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PBC-HOPE: A randomized controlled trial of hypnosis and psychoeducation in women with primary biliary cholangitis and fatigue

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Name of the trial registry: Trial of Psychoeducational and Hypnosis Interventions on the Fatigue Associated With PBC in Women (https://clinicaltrials.gov/study/NCT03630718?term=NCT03630718&rank=1)

Clinical trial number: NCT03630718

Study highlights:

WHAT IS KNOWN:

- Fatigue is the most frequent symptom of primary biliary cholangitis (PBC)
- It affects more than half of PBC patients
- However, no therapeutic intervention in PBC has yet proved effective for this symptom
- As demonstrated for other chronic diseases, psychoeducation and hypnosis could be relevant interventions

WHAT IS NEW HERE:

- In the short term, psychoeducation and hypnosis didn't result in a significant reduction in fatigue
- A positive qualitative change was observed in the perceptions of fatigue in both intervention groups
- Further research should explore the value of booster sessions and/or the combination of both interventions

Abbreviations

LT, liver transplantation; PBC, primary biliary cholangitis; SC, standard care; UDCA, ursodeoxycholic acid; VAS, visual analog scale.

Abstract

Objectives: Fatigue is the main symptom of primary biliary cholangitis (PBC), but has not yet been improved by any therapeutic intervention. This study evaluated the efficacy and safety of hypnosis and psychoeducation in improving fatigue associated with PBC (PBC-HOPE ClinicalTrial.gov number, NCT03630718).

Methods: Fifty-five women with PBC and significant fatigue, defined by a PBC-40 fatigue score ≥ 33, were randomly assigned to standard care (SC) alone (n=18), SC plus hypnosis (n=18) and SC plus psychoeducation (n=19), with four weekly sessions for the intervention groups. Self-report questionnaires, including the PBC-40, were completed at inclusion (D0) and Week 12 (W12). The first eight patients in each group were interviewed at both times. The primary outcome was the difference in PBC-40 fatigue score between D0 and W12. The secondary and exploratory outcomes were the psychometric scores and interview findings.

Results: The primary outcome was not achieved, with a median (interquartile range) difference in PBC-40 fatigue score of -3.0 (-10.0; 1.0), -6.0 (-8.0; -4.0), and -6.0 (-11.5; -4.8) for SC, SC-hypnosis, and SC-psychoeducation, respectively. The quantitative secondary outcomes were consistent with this result. The qualitative exploratory outcomes indicated that both interventions positively modified patients' perceptions of fatigue, underlining the appropriation of the intervention. No serious adverse events occurred.

Discussions: At 12 weeks, hypnosis and psychoeducation interventions were not associated with a significant reduction in quantitative measures of fatigue associated with PBC. However, the qualitative changes in perceived fatigue associated with these interventions suggest that maintenance sessions could be beneficial in the longer term.

Keywords: symptom; quality of life; PBC-40; psychosocial; interview.

INTRODUCTION

Primary biliary cholangitis (PBC) is a rare chronic, progressive, cholestatic liver disease of unknown etiology that mainly affects middle-aged women.[1] It is estimated that one in 1,000 women over the age of 40 has PBC. While the prognosis of the disease essentially depends on the risk of cirrhosis and its complications, the two main symptoms that impair patients' quality of life are pruritus and fatigue. Fatigue is the most frequent symptom and affects more than half of all patients. Fatigue is typically dissociated from PBC disease stage and severity, and can considerably impact quality of life, leading to social isolation and depression.[2-4] Unfortunately, none of the first or second-line drug therapies used in PBC patients, namely ursodeoxycholic acid (UDCA), obeticholic acid, or fibrates, have shown any significant beneficial effect on fatigue, although some improvement has been reported with bezafibrate.[5] Liver transplantation (LT) is associated with an improvement in fatigue in PBC patients, although a proportion of patients continue to suffer from significant fatigue after two years.[6] However, this last treatment option is only offered when the prognosis is at the vital stage.

Various drugs have been specifically evaluated to reduce fatigue in PBC patients. Inconsistent and/or anecdotal results have been reported with modafinil or methotrexate, whose efficacy, if it exists, seems limited or is hampered by side effects.[7-10] Other therapeutic approaches, such as selective serotonin reuptake inhibitors, serotonin receptor antagonists, antioxidants, or the B-cell-targeting biological agent, rituximab, have proved ineffective.[11-14] The lack of specific drug therapies for addressing fatigue in PBC has led to the following proposals: (a) advise patients on how to cope with limitations due to fatigue in daily living, (b) help patients learn how to reduce physical efforts in order to better perform some activities, (c) offer patients cognitive behavioral therapy, (d) maintain social interactions, as increased fatigue in PBC is particularly associated with social dysfunction.[15]

Despite these suggestions, the effects of psychosocial interventions have not been investigated for PBC, despite showing positive effects in the treatment of fatigue in other diseases. The most widely studied intervention is psychoeducation, which is based on cognitive and behavioral therapy and consists of education on fatigue, self-care or coping techniques, activity management, and learning to balance activities and rest.[16] Psychoeducation intervention has been shown to be effective in patients with various chronic diseases, such as cancer, chronic liver disease, inflammatory bowel disease, arthritis, and lupus, mainly through randomized controlled trials.[17-22] In a systematic review of the Cochrane Library, the efficacy of psychoeducation programs specifically designed to treat fatigue was found to be superior to the efficacy of non-specific interventions, such as those designed to improve overall disease management.[16]

