates of mental distress and impaired health related quality of life (HrQoL) than the general population. Given limited evidence, but a high need, our primary aim was to assess feasibility and acceptability of a 12-week, online, mind-body wellness program in people with PBC.

Methods: This was a single-group, sequential mixed-methods, pre-post feasibility and acceptability study. Core program components included follow-along movement, meditation and breathwork videos, and cognitive behavioral therapy informed activities. It was supplemented by weekly phone check-ins. Feasibility was assessed by recruitment, adherence and retention. The pre-post exploratory efficacy assessment included surveys for fatigue, perceived stress, anxiety, depression, HrQoL, and resilience. A qualitative descriptive approach with semi-structured interviews was used to evaluate study experiences.

Results: Thirty-two participants were recruited within 30 days and 29 (91%) were retained to end-of-study. Of these, 25 (86%) adhered to carrying out the mind-body practice at least 2-3 days per week. Feedback supported acceptability (satisfaction score 90%). Significant improvements were observed in fatigue (13%, p=0.004), anxiety (30%, p=0.005), depression (28%, p=0.022) and five PBC-40 domains (itch, fatigue, cognitive, emotional, general symptoms). Qualitative interviews revealed improved stress management, better coping, and a more positive mindset. Fatigue and self-sabotaging thoughts were cited as barriers to participation.

Conclusions: These findings suggest that a 12-week online mind-body intervention is feasible and acceptable in patients with PBC. After iterative refinement, a randomized controlled trial will be designed using this feedback.

4.2 Introduction

Primary biliary cholangitis (PBC) is a female predominant autoimmune liver disease typified by chronic progressive damage to intrahepatic bile ducts[1,36]. Though PBC is relatively uncommon, global incidence and prevalence rates are on the rise[1,28]. Common symptoms include fatigue, pruritus, social isolation, emotional dysfunction, and impaired health related quality of life (HrQol)[1,12], the latter occurring in 35% of patients as compared to 6% of healthy controls[12]. Fatigue is the strongest predictor of impaired HrQol[12,83]. Moreover, individuals with PBC experience significantly higher rates of anxiety, stress, and depression as compared to the general population, with studies estimating a 30-45% prevalence of depressive symptoms[3,25,45]. Across a range of chronic disease populations, these psychiatric comorbidities have been associated with impaired coping, poor prognosis, and increased mortality[25,46].

Mind-body wellness programming including practices such as mindful movement, meditation, breathwork, and cognitive behavioral therapy (CBT) has been shown to decrease fatigue, and improve HrQol and mental wellness in a variety of other chronic disease populations[16,18,19,64]. Delivering this programming on web-based platforms reduces barriers associated with attending person visits. This enhanced accessibility may be especially beneficial for populations who experience fatigue. Although mental health has been prioritized as an adjunct to medical therapy by both patients with PBC (GW, personal communication), and by guidelines[25], to date, we lack practical online mental wellness interventions specific to this population. To address this unmet need, we worked with a patient advisory team from the Canadian PBC Society to get feedback on developed content, and to co-develop the recruitment and evaluation strategy of a 12-week, online, mind-body wellness program for people with PBC (Peace Power Pack (PPP)). As a pilot study, our aim was to assess intervention feasibility

(through recruitment, adherence and retention rates), and acceptability. We also aimed to explore pre-post changes in measures of wellbeing including fatigue, perceived stress, anxiety and depression, and HrQol. Recognizing the complexities of a mind-body intervention, the need to explore participants' experiences, and our desire to obtain feedback on the intervention, an explanatory sequential mixed-methods design was employed[103].

4.3 Methods

4.3.1 Study Design

This was a single group, pre-post, feasibility study. Ethics approval was received from the Health Research Ethics Board of Alberta on January 14th, 2021 (Pro00106526). The study was registered at www.clinicaltrials.gov (NCT04791527). Informed written consent was obtained from each participant prior to enrollment.

4.3.2 Recruitment and Participants

Eligible participants (≥18 years of age) with a self-identified diagnosis of PBC) were recruited across Alberta and British Columbia in January 2021. Potential participants were made aware of the study through a recruitment email sent to members of the Canadian PBC Society's email list. The email provided study contact information that participants could reach out to if interested. Participants were excluded if they had a Hospital Anxiety and Depression Scale (HADS)[104] depression subcomponent score > 10 (at risk for severe depression), or inability to provide informed consent in English. Patients with (HADS) score > 10 were referred to resources for psychiatric follow-up. To increase generalizability of the results to the real-world, participants were not excluded based on a history of co-existing physical or mental comorbidities.

4.3.3 Intervention

Development of the 12-week online intervention was theoretically informed by the Behaviour Change Wheel (BCW), a framework for intervention development that is centered around the capability, opportunity, motivation model of behaviour (COM-B)[88]. The COM-B model outlines that for a behaviour to occur an individual must have the capability (physical and psychological), opportunity (physical and social), and motivation (reflective and automatic) to perform the behaviour[88]. The development of these behavioral components are reported separately in detail[105]. Delivered via an online web platform, the program included two core components: i) a 20-30 minute "daily routine" video containing progressive follow-along low intensity mindful movement, breathwork, and a guided meditation, and ii) a 5-15 minute weekly behaviour change video and activity informed by cognitive behavioural therapy. Participants were informed that the adherence goal for the program was based on completion of the daily routine video at least 2-3 times/week. Supplementary, optional content was added at the request of our patient partners and included a weekly video tip from a PBC physician (3-5 min each week) and a weekly PBC nutrition tip (3-5 min each week) (**Appendix B).** The online programming was accompanied by brief (10-15 minute) once weekly phone check-ins from a member of the study team. These check-ins were intended to review progress, support motivation, and answer any program-related questions. Participants were also invited to take part in voluntary once monthly zoom group sessions (1 hour) hosted by the Canadian PBC Society.

4.3.4 Data Collection and Outcome Measures

4.3.4.1 Quantitative

Demographic and disease related information was gathered at baseline from patient self-report.

The primary outcomes were feasibility (assessed by recruitment rate, retention rate, and adherence), and acceptability. A recruitment rate indicating feasibility was set at ≥ 30 participants consenting to the study over a 1-month period. Consistent with other studies[106,107], a retention rate indicating feasibility was set at ≥ 70% of consenting participants completing the end-of-study surveys. Adherence was defined as > 70% of participants meeting the adherence goal of 2-3x per week, and was assessed using a survey at the end of the study period as well as supplemented using the information gathered in the weekly-check ins. Acceptability was assessed through a survey at the end of the study period.

Additional exploratory outcome measures were collected to assess preliminary efficacy of the intervention and support sample size calculations for a future randomized controlled trial (RCT). Baseline and end-of-study surveys (12-weeks) assessed the change in patient-reported outcome measures in anxiety and depression (Hospital Anxiety and Depression Scale [HADS])[104], perceived stress (Perceived Stress Scale [PSS])[108], fatigue (Modified Fatigue Impact Scale [MFIS])[109], HrQol [PBC-40])[110], resilience (Connor-Davidson Resilience Scale [CD-RISC])[111], and perceived capability, opportunity, and motivation (**Appendix C**) (adapted from Keyworth et al.)[112].

4.3.4.2 Qualitative

End-of-study semi-structured interviews were carried out by MW and EJ using a qualitative description approach[113]. Purposive sampling methods[114] were used to ensure diversity

in age, retirement status, and time from PBC diagnosis. Interviews lasted an average of 40 minutes and were carried out by telephone. The interview guide, informed by the capability, opportunity, motivation model of behaviour (COM-B)[88], is detailed in **Appendix D**. All interviews were recorded and transcribed verbatim. Following each interview, field notes were recorded that detailed the interviewer's preliminary impressions.

4.3.5 Data Analysis

4.3.5.1 Sample Size and Statistical Analysis

To determine feasibility and acceptability, and inform a future efficacy trial, the target sample size was set to at least 30 participants, in the range of other studies of this nature[115,116]. Demographics, feasibility, and acceptability measures are presented using descriptive statistics (mean ± SD for continuous variables, frequency [%] for nominal variables). The normality of all exploratory effectiveness outcomes was examined using histograms and Q-Q plots. In the absence of non-normality, pre-post changes to exploratory effectiveness variables were analyzed using paired sample t-tests. All statistical analyses were performed using SPSS[117], with alpha set to 0.05.

4.3.5.2 Qualitative Analysis

Data collection and analysis occurred iteratively to enable refinement of our interview guide and exploration of emerging themes. Interviews were analyzed using a theoretical thematic approach, whereby data were analyzed inductively, with transcripts coded, then grouped into larger categories, then themes[118,119]. Analysis was completed by two members of the study team (MW, AH) who developed a coding framework, with disagreements resolved through consensus. NVivo was used for data management[119].

4.4 Results

4.4.1 Participants

Thirty-seven individuals were screened, and 32 met eligibility criteria and completed baseline surveys. Three individuals were excluded due to a HADS depression subcomponent score > 10, and 2 were excluded because they had received a liver transplant after their PBC diagnosis **(**Error! Reference source not found.**).** The mean age of participants was 57.7 ± 11.2 y ears. All participants were female. The mean number of years since PBC diagnosis was 8.5 ± 8.0. Further demographic information is reported in Error! Reference source not found.**.**

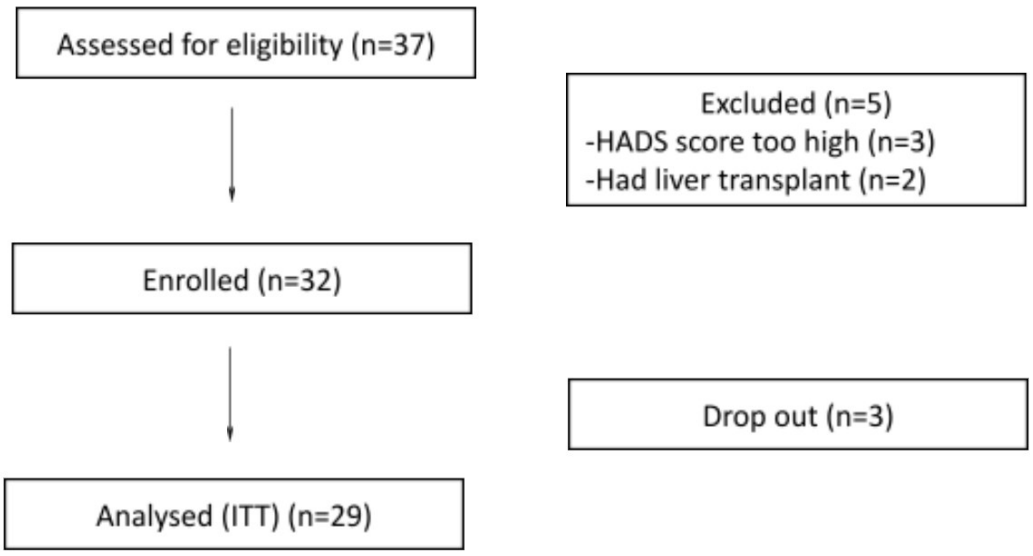

Figure 2. Patient recruitment and flow through the study. Abbreviations: HADS, hospital anxiety and depression scale

Table 2. Patient Baseline Characteristics

Relationship status	
Single	4 (12.5%)

Married/Common Law	21 (65.6%)
Divorced/Separated	5 (15.6%)
Widowed	2 (6.3%)
Employment status	
Employed	13 (40.6%)
Unemployed	14 (43.8%)
Prefer not to answer	5 (15.6%)
Highest education achieved	
Less than high school	0 (0%)
High school graduate/GED	2 (6.3%)
Some college	18 (56.3%)
University degree	12 (37.5%)
Sex	
Female	32 (100%)
Age	57.7 ± 11.2
Years since diagnosis	8.5 ± 8.0

Cirrhosis status	
No cirrhosis	14 (43.8%)
Cirrhosis	5 (15.6%)
Unsure	13 (40.6%)
Meditation in past 6 months	
Yes	12 (37.5%)
Yoga in the past 6 months	
Yes	6 (18.8%)

4.4.2 Primary Feasibility and Acceptability Outcomes

Recruitment of 32 eligible participants was within our target recruitment for 30 participants within 4 weeks. Of the 32 participants who met eligibility criteria and completed baseline surveys, 29 completed the 12-week program and follow-up surveys (90.6% retention). All three individuals who did not complete the programming cited lack of time commitment as their primary reason for non-completion. Of the 29 participants who completed the intervention, 25 (86.2%) met the pre-specified adherence target (completing the core programming at least 2-3 times per week). Weekly adherence rates to the core programming, self-reported at the end of the study period, were: once per week or less (n=4, 13.8%), 2-3 times per week (n=11, 37.9%), 4-5 times per week (n=12, 41.4%), and daily (n=2, 6.9%).

The mean satisfaction score, rated on a 0-100 visual scale with 0 representing "Not Satisfied" and 100 representing "Extremely Satisfied," was 89.7 ± 10.9. Participant satisfaction with different elements of the programming is illustrated in Error! Reference source not found.. The mean likelihood of continuing with elements of the programming, rated on a 0-100 visual scale with 0 representing "Not Likely" and 100 representing "Extremely Likely," was 88.2 ± 18.8. Seventeen (73.9%) of participants ranked the amount of information as just right, with 5 (21.7%) indicating too little information, and 1 (4.3%) indicating too much information. Seven (38.9%) of participants ranked the time commitment of 2-3 times per week for the programming as just right, with 7 (38.9%) indicating the time commitment was too little, and 11 (61.1%) indicating the time commitment was too much.

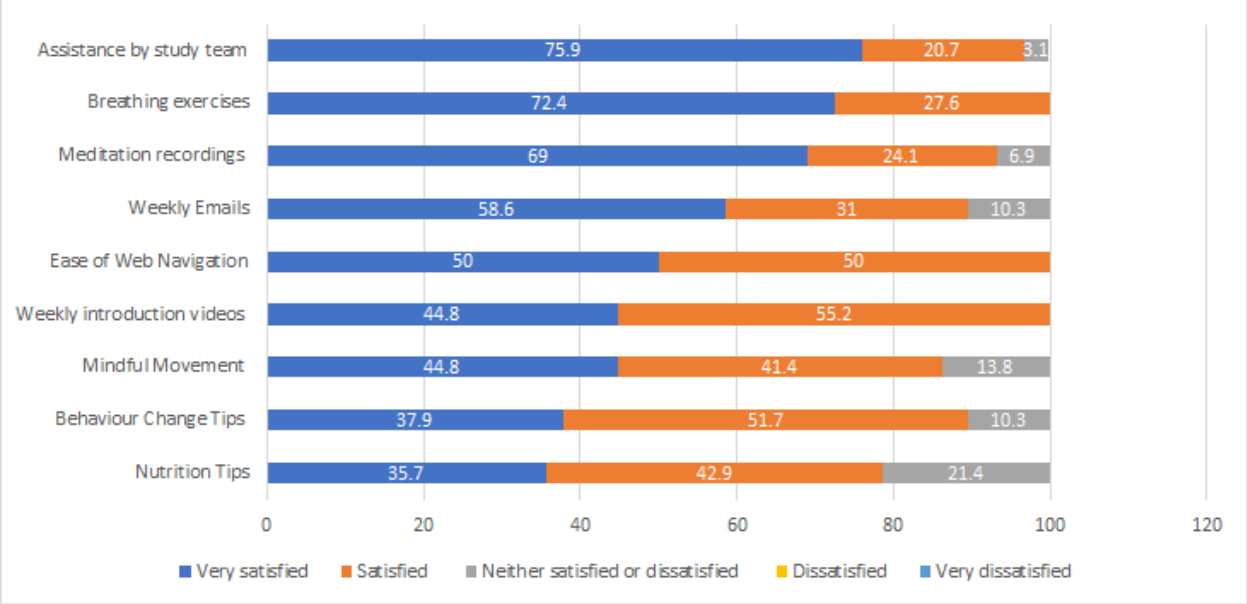

Figure 3. Participant satisfaction with core and optional elements of the Peace Power Pack program, scored using a 5-Point Likert Scale from Very Satisfied to Very Dissatisfied

4.4.3 Exploratory Indicators of Impact

From baseline to 12 weeks, the HADS total score improved by 27.6% (p=0.022), the HADS depression domain score improved by 29.5% (p=0.005), and HADS anxiety domain score improved by 28.3% (p=0.004). From baseline to 12 weeks, the MFIS total score improved by 13.4% (p=0.004), with significant improvements across the physical, cognitive and psychosocial domains. From baseline to 12 weeks, several PBC-40 domain scores improved, including itch by 22.0% (p=0.043), fatigue by 13.0% (p=0.005), cognitive function by 16.7% (p=0.006), emotional function by 17.9% (p=0.001), and general symptoms by 9.6% (p=0.018). No significant changes were observed from baseline to 12 weeks in the Perceived Stress Scale or Connor Davidson Resilience Scale. Significant changes were seen from baseline to 12 weeks in the COM-B domains, including physical opportunity which decreased by 9.9% (p=0.039), reflective motivation which decreased by 7.2% (p=0.046), automatic motivation which decreased by 15.0% (p=0.025), and psychological capability which decreased by 14.1% (p=0.009) **(Table 3, Figure 4**).

