Current Hepatology Reports (2019) 18:127–133
https://doi.org/10.1007/s11901-019-00458-0

AUTOIMMUNE, CHOLESTATIC, AND BILIARY DISEASES (S GORDON AND C BOWLUS, SECTION EDITORS)

Management of Fatigue in Primary Biliary Cholangitis

Amardeep Khanna[1] · Vinod S. Hegade[2] · David E. Jones[1]

Published online: 23 May 2019

Abstract

Purpose of Review Fatigue in primary biliary cholangitis patients is a frequently encountered and often debilitating symptom. With no currently approved drug therapies available to target fatigue as a symptom, managing these patients can be very challenging in a day-to-day clinical practise. We have critically appraised currently available evidence on various pharmacological agents trialled in the management of fatigue in PBC.

Recent Findings Most recently, a randomised controlled trial from Newcastle group using Rituximab in high fatigue patients has shown equivocal results for the improvement of fatigue, with a significant placebo effect. The data suggest that the general use of Rituximab for the treatment of fatigue in PBC is not supported; however, there was evidence suggesting improvement of muscle metabolic dysfunction linked to peripheral fatigue, and it may be that the agent has value in a carefully selected subgroup of patients with, in particular, peripheral fatigue. Further work is needed in this area. In addition, there are several non-pharmacological interventions which are available and can be considered in management of fatigue in PBC patients.

Summary A combination of non-pharmacological and currently non-licenced pharmacological therapies may be required in managing fatigue in PBC patients.

Keywords Primary biliary cirrhosis · Fatigue · Rituximab · Modafinil · PBC-40 questionnaire

Introduction

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease with a significant autoimmune component. It is characterised by progressive immune-mediated small and intermediate intrahepatic duct damage leading eventually to cirrhosis and associated complications. PBC has a female preponderance with a female/male ratio of 9:1. Diagnostic criterions set out in the EASL 2017 guidelines suggest that, in adult patients with cholestasis and no likelihood of systemic disease, a diagnosis of PBC can be made based on elevated ALP and the presence of anti-mitochondrial antibody (AMA) at a titre ≥ 1:40 [1].

Clinical presentation of PBC ranges from asymptomatic patients who have been found incidentally to have abnormal liver chemistry to patients presenting with complications of cirrhosis [2, 3]. It is now increasingly recognised that there is an additional clinical problem related to systemic symptoms of PBC, namely fatigue, pruritus, cognitive symptoms leading to social isolation and emotional dysfunction [4]. A patient-derived and fully validated assessment tool, the PBC-40, with domains covering localised symptoms, itch, fatigue, social, cognition and emotional dysfunction, is widely used in clinical practise and clinical trials as a patient-derived measure of quality of life [5]. Importantly, currently available first-line therapy Ursodeoxycholic acid (UDCA) and second-line therapies Obeticholic acid (OCA) are both ineffective in improving PBC-related symptoms [6, 7]. In this article, we focus on understanding the pathophysiology, impact on quality of life and available evidence on management of fatigue in PBC.

This article is part of the Topical Collection on *Autoimmune, Cholestatic, and Biliary Diseases*

✉ Amardeep Khanna
amardeep.khanna@newcastle.ac.uk

[1] Institute of Cellular Medicine and NIHR Biomedical Centre, Newcastle University and Freeman Hospital, Newcastle upon and Tyne, UK

[2] Institute of Cellular Medicine and NIHR Biomedical Centre, Newcastle University, Newcastle upon and Tyne, UK