Whereas psychoeducation involves informing, supporting, and counseling patients, another psychological intervention is hypnosis, which is defined as a state of consciousness involving focused attention and reduced peripheral awareness that is characterized by an enhanced ability to respond to suggestion (Society of Psychological Hypnosis, 2014) and involves cognitive procedures such as imagination. Hypnosis has proved effective in several areas, including acute and chronic pain management.[23] In the treatment of fatigue, positive effects have also been demonstrated in patients who have undergone coronary surgery, suffer from fibromyalgia, or have chronic kidney disease treated by hemodialysis.[24-26]

The main objective of the present randomized controlled trial was to evaluate the 12-week efficacy and safety of psychoeducation and hypnosis interventions in addition to standard care (SC), compared with standard care alone (SC-alone), on fatigue associated with PBC. This is the first trial to explore these types of interventions in PBC. The secondary objectives of the study were to evaluate the effects of these interventions on different dimensions of fatigue, quality of life, sleep quality, sleepiness, anxiety, and depression symptoms, and to explore changes in patients' discourse on their perceptions of their fatigue.

METHODS

Study design and participants

The PBC-HOPE trial, designed as a three-arm randomized trial, was conducted in the Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis of Saint Antoine Hospital, Paris, France, between 2019 and 2023 (see the Consort Checklist in the **Supplemental content**). The study protocol and its amendments were approved by the Ile-de-France Ethics Committee (IRB No. 2018-A00294-51). The trial registration number is NCT03630718. All the research was conducted in accordance with both the Declarations of Helsinki and Istanbul. Written consent was given by all the participants.

The eligibility criteria were as follows: 1) a woman over 18 years of age; 2) diagnosed with PBC according to recommended criteria;[27] 3) medically stable for a minimum of six months; 4) a high level of fatigue defined by a PBC-40 fatigue domain score ≥ 33;[28] 5) internet access to complete the online questionnaires; 6) a good understanding of the French language; and 7) a social security affiliation and signed informed consent.

The non-eligibility criteria were the following: 1) age over 75 years of age; 2) a history of LT; 3) on the waiting list for LT; 4) a Child-Pugh score of B or C;[29] 5) hepatic decompensation within the last six months, including ascites, variceal bleeding or hepatic encephalopathy; 5) hepatocellular

carcinoma; 6) serum total bilirubin > 50 µmoles/L; 7) disabling pruritus defined by permanent itch, itching skin lesions, or an itch score ≥ 7 over the last three weeks on a visual analog scale (VAS) of 0 to 10 (0 = the absence of pruritus, 10 = highest level of itching imaginable); 8) untreated depressive disorder reported in medical records; 9) any psychiatric disorder modifying perception of reality reported in medical records; and 10) any comorbidity that may explain the fatigue, not be medically controlled, or be potentially life-threatening within two years.

Randomization

Eligible patients were randomly assigned in a 1:1:1 ratio to receive SC-alone, SC plus psychoeducation intervention (SC-psychoeducation), or SC plus hypnosis intervention (SC-hypnosis). Block-balanced randomization was prepared by an independent statistician from the hospital. The block width and sequence were not disclosed to the investigators. Due to the nature of the interventions, the clinicians and patients were not blinded to treatment allocation. Individuals directly involved in data analysis did not participate in the interventions.

Procedure and follow-up

Eligible patients were first identified by checking medical records (i.e., patients identified as having expressed fatigue symptoms in routine care). These patients were then informed of the study objective and methods during a telephone screening session, and invited to complete the fatigue domain items of the PBC-40 questionnaire. Patients with a score ≥ 33 were invited to participate in the study and attended a medical visit to verify their eligibility and provide their signed informed consent. Randomization was then carried out.

The first measurement point occurred just after the medical visit (D0). Participants were asked to complete online self-report questionnaires. The first eight patients in each group participated in a first telephone interview with a research psychologist *before* they completed the online self-report questionnaires. The sample size of 24 interview patients was chosen because, in qualitative studies, data saturation (i.e., no new information emerges from the participants' discourse) is expected at around 12 to 20 participants. Having slightly that this number in this study ensured data saturation and appropriate performance of the group comparisons.

All the included patients were then informed of their group. For those randomly assigned to an intervention group (i.e., SC-psychoeducation or SC-hypnosis), a clinical psychologist contacted them to schedule sessions over the following four weeks. Participants assigned to the SC-alone group were followed up at the usual frequency of care visits and were informed that they would be offered a dedicated meeting at the end of the study so that they also experienced the both

interventions. For all patients, data were collected five (W5), 12 (W12), and 24 (W24) weeks after inclusion in the study, using the same self-report questionnaires. These measures were post-intervention for SC-psychoeducation and SC-hypnosis groups. The first eight patients from each group participated in a second telephone interview at W12 (**Supplemental Figure S1)**. These interviews were performed by CV.

Interventions

The psychoeducation and hypnosis interventions consisted of four weekly one-hour individual sessions. Two trained and experienced psychologists, one for psychoeducation and the other for hypnosis, delivered the interventions. At the beginning of the study, the sessions were held at Saint Antoine Hospital. However, during the COVID-19 pandemic, they were delivered by videoconference. The manual for each intervention is available in French on request from the corresponding author.