Table 3. Paired t-test comparison of the mean ± SD depression, resilience, stress, fatigue, quality of life, and perceived capability, opportunity, and motivation scores from baseline to end of study.

	Baseline (n=29)	**End-of-study (n=29)**	**Percent improvement**	**P value for the paired t-test**
Hospital anxiety and depression scale				

Total	13.4 ± 5.8	9.7 ± 6.1	27.6%	0.022*
Anxiety subcomponent	7.8 ± 3.7	5.5 ± 3.7	29.5%	0.005*
Depression subcomponent	6.0 ± 2.6	4.3 ± 3.2	28.3%	0.004*
Connor Davidson resilience scale	27.7 ± 5.3	29.2 ± 4.4	5.4%	0.256
Perceived stress scale	16.4 ± 7.5	14.0 ± 6.5	14.6%	0.082
Modified fatigue impact scale				
Total	65.5 ± 11.9	56.7 ± 12.3	13.4%	0.004*
Physical	30.2 ± 6.4	27.1 ± 5.5	10.2%	0.025*
Cognitive	28.5 ± 7.7	24.1 ± 7.8	15.4%	0.001*
Psychosocial	5.9 ± 1.7	4.7 ± 1.7	20.3%	0.029*
PBC-40				
Itch	5.0 ± 3.2	3.9 ± 3.1	22.0%	0.043*

Fatigue	33.1 ± 8.8	28.8 ± 7.2	13.0%	0.005*
Cognitive	16.2 ± 4.6	13.5 ± 4.7	16.7%	0.006*
Emotional	8.4 ± 2.1	6.9 ± 2.5	17.9%	0.001*
Social	26.8 ± 7.6	24.4 ± 6.4	9.0%	0.104
Symptom	16.7 ± 4.2	15.1 ± 5.1	9.6%	0.018*
Capability, opportunity, motivation model of behaviour				
Physical Opportunity	9.1 ± 1.1	8.2 ± 2.3	-9.9%	0.039*
Social Opportunity	8.4 ± 2.3	7.3 ± 3.0	-13.1%	0.057
Reflective Motivation	9.7 ± 0.7	9.0 ± 1.9	-7.2%	0.046*
Automatic Motivation	8.0 ± 2.0	6.8 ± 2.8	-15.0%	0.025*
Physical Capability	8.9 ± 1.3	7.8 ± 2.9	-12.4%	0.071
Psychological Capability	9.2 ± 0.8	7.9 ± 2.9	-14.1%	0.009*

Abbreviations: PBC, primary biliary cholangitis

* $p < 0.05$

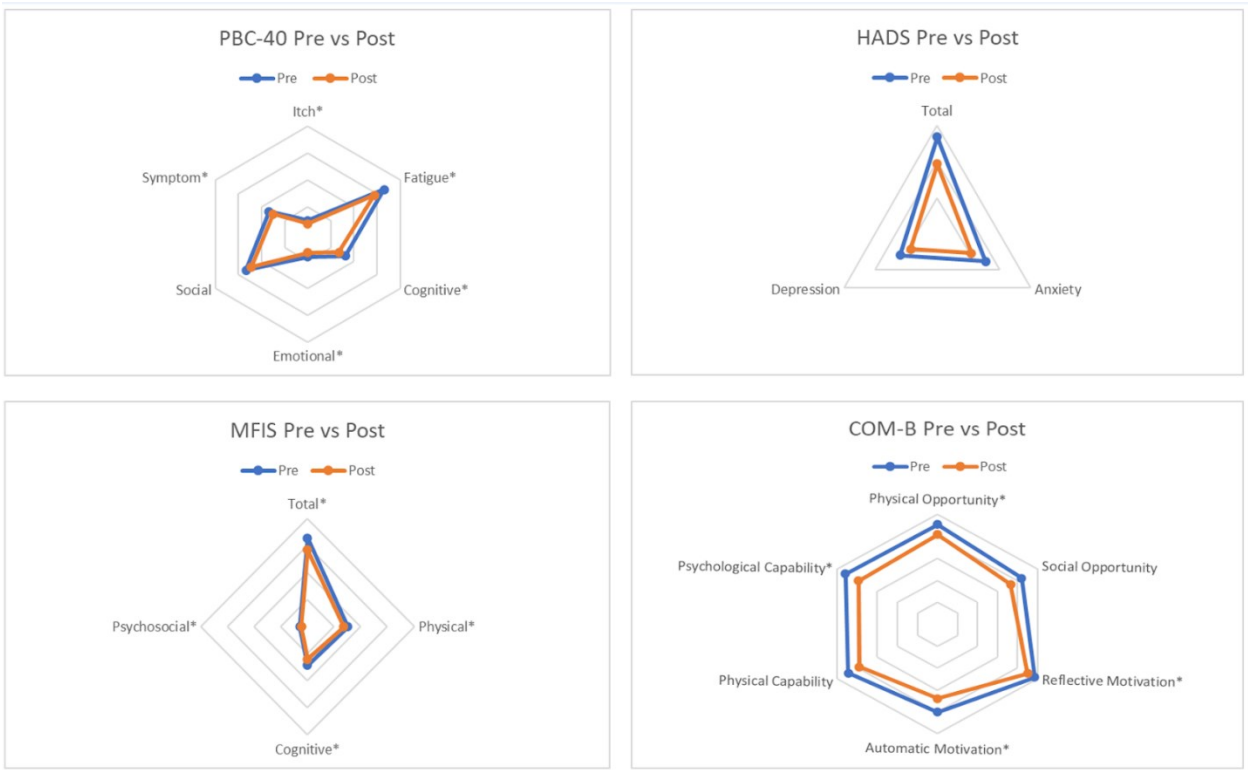

Figure 4. Estimated mean PBC-40, Hospital Anxiety and Depression Scale (HADS), Modified Fatigue Impact Scale (MFIS), and COM-B domain scores by timepoint. Lower scores indicate improvement on the PBC-40, HADS, and MFIS, higher scores indicate improvement on the COM-B, and * indicates statistical significance at alpha = 0.05

4.4.4 Qualitative Findings

Eleven individuals participated in the end-of-study qualitative interviews. They ranged in age from 34 to 71 years (56.8 ± 13.6 years), and had been diagnosed with PBC (12.8 ± 10.6 years ago). Six participants (54.5%) were employed, four were unemployed (36.4%), and one (9.1%) preferred not to specify employment status. These baseline characteristics were similar to

participants in the main study, and are reported in full in **Appendix E.** We identified three main themes: (i) Learning to live with PBC: appreciating the physical and emotional impacts (ii) Understanding impacts of the mind-body program, and (iii) Acknowledging barriers and facilitators to program participation.

4.4.4.1 Theme #1: Learning to live with PBC: appreciating the physical and emotional impacts

Participants described the physical, mental and emotional side effects of PBC, with many naming fatigue as "the biggest limitation." One individual described their fatigue, saying: "It's almost like there's an energy pump attached to me and sucking all of the energy out" (29). Others compared their fatigue to "hitting a wall where you just can't go any further" or "trying to wade through water." They acknowledged that this fatigue shaped their daily routines with one participant sharing: "Everything that I want to do in the day has to be done in the morning. And the morning doesn't have all that many hours in it" (24). Similarly, another reflected on the need to limit activity during episodes of fatigue: "If I am really, really fatigued, I don't want to go out and make myself worse for the following day" (10). Participants also spoke of physical symptoms including, dry eyes and mouth, and itching. On the other hand, a few participants did not experience physical symptoms with their PBC, describing their disease as something that was "there in the background."

Aside from the physical symptoms, participants described the mental toll associated with having an uncertain prognosis: "Mentally it plays on you when you think that there is a possibility that your lifespan could be shortened. Or that you might need a liver transplant in the future, that's frightening" (22). Some participants shared that coping with this uncertainty became easier as they got further from their diagnosis. One individual said the following of adapting to having PBC: "I feel like the farther away I get from my diagnosis, the less daily

anxiety I have about it, just because you sort of get used to PBC and learn to live with it" (22). For others, coping with PBC entailed "making the decision to give PBC as little energy as possible" while "doing everything possible to keep healthy." One participant reflected on this:

> *I try not to spend a lot of time thinking about it . . . sometimes your brain goes there. But there's really nothing I can do to affect the outcome, other than stay on my medication, try and stay healthy (14).*

Though participants largely acknowledged that they had learned to live with PBC, they expressed a desire to "stay healthy" and "continue striving toward living better with PBC". For some, this desire to "live better" with PBC and gather physical and mental tools to cope with their illness motivated them to enroll in the PPP program.

4.4.4.2 Theme #2: Understanding impacts of the mind-body program

Participants noted the positive impacts of the PPP program, with some describing that the PPP increased their knowledge of tools that could be used to effectively cope with the stress. One participant reflected on this, sharing how the breathwork practices in the program helped her to manage disease-related stress: "I was pretty stressed out about health and I just really needed that stress reliever. To breathe through something made me feel like I was more in control" (10). Many appreciated how acquiring these tools to manage stress helped to "conserve energy," which they noted was "way more limited with PBC." Of this, one participant shared:

> *I don't have extra energy to burn. So, if I can stay more focused and calmer, then I've got more energy to put into the things I want to put energy into (22).*

Participants went on to describe that these self- management skills gave them the ability to "start fresh and have a more positive attitude," comparing the program techniques to a

"booster shot" or a "stop gap" in their "circuit of anxious thoughts." One individual spoke of this shift in mindset in the following manner:

> *On the outside, I always project a positive attitude. But I do have an inside head voice that's constantly running a stream of negative thoughts. And [the PPP program] actually helped the inside voice (22).*

Another participant reflected on how adopting a more positive mindset impacted her personal and professional life:

> *The positive mindset has left me better prepared to be a positive force in the life of my family, my husband, my colleagues, my students. So, the benefits actually radiate out from me personally feeling better in my mind to how I impact other people around me (29).*

Adopting a positive mindset through the program impacted the way participants viewed themselves, with some participants sharing that "overcoming the limits" they had imposed on themselves, and feeling "proud and accomplished" was the most "profound" part of the program. Others acknowledged the mind-body effects of the program practices, noticing that they could use these techniques to "fall asleep with a clearer mind," which made them feel "more energized" and "like the world was brighter."

4.4.4.3 Theme #3: Acknowledging barriers and facilitators to program participation

While participants reflected that taking part in the program "made life considerably better," they also acknowledged some challenges to their participation, one of which was fatigue: "I thoroughly enjoyed [the PPP program]. It's just, you know, sometimes the body's unwilling to follow what you want it to do (10)." Participants shared that during times when their "energy wasn't as high" they found it "more difficult to participate" and "got out of the habit." Some

participants also spoke about “self-sabotaging thoughts” and “inner chatter” that made it difficult to participate in the programming. One participant described this in the following manner:

> *It’s a matter of giving myself a pass, which I don't want to do. It's that inner conflict, that inner turmoil that everyone experiences. It's always easier to do the fun, passive thing (29).*

While reflecting on these challenges, many participants spoke about things that helped them to maintain consistency, including the weekly phone check-ins with a program facilitator: “The weekly check-in made me accountable. And helped me track progress, because I would jot down a few notes before [program facilitator] called as a little recap of the week (16).” Participants also reflected on how connecting with study peers during the monthly group sessions made them feel supported:

> *It normalized my struggles and it was interesting to hear about other people's successes and where those commonalities are in the benefits . . . so the support of my peers participating in the study was really a huge part of the program (29).*

Others described that doing the program at the same time each day helped them to avoid the “psychological argument that causes self-sabotage.” One participant shared:

> *I used a discipline technique of choosing to do my yoga at the exact same time every day, and so I do it first thing in the morning. And then it's not in the back of my mind, my little self-argument of, "You don't have to do yoga today. Yes you do. No I don't." It's just automatic, so that helps to keep the routine (29).*

Many participants found that adopting a morning routine worked best, as they “ran out of steam” by the afternoon. Finally, participants described how the accessibility of the web-based intervention facilitated their participation. One participant reflected on the benefits of web-based

delivery: “I love the flexibility in the web based, because I can fit into my schedule, rather than me trying to fit into somebody else's schedule (14).” Others furthered this, reflecting that the program was “there waiting for them” and that they could “fit it in” wherever they had time.

Many participants felt that the routine they built during the study allowed them to continue with the program techniques after the study period. One participant reflected on the transition associated with continuing her practice after the study period:

> *Now I don't need you checking in with me, because I'm checking in with myself . . . I do my meditation every morning and if I'm starting to feel stressed, I'm thinking, just go back to that feeling you had this morning, take some breaths, close your eyes, do some deep breathing, and off I go and do whatever I need to do (14).*

Others described that while they had “good intentions” to continue with the program practices they “lost motivation” after the study ended. Participants suggested that being left with suggestions for “things to do in the future” may have helped them continue with the practices.

4.5 Discussion

The findings of this study indicate that the 12-week mind-body intervention was feasible and acceptable for people with PBC. Results also highlight that the online intervention may positively impact measures of wellbeing including anxiety, depression, fatigue, and quality of life. This was furthered by our qualitative findings, which found improvements to stress management and development of a more positive mindset. While mind-body interventions have been trialed in other chronic disease populations, this is the first study to assess the feasibility and acceptability of a mind-body intervention in people with PBC. The findings of this study provide lessons that can be grouped into two main categories.

4.5.1 Feasibility and acceptability of the web-based intervention

This study was associated with high adherence and retention rates. Given the high dropout rates and low adherence rates traditionally observed with web-based, health management interventions[120] such findings are encouraging. For instance, one study evaluating a 12-week, web-based health management program for people with anxiety disorders reported a retention rate of 1.0% at the end of the study period[121]. Another study evaluating engagement with 93 mental health apps reported a median 30-day retention rate of 3%[122]. End of study interviews highlighted various factors that may have contributed to the relatively high adherence and retention observed in this study. Similar to what has been identified in the literature[123,124] participants reported that taking part in weekly check-ins with a program administrator positively contributed to their adherence. Second, participants described that engaging in the optional monthly group sessions with study peers helped them to feel supported throughout the study. Though evidence on group sessions within web-based interventions is limited, a study by Ho et al evaluating a web-based intervention designed to target depression in adolescence reported a positive correlation between adherence, and engagement with study peers during the intervention period[125]. Third, participants were satisfied with the ease of navigating the intervention, and described that the online nature of the intervention allowed them to conveniently fit the program into their daily routine. In other studies, the use of a clear theoretical framework during the design of an intervention has been associated with increased adherence rates, and sustained changes to health-related behaviours[76,86]. We can hypothesize that this use of behavioural theory to inform the intervention contributed here as well. Finally, as demonstrated in other work, we speculate that the involvement of patient partners in the roll out of this intervention promoted usability,

acceptability and adherence[77]. Participants highlighted that incorporating different levels and styles of movement, and gamifying the weekly behaviour activities may further increase their satisfaction with, and adherence to the intervention.

4.5.2 Preliminary evidence for efficacy of the web-based intervention

Participants experienced improvements in measures of mental health, symptom burden, and quality of life. Significant improvements were observed in anxiety and depression, echoing studies of mind-body intervention in other chronic disease population[19,64]. These findings are particularly important, as mental health comorbidities such as anxiety and depression have been associated with increased mortality rates in people with chronic liver disease[25,46]. Participants also experienced significant improvements in fatigue, a symptom that has been estimated to affect up to 68% of patients with PBC[83]. This is notable, as fatigue has been recognized as the most limiting symptom of PBC by participants in our study, and in the literature[12,83]. End of study interviews suggest that improved stress management may have contributed to reductions in fatigue by enabling participants to conserve their limited energy. Similarly, a study of 117 patients with chronic fatigue syndrome found that patients with higher perceived stress management skills displayed less fatigue[126]. The changes to fatigue observed in our study are comparable to those observed in pharmacological studies in PBC[56,57]. Notably only the study by Khanna et al had a control group. This study observed improvements to fatigue in both the treatment and control arm with no significant difference between arms, highlighting the need for a future controlled mind-body interventional study[56]. Further to changes in mental wellness and fatigue, participants experienced significant improvement to HrQoL, indicated through the PBC-40 itch, fatigue, cognitive, emotional, and general symptom domains. Though significant changes in stress (PSS) and resilience (CD-RISC) were not observed from baseline to end of

study, interviews highlighted that taking part in the mind-body intervention increased participants' perceived ability to manage their stress, and adopt a more positive mindset.