Impact of Fatigue in PBC

Fatigue is the most commonly reported symptom in PBC patients with 40–80% of patients encountering the symptom during the course of their illness. In addition to having debilitating physical effect on patients' ability to perform usual day-to-day activities, fatigue also significantly impacts on mental health, social life, family life, sexual life and job performance [4, 8, 9]. This is exemplified by an early Canadian study by Cauch-Dudek and colleagues which reported fatigue in 81% of PBC patients, with 7% reporting fatigue interfering with their physical activity, 57% family life and 30% job performance [10]. Poor sleep quality and depression were frequently reported to be related to fatigue. Verbally reported fatigue of longer than 6-month duration was reported in 68% patients with equal rates in UDCA-treated and -untreated patients. Furthermore, no correlation was seen with patient age, duration of disease, level of daily physical activity, bilirubin levels or Mayo Risk Score. Fatigued patients had more difficulty with global sleep quality as measured by Pittsburgh Sleep Quality Index, reporting greater impairment in subjective sleep quality, habitual sleep efficiency, sleep disturbances and daytime dysfunction. Fatigued patients reported higher rates of depression symptoms (71%) compared to 18% in non-fatigued patients [10]. Similar findings have been reported in other studies [11, 12] including the nationwide UK-PBC study, which added the observation that the impact of fatigue on quality of life is greatest in younger patients [13•].

Pathogenesis of Fatigue in PBC

The pathophysiology of fatigue is poorly understood [14••]. PBC patients exhibit both peripheral and central components to their fatigue (Table 1); the latter is characterised by neurophysiological abnormalities and is shown to be related to cognitive symptoms, sleep disturbance and depression [10].

Table 1 Pathogenesis of fatigue in PBC

Central causes of fatigue:
Depression
Sleep disturbance
Autonomic dysfunction
Organic changes in the brains (based on MRI studies)
Peripheral causes of fatigue:
Excessive deviation from aerobic to anaerobic metabolism and resulting lactate accumulation.
Abnormal serum amino acid levels:
Decreased levels of valine, isoleucine, leucine and tryptophan.
Increased levels of tyrosine and phenylalanine
Autoimmune

A complex interaction exists between depression, sleep disturbance and fatigue in these patients and correlates with the fatigue severity. In the UK-PBC studies of 2353 patients, the investigators used the PBC-40 measure, the Epworth Sleepiness Scale [ESS; a measure of daytime somnolence (score range of 0–24) and an ESS of 10 or more indicates clinically significant daytime somnolence], the Orthostatic Grading Scale [OGS; a measure of vasomotor autonomic dysfunction (score range 0–20 and a score of ≥ 4 indicates significant vasomotor autonomic dysfunction)] and the Hospital Anxiety & Depression Scale (HADS; a measure of depression and anxiety) [15, 16]. Significant numbers of PBC patients reported increased daytime somnolence contributing, in part, to their fatigue. A significant correlation was seen between fatigue severity and HADS-D score ($p < 0.0001$). In addition, autonomic dysfunction showed significant correlation with fatigue, cognitive impairment and sleep disturbance.

The role of autonomic dysfunction in fatigue development has been explored in detail. In one study, autonomic dysfunction was assessed using the Composite Autonomic Symptom Scale (COMPASS) and fatigue was assessed using the Fatigue Impact Scale (FIS) in two groups. Phase 1 (derivation phase), 40 chronic fatigue syndrome (CFS) patients and 40 age- and sex-matched controls; phase 2 (validation phase), 30 CFS patients, 37 normal controls and 60 patients with primary biliary cirrhosis. Symptoms of autonomic dysfunction were strongly and reproducibly associated with the presence of fatigue and correlated with severity of fatigue. Total COMPASS score > 32.5 was identified to have a positive predictive value of 0.96 (95%CI 0.86–0.99) and a negative predictive value of 0.84 (0.70–0.93) for the diagnosis of CFS and PBC patients and can be used to identify patients for targeted intervention studies [29]. The combination of depression with sleep disturbance and autonomic symptoms was seen more in patients with severe fatigue. In a related study, around 35% patient reported impaired perceived quality of life (QoL) (compared from 6% in healthy controls, $p < 0.0001$) [30].