Psychoeducation intervention

The psychoeducation intervention consisted of a structured program designed to inform participants about the fatigue dimensions, and its etiology and treatments, to help them develop new strategies to better manage their fatigue and teach them how to find a balance between activity and rest. The program was inspired by a program developed by Reif et al. through group sessions in the field of oncology.[17] The format was adapted to individual sessions, which were more appropriate for this study, in order to personalize the intervention according to the participants' difficulties and needs. Each session had a theme: (1) Fatigue and its Dimensions; (2) Energy and its Management; (3) Fatigue and Emotions; (4) Fatigue and Sleep. Between each session, the participants were encouraged to rate their activities, level of fatigue and energy, and their emotions in an "energy notebook" given to them at the first session. Exercises were undertaken during each session and home exercises for between sessions were assigned to help participants become more attentive and aware of their own fatigue and energy levels and facilitate the implementation of behavior changes.

Hypnosis intervention

The hypnosis intervention aimed to decrease participants' fatigue and associated distress, promote feelings of energy and well-being, and promote self-hypnosis. The objective of the first session was to introduce participants to the hypnosis intervention, and its framework and goals.

During this initial session, the psychologist provided details of upcoming sessions, answered questions, explained the need to replicate the session exercises at home, and discussed the patient's perceptions and myths about hypnosis. A first hypnosis exercise was then proposed, with a hypnotic induction for mental and physical relaxation. Two metaphors were proposed that favored deep trance: a botanic metaphor and a second one more centered on fatigue. Finally, posthypnotic suggestions focused on the patient's feelings of energy beyond the session and her ability to recapture these feelings. This exercise was audio-recorded and provided to each participant at the end of the first session for them to use at home. The importance of developing self-hypnosis was discussed with the participants. The psychologist also advised the participants how they could practice self-hypnosis at home and helped them identify the best time to perform it each day. The following three weekly sessions aimed to deepen the exercises from the first session and continue the self-hypnosis learning, taking into account each patient's difficulties.

For each session, each psychologist indicated if the participant had attended to the session, if session objectives had been achieved and if exercises had been done at home.
For all patients, standard care was provided according to the severity of the patient's liver condition, at the pace deemed necessary by the hepatologist.

Outcomes

Primary outcome (self-reported questionnaire)

The primary outcome measure was the difference in the PBC-40 fatigue domain score between D0 and W12. The PBC-40 is a quality-of-life measure specifically designed for PBC patients.[28] It measures six domains through 40 items focused on symptoms, itching, fatigue, cognitive issues, emotional issues, and social quality of life. The fatigue domain is made up of 11 items and a 5-point Likert scale. The fatigue score ranges from 11 to 55, with higher values indicating worse fatigue. The French adaptation was previously used in an unpublished study, in which internal consistency for the PBC-40 fatigue domain was satisfactory (Cronbach's alpha = 0.84).

It is to note that the assessment at W24 was done because standard care usually consists in one medical consultation every six months. Thus, the measure at W24 was decided according to this practice and the final visit to close participation to the study was done at this time point.

Secondary outcomes (self-reported questionnaire)

The secondary outcomes were the differences between D0 and W12 in several specific or generic quality of life scores: the other domains of the PBC-40, the fatigue dimensions from the Multidimensional Fatigue Inventory, quality of life as measured by the Short Form Health Survey, sleep quality as measured by the Pittsburgh Sleep Quality Inventory, sleepiness, as measured by the Epworth Sleeping Scale, and anxiety and depression, as measured by the Hospital Anxiety and Depression Scale.[30-33] (see **Supplemental Table S3**).

Exploratory outcomes

For the first eight patients in each group, a qualitative evaluation of their fatigue experience was undertaken through telephone interviews at D0 and W12. Being structured in a funnel shape, the interview opened with a main question: "Can you tell me about your fatigue?" This question was broad and open enough for participants to take ownership of the theme of fatigue and approach it in whatever way suited them. The topic of fatigue was then explored through rephrasing, follow-up, and probing questions. Participants were asked to be alone and in a calm place during the interview.

Amendments to the study protocol

The initial inclusion criterion for fatigue was a PBC-40 fatigue score greater than 40 (in line with Jones and Newton[8]). However, this threshold was too restrictive with regard to the screened population and was reduced to a score ≥ 33 (in line with a previous French study for which the mean fatigue score was 32.5 ± 10.2; see the Sample Size Calculation section below). Other changes were made in this study, such as extending the inclusion period and carrying out the interventions by videoconference, given the health conditions associated with the Covid-19 pandemic (**Supplemental Table S7**).[34]

Sample size calculation

Jones and Newton showed that treatment with Modafinil reduced the fatigue score of PBC patients by 12 points after two months.[8] In this study, the sample size calculation relied on comparing the SC-alone group with the SC-psychoeducation group on the one hand, and with the SC-hypnosis group on the other hand. The same hypothesis was formulated for each intervention group: there would be a decrease of at least 11 points on the PBC-40 fatigue score at 12 weeks (i.e., eight weeks after the fourth and last intervention) and a standard error of the difference equal to 12. In a previous French unpublished study conducted among 144 women with PBC, the mean PBC-40 fatigue score was 32.5 ± 10.2. An 11-point drop in this score seemed at least realistic. Based on

this assumption, and assuming a 10% rate of loss to follow-up or patients not being evaluable, we calculated that we needed a total of 54 patients, or 18 patients per group, to achieve a power of 80%, with a two-sided significance level of 0.025%.

Statistical analysis

Primary outcome

The main analysis of the primary outcome was performed on the intent-to-treat (ITT) population, i.e., all participants randomized and as randomized. Descriptive analyses—median, interquartile range (IQR), and range—of the PBC-40 fatigue domain scores were performed by group at D0, W5, W12, and W24. The difference in the PBC-40 fatigue score between D0 and W12 (W12 minus D0) was calculated for each group and compared using the non-parametric Mann–Whitney test. Two sensitivity analyses were performed to assess the primary outcome: one for the per-protocol (PP) population (i.e., all randomized patients without major protocol violation) and the other for the ITT population with complete data. Single imputation was performed for the missing values using the median score of the group.