Despite these positive findings, physical opportunity, reflective and automatic motivation, and psychological capability, assessed through the COM-B survey, significantly decreased throughout the course of the program. Notably, the majority of participants had not practiced yoga or meditation prior to beginning the intervention. We hypothesize that with the excitement and anticipation of a novel intervention, the decrease in the COM-B domains from baseline to study end was related to participants over-estimating their capability, opportunity and motivation at study baseline, instead of a true reduction in these parameters. A similar phenomenon was observed in a study by Spence et al. which reported that wearing a pedometer significantly reduced self-efficacy, and intention for future walking, again potentially related to participants becoming newly aware of barriers associated with what it meant to walk a given number of steps per day[127]. This decrease in COM-B, however, was reflected differently in our qualitative data which showed evidence of participants starting to rebuild capability, opportunity and motivation to achieve longer-term behavior change. For instance, they rebuilt their physical capability by prioritizing the program early in their day to ensure they had the energy to complete the program activities. Further, we saw evidence that participants were developing automatic motivation when some participants described building habits with the program techniques, and subconsciously returning to the program techniques during periods of stress. Other studies have similarly suggested that developing this automaticity fosters long-term behavior change[128].

4.5.3 Limitations

We acknowledge the following study limitations. First, 100% of the participants were female, making the results non-generalizable to male patients. This is not unexpected, as the female: male ratio of PBC patients has been estimated to be as high as 10:1[31], and other studies evaluating mind-body interventions have reported a higher prevalence of females as compared to males[129,130]. Second, adherence was self-reported at the end of study, which could potentially cause overestimation of adherence rates. Third, the purpose of this study was to assess feasibility and acceptability of an online intervention in PBC. It was not powered or designed to evaluate efficacy, which would require an adequately powered RCT.

4.5.4 Conclusions

To our knowledge, this is the first study to assess feasibility and acceptability of an online, multicomponent mind-body intervention in people with PBC. Our findings highlight the physical, mental, and emotional ramifications of PBC, and emphasize the value that individuals with PBC place on self-management tools. This study offers insight towards the feasibility and acceptability of delivering adjunctive wellness interventions to people with PBC, and provides an exploratory assessment of impact on efficacy. Recognizing the limitations of a single-arm study with a small sample size, these findings will be used to inform development of a future RCT.

CHAPTER 5: A RANDOMIZED CONTROL TRIAL EVALUATING THE IMPACT OF A WEB-BASED MIND-BODY WELLNESS INTERVENTION FOR PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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5.1 Abstract

Introduction: People with primary biliary cholangitis (PBC) experience high rates of mental distress, fatigue and impaired health related quality of life (HrQoL). Our previous pilot study of a novel online mind-body intervention in PBC demonstrated high feasibility and acceptability and promising exploratory efficacy. The current study aimed to assess the efficacy of the intervention.

Methods: This was a sequential mixed-methods randomized control trial (RCT). Participants were randomized to receive standard of care (SOC) or SOC alongside a 12-week online mind-body intervention involving mindful movement, breathwork, meditation, and supplementary content. The primary outcome was changes in the Hospital Anxiety and Depression Scale (HADS). Secondary outcomes evaluated fatigue, perceived stress, resilience and HrQoL. ANCOVA was used to determine between group differences. A qualitative descriptive approach with semi-structured interviews evaluated study experiences.

Results: Of the 123 patients screened, 87 were randomized (control group: n=44, intervention group: n=43). The between-group HADS total score improved by 20.0% (95% CI 4.7, 35.2, p=0.011) and the HADS depression score improved by 25.8% (95% CI 4.8, 46.8, , p=0.017). Significant improvements were seen in perceived stress (15.2%), and two PBC-40 domains (emotional symptoms (16.3%), and social symptoms (11.8%)) with a mean satisfaction of 82/100. While no significant improvements were observed in fatigue, interviews revealed improved coping with fatigue. Of the 36/43 participants who completed the intervention, 20 (56%) completed the program at least 3x per week.

Conclusion: This 12-week intervention improved measures of mental wellness and quality of life and demonstrated high satisfaction and reasonable adherence. Future studies could explore strategies to optimize adherence and target fatigue.

5.2 Introduction

Primary Biliary Cholangitis (PBC) is chronic autoimmune liver disease that affects primarily women[1,34,36]. North America has the highest prevalence of PBC in the world (21.8 per 100 000), and the incidence and prevalence rates of PBC in North America are rising[4]. PBC is initiated by immune-mediated damage to the small intrahepatic bile ducts[1,34,36]. This results in fibrosis that can progress to cirrhosis and end-stage liver disease[34]. Ursodeoxycholic acid (UDCA) is the first-line therapy for PBC and has been shown to improve transplant-free survival [1,131], but even with treatment it has been estimated that 30% of PBC cases progress to advanced liver disease, decompensated disease, or death[1]. Additionally, UDCA does not target the debilitating physical and emotional symptoms of PBC which include chronic fatigue, itch, impaired health-related quality of life (HRQoL)[12], and high rates of mental health comorbidities (anxiety, depression, and stress)[1,12,25]. The presence of these symptoms and mental health comorbidities predicts poor prognosis and increased mortality rates[25,46,132,133].

The need for self management tools to help people with PBC cope with their symptom burden has been identified by patients with PBC, and in the literature[25]. Mind body interventions (including movement, breathwork, meditation, and behaviour therapy) have been shown to improve fatigue, quality of life, and mental health in other chronic disease populations[16,18-20,64,134]. However, no randomized trials have observed whether these interventions impact mental health or symptoms in PBC. We previously conducted a pilot study of a novel online mind-body wellness intervention in PBC that demonstrated high feasibility and acceptability, as well as promising exploratory efficacy that could be further assessed in a randomized trial (Watt et al. submitted). Participants in the pilot study also highlighted areas for intervention refinement

including a revised chronic disease skills program, more options for mindful movement, and gamification elements including a leaderboard.

The purpose of the current study was to use an RCT design to assess the effects of a 12-week, online, mind-body intervention. The primary outcome was changes in the Hospital Anxiety and Depression Scale (HADS)[104]. Secondary outcomes evaluated fatigue, perceived stress, resilience, and HrQoL. We also assessed program outcomes, including adherence, retention, and acceptability. Recognizing the complexities of a mind-body intervention and the need to explore participants' experiences, an explanatory sequential mixed-methods design was employed[103]. We hypothesized that the program would positively affect the primary and secondary outcome measures as compared to the control group, and that the intervention would be associated with high adherence, retention, and acceptability.

5.3 Methods

5.3.1 Study Design

This was a two-arm, randomized controlled study. Ethics approval was received from the Health Research Ethics Board of Alberta on August 5th, 2021 (Pro00112622). The study was registered at www.clinicaltrials.gov. Informed written consent was obtained from each participant prior to enrollment.

5.3.2 Setting, Participants, and Randomisation Scheme

Participants were recruited between July 2021 and September 2021. A recruitment email was sent to all members of the Canadian PBC Society's email list. The email provided study contact information that participants could reach out to if interested. Inclusion criteria were: 1) age ≥ 18 years, and 2) a self-identified diagnosis of PBC. Exclusion criteria were: 1) a Hospital Anxiety and Depression Scale (HADS)[104] depression subcomponent score > 10 (at risk for

severe depression), and 2) inability to provide informed consent in English. Patients with (HADS) score > 10 were referred to resources for psychiatric follow-up. To increase generalizability of the results to the real-world, individuals were not excluded based on a history of co-existing physical or mental comorbidities apart from severe depression as detected by the HADS. Individuals who met eligibility criteria were invited to complete baseline assessments. Upon completing baseline assessments, participants were randomly assigned to the intervention or control group using a 1:1 ratio. REDcap was used for randomization. Control group participants were given the option to take part in the intervention after their 12-week control period.

5.3.3 Study Arms

5.3.3.1 Control arm

During the 12-week study period, participants assigned to the control arm continued to receive standard of care (SOC) treatment for their PBC from their treating hepatologist. They also received weekly emails containing a countdown to the end of their control period.

5.3.3.2 Intervention arm

Participants in the intervention arm received access to the 12-week mind-body intervention in addition to SOC. The intervention consisted of three components:

1. Core program video. Each week of the program included a core program video consisting of guided meditation, breathwork practices, and mindful movement (choice between yoga, tai chi, or chair movement). Participants were encouraged to complete the core program a minimum of three times per week.
2. Supplementary content. Each week also contained supplementary content as prioritized by patients. This included: 1) a 3–5-minute chronic disease skills video and activity

informed by acceptance and commitment therapy (ACT), and 2) a 3-5 minute "PBC tip" video from a PBC physician.

3. Weekly check-ins. Participants received weekly, 10-minute phone calls from a program facilitator. The purpose of these calls was to answer questions, review progress, and facilitate goal setting.

Participants were also invited to attend optional monthly group zoom sessions, hosted by the Canadian PBC Society.

5.3.4 Data Collection and Outcome Measures

5.3.4.1 Quantitative Data Collection

At study baseline, we collected participant demographic information including age, sex, relationship status, employment status, education, years since diagnosis, cirrhosis status, current PBC medications, and previous exposure to meditation, yoga, and tai chi.

We evaluated primary and secondary outcome measures at study baseline, and immediately after the 12-week study period. Our primary outcome was changes in the Hospital Anxiety and Depression Scale (HADS). The HADS is a 14-item scale used to detect the possible presence of anxiety and depression. The HADS differentiates anxiety symptoms from depressive symptoms and provides severity scores in each dimension in addition to an overall score[104]. Our secondary outcome measures were changes in the: Perceived Stress Scale (PSS-10) - a 10 item scale to assess the degree to which life has been experienced as unpredictable, uncontrollable, and overloaded[108]; Connor Davidson Resilience Scale (CD-RISC) - a 25 item scale to assess resilience[111]; Modified Fatigue Impact Scale (MFIS) - a 21 item scale to assess the extent to which fatigue has impacted life[109]; and PBC-40 - a 40 item disease HRQoL scale[110].

Adherence was assessed using a survey at end of program and confirmed through weekly check ins. To help understand adherence, we also assessed participants perceived capability, opportunity, and motivation to take part in the core programming at least three times per week at study baseline, and immediately after the 12-week study period (**Appendix C**) (adapted from Keyworth et al.)[110]. Satisfaction was assessed through a survey at the end of the study period. Participants were sent follow up surveys eight weeks after completing the intervention to assess continued engagement with the program practices.

5.3.4.2 Qualitative Data Collection

All participants were invited to engage in the qualitative portion of the study and 25 consented to an interview. Purposive sampling methods[31] were used to ensure diversity in adherence to and satisfaction with the programming. Semi-structured interviews were conducted using a qualitative descriptive approach[113] with 11 participants. Interviews were conducted via telephone by MW and EJ from February-March 2022 and lasted an average of 50 minutes. The interview guide was informed by the capability, opportunity, motivation model of behavior (COM-B)[88] and sought to explore participant experiences with the program and perceptions of novel program components including the chronic disease skills program and gamification **(Appendix F)**. All interviews were recorded and transcribed verbatim. Field notes were recorded after each interview to detail the interviewer's preliminary impressions.

5.3.5 Data Analysis

5.3.5.1 Sample Size and Statistical Analysis

The sample size calculation was based on the primary outcome, anxiety and depression (HADS total score). With a 0.05 alpha and 80% power, and accounting for a 15% dropout rate, 40 participants per group (80 participants in total) were deemed adequate to show a statistically

significant difference by independent t-test (d = 0.71 effect size). This potential effect was estimated from a previous RCT in individuals with inflammatory bowel disease where the mean (SD) of change in the HADS score for the intervention group was -7(7), and the mean change in the control group was 0.3, and from the previous pilot study in individuals with PBC where the mean (SD) of change in the HADS score was -4(7). Recognizing that revisions were being made to the intervention in an attempt to enhance its impact, I used a mean of change in the intervention group of -5.5 (7), a value in between the -4 and the -7 seen in each study's intervention group. Based on the study in inflammatory bowel disease, I conservatively used a mean change in the control group of -0.5.

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 21.0[117]. Demographics, feasibility, and acceptability measures are presented using descriptive statistics (mean ± SD for continuous variables, frequency [%] for nominal variables). The normality of all primary and secondary outcomes was examined using histograms and Q-Q plots. ANCOVA was used to analyze the impact of the intervention on the HADS after testing the assumptions that there were no differences in baseline HADS total values between groups and that the impact of the intervention did not differ depending on the baseline value. The absolute impact of the intervention was derived from a linear regression model predicting change in HADS adjusted for baseline HADS. The relative impact of the intervention was defined as the percentage change in the HADS total score at the end of the study compared to baseline. The same ANCOVA procedures were also used to test the secondary outcomes. Within group differences were also analyzed using paired-sample t-tests. Statistical significance was established at a 2-tailed p-value of <0.05. The intention-to-treat analyses (ITT) imputed missing values with the last observation carried forward method.

5.3.5.2 Qualitative Data Analysis

Data collection and analysis occurred iteratively to enable refinement of our interview guide and exploration of emerging themes. Interviews were analyzed using a theoretical thematic approach, whereby data were analyzed inductively, with transcripts coded, then grouped into larger categories, then themes[118,119]. Analysis was completed by two members of the study team (MW, AH) who developed a coding framework, with disagreements resolved through consensus. NVivo was used for data management[135].

5.4 Results

A total of 123 patients were screened for the study, 18 declined to participate and 14 were excluded. 87 patients were randomized to the intervention (n=43) and the control (n=44) group. After the 12-week intervention, the overall retention was 89.7% (n=6 unable to begin the intervention during the specified period, n=1 lost due to follow up in the intervention arm, n=2 lost due to follow up in the control arm) with 78 patients remaining at the end-of-study (**Figure 5**).

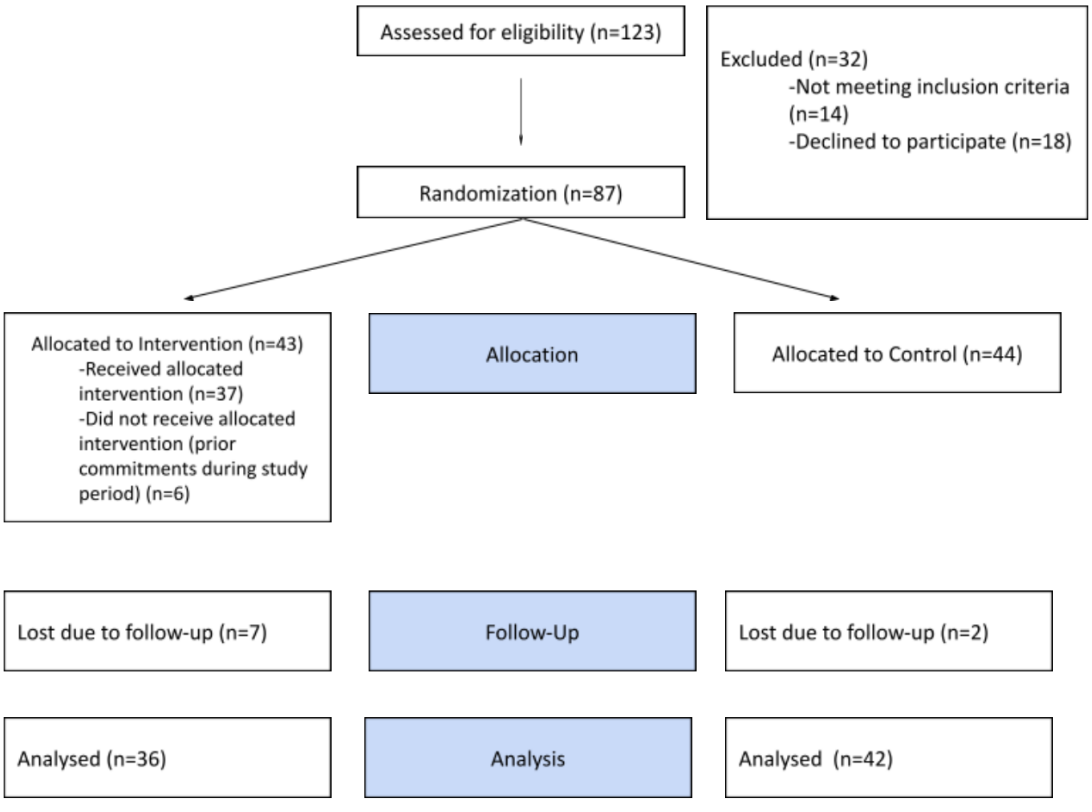

Figure 5. Patient recruitment and flow through the study

5.4.1 Patient Baseline Characteristics

The mean age of participants was 59.8 ± 10.6 years and 98% were female**.** The intervention group had a greater proportion of patients who were not on any medication for PBC (4 (9.3%) vs. 0), p=0.038). Further demographic characteristics are reported in **Table 4.**