There are also emerging data suggesting the presence of organic changes in the brains of PBC patients which may be associated with fatigue and linked cognitive symptoms [31, 32]. These fall into two groups, those demonstrating imaging

Table 2 Drugs/therapies trialled for management of fatigue in PBC

1. Rituximab [17••]
2. Modafinil [18, 19]
3. Fluoxetine [20]
4. Antioxidants [21]
5. Ondansetron [22]
6. Methotrexate [23, 24]
7. Corticosteroids [25]
8. Fluvoxamine [26]
9. Plasmapheresis [27, 28]

changes typically with advanced MR methodologies and those demonstrating neurophysiological and function abnormality [33, 34, 35•]. These changes suggest a fluid organic process which may be amenable to therapeutic intervention. Importantly, however, imaging change can be seen in the first few months following disease presentation suggesting that injury may start early in the disease process [36•]. It may be that effective treatment of the processes linked to fatigue requires early intervention.

The peripheral component of fatigue is described by PBC patients as the inability to sustain physical activity, loss of energy or feeling of "batteries being run down". Using a hand grip strength assessment protocol, it has been demonstrated that fatigued PBC patients show significantly accelerated decline in muscle function on repeated activity, with the rate of decline in grip strength being strongly correlated to severity of fatigue reported [37]. Intramuscular acidosis is a factor leading to muscle fatigue during prolonged and intense muscle activity; leading to reduction in contractile force and shortening velocity; and a prolongation of recovery time [38, 39].

Using cardio pulmonary exercise testing (CPET) in PBC patients undergoing transplant assessment, a baseline lowering in anaerobic threshold has been demonstrated compared with controls [40]. Over 95% of the PBC patients exhibit high titres of anti-PDH (pyruvate dehydrogenase) antibodies, directed against E2 and E3BP components of PDH, a key enzyme-regulating anaerobic metabolism. The level of bioenergetic mitochondrial abnormalities is directly related to anti-PDH levels [41, 42]. These findings suggest a possible excessive deviation from aerobic to anaerobic metabolism in fatigued PBC patients leading to excessive lactic acid accumulation.

Abnormal serum amino acid levels have also been implicated in the development of fatigue in PBC as observed in other chronic liver diseases. A study by Brog et al. demonstrated that PBC patients had significantly decreased levels of valine, isoleucine, and leucine. Tyrosine and phenylalanine were increased ($p < 0.0002$) and tryptophan decreased ($p < 0.0001$) in PBC. Furthermore, in fatigued PBC patients a significant inverse relation between tyrosine concentrations and fatigue and quality of life was found. Patients without fatigue and with good quality of life had increased tyrosine concentrations compared to fatigued patients [43].

In addition to directly disease mechanism-associated processes, it should be borne in mind that PBC is associated with other autoimmune conditions which are themselves associated with treatable fatigue [44]. There is high prevalence (up to 22%) of autoimmune hypothyroidism in PBC patients with a 20% prevalence of anti-thyroglobulin antibodies. Fatigue, lethargy and anorexia are among the array of symptoms that are common to hypothyroidism and PBC. Hence, in PBC patients who have concurrent hypothyroidism, the latter contributes at least partially to fatigue and is a very much treatable cause. It has been demonstrated that these symptoms improve with thyroxine supplementation [45].

Management of Fatigue in PBC

Currently, there is no recommended, licenced therapy available to treat fatigue in PBC patients, though various agents have been trialled (Table 2). Our approach to management is therefore supportive, aimed at treating reversible contributors to fatigue and co-morbid diseases which may exacerbating it; the "so called treatable causes contributing to the fatigue". These include, for example, hypothyroidism, itch (causing sleep disturbance and resultant day time fatigue and somnolence) and depression **(**Table 3**)**. In addition, various non-pharmacological measures can help provide patients with coping and supportive strategies (Table 4). These include energy pacing and daytime planning (fatigue is typically worse later in the day meaning that it is helpful for patients to plan important activities for the morning. This structured approach, although lacking the headline impact of an effective drug can, nonetheless, lead to significant quality of life improvement [14••, 46].

Drug Therapy and Other Interventions for Fatigue in PBC Patients

There are currently no licenced drug therapies for the treatment of fatigue in PBC. Furthermore, there is no evidence to suggest that either of the currently licenced treatments (UDCA and OCA) for progression prevention is effective in reducing fatigue. A number of agents have been evaluated in clinical trials for the treatment of fatigue in PBC (Table 2).