Secondary outcomes

The same analyses as for the primary outcome were performed for all the self-reported questionnaires described above. A p-value < 0.05 indicates statistical significance except in the case of multiple comparisons, for which the Bonferroni correction was applied ($p < 0.025$). No adjustment was made for multiplicity. All the statistical analyses were performed using IBM SPSS Statistics software (version 24.0).

Exploratory outcomes

The interviews were audio recorded and transcribed verbatim (eight participants in each group at D0 and W12, giving a total of 48 interviews). The interviews lasted a median of 21 min. [range 10–45 min]. The analyzed corpus (i.e., patient discourse) was derived from these transcripts after the researcher's questions and comments were deleted. Statistical textual analyses were conducted using the free software IraMuTeQ (R Interface for Multidimensional Analysis of Texts and Questionnaires), which automatically identifies lexical patterns in qualitative data based on word count and co-occurrences.[35] To put the results into better perspective, the D0 and W12 interviews were analyzed separately. A chi-square test was performed to assess the strength of the association between the treatment group and classes. The data were analyzed in accordance with the Consolidated criteria for reporting qualitative studies checklist (COREQ, see the **Supplemental Text S1-2** for additional information about these analyses).

Post hoc analyses

The proportions of participants who achieved a 5.5-point reduction in the PBC-40 fatigue score[37] or a score of less than 29 at W5 and W12 were evaluated and compared between groups. A linear regression analysis was performed to estimate group effect on the on PBC-40 fatigue difference score between D0 and W12.

RESULTS

Trial population

The participants were recruited from May 2019 to December 2022 and the last follow-up visit was in May 2023. A flowchart of the study is presented in **Figure 1**. Fifty-five women with PBC and significant fatigue were randomly assigned to the SC-alone group (n = 18), SC-psychoeducation group (n = 19), and SC-hypnosis group (n = 18). One participant assigned to the SC-psychoeducation group prematurely withdrew her consent and did not benefit from the intervention. All the other participants (98%) completed the trial. Two participants, one in the SC-alone group and the other in the SC-psychoeducation group, did not fully meet the eligibility criteria for inclusion. In total, the ITT and PP populations comprised 55 (100%) and 52 (95%) patients, respectively. All the proposed interview participants consented to take part in interviews at D0 and W12. The characteristics of the participants at inclusion are shown in **Table 1**. Most of the participants had non-advanced PBC with normal levels of total bilirubin, albumin, and platelets, and a Fibroscan-based liver stiffness measurement (LSM) < 10 kPa. In addition, most of the participants had normal or subnormal ALP and aminotransferase levels on treatment, and no or minimal pruritus, suggesting that the disease was inactive and under medical control. All but three participants (95%) were treated with UDCA, and a third of patients received second-line treatment (fibrates or obeticholic acid). None received specific treatment for pruritus. The three groups were broadly comparable, with the participants in the SC-hypnosis group being slightly older. Information on the participants' investment in the interventions and the characteristics of those who took part in the interviews are presented in the **Supplemental Tables S1, S2, S8**.

Primary outcome

Changes in the PBC-40 fatigue score for the different treatment groups are presented in **Table 2** and **Figure 2**. The PBC-40 fatigue score progressively decreased in all groups up to W12, then increased again at W24, although it remained below the initial score. In the ITT population, there was no absolute difference in the fatigue score between D0 and W12 between the SC-alone group and the

SC-psychoeducation group (-3 vs. -6; U = 137.0; p = 0.30), nor between the SC-alone group and the SC-hypnosis group (-3 vs. -6; U = 117.0; p = 0.15). These results did not change when the analysis focused on the PP population (U = 105.5; p = 0.17: SC-alone group vs. SC-psychoeducation group; U = 104.0; p = 0.10: SC-alone group vs. SC-hypnosis group) or the ITT complete cases.

In post-hoc analysis (**Table 3**), the proportion of patients with a score lower than 29 at W5 and W12 was higher in the SC-hypnosis group (28.6% and 33.3%, respectively) than in the SC-psychoeducation group (7.7% and 5.3%) and the SC-alone group (0% and 5.6%) (p-values for Fisher's Exact test 0.045 at W5 and 0.022 at W12). However, the proportion of patients achieving a reduction of 5.5 points in the PBC-40 fatigue score did not differ between groups at each time point. Finally, the results of the regression analysis aligned with the primary outcome (**Table S9**).

Secondary outcomes

All the quantitative self-report questionnaires assessing quality of life, sleep quality, anxiety, and depression were consistent with the primary outcome, showing no statistically significant differences between groups (**Supplemental Table S4**).

Exploratory outcomes

At inclusion, participants' discourse was classified into two classes: (1) subjective experience of illness and (2) organization of daily life around fatigue. At W12, participants' discourse was classified into three classes: (1) experience and evolution of fatigue; (2) hypnosis sessions; (3) organization and routines of daily life in relation to fatigue (detailed results are presented in **Table 4**, **Supplemental Text S3-S4, Figure S2-4, Table S5-6**).