Table 4. Patient Baseline Characteristics

	Total (n=87)	**Control Group (n=44)**	**Intervention Group (n=43)**	**P-Value**
Age (years)	59.8 ± 10.6	59.4 ± 9.9	60.2 ± 11.4	0.72
Sex				0.99
Male	2 (2.3%)	1 (2.3%)	1 (2.3%)	
Female	85 (97.7%)	43 (97.7%)	42 (97.7%)	
Other	0 (0%)	0 (0%)	0 (0%)	
Relationship status				0.46
Married	55 (63.2%)	30 (68.2%)	25 (58.1%)	
Living common-law	7 (8.0%)	3 (6.8%)	4 (9.3%)	
Divorced/Separated	14 (16.1%)	6 (13.6%)	8 (18.6%)	
Widowed	4 (4.6%)	2 (4.5%)	2 (4.7%)	
Single/Never Married	5 (5.7%)	1 (2.3%)	4 (9.3%)	
Prefer not to answer	2 (2.3%)	2 (4.5%)	0 (0%)	

Employment status				0.35
Employed	40 (46.0%)	19 (43.2%)	21 (48.8%)	
Unemployed	34 (39.1%)	16 (36.4%)	18 (41.9%)	
Prefer not to answer	13 (14.9%)	9 (20.5%)	4 (9.3%)	
Highest Education Achieved				0.19
No post-secondary degree, certificate, or diploma	21 (24.1%)	12 (27.3%)	9 (20.9%)	
Trade certificate or diploma from a vocational school of apprenticeship training	4 (4.6%)	3 (6.8%)	1 (2.3%)	
Non-university certificate or diploma from a community college, CEGEP, school of nursing, ect.	22 (25.3%)	15 (34.1%)	7 (16.3%)	
University certificate below bachelor's level	3 (3.4%)	1 (2.3%)	2 (4.7%)	
Bachelor's degree	16 (18.4%)	7 (15.9%)	9 (20.9%)	
University degree or certificate above bachelor's degree	18 (20.7%)	5 (11.0%)	13 (30.2%)	
Unknown	3 (3.4%)	1 (2.3%)	2 (4.7%)	
Years since diagnosis	9.63 ± 8.36	9.70 ± 7.93	9.56 ± 8.88	0.94
Cirrhosis Status				0.67
No cirrhosis	50 (57.5%)	26 (59.1%)	24 (55.8%)	
Cirrhosis	20 (23.0%)	11 (25.0%)	9 (20.9%)	

Unsure	17 (19.5%)	7 (15.9%)	10 (23.3%)	
Current PBC Medications				
None	4 (4.6%)	0 (0%)	4 (9.3%)	**0.04***
UDCA	75 (86.2%)	38 (86.4%)	37 (86.0%)	0.97
Obeticholic acid	15 (17.2%)	11 (25.0%)	4 (9.3%)	0.05
Fenofibrate	3 (3.4%)	2 (4.5%)	1 (2.3%)	0.57
Bezafibrate	6 (6.9%)	3 (6.8%)	3 (7.0%)	0.98
Colchicine	0 (0%)	0 (0%)	0 (0%)	
Other	12 (13.8%)	9 (20.5%)	3 (7.0%)	0.07
Meditation in past 6 months				0.44
Yes	36 (41.4%)	20 (45.5%)	16 (37.2%)	
Yoga in past 6 months				0.44
Yes	36 (41.4%)	20 (45.5%)	16 (37.2%)	
Tai Chi in past 6 months				0.25
Yes	7 (8.0%)	5 (11.4%)	2 (4.7%)	

Abbreviations: CEGEP –Collège d'enseignement général et professionnel; PBC –primary biliary cholangitis; UDCA – ursodeoxycholic acid

5.4.2 Primary Outcomes

After adjusting for HADS total at baseline, there was a significant change in the HADS total and HADS depression scores between baseline and end of study in the intervention arm compared to the control arm. This translated to an absolute improvement of 2.66 (95% CI, 0.628-4.69) and a relative improvement of 20.0% (4.72, 35.2), p= 0.011 for the HADS total score, and an absolute improvement of 1.44 (95% CI, 0.266-2.61) and a relative improvement of 25.8% (95% CI, 4.77-46.8), p= 0.017 for the HADS depression score. No significant differences existed between study groups in HADS anxiety **(Table 5)**.

Table 5. Anxiety, depression, stress, resilience, fatigue, quality of life, and behavioural outcomes

	Control group (n=44)			**Intervention group (n=43)**			**Between group absolute improvement (95% CI)**	**Between group relative improvement (95% CI)**	**ANCOVA p value Between groups**
	Baseline	**End of study**	**Within group p-value**	**Baseline**	**End of study**	**Within group p-value**			
HADS Total	11.6 ± 5.30	13.0 ± 5.56	0.073	12.7 ± 5.67	11.0 ± 5.79	**0.044***	2.66 (0.628, 4.69)	20.0 (4.72, 35.2)	**0.01***
HADS anxiety	6.89 ± 3.42	7.59 ± 3.37	0.193	7.37 ± 3.63	6.60 ± 3.61	0.144	1.30 (-0.045, 2.65)	16.8 (-0.581, 34.2)	0.06
HADS depression	4.73 ± 2.80	5.41 ± 2.88	**0.047***	5.28 ± 3.07	4.30 ± 3.46	**0.026***	1.44 (0.266, 2.61)	25.8 (4.77, 46.8)	**0.02***
Connor-Davidson Resilience Scale	26.1 ± 6.27	26.2 ± 5.63	0.974	27.7 ± 6.55	28.3 ± 6.62	0.401	2.54 (-0.016, 5.09)	9.78 (-0.062, 19.6)	0.05

PSS	17.7 ± 6.54	17.9 ± 6.52	0.845	17.5 ± 6.12	15.7 ± 6.13	**0.038***	2.76 (0.231, 5.28)	15.2 (1.28, 29.2)	**0.03***
MFIS Total	59.0 ± 16.3	59.8 ± 15.5	0.472	59.1 ± 15.9	56.4 ± 16.5	0.059	5.07 (-0.908, 11.0)	8.37 (-1.50, 18.2)	0.10
MFIS Physical	27.4 ± 8.42	27.7 ± 7.64	0.691	27.4 ± 7.92	25.7 ± 7.45	**0.047***	2.63 (-0.348, 5.60)	9.40 (-1.24, 20.0)	0.08
MFIS Cognitive	26.1 ± 8.28	26.4 ± 8.46	0.668	26.4 ± 7.88	25.4 ± 8.35	0.141	1.85 (-1.362, 5.06)	6.91 (-5.09, 18.9)	0.26
MFIS Psychosocial	5.43 ± 1.93	5.73 ± 1.87	0.204	5.33 ± 2.02	5.30 ± 2.27	0.936	0.595 (-0.222, 1.41)	10.2 (-3.82, 24.3)	0.15
PBC-40 Itch	4.36 ± 3.16	4.55 ± 3.00	0.613	3.84 ± 3.15	3.40 ± 2.66	0.207	1.11 (-0.121, 2.35)	23.6 (-2.57, 50.0)	0.08
PBC-40 Fatigue	31.1 ± 8.63	31.1 ± 8.78	0.886	31.8 ± 9.13	30.4 ± 9.03	0.095	1.38 (-2.25, 5.01	4.39 (-7.16, 15.9)	0.45
PBC-40 Cognitive	14.5 ± 4.85	14.4 ± 5.04	0.779	14.8 ± 5.56	13.7 ± 5.81	**0.011***	1.14 (-1.11, 3.40)	7.86 (-7.66, 23.4)	0.32
PBC-40 Emotional	8.16 ± 2.32	8.25 ± 2.63	0.750	8.09 ± 2.72	7.19 ± 2.72	**0.006***	1.36 (0.306, 2.42)	16.3 (3.66, 29.0)	**0.01***
PBC-40 Social	25.8 ± 7.09	25.7 ± 7.47	0.990	24.9 ± 8.98	23.2 ± 8.34	**0.016***	3.08 (0.045, 6.17)	11.8 (0.173, 23.7)	**0.05***
PBC-40 Symptom	16.6 ± 4.17	16.7 ± 4.66	0.834	16.4 ± 4.01	15.9 ± 4.66	0.185	1.10 (-0.854, 3.05)	6.55 (-5.08, 18.2)	0.27
COM-B Physical Opportunity	8.59 ± 1.48	8.59 ± 1.45	1.000	8.45 ± 1.63	7.38 ± 2.08	**0.002***	1.24 (0.470, 2.01)	14.5 (5.48, 23.4)	**0.002***

COM-B Social Opportunity	8.05 ± 2.34	8.20 ± 2.11	0.643	7.62 ± 2.80	6.93 ± 2.74	0.156	1.25 (0.220, 2.29)	15.3 (2.70, 28.1)	**0.02***
COM-B Reflective Motivation	9.18 ± 1.15	9.02 ± 1.27	0.368	9.36 ± 0.958	8.38 ± 1.83	**<0.001***	0.676 (-0.008, 1.36)	7.49 (-0.089, 15.1)	0.05
COM-B Automatic Motivation	7.61 ± 2.15	7.68 ± 1.97	0.760	7.12 ± 2.51	5.62 ± 2.76	**<0.001***	2.03 (1.06, 3.00)	26.7 (13.9, 39.4)	**<0.001***
COM-B Physical Capability	8.34 ± 1.68	8.30 ± 1.61	0.839	8.19 ± 1.92	7.05 ± 2.53	**0.003***	1.26 (0.357, 2.16)	15.3 (4.34, 26.3)	**0.007***
COM-B Psychological Capability	8.68 ± 1.44	8.77 ± 1.31	0.643	8.83 ± 7.55	1.51 ± 2.52	**0.002***	1.23 (0.370, 2.08)	14.1 (4.23, 23.8)	**<0.001***

Abbreviations: HADS – Hospital anxiety and depression scale; PSS – Perceived stress scale; MFIS – modified fatigue impact scale; COM-B-capability, opportunity, motivation model of behaviour

5.4.3 Secondary Outcomes

Data on secondary outcomes are presented in **Table 5**. There was a significant absolute improvement in the PSS (2.76; 95% CI: 0.231-5.28, p = 0.033), PBC-40 emotional domain (1.36; 95% CI: 0.306-2.42, p = 0.012), and PBC-40 social domain (3.08; 95% CI: 0.045-6.17, p = 0.047). Relative scores are presented in **Table 5**. No significant differences existed between study groups in CD-RISC, MFIS, PBC-40 itch, fatigue, cognitive, or general symptom domain **(Table 5).**

5.4.4 Program Outcomes

5.4.4.1 Adherence

Of the 36 participants who completed the intervention, 20 (56%) achieved the pre-specified adherence goal of completing the core programming at least three times per week (3-3.5 times per week n=10, 4-4.5 times per week n=3, 5-5.5 times per week n=2, 6-6.5 times per week n=3, 7 times per week n=2). The remaining 16 (44.4%) of participants were classified as non adherers (>1 time per week n=3, 1-1.5 times per week n=7, 2-2.5 times per week n=6). All patients who completed the core programming at least once per week also reported watching the supplementary program content.

There was a significant absolute decrease in COM-B domains, including physical opportunity (1.24; 95% CI: 0.470-2.01), social opportunity (1.25; 95% CI: 0.220-2.29), automatic motivation (2.03; 95% CI: 1.06-3.00), physical capability (1.26; 95% CI: 0.356-2.16), and psychological capability (1.23; 95% CI: 0.370-2.08) **(Table 5).**

5.4.4.2 Satisfaction

Rated from 0 to 100 ("Not Satisfied" to "Extremely Satisfied"), the mean satisfaction score was 81.5% (standard deviation 15.7%). Participant satisfaction with different elements of the programming is illustrated in **Figure 6**. Thirty-three (91.7%) of participants ranked the amount of information as just right, with 2 (5.6%) indicating too little information, and 1 (2.8%) indicating too much information. Twenty-eight (77.8%) of participants ranked the time commitment of 3 times per week for the programming as just right, with 0 (0%) indicating the time commitment was too little, and 8 (22.2%) indicating the time commitment was too much.

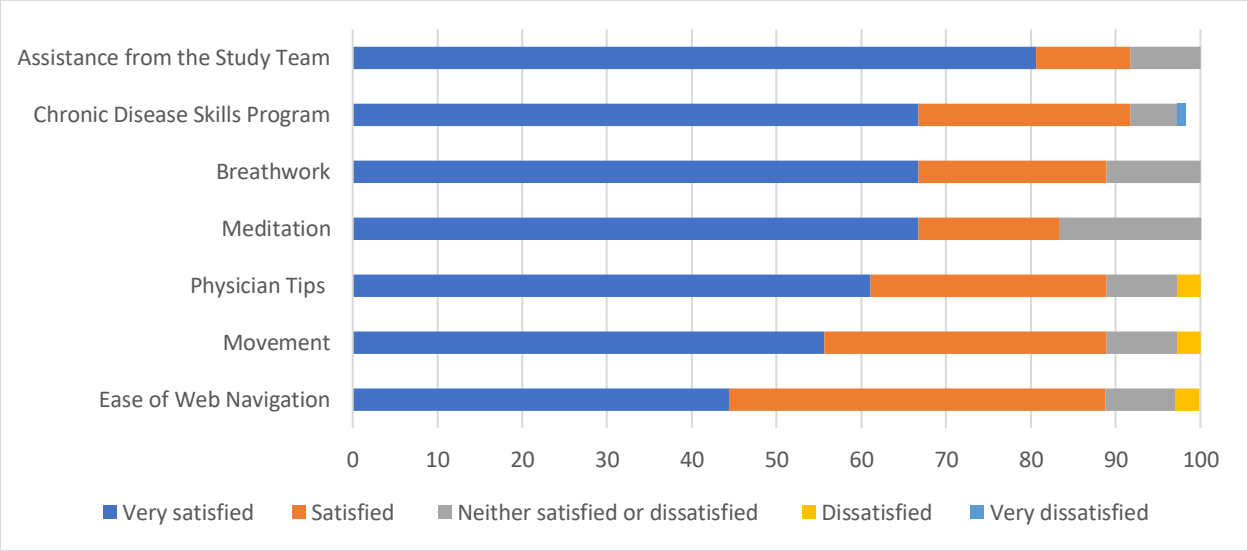

Figure 6. Participant satisfaction with core and optional elements of the Peace Power Pack program, scored using a 5-Point Likert Scale from Very Satisfied to Very Dissatisfied

5.4.4.3 Continuation

After completing the 12-week intervention, participants' mean perceived likelihood of continuing any element of the program (Rated from 0 "Not Likely" to 100 "Extremely likely") was 82.1% with a standard deviation of 16.4. Eight week follow up data was available for 24/36 of the participants who completed the intervention period. Of these 24 participants, 15 (62.5%) indicated that they had accessed techniques from the program in the 8 weeks after completing the programming.

5.4.5 Qualitative Findings

Eleven individuals participated in the end-of-study qualitative interviews. They ranged in age from 32 to 82 years (61.1 ± 13.0 years), and 91% were female. These baseline characteristics were similar to participants in the main study, and are reported in full in **Appendix G**. We identified three main themes: (i) Understanding the impact of program components on disease

management (ii) Mixed reception: exploring experiences with gamification, and (iii) Bridging the transition: long-term adoption of program practices.

5.4.5.1 Theme # 1: Understanding the impact of program components on disease management

Participants experienced fatigue that limited their ability to work, interact with family, and perform day to day tasks. Many highlighted the unpredictable nature of this fatigue: “It's kind of like from Forrest Gump, life is like a box of chocolates. I never know what my energy is going to be like when I wake up” (57). Some participants recognized that they tended to “overdo it on good days” which resulted in them “crashing and needing days to recover.” Participants went on to describe how learning about pacing their activity through the chronic disease skills program helped them to combat this “boom and bust cycle.” One participant spoke about this in the following manner: “We learned about holding yourself back and just doing the same amount of stuff on days where you feel normal. And that was quite a profound thing to learn about (135).” Participants clarified that while the “fatigue was still there” pacing allowed them to “manage energy better.” One participant described how this allowed her to spend energy on things that were important to her:

> *I'm saying no to some things. And just using the energy that I do have in a better way on the things that bring me joy. I guess that’s how it should be instead of always feeling like you’re the one who has to step up (135).*

Participants also spoke of the “underlying stress and anxiety” that came from wondering if their disease would progress which they felt was “every bit as debilitating if not more than the disease itself” (57). One participant said the following of how the breathwork techniques she learned in the program helped her to cope during stressful times:

I sometimes even just do the breathwork if I feel myself getting stressed during the day. The stuff heard on social media is just crazy and the news is horrible right now and sometimes I just unconsciously find myself just doing a little bit of breathwork to escape (42).

Others furthered this, speaking about how the program techniques allowed them to relax when their "mind is racing" and "approach the day differently."

5.4.5.2 Theme # 2: Mixed reception: exploring experiences with gamification

Some participants chose not to participate in the leaderboard, expressing that competing with others felt like "the wrong way to go into wellness," and that they were instead motivated by their "commitment to the program" and "curiosity about how it would feel to do the practices." For others, participating in the leaderboard offered a way to receive "acknowledgement for putting in the effort" while connecting and competing with their study peers.