Table 3 Other pharmacological interventions (adapted from Best Practice & Research Clinical Gastroenterology, Vol 34, Amardeep Khanna, et al., Symptoms of PBC–Pathophysiology and management, 41–47, June–August 2018, with permission from Elsevier)

1. Treat depression
2. Treat Sicca syndrome
3. Treat vitamin D deficiency
4. Treat restless leg syndrome
5. Manage autonomic dysfunction:
   - Stop inappropriate anti-hypertensives
   - Keep well hydrated
   - TED stockings
6. Rule out obstructive sleep apnoea

Table 4 Non-pharmacological interventions (adapted from Best Practice & Research Clinical Gastroenterology, Vol 34, Amardeep Khanna, et al., Symptoms of PBC–Pathophysiology and management, 41–47, June–August 2018, with permission from Elsevier)

1. Patient engagement and encouraging patients to take ownership of their problem
2. Energy management-plan the daily activities and tailor them according to the hours and activities' where most fatigue is experienced.
3. Graded exercise
4. Physiotherapy
5. Occupational therapist
6. Psychologist
7. Smoking cessation advice
8. Engaging with employers to develop supportive work patterns
9. Engagement in patient awareness groups

Rituximab Rituximab, an anti-CD20 monoclonal antibody that selectively depletes B cells, is an effective immunotherapy in autoimmune disease with a strong autoantibody response. B cell and T cell responses to the E2 subunit of the inner mitochondrial membrane enzyme pyruvate dehydrogenase complex have been implicated in the pathogenesis of PBC. Rituximab has shown to significantly decrease serum levels of total IgG, IgM and IgA as well as AMA [47, 48]. In a single-centre double-blinded placebo-controlled trial, 57 participants (aged ≥ 18 years with PBC and moderate or severe fatigue (PBC-40 fatigue domain score of > 33)) were randomised to receive two doses of either rituximab (1000 mg) or saline (placebo). The primary outcome measure was the difference between intervention and control groups at 12 weeks in the fatigue domain score of the PBC-40. Improvement in fatigue was seen in the Rituximab-treated group ($n = 28$, falling from 41.2 ± 5.5 to 36.2 ± 8.4 at 3 months). A similar magnitude fall was, however, also seen in the placebo group (43.0 ± 5.9 to 38.1 ± 8.7). Following adjustment for baseline characteristics, fatigue severity was lower in the Rituximab-treated group; however, this was not statistically significant. Rituximab therapy was safe with no serious adverse events [17••].

Modafinil The CNS stimulant drug modafinil has an established role in the treatment of excessive daytime somnolence in non-liver disease states. An open label study explored the responses of modafinil therapy in 21 PBC patients suffering from significant daytime somnolence as assessed by Epworth Sleepiness Scale [18]. In keeping with previous observations, this group had very prominent fatigue when assessed using the PBC-40. Significant improvement was seen in Epworth Sleepiness Scale scores (15 ± 3 vs. 8 ± 6, $P < 0.0005$), was seen with modafinil therapy, and this was accompanied in improvement in fatigue severity [PBC-40 fatigue domain score (46 ± 6 vs. 34 ± 12, $P < 0.0001$)] [18]. A further study, exploring the utility of modafinil in patients not characterised by significant daytime somnolence, showed, unsurprisingly, given the mode of action of the drug, no benefit for fatigue [19]. Taken together, the data suggest that modafinil should not be used as a treatment for fatigue per se but may have value in the subgroup of patients where fatigue is contributed to by significant daytime somnolence.

Fluoxetine A double-blind, placebo-controlled study analysed the safety and efficacy of fluoxetine for the treatment of fatigue in PBC. Patients were randomised to two groups to receive 20 mg fluoxetine once daily, or matched placebo for 8 weeks. The primary study endpoint was a > or = 50% reduction in overall Fisk Fatigue Impact Scale FFIS score at the end of treatment (a very high bar for a fatigue trial end-point). Health-related quality of life (HRQL) was assessed as a secondary endpoint. No statistically significant change in median FFIS score and HRQL was observed in the fluoxetine group after 8 weeks of therapy [20].