Safety

Four adverse events occurred during the trial, although none were serious. All occurred in the intervention groups, but none were considered to be related to the interventions. One participant from the SC-psychoeducation group contracted non-severe COVID-19 and recovered without sequelae. Three participants from the SC-hypnosis group had issues. One experienced diarrhea, which necessitated transient discontinuation of UDCA. Another had to start second-line therapy with bezafibrate because of an increase in their serum liver tests on UDCA alone. The third had an asthma attack requiring treatment with inhaled corticosteroids.

DISCUSSION

This is the first randomized controlled trial comparing standard care with two psychological interventions—psychoeducation and hypnosis—for treating fatigue in PBC. A reduction of fatigue was observed in all groups after 12 weeks. However, our hypothesis of better improvement after four weekly sessions of psychological interventions in addition to SC, compared to SC-alone, was not met. This result, based on a quantitative assessment of fatigue and its daily-life repercussions, was consistent whether the analysis was performed for the ITT population or the PP population. However, using a more qualitative evaluation (i.e., based on the corpus of words associated with perceived fatigue), a positive change in the discourses of participants in both intervention groups was observed, which may suggest that a longer intervention might evidence improved fatigue scores.

Fatigue is a frequent symptom of PBC, and can have a major impact on patients' quality of life and social interactions. To date, no pharmacological strategy for PBC, including those approved as disease-modifying therapies, has been shown to unquestionably reduce symptoms of fatigue.[7, 11, 12, 14] These results and those presented here show just how difficult it is to treat fatigue in PBC. Interestingly, participating in our study seemed to have an overall positive impact on participants, as fatigue decreased in all three groups between inclusion and Week 12. The explanation for this could lie in the fact that the self-report questionnaires completed during the study, as well as the interviews for those who took part, encouraged participants to reflect on their fatigue, become more aware of it, and undertake changes in their daily lives. This could be particularly the case for the SC-alone group, where participants might have been disappointed not to be assigned to an intervention group, despite being informed they would be offered a dedicated meeting at the end of the study to experience both interventions. It remains to be demonstrated whether the reduction in fatigue is linked to a clinically significant change in participants' experience.

In terms of intervention modalities, four sessions may not have been enough to implement significant changes in the participants' lives and alter their fatigue scores, especially in the SC-psychoeducation participants, for whom the proportion of participants having a score lower than 29 post intervention was lower than for the SC-hypnosis participants. Our psychoeducation program was based on Reif et al., although their format was adapted for use here.[17] Our intervention consisted of four 60-minute individual sessions, whereas Reif et al.'s program consisted of six 90-minute group sessions. The advantage of individual sessions is that they allow the intervention to be tailored to patients' individual difficulties and needs, as well as practical constraints, although group sessions help patients to feel less isolated through meeting others with similar difficulties and providing mutual support, which also stimulates behavioral change. The longer intervention in the

Reif et al. program could have also improved the implementation of changes in fatigue management. The Reif et al. program also included two follow-up sessions (three and six months later), during which participants shared their experiences. These sessions are in line with the reinforcement sessions designed to improve the results of therapy. For example, in multiple sclerosis, the efficacy of cognitive behavioral therapy has been observed in the short and medium term, and the relevance of booster sessions is currently being explored.[38-39] The combination of psychoeducation and hypnosis might also be relevant.[40] For example, to maximize the potential clinical benefit for patients, this combination has been offered to breast cancer patients undergoing radiotherapy, who showed lower levels of fatigue compared to control groups, both after treatment and six months later.[18, 41]More globally, using body-mind approaches might be a key ingredient to improving fatigue in many chronic conditions. Very recently, an online mind–body program trial showed improvements to mental health and quality of life in PBC patients.[36] Fatigue was also evaluated but not an inclusion criterion and results showed that patients who did the exercise videos three days a week or greater did experience improvements in fatigue. Although the primary outcome was not reached in this study, analysis of the interviews revealed a positive shift in women's experience of fatigue at 12 weeks, particularly in the two intervention groups. At inclusion, the search for meaning appeared as an attempt to overcome the lack of understanding and cope with illness,[42] while the perception of fatigue was linked to difficulties in daily life.[3,43] Patients organized their lives around fatigue by implementing coping strategies such as restricting activities, allowing recovery time, and maintaining energy for essential activities.[44] Finally, the participants' discourse showed difficulties related to sleep disorders, such as difficulty falling asleep, daytime sleepiness, and poorer sleep quality.[43, 45-47] However, at 12 weeks, the participants' discourse in both intervention groups had changed. Participants assigned to the SC-psychoeducation group spoke more about improved fatigue and energy through the application of strategies in daily life, as well as having a better understanding of the symptoms of fatigue, while those assigned to the SC-hypnosis group spoke more about their satisfaction with the intervention and the benefits felt during the sessions, particularly on their general well-being. This improvement is in line with the literature evaluating the effects of psychoeducation and hypnosis on fatigue in other chronic diseases.[17, 18, 20, 22, 24, 48-50]

This study has some limitations. First, the main eligibility criterion, the PBC-40 fatigue score threshold, had to be reduced from 40 to 33 due to insufficient recruitment. The initial hypothesis, on which the study sample size was estimated, was an 11-point decrease from 40 in the PBC-40 fatigue score (i.e., a decrease to 29). As a result of the reduced criterion score, the trial may not have had adequate power to detect a beneficial effect of intervention. The COVID-19 pandemic resulted in the

second limitation. Around a third of the participants were recruited before the first containment in France, and the inclusions were interrupted from March to August 2020. Therefore, participants took part in the study in different care settings, which may have impacted their fatigue levels and daily activities. A third limitation is related to the heterogeneity in the intervention modalities, in that the interventions were first delivered at the Hospital, but this changed to videoconference because of the COVID-19 pandemic. Despite these limitations, this study showed a high degree of patient acceptance of the intervention sessions.