After gaining experience with the leaderboard, some felt that their "competitive nature responded well," describing that seeing others who were "way ahead" motivated them to participate more. One participant reflected on this in the following manner:

The leaderboard obviously motivated me. Ironically, when I first started [facilitators] were telling me about the leaderboard and I thought: 'I probably won't use it because I motivate myself.' But I was watching people accumulate points and I thought: 'I want them. I want those points' (111).

One the other hand, many participants felt that the leaderboard "stopped being motivating" as they "fell behind." One participant described this saying:

I thought at the beginning the leaderboard would be fun. After about the first week or two I said: 'This feels like a competition where you can never catch up.' If you missed a few days, and somebody else is way ahead, it's sort of like, why am I doing this?' (196).

Participants also spoke about exchanging automated "kudos" messages with their study peers, with many describing that these messages didn't feel connected. One participant elaborated on this:

There was a thing on the dashboard where people were supposed to give you a thumbs up and I received a number of them. It didn't seem connected to anything . . . it's like why are these people giving me a thumbs up? There's no discussion. And I didn't give any thumbs up. Not because I'm not a supportive person, because it didn't seem connected (196).

Participants suggested that having the ability to write personalized comments to their study peers may have helped create a "more in-depth connection" while allowing them to "offer more encouragement".

5.4.5.3 Theme # 3: Bridging the transition: long-term adoption of program practices

While reflecting on their use of the program practices after the study period, a few participants shared that they return to the practices as an "automatic response" when "things get tough." One participant said the following of this automaticity:

I went through a very stressful moment in my workplace and the first thing that went through my mind was: ' I will run to my car and start that meditation.' The fact that I think about it in the same exact moment . . . that almost automatic reflection was a very big thing for me (61).

Another participant furthered this, describing that experiencing positive changes as a result of the practices made it natural to continue after the study period: " I noticed a difference in myself. The breathing helps relax me when my mind's racing, and the exercise helps my body feel better. So why wouldn't I keep doing it?" (135). Others described that while the practices were "not a habit quite yet," they had used strategies including signing up for fitness classes, returning to the program website, and tracking their activity to help them "keep up the momentum" after the study.

Contrastingly, the majority of participants shared that despite having the intention to "maintain the benefits of the program," they hadn't stayed consistent after the study period. Some spoke about the "hard adjustment" of losing the "input and support" that was available during the program:

> *The program was like a class. You're fully engaged and fully immersed and then your class is over and it's like, boom, done. There was no more information from the tips and videos and there was no more involvement from the team (103).*

Others described how they "got off track" and found it "hard to get back in it" after the program ended. One participant said the following of how finishing the program around Christmas disrupted her routine:

> *I found the structure of the program helpful because I thought: 'I'm going to continue, this is something so great I'm going to continue with every day.' And then Christmas happened, and then the cold weather happened and I have to confess I'm not doing it every day (45).*

Many participants expressed feeling "disappointed" and "confused" that they had not continued with the practices, and suggested that being matched with a study peer who could "share

feedback about working around obstacles" and serve as a "link between the program and the post-program" may facilitate continuation.

5.5 Discussion

This is the first RCT to evaluate the impact of a multi-component mind-body wellness intervention in individuals with PBC. Statistically significant between group differences were seen in the primary outcome of depression (HADS total and depression domains), and the secondary outcomes of stress (PSS), and quality of life (PBC-40 emotional symptoms and social symptoms domains). Although no significant improvements were observed in fatigue, interviews revealed improved ability to cope with fatigue through pacing. Of the 78 participants who completed the intervention, 20 (55.6%) adhered to the program goal of completing the program at least 3x per week. Participants reflected on how tracking could be used to increase their adherence, and highlighted enhanced group support as a way to increase engagement with the practices both during and after the intervention period. The findings of this study provide lessons that can be grouped into three main categories.

5.5.1 Impact on Mental Health and Quality of Life

Participants experienced statistically significant improvements in measures of mental health and quality of life. Clinical significance of changes in mental health can be understood through the HADS total, with past literature identifying a change of 1.5-2 as a clinically important difference[136,137]. Our study was in range of clinical significance, demonstrating an absolute improvement in the HADS total of 2.66. In the qualitative portion, participants described these improvements in mental health, speaking about how the program gave them tools to cope with their disease and manage day to day stressors. This echoed findings from our pilot study (Watt et al. submitted). Given the abundance of research demonstrating positive impacts of

mind-body practices on mental health and HrQoL in other chronic disease populations[64,134,138,139], past literature has acknowledged the potential of these practices in PBC[25,140]. Our study adds to the existing literature as the first RCT in PBC to assess mind-body practices as a way to help patients manage mental health comorbidities and improve quality of life and one of the few studies to use mixed methodology. Participants in our study highlighted the importance of articulating their experience through qualitative interviews, expressing that the pre-post surveys did not allow them to comprehensively express the impacts that the mind-body intervention had on their day to day lives.

5.5.2 Lack of Impact on Fatigue

Despite the significant impact on mental health and HRQoL measures, there was no impact on fatigue, a symptom that has been highlighted as a research priority by patients with PBC[56]. This echoes findings of pharmacological studies in PBC, which have not shown significant improvements in fatigue in patients taking medications (rituximab or fluvoxamine) as compared to control[55,56]. Interestingly, randomized controlled studies in people with cancer related fatigue and chronic fatigue syndrome have reported significant improvements in fatigue after participation in exercise, yoga, and qigong[16,66,141]. The absence of an effect in our study may be attributable to the relatively low dose of the mindful-movement intervention (45 minutes per week). Notably, in the qualitative portion of our study, participants highlighted that while they still experienced fatigue, learning to pace through the 12-week program improved their fatigue management. Adaptive pacing therapy has been used in a variety of other chronic disease populations to help patients avoid fatigue and achieve prioritized activities[142]. Patients have reported positive perceptions of pacing therapy, with individuals with chronic fatigue syndrome ranking pacing as the most helpful symptom management tool on a 2008 national survey[142].

5.5.3 Engagement with the Practices During and After the Intervention

Our study demonstrated relatively high adherence, with other studies that have assessed online mind-body interventions for patients with chronic liver disease reporting adherence ranging from 14-55%[143,144]. This is notable, as low adherence has been widely recognised as a challenge to delivering wellness interventions on web-based platforms[120]. One way that past studies have attempted to increase engagement with online wellness interventions is through implementing behaviour change techniques (BCTs), which are active components of an intervention[91,145]. These techniques may include providing feedback on behaviour, providing rewards, and social comparison[91], all of which can be implemented through gamified program elements such as leaderboards, points, and badges[145]. Past literature has echoed the results of our study, reporting varying perceptions of gamification in wellness interventions[146,147]. A qualitative study of gamification reported that older adults did not see value in points, badges, and leaderboards, and were instead motivated by connecting and collaborating with others[146]. Participants in our study also suggested that connecting with study peers online could help them to encourage and motivate each other. Despite the high adherence observed in this study, there were significant between group reductions in aspects of capability, opportunity, and motivation in the COM-B survey, echoing findings from our pilot study (Watt et al. submitted). We hypothesize that as observed in past studies[127], this decrease in the COM-B domains was a result of participants over-estimating their capability, opportunity and motivation for engaging in relatively novel behaviours at study baseline, and then encountering unanticipated barriers to participation. Based on our interview data, we speculate that administering the COM-B survey after participants had become familiar with the intervention may allow for a more realistic baseline assessment of capability, opportunity and motivation. Future studies could focus on

additional support for participants to rebuild capability, opportunity, and motivation after initial exposure to novel programming.

Our study also offers important insights about continued engagement with wellness practices after an intervention period, which is of interest given that changes in behaviour during an intervention period often do not translate to long-term behaviour change[148]. Qualitative data from our study highlighted habit formation as a factor that promoted continuation, adding to the existing literature that outlines habit formation as an important goal of behaviour change[128,149,150]. Participants in our study also highlighted continued group support as a way to facilitate long-term adoption of practices. This is valuable, as intervention strategies that facilitate long-term behaviour change are poorly understood[148].

5.5.4 Limitations

We acknowledge the following limitations to our study. First, 98% of the participants in our study were female, making our results less generalizable to male patients. This is not unexpected, given that the female: male ratio of PBC patients has been estimated to be as high as 10:1[31], and other studies evaluating mind-body interventions have reported a higher prevalence of females as compared to males[129,130]. Second, six of the patients who were randomized to the intervention arm dropped out before the study period due to prior commitments. This represented a considerable proportion of patients who were counted as having no change using an intention to treat design causing potential underestimation of the intervention effects. Third, eight-week follow up data was only available in 67% of participants who completed the intervention, potentially contributing to an overestimation of percentage of participants who continued with the practices after the study period.

5.5.6 Conclusions

To our knowledge, this is the first RCT to evaluate the impact of a multicomponent mind-body intervention in people with PBC. Our findings offer insight towards the efficacy of adjunctive mind-body interventions to help people with PBC manage their mental health, quality of life, and symptom burden. Future studies could explore strategies to optimize adherence including group support and making gamification more appealing, and could increase the physical activity intervention, which may result in a greater impact on fatigue.

CHAPTER 6: DISCUSSION

Chapter three of this thesis includes a formative study summarizing the development of a 12-week mind-body wellness intervention for people with PBC. Chapter four discusses a single arm pilot study which demonstrated that the intervention was feasible and acceptable to people with PBC. Finally, chapter five describes an RCT that found positive impact on measures of mental health and quality of life, with no impact on fatigue. To our knowledge, this thesis contains the first studies describing the development, feasibility and acceptability, and efficacy of a multicomponent mind-body intervention for people with PBC. Important learnings from this thesis include: (1) feasibility and acceptability (2) impact on mental health and symptom burden, and (3) sustainability.

6.1 Feasibility and acceptability

In chapter 4, the primary outcome measures of feasibility (assessed through adherence, retention, and recruitment) and acceptability were achieved. Relatively high adherence, retention, and satisfaction rates were also observed in chapter 5. This is an important finding, because web-based health management interventions are typically associated with high dropout and low adherence rates[120]. A few factors contributed to the high feasibility and acceptability of this mind-body intervention.

First, we hypothesize that inclusion of the patient voice promoted acceptability and therefore uptake of the intervention. Past literature has acknowledged that involving end-users improves success of web-based health interventions[77,151,152], with de Beurs et al. suggesting that end-user involvement should be the standard in web-based health interventions[77]. This thesis involved end users through engaging patient partners, and gathering feedback through qualitative interviews. The engagement of patient partners began early, when patient representatives from

the Canadian PBC Society expressed a need for programming to help people with PBC manage their mental health and symptoms. Two patient representatives from the Canadian PBC Society were then actively involved in developing the 12-week mind-body intervention. As reported in other studies, this allowed the intervention to appropriately reflect the unique needs of the target patient population[152]. An example of this is that patient partners advocated for supplementary content, including tips and information from PBC physicians, and positive psychology tips. Patient partners were also actively involved in implementation of the intervention by sending recruitment advertisements to their members, and providing feedback on the assessment instruments. End -user involvement was furthered by conducting interviews with participants in the pilot study (chapter 4) to help guide iterative refinement of the intervention. In these interviews participants highlighted areas for intervention refinement including a revised chronic disease skills program, more options for mindful movement, and gamification elements including a leaderboard. While participants in the RCT (chapter 5) had mixed experiences with the leaderboard, they described the chronic disease skills program and the variation in mindful movement as elements that enhanced their participation and enjoyment of the program. This supports past literature which has highlighted that engaging end-users in qualitative research can lead to effective interventions that are sensitive to the unique needs of participants[79].

Second, we hypothesize that, as observed in past studies[76,86,87], using a theoretical framework to develop the intervention led to increased adherence. When developing the intervention, we selected standardized BCTs from the behavior change technique taxonomy (v1)[91]. For example, during the weekly phone calls with a program facilitator (implemented in chapters 4 and 5) we used the behavior change techniques: review behavior goal(s), and social support (unspecified). In chapter 5, we also used gamification (i.e., points, badges, leaderboard)

to incorporate the BCTs: feedback on behavior, rewards (unspecified), and social comparison. The qualitative components of chapter 4 and 5 helped us to understand how these BCTs may have impacted adherence. Specifically, participants highlighted that the weekly check-ins prompted them to reflect on their participation, and helped them to feel supported, which in turn enhanced their participation. Other studies have similarly highlighted that telephone check-ins increase adherence to web-based programming[123,124]. Interestingly, perceptions of how gamification impacted engagement with the practices were mixed. Past literature builds on this, suggesting that older adults may find social connections more motivating than earning points and competing on a leaderboard[145].

Incorporating behavior change theory into the quantitative and qualitative assessment in chapters 4 and 5 helped further our understanding of adherence. While other studies have used the COM-B model to inform their assessment framework[112,153], these are the first known studies to include qualitative and quantitative assessment of COM-B domains. In chapter 4, pre-post assessment of participants' perceived capability, opportunity, and motivation to take part in the intervention showed that elements of capability, opportunity, and motivation significantly decreased during the 12-week study period. We speculate that, as observed in past studies[127], this decrease in the COM-B domains was a result of participants over-estimating their capability, opportunity and motivation for engaging in novel behaviours at study baseline, and then encountering unexpected barriers to participation. In the qualitative component of chapter 4, participants spoke about how fatigue and self-sabotaging thoughts made it more difficult for them to participate in the practices than anticipated. This hypothesis was further supported in chapter 5, in which the intervention group again experienced significant decreases in COM-B

domains as compared to control. Future programming may focus on ways to further support participation in spite of these barriers.

6.2 Impact on mental health and symptom burden

Changes in measures of mental health and quality of life were observed in the pilot study (chapter 4) and the RCT (chapter 5). In chapter 4, our exploratory assessment highlighted significant pre-post changes in depression, anxiety, and quality of life (through the PBC-40 itch, fatigue, cognitive, emotional, and general symptoms domains). In the RCT (chapter 5), ANCOVA analysis revealed significant end of study between group differences in depression, stress, and quality of life (through the PBC-40 emotional and social domains). The improvements in depression, stress, and quality of life observed in chapter 5 are comparable to studies that have looked at mind-body techniques (including mindful movement, breathwork, meditation, and behavior therapy) in other chronic disease populations[23,64,65,70,72]. Improvements in mental health and quality of life are of importance in this population, as people with PBC experience high rates of mental health comorbidities and impaired health related quality of life (HrQoL) as compared to the general population[25]. These psychiatric comorbidities have been associated with impaired coping, poor prognosis, and increased mortality across a range of chronic disease populations. Given this association, targeting mental health in PBC has potential to improve long-term outcomes.

While significant pre-post changes to fatigue were observed in chapter 4, the ANCOVA analysis in chapter 5 did not reveal significant improvements in fatigue as compared to control. It is possible that the pre-post change in fatigue observed in the pilot study resulted from a placebo effect. A similar effect was observed in a pharmacological study of rituximab in PBC that reported significant changes to fatigue in both the intervention and control arm with no

significant difference between arms[56]. RCTs of pharmacological treatments have yet to report changes to fatigue in PBC. However, RCTs in people with cancer related fatigue and chronic fatigue syndrome have reported significant improvements in fatigue after participation in exercise, yoga, and qigong[16,66,141]. The absence of an effect in our study may be attributable to the relatively low dose of the mindful-movement intervention (45 minutes per week). Given the high prevalence and recognized burden of fatigue in PBC[41], the effect of a higher dose of mindful movement on fatigue in PBC warrants further investigation.

6.3 Sustainability

Another key learning from chapters 4 and 5 was the value that participants placed on sustaining the mind-body practices. They recognized benefits to their participation, and expressed an intention to continue with the practices after the study period. This is interesting because past literature has acknowledged that adherence to an intervention does not correlate to long-term adoption of practices[148]. Participants in our study furthered this, highlighting that while they could still access the intervention, losing the gamification elements and support from the study team created a difficult transition. Currently, there are a lack of strategies that have been shown to successfully facilitate sustainability of wellness practices after an intervention[148]. Some participants in our studies recognized the importance of habit formation in their continued engagement with the practices. Other studies have also highlighted the importance of habit formation to long-term behavior change[128,149,150]. As habit formation is an important component of automatic motivation, future mind-body interventions might prioritize using behavior change techniques to help participants build automatic motivation during an intervention. Participants in our study also felt that continued support from their peers could help with long-term adoption of the mind-body practices.