In conclusion, the psychoeducation and hypnosis interventions did not result in a significantly greater short-term reduction in fatigue associated with PBC than SC-alone. However, a positive change was observed in the perceptions of fatigue in both intervention groups. Further research should explore the value of booster sessions and/or the combination of both interventions for improving fatigue management.

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Figure 1. Flowchart of the study

Note: * One participant did not fully meet the eligibility criteria for inclusion

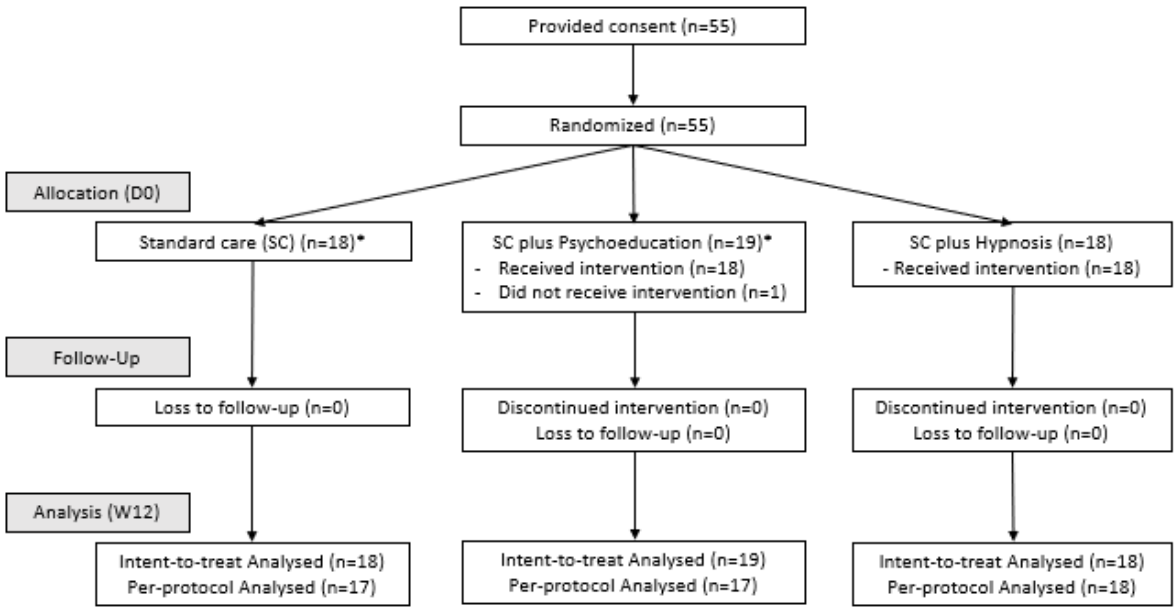
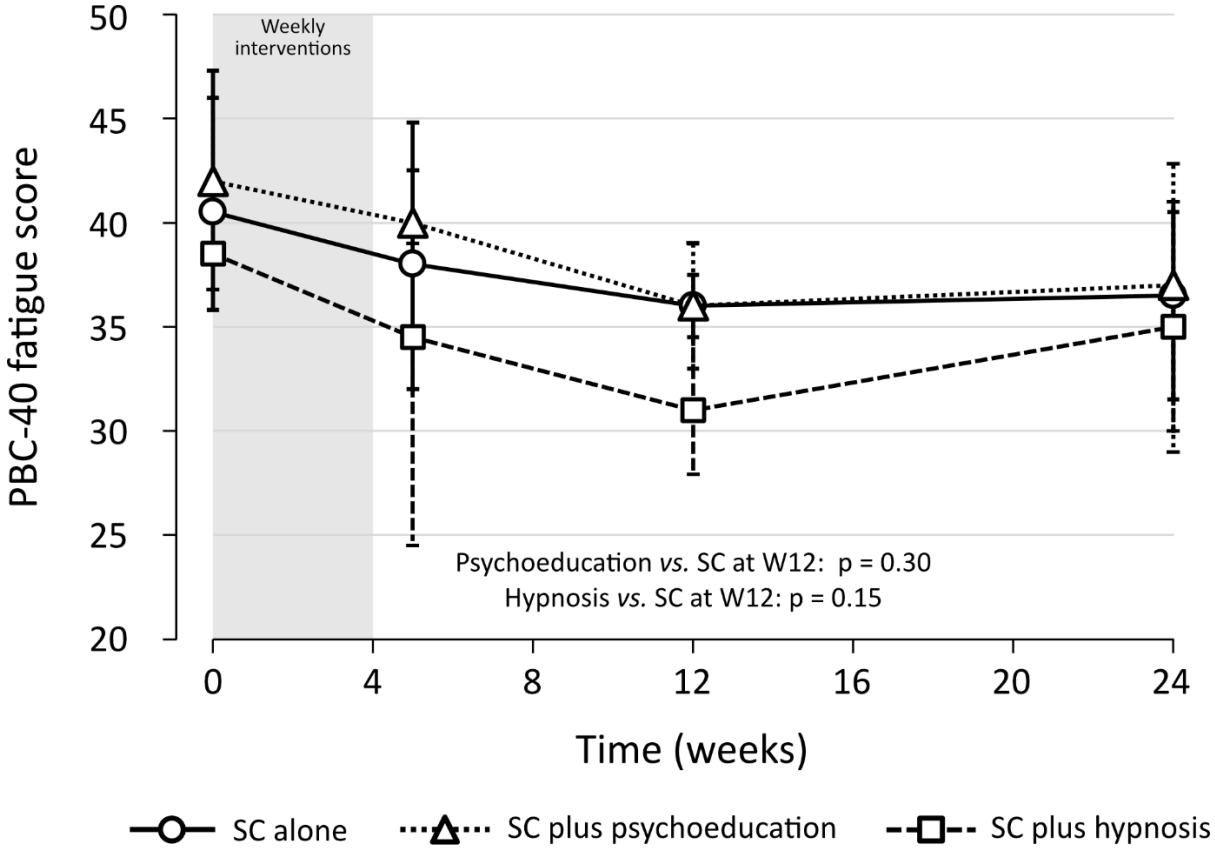


Figure 2. Evolution of PBC-40 fatigue score according to time and treatment group



Supplementary_CBP-HOPE_AJG_R1-http://links.lww.com/AJG/D703

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Table 1. Demographic and clinical characteristics of the participants at inclusion.

	SC-alone Group (n=18)	SC-psychoed. Group (n=19)	SC-hypnosis Group (n=18)
Age (years)	55.0 (43.8 – 61.0)[0]	57.0 (48.0 – 62.0)[0]	61.5 (55.0 – 65.0)[0]
Time since diagnosis (years)	4.0 (2.5 – 8.5)[1]	5.0 (2.8 – 10.8)[1]	6.0 (4.0 – 8.5)[1]
UDCA (present)	17 (100)[1]	18 (100)[1]	17 (94.4)[1]
Obeticholic acid (present)	0 (0.0)[1]	3 (16.6)[1]	1 (5.8)[1]
Bezafibrate (present)	4 (23.5)[1]	4 (22.2)[1]	3 (17.6)[1]
Fenofibrate (present)	1 (5.8)[1]	1 (5.5)[1]	2 (11.7)[1]
Budesonide (present)	1 (5.8)[1]	0 (0)	1 (5.8)[1]
Prednisone (present)	1 (5.8)[1]	0 (0)	0 (0)
Azathioprine (present)	0 (0)	1 (5.5)[1]	0 (0)
Mycophenolate mofetil (present)	0 (0)	2 (11.1)[1]	0 (0)
Sertraline (present)	0 (0)	1 (5.5)[1]	1 (5.8)[1]
Vitamin D (present)	12 (70.5)[1]	12 (66.6)[1]	11 (64.7)[1]
Fibrates (present)	5 (29.4)[1]	5 (27.8)[1]	5 (29.4)[1]
0-10 VAS itch score	0.0 (0.0 – 3.7)[2]	1.0 (0.0 – 4.0)[1]	0.0 (0.0 – 2.0)[3]
PBC-40 fatigue score †	39.0 (36.0 – 43.0)[1]	41.5 (37.5 – 45.6)[1]	38.5 (37.0 – 43.8)[2]
Total bilirubin (µmol/L)	9.0 (6.0 – 15.5)[5]	9.8 (7.3 – 12.0)[3]	8.0 (6.0 – 10.0)[3]
Alkaline Phosphatase (U/L)	82.0 (56.0 – 116.5)[5]	105.5 (89.3 – 120.3)[1]	85.0 (58.0 – 106.5)[4]
ALT (U/L)	25.0 (18.0 – 44.0)[5]	30.0 (20.0 – 54.5)[2]	23.0 (18.0 – 32.0)[3]
Albumin (g/L)	42.0 (38.5 – 44.8)[6]	41.0 (37.8 – 43.3)[5]	41.0 (37.0 – 42.0)[8]
Platelets count (G/L)	264.0 (215.5 – 323.5)[5]	229.0 (195.0 – 298.5)[2]	273.0 (233.0 – 291.0)[3]
LSM (kPa)	9.0 (5.1 – 10.4)[3]	6.9 (4.9 – 11.1)[1]	5.8 (5.2 – 7.0)[3]

Data are expressed in median (IQR) for quantitative variables and in number (%) for qualitative variables. SC, standard care; Psychoed., psychoeducation; UDCA, ursodeoxycholic acid; VAS, visual analogue scale; ALT, alanine aminotransferase; LSM, liver stiffness measurement. Exponent numbers are missing values; † At the screening visit.

Table 2. PBC-40 Fatigue score according to time and randomized group.

		SC-alone Group		**SC-psychoed. Group**		**SC-hypnosis Group**
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
Baseline (D0)*	18	40.5 (35.8 – 47.3)	19	42.0 (38.0 – 46.0)	18	38.5 (36.8 – 42.0)
Week 5 (W5)	16	38.0 (35.0 – 44.8)	13	40.0 (32.0 – 42.5)	14	34.5 (24.8 – 39.0)
Week 12 (W12)	18	36.0 (34.5 – 37.5)	19	36.0 (33.0 – 39.0)	18	31.0 (27.8 – 35.5)
Week 24 (W24)	14	36.5 (31.5 – 40.5)	14	37.0 (29.0 – 42.8)	15	35.0 (30.0 – 41.0)
W12 – D0†	18	-3.0 (-10.0 – 1.0)	19	-6.0 (-8.0 – -4.0)	18	-6.0 (-11.5 – -4.8)

SC, standard care; Psychoed., psychoeducation; IQR; interquartile range.

* At randomization; † Primary outcome measure with imputation of 9 missing values (2 at W12 for SC-alone group; 1 at D0 and 5 at W12 for SC-psychoeducation group; 1 at W12 for SC-hypnosis group)

Table 3. Post-hoc analysis of PBC-40 Fatigue score and its dichotomized absolute change over time according to intervention group.