6.4 Limitations

This thesis has some limitations that should be identified. First, in the formative study (chapter 3) the qualitative feedback used to inform barriers and facilitators to participating in the intervention was provided by participants with IBD, with no large-scale data collection occurring from individuals with PBC. Given the similarity of the symptom burden experienced with IBD and PBC, the barriers and facilitators provided in the interviews were deemed to be applicable to PBC. To further mitigate this limitation, we worked with an advisory team of patients with PBC to better understand how intervention design needed to be tailored to meet the specific needs of this population. Second, in both the pilot study (chapter 4) and the RCT (chapter 5), at least 98% of participants were female, making the results less-generalizable to male patients. This is not unexpected, as the female: male ratio of PBC patients has been estimated to be as high as 10:1[31], and other studies evaluating mind-body interventions have reported a higher prevalence of females as compared to males[65,130]. Third, in the pilot study (chapter 4), adherence was self-reported at the end of study, which could potentially cause overestimation of adherence rates. In the RCT (chapter 5) adherence was assessed during weekly check-ins and at end of study, and no notable differences in adherence were observed between the two methods.

6.5 Conclusions & Future Directions

The findings of this thesis support the feasibility, acceptability, and positive impact on mental health of a 12-week web-based mind-body wellness program for people with PBC. While the adherence rates reported in the pilot study (chapter 4) and the RCT (chapter 5) were high in comparison to other online mind-body interventions, future research could focus on further enhancing adherence. The findings highlight the value of a theoretical framework and patient partnership in achieving adherence. Patients in our study also highlighted that enhancing group

support and making gamification more appealing could further support their adherence. Further qualitative studies with end-users could provide direction on incorporating these elements. Future research could also focus on enhancing scalability of the mind-body programming. Web-based delivery of this intervention promoted scalability, and was positively perceived by users. Scalability could be further enhanced if group support proved to be a sufficient alternative to the 1-1 support from the study team that was provided in chapters 4 and 5. Moreover, finding ways to promote long-term adoption of the mind-body practices would promote scalability. Finally, as fatigue remains a prominent and unaddressed symptom in PBC, future mind-body interventions could focus on incorporating elements to reduce fatigue, such as a higher dose of mindful movement programming.

REFERENCES

1. CADTH Common Drug Reviews. *Clinical Review Report: Obeticholic Acid (Ocaliva): (Intercept Pharmaceuticals Canada, Inc): Indication: For the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA*. Canadian Agency for Drugs and Technologies in Health

2. Younossi Z, Henry L. Overall health-related quality of life in patients with end-stage liver disease. *Clin Liver Dis (Hoboken)*. Jul 2015;6(1):9-14. doi:10.1002/cld.480

3. Shaheen AA, Kaplan GG, Almishri W, et al. The impact of depression and antidepressant usage on primary biliary cholangitis clinical outcomes. *PLoS One*. 2018;13(4):e0194839. doi:10.1371/journal.pone.0194839

4. Huet PM, Deslauriers J, Tran A, Faucher C, Charbonneau J. Impact of fatigue on the quality of life of patients with primary biliary cirrhosis. *Am J Gastroenterol*. Mar 2000;95(3):760-7. doi:10.1111/j.1572-0241.2000.01857.x

5. Valtýsdóttir ST, Gudbjörnsson B, Hällgren R, Hetta J. Psychological well-being in patients with primary Sjögren's syndrome. *Clin Exp Rheumatol*. Sep-Oct 2000;18(5):597-600.

6. Tarrants M, Oleen-Burkey M, Castelli-Haley J, Lage MJ. The impact of comorbid depression on adherence to therapy for multiple sclerosis. *Mult Scler Int*. 2011;2011:271321. doi:10.1155/2011/271321

7. Carta MG, Hardoy MC, Boi MF, Mariotti S, Carpiniello B, Usai P. Association between panic disorder, major depressive disorder and celiac disease: a possible role of thyroid

autoimmunity. *J Psychosom Res*. Sep 2002;53(3):789-93. doi:10.1016/s0022-3999(02)00328-8

8. Zyrianova Y, Kelly BD, Gallagher C, et al. Depression and anxiety in rheumatoid arthritis: the role of perceived social support. *Ir J Med Sci*. Apr-Jun 2006;175(2):32-6. doi:10.1007/bf03167946

9. Nery FG, Borba EF, Viana VS, et al. Prevalence of depressive and anxiety disorders in systemic lupus erythematosus and their association with anti-ribosomal P antibodies. *Prog Neuropsychopharmacol Biol Psychiatry*. Apr 1 2008;32(3):695-700. doi:10.1016/j.pnpbp.2007.11.014

10. Lewinson RT, Vallerand IA, Lowerison MW, et al. Depression Is Associated with an Increased Risk of Psoriatic Arthritis among Patients with Psoriasis: A Population-Based Study. *J Invest Dermatol*. Apr 2017;137(4):828-835. doi:10.1016/j.jid.2016.11.032

11. Mullish BH, Kabir MS, Thursz MR, Dhar A. Review article: depression and the use of antidepressants in patients with chronic liver disease or liver transplantation. *Aliment Pharmacol Ther*. Oct 2014;40(8):880-92. doi:10.1111/apt.12925

12. Mells GF, Pells G, Newton JL, et al. Impact of primary biliary cirrhosis on perceived quality of life: the UK-PBC national study. *Hepatology*. Jul 2013;58(1):273-83. doi:10.1002/hep.26365

13. Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gluud C. Ursodeoxycholic acid for primary biliary cirrhosis. *Cochrane Database Syst Rev*. Dec 12 2012;12(12):Cd000551. doi:10.1002/14651858.CD000551.pub3

14. Nevens F, Andreone P, Mazzella G, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. *N Engl J Med*. Aug 18 2016;375(7):631-43. doi:10.1056/NEJMoa1509840

15. Jacobsen PB, Donovan KA, Vadaparampil ST, Small BJ. Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. *Health Psychol*. Nov 2007;26(6):660-7. doi:10.1037/0278-6133.26.6.660

16. Hilfiker R, Meichtry A, Eicher M, et al. Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis. *Br J Sports Med*. May 2018;52(10):651-658. doi:10.1136/bjsports-2016-096422

17. Yancey JR, Thomas SM. Chronic fatigue syndrome: diagnosis and treatment. *Am Fam Physician*. Oct 15 2012;86(8):741-6.

18. Yudhawati R, Rasjid Hs M. Effect of yoga on FEV1, 6-minute walk distance (6-MWD) and quality of life in patients with COPD group B. *Adv Respir Med*. 2019;87(5):261-268. doi:10.5603/arm.2019.0047

19. Tong J, Qi X, He Z, et al. The immediate and durable effects of yoga and physical fitness exercises on stress. *J Am Coll Health*. Aug-Sep 2021;69(6):675-683. doi:10.1080/07448481.2019.1705840

20. Jayawardena R, Ranasinghe P, Ranawaka H, Gamage N, Dissanayake D, Misra A. Exploring the Therapeutic Benefits of Pranayama (Yogic Breathing): A Systematic Review. *Int J Yoga*. May-Aug 2020;13(2):99-110. doi:10.4103/ijoy.IJOY_37_19

21. Araujo RV, Fernandes AFC, Nery IS, Andrade E, Nogueira LT, Azevedo FHC. Meditation effect on psychological stress level in women with breast cancer: a systematic review.

Rev Esc Enferm USP. 2019;53:e03529. Efeito da meditação no nível de estresse psicológico de mulheres com neoplasia mamária: revisão sistemática. doi:10.1590/s1980-220x2018031303529

22. Vanage SM, Gilbertson KK, Mathiowetz V. Effects of an energy conservation course on fatigue impact for persons with progressive multiple sclerosis. *Am J Occup Ther*. May-Jun 2003;57(3):315-23. doi:10.5014/ajot.57.3.315

23. Chan RR, Larson JL. Meditation Interventions for Chronic Disease Populations: A Systematic Review. *J Holist Nurs*. Dec 2015;33(4):351-65. doi:10.1177/0898010115570363

24. Greenlee H, Balneaves LG, Carlson LE, et al. Clinical practice guidelines on the use of integrative therapies as supportive care in patients treated for breast cancer. *J Natl Cancer Inst Monogr*. Nov 2014;2014(50):346-58. doi:10.1093/jncimonographs/lgu041

25. Sivakumar T, Kowdley KV. Anxiety and Depression in Patients with Primary Biliary Cholangitis: Current Insights and Impact on Quality of Life. *Hepat Med*. 2021;13:83-92. doi:10.2147/hmer.S256692

26. Tanaka A. Current understanding of primary biliary cholangitis. *Clin Mol Hepatol*. Jan 2021;27(1):1-21. doi:10.3350/cmh.2020.0028

27. Beuers U, Gershwin ME, Gish RG, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. *Hepatology*. Nov 2015;62(5):1620-2. doi:10.1002/hep.28140

28. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol*. May 2012;56(5):1181-1188. doi:10.1016/j.jhep.2011.10.025

29. Trivedi PJ, Hirschfield GM. Recent advances in clinical practice: epidemiology of autoimmune liver diseases. *Gut*. Oct 2021;70(10):1989-2003. doi:10.1136/gutjnl-2020-322362

30. Witt-Sullivan H, Heathcote J, Cauch K, et al. The demography of primary biliary cirrhosis in Ontario, Canada. *Hepatology*. Jul 1990;12(1):98-105. doi:10.1002/hep.1840120116

31. Lleo A, Jepsen P, Morenghi E, et al. Evolving Trends in Female to Male Incidence and Male Mortality of Primary Biliary Cholangitis. *Sci Rep*. May 19 2016;6:25906. doi:10.1038/srep25906

32. Gerussi A, Cristoferi L, Carbone M, Asselta R, Invernizzi P. The immunobiology of female predominance in primary biliary cholangitis. *J Autoimmun*. Dec 2018;95:124-132. doi:10.1016/j.jaut.2018.10.015

33. Hirschfield GM, Dyson JK, Alexander GJM, et al. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut*. Sep 2018;67(9):1568-1594. doi:10.1136/gutjnl-2017-315259

34. Li H, Guan Y, Han C, et al. The pathogenesis, models and therapeutic advances of primary biliary cholangitis. *Biomed Pharmacother*. Aug 2021;140:111754. doi:10.1016/j.biopha.2021.111754

35. Gulamhusein AF, Hirschfield GM. Primary biliary cholangitis: pathogenesis and therapeutic opportunities. *Nat Rev Gastroenterol Hepatol*. Feb 2020;17(2):93-110. doi:10.1038/s41575-019-0226-7

36. Tsuneyama K, Baba H, Morimoto Y, Tsunematsu T, Ogawa H. Primary Biliary Cholangitis: Its Pathological Characteristics and Immunopathological Mechanisms. *J Med Invest*. 2017;64(1.2):7-13. doi:10.2152/jmi.64.7

37. Örnolfsson KT, Olafsson S, Bergmann OM, Gershwin ME, Björnsson ES. Using the Icelandic genealogical database to define the familial risk of primary biliary cholangitis. *Hepatology*. Jul 2018;68(1):166-171. doi:10.1002/hep.29675

38. Tanaka A, Leung PS, Gershwin ME. Environmental basis of primary biliary cholangitis. *Exp Biol Med (Maywood)*. Jan 2018;243(2):184-189. doi:10.1177/1535370217748893

39. Selmi C, Mayo MJ, Bach N, et al. Primary biliary cirrhosis in monozygotic and dizygotic twins: genetics, epigenetics, and environment. *Gastroenterology*. Aug 2004;127(2):485-92. doi:10.1053/j.gastro.2004.05.005

40. Al-Harthy N, Kumagi T. Natural history and management of primary biliary cirrhosis. *Hepat Med*. Dec 4 2012;4:61-71. doi:10.2147/hmer.S25998

41. Younossi ZM, Bernstein D, Shiffman ML, et al. Diagnosis and Management of Primary Biliary Cholangitis. *Am J Gastroenterol*. Jan 2019;114(1):48-63. doi:10.1038/s41395-018-0390-3

42. Jopson L, Jones DE. Fatigue in Primary Biliary Cirrhosis: Prevalence, Pathogenesis and Management. *Dig Dis*. 2015;33 Suppl 2:109-14. doi:10.1159/000440757

43. Carbone M, Mells GF, Pells G, et al. Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid. *Gastroenterology*. Mar 2013;144(3):560-569.e7; quiz e13-4. doi:10.1053/j.gastro.2012.12.005

44. De Vloo C, Nevens F. Cholestatic pruritus : an update. *Acta Gastroenterol Belg*. Jan-Mar 2019;82(1):75-82.

45. Ojo SO, Bailey DP, Brierley ML, Hewson DJ, Chater AM. Breaking barriers: using the behavior change wheel to develop a tailored intervention to overcome workplace

inhibitors to breaking up sitting time. *BMC Public Health*. Aug 16 2019;19(1):1126. doi:10.1186/s12889-019-7468-8

46. Huang X, Liu X, Yu Y. Depression and Chronic Liver Diseases: Are There Shared Underlying Mechanisms? *Front Mol Neurosci*. 2017;10:134. doi:10.3389/fnmol.2017.00134

47. Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. The UDCA-PBC Study Group. *N Engl J Med*. May 12 1994;330(19):1342-7. doi:10.1056/nejm199405123301903

48. Corpechot C, Poupon R, Chazouillères O. New treatments/targets for primary biliary cholangitis. *JHEP Rep*. Sep 2019;1(3):203-213. doi:10.1016/j.jhepr.2019.05.005

49. Hirschfield GM, Mason A, Luketic V, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. *Gastroenterology*. Apr 2015;148(4):751-61.e8. doi:10.1053/j.gastro.2014.12.005

50. Harms MH, van Buuren HR, Corpechot C, et al. Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. *J Hepatol*. Aug 2019;71(2):357-365. doi:10.1016/j.jhep.2019.04.001

51. Trauner M, Nevens F, Shiffman ML, et al. Long-term efficacy and safety of obeticholic acid for patients with primary biliary cholangitis: 3-year results of an international open-label extension study. *Lancet Gastroenterol Hepatol*. Jun 2019;4(6):445-453. doi:10.1016/s2468-1253(19)30094-9

52. Corpechot C, Chazouillères O, Rousseau A. Bezafibrate in Primary Biliary Cholangitis. *N Engl J Med*. Sep 6 2018;379(10):985. doi:10.1056/NEJMc1809061

53. Honda A, Tanaka A, Kaneko T, et al. Bezafibrate Improves GLOBE and UK-PBC Scores and Long-Term Outcomes in Patients With Primary Biliary Cholangitis. *Hepatology*. Dec 2019;70(6):2035-2046. doi:10.1002/hep.30552

54. Phaw NA, Leighton J, Dyson JK, Jones DE. Managing cognitive symptoms and fatigue in cholestatic liver disease. *Expert Rev Gastroenterol Hepatol*. Mar 2021;15(3):235-241. doi:10.1080/17474124.2021.1844565

55. ter Borg PC, van Os E, van den Broek WW, Hansen BE, van Buuren HR. Fluvoxamine for fatigue in primary biliary cirrhosis and primary sclerosing cholangitis: a randomised controlled trial [ISRCTN88246634]. *BMC Gastroenterol*. Jul 13 2004;4:13. doi:10.1186/1471-230x-4-13

56. Khanna A, Jopson L, Howel D, et al. Rituximab Is Ineffective for Treatment of Fatigue in Primary Biliary Cholangitis: A Phase 2 Randomized Controlled Trial. *Hepatology*. Nov 2019;70(5):1646-1657. doi:10.1002/hep.30099

57. Ian Gan S, de Jongh M, Kaplan MM. Modafinil in the treatment of debilitating fatigue in primary biliary cirrhosis: a clinical experience. *Dig Dis Sci*. Oct 2009;54(10):2242-6. doi:10.1007/s10620-008-0613-3

58. Ataei S, Kord L, Larki A, et al. Comparison of Sertraline with Rifampin in the treatment of Cholestatic Pruritus: A Randomized Clinical Trial. *Rev Recent Clin Trials*. 2019;14(3):217-223. doi:10.2174/1574887114666190328130720

59. Shen N, Pan J, Miao H, Zhang H, Xing L, Yu X. Fibrates for the treatment of pruritus in primary biliary cholangitis: a systematic review and meta-analysis. *Ann Palliat Med*. Jul 2021;10(7):7697-7705. doi:10.21037/apm-21-1304

60. Bolier R, de Vries ES, Parés A, et al. Fibrates for the treatment of cholestatic itch (FITCH): study protocol for a randomized controlled trial. *Trials*. May 23 2017;18(1):230. doi:10.1186/s13063-017-1966-8

61. Krawczyk M, Liebe R, Wasilewicz M, Wunsch E, Raszeja-Wyszomirska J, Milkiewicz P. Plasmapheresis exerts a long-lasting antipruritic effect in severe cholestatic itch. *Liver Int*. May 2017;37(5):743-747. doi:10.1111/liv.13281

62. Wahbeh H, Elsas SM, Oken BS. Mind-body interventions: applications in neurology. *Neurology*. Jun 10 2008;70(24):2321-8. doi:10.1212/01.wnl.0000314667.16386.5e