		SC-alone Group	SC-psychoed. Group	SC-hypnosis Group	p[+]
Week 5 (W5)					
Score < 29	Yes	0% (0)	7.7% (1)	28.6% (4)	.045
	No	100% (16)	92.3% (12)	71.4% (10)	
Reduction > 5.5	Yes	31.3% (5)	30.8% (4)	42.9% (6)	.748
	No	68.8% (11)	69.2% (9)	57.1% (8)	
Missing data		2	6	4	
Week 12 (W12)*					
Score < 29	Yes	5.6% (1)	5.3% (1)	33.3% (6)	.022
	No	94.4% (17)	94.8% (17)	66.7% (12)	
Reduction > 5.5	Yes	44.4% (8)	57.9% (11)	55.6% (10)	.685
	No	55.6% (10)	42.1% (8)	44.4% (8)	
Missing data		0	0	0	
Week 24 (W24)					
Score < 29	Yes	21.4% (3)	14.4% (2)	13.3% (2)	.815
	No	78.6% (11)	85.7% (12)	86.7% (13)	
Reduction > 5.5	Yes	50.0% (7)	42.9% (6)	46.7% (7)	.931
	No	50.0% (7)	57.1% (8)	53.3% (8)	
Missing data		4	5	3	

SC, standard care; Psychoed., psychoeducation

* Primary outcome measure with imputation of 9 missing values (2 at W12 for SC-alone group; 1 at D0 and 5 at W12 for SC-psychoeducation group; 1 at W12 for SC-hypnosis group)

[+] p-value for Chi-2 test or Fisher's exact test

Table 4. Results from the statistical textual analyses on the interviews at inclusion and week 12

Class	Theme of the class	Corpus percentage	Most representative words	Description of the class	Association with groups
First interview (Inclusion, D0)					
Class 1	Subjective experience of illness	84%	"illness" "see" "understand" "find" "doctor"	Participants expressed a significant difficulty in understanding PBC and its issues, as well as its main symptom, fatigue, and attempted to make sense about the illness. The patients' discourse showed the importance of self-observation linked to how they perceive themselves, changes since the diagnosis of their illness, and fatigue experienced in their daily lives. Patients also reported how their fatigue was perceived by those around them, while the illness itself seemed invisible.	Associated with the SC-hypnosis group and the the SC-psychoeducation group
Class 2	Organization of daily life around fatigue	16%	"morning" "sleep" "(after)noon" "get up" "go to bed"	The discourse showed the importance of finding rest periods during the day, daytime sleepiness, and a lack of motivation.	Associated with the SC-alone group
Second interview (Week 12)					
Class 1	Experience and evolution of fatigue	62%	"fatigue" "thing" "illness" "thinking" "trying"	The words expressed how the participants reiterated the experience and evolution of their fatigue since the first interview, with a more experimental component being linked to the implementation of management strategies. This shows how participants had evolved in their understanding of their fatigue. Through self-observation and	Associated with the SC-psychoeducation group

				analysis of their feelings, they tried to understand the intertwining of the different types of fatigue in their illness. Most participants emphasized the unpredictability and intensity of fatigue.	
Class 2	Hypnosis sessions	13%	"session" "find" "hypnosis" "part" "frankly"	The discourse showed attempts to find explanations and solutions for managing fatigue. The participants talked about improving their symptoms of fatigue thanks to hypnosis (which to them, appeared to be a solution), their evolution over the course of the sessions, and the setting in which the sessions took place. They also talked about their perceptions of how their fatigue evolved, as well as their satisfaction with hypnosis, adoption of the exercises, and for some, maintaining its management.	Associated with the SC-hypnosis group
Class 3	Organization and routines of daily life in relation to fatigue	25%	"time" "morning" "get up" "wake up" "(after)noon"	The discourse showed how the patients felt and were tired throughout the day, and how their daily life was organized around this symptom. In connection with the fluctuating nature of fatigue, the patients tried to preserve their energy, for work, for example. Their discourse also showed how fatigue upon awakening impacted the rest of the day and how sleep seemed to be an important issue for the participants in managing their fatigue.	Associated with the SC-alone group

HOPE Trial of Hypnosis and Psychoeducation for Fatigue in PBC

Open-Label Randomized Trial

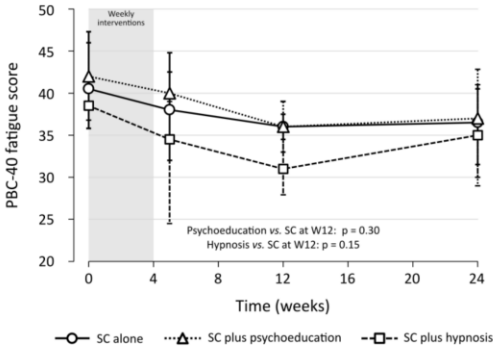
+ Stable PBC + PBC-40 Fatigue Score ≥ 33

- 4 sessions Hypnosis n=18 → Interviews + Self-Report Quest.
- 4 sessions Psychoed. n=19 → Interviews + Self-Report Quest.
- Std. Care n=18 → Interviews + Self-Report Quest.

W0 W4 W8 **W12** W24

Primary Outcome: Fatigue Score at W12
Explor. Outcome: Interview Findings at W12

Findings



The quantitative primary outcome was unmet, but both interventions improved patients' perceptions of fatigue in exploratory analyses

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