63. Bower JE, Irwin MR. Mind-body therapies and control of inflammatory biology: A descriptive review. *Brain Behav Immun*. Jan 2016;51:1-11. doi:10.1016/j.bbi.2015.06.012

64. Li Z, Liu S, Wang L, Smith L. Mind-Body Exercise for Anxiety and Depression in COPD Patients: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. Dec 18 2019;17(1)doi:10.3390/ijerph17010022

65. Cramer H, Lauche R, Klose P, Lange S, Langhorst J, Dobos GJ. Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer. *Cochrane Database Syst Rev*. Jan 3 2017;1(1):Cd010802. doi:10.1002/14651858.CD010802.pub2

66. Oka T, Tanahashi T, Chijiwa T, Lkhagvasuren B, Sudo N, Oka K. Isometric yoga improves the fatigue and pain of patients with chronic fatigue syndrome who are resistant to conventional therapy: a randomized, controlled trial. *Biopsychosoc Med*. 2014;8(1):27. doi:10.1186/s13030-014-0027-8

67. Izgu N, Gok Metin Z, Karadas C, Ozdemir L, Metinarikan N, Corapcıoglu D. Progressive Muscle Relaxation and Mindfulness Meditation on Neuropathic Pain, Fatigue, and Quality of Life in Patients With Type 2 Diabetes: A Randomized Clinical Trial. *J Nurs Scholarsh*. Sep 2020;52(5):476-487. doi:10.1111/jnu.12580

68. Chakrabarty J, Vidyasagar M, Fernandes D, Joisa G, Varghese P, Mayya S. Effectiveness of pranayama on cancer-related fatigue in breast cancer patients undergoing radiation therapy: A randomized controlled trial. *Int J Yoga*. Jan 2015;8(1):47-53. doi:10.4103/0973-6131.146062

69. Chakrabarty J, Vidyasagar MS, Fernandes D, Mayya S. Emotional Aspects and Pranayama in Breast Cancer Patients Undergoing Radiation Therapy: A Randomized Controlled Trial. *Asia Pac J Oncol Nurs*. Apr-Jun 2016;3(2):199-204. doi:10.4103/2347-5625.177390

70. Prem V, Sahoo RC, Adhikari P. Comparison of the effects of Buteyko and pranayama breathing techniques on quality of life in patients with asthma - a randomized controlled trial. *Clin Rehabil*. Feb 2013;27(2):133-41. doi:10.1177/0269215512450521

71. Graham CD, Gouick J, Krahé C, Gillanders D. A systematic review of the use of Acceptance and Commitment Therapy (ACT) in chronic disease and long-term conditions. *Clin Psychol Rev*. Jun 2016;46:46-58. doi:10.1016/j.cpr.2016.04.009

72. Ma RC, Yin YY, Wang YQ, Liu X, Xie J. Effectiveness of cognitive behavioural therapy for chronic obstructive pulmonary disease patients: A systematic review and meta-analysis. *Complement Ther Clin Pract*. Feb 2020;38:101071. doi:10.1016/j.ctcp.2019.101071

73. Courneya KS, Friedenreich CM, Quinney HA, et al. A longitudinal study of exercise barriers in colorectal cancer survivors participating in a randomized controlled trial. *Ann Behav Med*. Apr 2005;29(2):147-53. doi:10.1207/s15324796abm2902_9

74. Wangberg SC, Bergmo TS, Johnsen JA. Adherence in Internet-based interventions. *Patient Prefer Adherence*. Feb 2 2008;2:57-65.

75. Kok B, McNeely M, Watt M, Tandon P. Exercise Only Works If You Do It! The Holy Grail of Adherence. *Am J Gastroenterol*. Apr 2021;116(4):673-674. doi:10.14309/ajg.0000000000001198

76. Jennings HM, Morrison J, Akter K, et al. Developing a theory-driven contextually relevant mHealth intervention. *Glob Health Action*. 2019;12(1):1550736. doi:10.1080/16549716.2018.1550736

77. de Beurs D, van Bruinessen I, Noordman J, Friele R, van Dulmen S. Active Involvement of End Users When Developing Web-Based Mental Health Interventions. *Front Psychiatry*. 2017;8:72. doi:10.3389/fpsyt.2017.00072

78. Lewin S, Glenton C, Oxman AD. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. *Bmj*. Sep 10 2009;339:b3496. doi:10.1136/bmj.b3496

79. O'Cathain A, Thomas KJ, Drabble SJ, Rudolph A, Hewison J. What can qualitative research do for randomised controlled trials? A systematic mapping review. *BMJ Open*. Jun 20 2013;3(6)doi:10.1136/bmjopen-2013-002889

80. Khanna A, Hegade VS, Jones DE. Management of Fatigue in Primary Biliary Cholangitis. *Current Hepatology Reports*. 2019/06/01 2019;18(2):127-133. doi:10.1007/s11901-019-00458-0

81. Reshetnyak VI. Primary biliary cirrhosis: Clinical and laboratory criteria for its diagnosis. *World J Gastroenterol*. Jul 7 2015;21(25):7683-708. doi:10.3748/wjg.v21.i25.7683

82. Lee JY, Danford CJ, Trivedi HD, Tapper EB, Patwardhan VR, Bonder A. Treatment of Fatigue in Primary Biliary Cholangitis: A Systematic Review and Meta-Analysis. *Dig Dis Sci*. Aug 2019;64(8):2338-2350. doi:10.1007/s10620-019-5457-5

83. Cauch-Dudek K, Abbey S, Stewart DE, Heathcote EJ. Fatigue in primary biliary cirrhosis. *Gut*. Nov 1998;43(5):705-10. doi:10.1136/gut.43.5.705

84. Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. *Lancet*. Oct 17 2015;386(10003):1565-75. doi:10.1016/s0140-6736(15)00154-3

85. Shohani M, Kazemi F, Rahmati S, Azami M. The effect of yoga on the quality of life and fatigue in patients with multiple sclerosis: A systematic review and meta-analysis of randomized clinical trials. *Complement Ther Clin Pract*. May 2020;39:101087. doi:10.1016/j.ctcp.2020.101087

86. Cotter AP, Durant N, Agne AA, Cherrington AL. Internet interventions to support lifestyle modification for diabetes management: a systematic review of the evidence. *J Diabetes Complications*. Mar-Apr 2014;28(2):243-51. doi:10.1016/j.jdiacomp.2013.07.003

87. Hagger MS, Weed M. DEBATE: Do interventions based on behavioral theory work in the real world? *Int J Behav Nutr Phys Act*. Apr 25 2019;16(1):36. doi:10.1186/s12966-019-0795-4

88. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci*. Apr 23 2011;6:42. doi:10.1186/1748-5908-6-42

89. Robinson E, Higgs S, Daley AJ, et al. Development and feasibility testing of a smart phone based attentive eating intervention. *BMC Public Health*. Jul 9 2013;13:639. doi:10.1186/1471-2458-13-639

90. Mangurian C, Niu GC, Schillinger D, Newcomer JW, Dilley J, Handley MA. Utilization of the Behavior Change Wheel framework to develop a model to improve cardiometabolic screening for people with severe mental illness. *Implement Sci*. Nov 14 2017;12(1):134. doi:10.1186/s13012-017-0663-z

91. Michie S, Richardson M, Johnston M, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med*. Aug 2013;46(1):81-95. doi:10.1007/s12160-013-9486-6

92. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implement Sci*. Apr 24 2012;7:37. doi:10.1186/1748-5908-7-37

93. Watt M, Hyde A, Madsen K, Peerani F, Tandon P. A169 EXPLORING PATIENT PERSPECTIVES ON AN ONLINE STRESS REDUCTION BASED WELLNESS INTERVENTION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD). *Journal of the Canadian Association of Gastroenterology*. 2021;4(Supplement_1):179-180. doi:10.1093/jcag/gwab002.167

94. Borren NZ, van der Woude CJ, Ananthakrishnan AN. Fatigue in IBD: epidemiology, pathophysiology and management. *Nat Rev Gastroenterol Hepatol*. Apr 2019;16(4):247-259. doi:10.1038/s41575-018-0091-9

95. Knowles SR, Graff LA, Wilding H, Hewitt C, Keefer L, Mikocka-Walus A. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses-Part I. *Inflamm Bowel Dis*. Mar 19 2018;24(4):742-751. doi:10.1093/ibd/izx100

96. Webster R, Michie S, Estcourt C, Gerressu M, Bailey JV. Increasing condom use in heterosexual men: development of a theory-based interactive digital intervention. *Transl Behav Med*. Sep 2016;6(3):418-27. doi:10.1007/s13142-015-0338-8

97. Tombor I, Shahab L, Brown J, Crane D, Michie S, West R. Development of SmokeFree Baby: a smoking cessation smartphone app for pregnant smokers. *Transl Behav Med*. Dec 2016;6(4):533-545. doi:10.1007/s13142-016-0438-0

98. The Wellness Toolbox. Accessed May 15, 2022.

99. Inouye SK, Bogardus ST, Jr., Williams CS, Leo-Summers L, Agostini JV. The role of adherence on the effectiveness of nonpharmacologic interventions: evidence from the delirium prevention trial. *Arch Intern Med*. Apr 28 2003;163(8):958-64. doi:10.1001/archinte.163.8.958

100. Blackburn P, Freeston M, Baker CR, Jones DE, Newton JL. The role of psychological factors in the fatigue of primary biliary cirrhosis. *Liver Int*. Jun 2007;27(5):654-61. doi:10.1111/j.1478-3231.2007.01500.x

101. Wood CE, Hardeman W, Johnston M, Francis J, Abraham C, Michie S. Reporting behaviour change interventions: do the behaviour change technique taxonomy v1, and training in its use, improve the quality of intervention descriptions? *Implement Sci*. Jun 7 2016;11(1):84. doi:10.1186/s13012-016-0448-9

102. Bourne JE, Ivanova E, Gainforth HL, Jung ME. Mapping behavior change techniques to characterize a social cognitive theory informed physical activity intervention for adults at risk of type 2 diabetes mellitus. *Transl Behav Med*. Aug 7 2020;10(3):705-715. doi:10.1093/tbm/ibz008

103. Ivankova NV, Creswell JW, Stick SL. Using mixed-methods sequential explanatory design: From theory to practice. *Field methods*. 2006;18(1):3-20.

104. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med*. Mar 1997;27(2):363-70. doi:10.1017/s0033291796004382

105. Watt M, Spence JC, Tandon P. Development of a Theoretically Informed Web-Based Mind-Body Wellness Intervention for Patients With Primary Biliary Cholangitis: Formative Study. *JMIR Form Res*. Oct 8 2021;5(10):e29064. doi:10.2196/29064

106. Robinson E, Titov N, Andrews G, McIntyre K, Schwencke G, Solley K. Internet treatment for generalized anxiety disorder: a randomized controlled trial comparing clinician vs. technician assistance. *PLoS One*. Jun 3 2010;5(6):e10942. doi:10.1371/journal.pone.0010942

107. Titov N, Andrews G, Davies M, McIntyre K, Robinson E, Solley K. Internet treatment for depression: a randomized controlled trial comparing clinician vs. technician assistance. *PLoS One*. Jun 8 2010;5(6):e10939. doi:10.1371/journal.pone.0010939

108. Lee EH. Review of the psychometric evidence of the perceived stress scale. *Asian Nurs Res (Korean Soc Nurs Sci)*. Dec 2012;6(4):121-7. doi:10.1016/j.anr.2012.08.004

109. Larson RD. Psychometric properties of the modified fatigue impact scale. *International journal of MS care*. 2013;15(1):15-20.

110. Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. *Gut*. Nov 2005;54(11):1622-9. doi:10.1136/gut.2005.065862

111. Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). *Depress Anxiety*. 2003;18(2):76-82. doi:10.1002/da.10113

112. Keyworth C, Epton T, Goldthorpe J, Calam R, Armitage CJ. Acceptability, reliability, and validity of a brief measure of capabilities, opportunities, and motivations ("COM-B"). *Br J Health Psychol*. Sep 2020;25(3):474-501. doi:10.1111/bjhp.12417

113. Bradshaw C, Atkinson S, Doody O. Employing a Qualitative Description Approach in Health Care Research. *Glob Qual Nurs Res*. Jan-Dec 2017;4:2333393617742282. doi:10.1177/2333393617742282

114. Pope C, van Royen P, Baker R. Qualitative methods in research on healthcare quality. *Qual Saf Health Care*. Jun 2002;11(2):148-52. doi:10.1136/qhc.11.2.148

115. Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *Bmj*. Oct 24 2016;355:i5239. doi:10.1136/bmj.i5239

116. Schoenfeld D. Statistical considerations for pilot studies. *Int J Radiat Oncol Biol Phys*. Mar 1980;6(3):371-4. doi:10.1016/0360-3016(80)90153-4

117. IBM SPSS Statistics for Windows, Version 16.0. Chicago, SPSS Inc.

118. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. *Nurs Health Sci*. Sep 2013;15(3):398-405. doi:10.1111/nhs.12048

119. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative research in psychology*. 2006;3(2):77-101.

120. Eysenbach G. The law of attrition. *J Med Internet Res*. Mar 31 2005;7(1):e11. doi:10.2196/jmir.7.1.e11

121. Farvolden P, Denisoff E, Selby P, Bagby RM, Rudy L. Usage and longitudinal effectiveness of a Web-based self-help cognitive behavioral therapy program for panic disorder. *J Med Internet Res*. Mar 26 2005;7(1):e7. doi:10.2196/jmir.7.1.e7

122. Baumel A, Muench F, Edan S, Kane JM. Objective User Engagement With Mental Health Apps: Systematic Search and Panel-Based Usage Analysis. *J Med Internet Res*. Sep 25 2019;21(9):e14567. doi:10.2196/14567

123. Beintner I, Jacobi C. Impact of telephone prompts on the adherence to an Internet-based aftercare program for women with bulimia nervosa: A secondary analysis of data from a randomized controlled trial. *Internet Interv*. Mar 2019;15:100-104. doi:10.1016/j.invent.2017.11.001

124. Dennison L, Morrison L, Lloyd S, et al. Does brief telephone support improve engagement with a web-based weight management intervention? Randomized controlled trial. *J Med Internet Res*. Mar 28 2014;16(3):e95. doi:10.2196/jmir.3199

125. Ho J, Corden ME, Caccamo L, et al. Design and evaluation of a peer network to support adherence to a web-based intervention for adolescents. *Internet Interv*. Nov 2016;6:50-56. doi:10.1016/j.invent.2016.09.005

126. Lattie EG, Antoni MH, Fletcher MA, et al. Stress management skills, neuroimmune processes and fatigue levels in persons with chronic fatigue syndrome. *Brain Behav Immun*. Aug 2012;26(6):849-58. doi:10.1016/j.bbi.2012.02.008

127. Spence JC, Burgess J, Rodgers W, Murray T. Effect of pretesting on intentions and behaviour: a pedometer and walking intervention. *Psychol Health*. Sep 2009;24(7):777-89. doi:10.1080/08870440801989938

128. Lally P, Wardle J, Gardner B. Experiences of habit formation: a qualitative study. *Psychol Health Med*. Aug 2011;16(4):484-9. doi:10.1080/13548506.2011.555774

129. Cramer H, Ward L, Steel A, Lauche R, Dobos G, Zhang Y. Prevalence, Patterns, and Predictors of Yoga Use: Results of a U.S. Nationally Representative Survey. *Am J Prev Med*. Feb 2016;50(2):230-5. doi:10.1016/j.amepre.2015.07.037

130. Upchurch DM, Johnson PJ. Gender Differences in Prevalence, Patterns, Purposes, and Perceived Benefits of Meditation Practices in the United States. *J Womens Health (Larchmt)*. Feb 2019;28(2):135-142. doi:10.1089/jwh.2018.7178

131. Schattenberg JM, Pares A, Kowdley KV, et al. A randomized placebo-controlled trial of elafibranor in patients with primary biliary cholangitis and incomplete response to UDCA. *J Hepatol*. Jun 2021;74(6):1344-1354. doi:10.1016/j.jhep.2021.01.013

132. Björnsson E, Kalaitzakis E, Neuhauser M, et al. Fatigue measurements in patients with primary biliary cirrhosis and the risk of mortality during follow-up. *Liver Int*. Feb 2010;30(2):251-8. doi:10.1111/j.1478-3231.2009.02160.x

133. Jones DE, Al-Rifai A, Frith J, Patanwala I, Newton JL. The independent effects of fatigue and UDCA therapy on mortality in primary biliary cirrhosis: results of a 9 year follow-up. *J Hepatol*. Nov 2010;53(5):911-7. doi:10.1016/j.jhep.2010.05.026

134. Williams H, Simmons LA, Tanabe P. Mindfulness-Based Stress Reduction in Advanced Nursing Practice: A Nonpharmacologic Approach to Health Promotion, Chronic Disease Management, and Symptom Control. *J Holist Nurs*. Sep 2015;33(3):247-59. doi:10.1177/0898010115569349

135. NVivo Qualitative Data Analysis Software [Software].

136. Vaganian L, Bussmann S, Gerlach AL, Kusch M, Labouvie H, Cwik JC. Critical consideration of assessment methods for clinically significant changes of mental distress after psycho-oncological interventions. *Int J Methods Psychiatr Res*. Jun 2020;29(2):e1821. doi:10.1002/mpr.1821

137. Lemay KR, Tulloch HE, Pipe AL, Reed JL. Establishing the Minimal Clinically Important Difference for the Hospital Anxiety and Depression Scale in Patients With Cardiovascular Disease. *J Cardiopulm Rehabil Prev*. Nov 2019;39(6):E6-e11. doi:10.1097/hcr.0000000000000379

138. Venkatesh HN, Ravish H, Wilma Delphine Silvia CR, Srinivas H. Molecular Signature of the Immune Response to Yoga Therapy in Stress-related Chronic Disease Conditions: An Insight. *Int J Yoga*. Jan-Apr 2020;13(1):9-17. doi:10.4103/ijoy.IJOY_82_18

139. Song R, Grabowska W, Park M, et al. The impact of Tai Chi and Qigong mind-body exercises on motor and non-motor function and quality of life in Parkinson's disease: A systematic review and meta-analysis. *Parkinsonism Relat Disord*. Aug 2017;41:3-13. doi:10.1016/j.parkreldis.2017.05.019

140. Hallsworth K, Jopson L, Jones DE, Trenell MI. Exercise therapy in primary biliary cirrhosis: the importance of moving while sitting on a surgical waiting list-a case study. *Frontline Gastroenterol*. Jul 2016;7(3):167-169. doi:10.1136/flgastro-2015-100672

141. Chan JS, Ho RT, Chung KF, et al. Qigong exercise alleviates fatigue, anxiety, and depressive symptoms, improves sleep quality, and shortens sleep latency in persons with chronic fatigue syndrome-like illness. *Evid Based Complement Alternat Med*. 2014;2014:106048. doi:10.1155/2014/106048

142. White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet*. Mar 5 2011;377(9768):823-36. doi:10.1016/s0140-6736(11)60096-2

143. Lai JC, Dodge JL, Kappus MR, et al. A Multicenter Pilot Randomized Clinical Trial of a Home-Based Exercise Program for Patients With Cirrhosis: The Strength Training Intervention (STRIVE). *Am J Gastroenterol*. Apr 2021;116(4):717-722. doi:10.14309/ajg.0000000000001113

144. Kruger C, McNeely ML, Bailey RJ, et al. Home Exercise Training Improves Exercise Capacity in Cirrhosis Patients: Role of Exercise Adherence. *Sci Rep*. Jan 8 2018;8(1):99. doi:10.1038/s41598-017-18320-y

145. Edwards EA, Lumsden J, Rivas C, et al. Gamification for health promotion: systematic review of behaviour change techniques in smartphone apps. *BMJ Open*. Oct 4 2016;6(10):e012447. doi:10.1136/bmjopen-2016-012447

146. Altmeyer M, Lessel P, Krüger A. Investigating gamification for seniors aged 75+. 2018:453-458.

147. Arigo D, Brown MM, Pasko K, Suls J. Social Comparison Features in Physical Activity Promotion Apps: Scoping Meta-Review. *J Med Internet Res*. Mar 27 2020;22(3):e15642. doi:10.2196/15642

148. Rothman AJ. Toward a theory-based analysis of behavioral maintenance. *Health Psychol*. Jan 2000;19(1s):64-9. doi:10.1037/0278-6133.19.suppl1.64

149. Gardner B, Lally P, Wardle J. Making health habitual: the psychology of 'habit-formation' and general practice. *Br J Gen Pract*. Dec 2012;62(605):664-6. doi:10.3399/bjgp12X659466

150. Rothman AJ, Sheeran P, Wood W. Reflective and automatic processes in the initiation and maintenance of dietary change. *Ann Behav Med*. Dec 2009;38 Suppl 1:S4-17. doi:10.1007/s12160-009-9118-3

151. Glasgow RE. eHealth evaluation and dissemination research. *Am J Prev Med*. May 2007;32(5 Suppl):S119-26. doi:10.1016/j.amepre.2007.01.023

152. van Bruinessen IR, van Weel-Baumgarten EM, Gouw H, Zijlstra JM, van Dulmen S. An Integrated Process and Outcome Evaluation of a Web-Based Communication Tool for Patients With Malignant Lymphoma: Randomized Controlled Trial. *J Med Internet Res*. Jul 29 2016;18(7):e206. doi:10.2196/jmir.5877

153. Atkins L, Kelly MP, Littleford C, Leng G, Michie S. Reversing the pipeline? Implementing public health evidence-based guidance in english local government. *Implement Sci*. May 12 2017;12(1):63. doi:10.1186/s13012-017-0589-5

APPENDICES

Appendix A: Description of the online intervention

Week number	Theme of the week	Positive psychology activity of the week	Breathwork practices introduced	Standing mindful movement postures introduced	Chair mindful movement postures introduced
Week 1	Understanding behaviour change and prioritizing self care	Plan program participation. Brainstorm potential barriers and facilitators to program participation	Shining skull breath, bellows breath, full breath, breath awareness, diaphragmatic breathing, alternate nostril breathing	Cat cow, yoga namaskar, tree, thunderbolt	Marching flow, mountain pose, seated oblique crunch, seated chest press with band, cow face, lateral line stepovers, seated boat pose, seated hammer curls, staggered sit to stand, step backs with support

Week 2	Connecting with your breath	Select 5 core values			Seated jacks
Week 3	Connecting with your emotional body	Complete life wheel activity	Sitali	Yogi squat, yoga namaskar in goddess	Seated skiers
Week 4	End of program goal setting	Set end of program SMART goals		Triangle	Seated skaters
Week 5	Affirmations and personal power	Select and practice affirmations		Seated twist	Standing march with support
Week 6	Managing thoughts	Learn and practice strategies to manage thoughts		Happy baby, reclining twist, wind removing pose	Seated reverse fly
Week 7	Managing feelings	Learn and practice strategies to manage thoughts		Beauty pose	Seated triceps kickbacks

Week 8	Sleep	Select and practice sleep hygiene tips			Seated good morning
Week 9	Self compassion	Complete self-compassion journaling, or choose a self compassion pathway to work on		Locust pose	3 way foot reach
Week 10	Gratitude	Roll a dice to receive ideas for expressing gratitude			Staggered stance bent over row
Week 11	Social connectedness	Build a social support village			Seated wide leg forward bend with twist
Week 12	End-of-program review and long term goal setting	Set end of program SMART goals			Seated toe touches

Appendix B: Description of the supplementary intervention content

Week number	Behaviour Theme of the Week	Nutrition topic	PBC tip of the week
Week 1	Connecting with your breath and core values	Canada's food guide and eating balanced meals.	What causes PBC?
Week 2	Connecting with your body and moving towards core values	Experimenting with a lower sodium diet.	How is PBC diagnosed?
Week 3	Grounding	Learning about reducing sugar intake.	What is ursodeoxycholic acid? How does it work and why is it so important to take?
Week 4	Managing your thoughts	Boosting fibre intake.	Are there certain questions I should be asking at my doctor's appointment?
Week 5	Personal power	Learn about dietary protein intake.	Is my family at risk of getting PBC?
Week 6	Social connectedness and gratitude	Learn about nutrition and bone health	Does having PBC put me at a higher risk for other diseases?
Week 7	Self-expression	Learning about meal planning.	What can I do for itch (pruritus)?

Week 8	Letting go	Learning about healthy fats.	Are COVID-19 vaccines effective and safe for individuals with PBC?
Week 9	Forgiveness	Learning how to set healthy nutrition goals.	What is known about fatigue and PBC?
Week 10	Visualization for health	Learning about maintaining a healthy weight?	What care should I expect for my PBC?
Week 11	Visualization for other life goals	Dietary trends- should I ditch them or try them out?	How does drinking alcohol affect my PBC?
Week 12	End of program review	Learn about label reading.	How can the PBC society support me moving forward.

Appendix C. COM-B Survey

Please mark the appropriate response with an x.

1. I (will) have enough time, information and reminders in place to ensure I can do the program at least 3 times a week

Please rate

Strongly disagree — Strongly Agree

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

2. I (will) have the support of others (my partner/ family and healthcare providers) to do the program at least 3 times a week

Please rate

Strongly disagree — Strongly Agree

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

3. I want to, and know I need to do the program at least 3 times a week

Please rate

Strongly disagree — Strongly Agree

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

4. Completing the program at least 3 times a week is something I (will) do without

thinking

Please rate	Strongly disagree										Strongly Agree
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

5. I (will) have the energy and physical ability to do the program at least 3 times a week

Please rate	Strongly disagree										Strongly Agree
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

6. I (will) remember and know how to do the program at least 3 times a week

Please rate	Strongly disagree										Strongly Agree
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Appendix D. Qualitative Interview Guide

1. Can you tell me what it means to you to have Primary Biliary Cholangitis (PBC)? What symptoms do you deal with day to day? (Probes: physical symptoms, social, emotional) How has it impacted your daily life?

1. Prior to joining this study, where were you physically and psychologically?
    0. What were you hoping to gain from the program?
    1. Were there any goals that you set for yourself?

1. How many times did you complete the program per week?

1. What helped you to do the program on the days that you did?

1. Can you tell me about a time when you had difficulty fitting the program into your daily life? What could have made it easier for you?

1. Were there any points during the program where you thought about quitting or weeks where you didn't participate as much? Why? What made you keep going?

1. Can you tell me about how your physical abilities changed over the course of the program?
    0. Do you have an example of something that you couldn't do before the program that you can do now?
    1. What was difficult for you?
    2. What will you continue now that the program is over? Why?

1. How challenging did you find the program overall?
    0. What kinds of challenges did you experience?
    1. How did these challenges make you feel?
    2. How did you overcome these challenges?

1. I want to ask you about specific components of the program now.
    0. Stress reduction techniques: What did you learn that you didn't know before? Which were most helpful to you? Were there any that didn't work for you? Why?
    1. Weekly phone calls with facilitator: How did these calls impact your participation in the program? What did you like about them? What didn't you like?
    2. Nutrition: What was new for you with the nutrition aspect of the study? What nutrition practices will you carry forward?

1. How did participating in this program impact your:
    0. Overall health?
    1. PBC?

2. Mental/Psychological well-being?
3. Relationships?

1. Which part of the study had the biggest impact on your:
    0. knowledge? Why?
    1. Physical abilities?
    2. Daily routine?
    3. Personal outlook on life/mindset? How has this program impacted your PBC management?

1. What is the biggest change that you have seen in yourself because of completion of this program?

1. Looking towards the future, which aspects of the program have you incorporated into your everyday life?
    0. Are there any program aspects that you are still planning to incorporate? Why? Why have you not done so already?

1. What was the best part of being a part of this study? Why?

1. What would you change about the program?

1. Is there anything else that you'd like to share with us?

Appendix E. Qualitative Interview Participant Baseline Characteristics

Relationship status	
Single	0 (0%)
Married/Common Law	9 (81.8%)
Divorced/Separated	2 (18.2%)
Widowed	0 (0%)
Employment status	
Employed	6 (54.5%)
Unemployed	4 (36.4%)
Prefer not to answer	1 (9.1%)
Highest Education Achieved	
Less than high school	0 (0%)
High school graduate/GED	2 (18.2%)
Some college	6 (54.5%)
University degree	3 (27.3%)
Sex	
Female	11 (100%)

Age	56.8 ± 13.6
Years since diagnosis	12.8 ± 10.6
Cirrhosis Status	
No cirrhosis	5 (45.5%)
Cirrhosis	1 (9.1%)
Unsure	5 (45.5%)
Meditation in past 6 months	
Yes	3 (27.3%)
Yoga in past 6 months	
Yes	1 (9.1%)

Appendix F. Qualitative Interview Guide

1. Can you tell me what it means to you to have Primary Biliary Cholangitis (PBC)? What symptoms do you deal with day to day? (probes: physical symptoms, social, emotional) How has it impacted your daily life?

1. Prior to joining this study, where were you physically and psychologically?
    0. What were you hoping to gain from the program?
    1. Which elements drew you to the program? What appealed to you as being able to potentially impact your PBC?
    2. Were there any goals that you set for yourself? Why was it important to you to set this particular goal?

1. What helped you to do the program on the days that you did?

1. How did your participation change through the course of the program?
    0. At what point during the program did you feel the most motivated? Why do you think this was?

1. Can you tell me about a time when you had difficulty fitting the program into your daily life?
    0. What could have made it easier for you? (*PROBES*: coaching around adopting new habits, doing a shorter program more often, changes to the program content)

1. Were there any points during the program where you thought about quitting or weeks where you didn't participate as much? Why? What made you keep going?

1. How challenging did you find the program overall?
    0. What kinds of challenges did you experience?
    1. Were you surprised by any of these challenges?
    2. How did these challenges make you feel?
    3. How did you overcome these challenges?

1. I want to ask you about certain elements of the study now:
    0. Weekly phone calls with facilitator: How did these calls impact your participation in the program? What did you like about them? What didn't you like?

1. Group sessions: Did you attend any group sessions?
    0. If yes, what motivated you to attend? How did these sessions impact you? Can you tell me about a group session that you enjoyed? What did you enjoy about this session?
    1. If not, what got in the way? What could make these sessions more appealing to you?
    2. We're exploring potentially eliminating individual check ins, and adding more frequent group sessions instead. How do you think this would impact your program experience?

a. Study dashboard:

.Did you opt to be a part of the study leaderboard? Why or why not?

0. How did the leaderboard affect your experiences with the program? (*PROBES*: connection to study peers, competition, tracking)
    1. Did your feelings about the leaderboard change throughout the course of the program?

i. What other features could be added to the dashboard to enhance your motivation (*PROBES*: chatbox, streaks, notifications, other tracking mechanisms)

1. How do you plan on keeping yourself engaged in these practices in the absence of these things? Is there anything that could help facilitate your continued participation?

1. Looking towards the future, which aspects of the program have you incorporated into your everyday life? Why?
    0. Can you tell me more about this transition (from doing the practices during the study to doing them after the study)?
    1. Are there any program aspects that you are still planning to incorporate? Why? Why have you not done so already?
    2. What could be incorporated into the programming to support you to return to the program website? Carry on your practice outside of the program website? (*PROBES*: more content, a full level two)

1. How did participating in this program impact your:
    0. Overall health?
    1. PBC?
    2. Fatigue/Energy?
    3. Physical abilities?
    4. Mental/Psychological well-being? (probes: stress, anxiety, mood)
    5. Relationships?

1. How has this program impacted how you manage or cope with your PBC?

1. How has the program affected the way you think about your own abilities?
    0. Thinking back to when you joined the program, can you take me through how you felt about yourself and your abilities? (*PROBES*: ability to adhere to program, ability to stay motivated)
    1. How did this change throughout the program? Were there any points where you felt worse off than before?

1. What is the biggest change that you have seen in yourself because of completion of this program?

1. What was the best part of being a part of this study? Why?

1. What would you change about the program?

1. Is there anything else that you'd like to share with us?

Appendix G. Qualitative Interview Participant Baseline Characteristics

	Total (n=11)
Age (years)	61.1 ± 13.0
Sex	
Male	1 (9.1%)
Female	10 (90.9%)
Other	0 (0%)
Relationship status	
Married	9 (81.8%)
Living common-law	0 (0%)
Divorced/Separated	2 (18.2%)
Widowed	0 (0%)
Single/Never Married	0 (0%)
Prefer not to answer	0 (0%)
Employment status	
Employed	4 (45.5%)
Unemployed	5 (45.5%)
Prefer not to answer	0 (0%)
Highest Education Achieved	

No post-secondary degree, certificate, or diploma	1 (9.1%)
Trade certificate or diploma from a vocational school of apprenticeship training	0 (0%)
Non-university certificate or diploma from a community college, CEGEP, school of nursing, ect.	1 (9.1%)
University certificate below bachelor's level	1 (9.1%)
Bachelor's degree	1 (9.1%)
University degree or certificate above bachelor's degree	7 (63.6%)
Unknown	0 (0%)
Years since diagnosis	7.4 ± 6.8
Cirrhosis Status	
No cirrhosis	9 (81.8%)
Cirrhosis	1 (9.1%)
Unsure	1 (9.1%)
Current PBC Medications	
None	2 (18.2%)
UDCA	9 (81.8%)
Obeticholic acid	1 (9.1%)
Fenofibrate	0 (0%)
Bezafibrate	1 (9.1%)
Colchicine	0 (0%)

Other	0 (0%)
Meditation in past 6 months	
Yes	5 (45.5%)
Yoga in past 6 months	
Yes	5 (45.5%)
Tai Chi in past 6 months	
Yes	0 (0%)