Antioxidants A trial using two compound antioxidant preparations—Bio-Antox (containing the antioxidants selenium, methionine, beta-carotene, vitamin C and vitamin E and Bio-Quinone Q10 (containing the antioxidants coenzyme Q10 and alpha-tocopherol)—reported improvement in fatigue in 9 of 13 patients; at least in one domain of Fisk Fatigue Score ($r = 0.44$, $P < 0.05$), even more so when taken together (69% compared from 56% when bio-Antox taken alone) [49]. However, a placebo-controlled trial of oral antioxidant supplementation failed to confirm benefit [21].

Ondansetron Ondansetron is a selective 5-HT3 receptor antagonist with an effect on central serotonergic neurotransmission alterations which were believed to be implicated in the pathogenesis of fatigue in PBC. A multi-centre, randomised, double-blind, placebo-controlled, crossover trial evaluated the efficacy of ondansetron in fatigued PBC patients [22]. Sixty patients with clinically stable PBC, a Fatigue Severity Score > 4, and no other identifiable cause for fatigue were randomised to receive ondansetron (4 mg) or placebo orally 3 times daily for 4 weeks. Subjects then crossed over, after a 1-week washout period, for a further 4 weeks of ondansetron or placebo. In the placebo phase period 1, there was no significant fatigue reduction (as measured by a Fatigue Severity Score (FSS) and Fatigue Impact Scale (FIS) with ondansetron compared to placebo. During period 2, FSS and FIS decreased significantly in ondansetron group ($p = 0.001$). However, there is a widely held view that these results were influenced by drug side effects such as constipation unblinding subjects and later clinical experience would support the view that ondansetron has no role in treating PBC-related fatigue.

Methotrexate A pilot study of five patients with stage I-III PBC treated with weekly methotrexate (MTX) for 15 months reported improvement in fatigue in three (60%) patients [23]. Another study using a combination of UDCA and MTX reported conflicting results with no improvement in symptoms and one patient withdrawing from the study due to extreme fatigue [24].

Corticosteroids A study combining UDCA with prednisolone showed improvement in symptoms in conjunction with biochemical improvement with fatigue disappeared in four of six symptomatic patients [25]. There is no high-quality evidence to determine whether there is a clinically significant effect.

Fluvoxamine In a randomised placebo-controlled trial of the antidepressant fluvoxamine, 17 patients received fluvoxamine and 16 received placebo for a period of 6 weeks. Fatigue and quality of life were measured using a visual analogue scale, the Fisk Fatigue Severity Scale, the Multidimensional Fatigue Inventory and the SF-36 did not show any statistically significant beneficial effect of fluvoxamine [26].

Plasmapheresis A pilot study of six patients with stage III-IV PBC with symptoms refractory to pharmacological therapy and undergoing plasma exchange therapy for mean period of 40 weeks demonstrated improvement in fatigue in four of the six (67%) patients [50]. A similar study of five patients who underwent a mean of 63 plasmapheresis procedures over a mean of 112 weeks also showed moderate reduction in fatigue [27]. The significance of this effect is not clear and the approach has not entered clinical use for this indication.

Role of Liver Transplant in Treating Fatigue

Current evidence does not support liver transplantation for fatigue as a main indication in PBC. An earlier study reported a significant improvement in quality of life related to the symptoms of cholestatic liver diseases (PBC and PSC) when compared pre- and post-liver transplant ($p < 0.01$). Even though fatigue was still among the top rated most distressing symptoms even post-transplant, however, there was reduction in intensity (reported as quite a bit distressed pre-transplant to a little bit distressed post-transplant) [51]. Another study reported significantly higher levels of fatigue (measured by median FIS) in PBC patients ($n = 136$) compared to community controls ($P < 0.0001$) and chronic liver disease controls ($P < 0.05$) and did not show any significant changes in fatigue score in 11 patients undergoing liver transplantation compared to those in non-transplanted patients with advanced disease [4]. Therefore, current evidence is insufficient to support the routine use of liver transplantation in the management of fatigued PBC patients [52].

Conclusion

Fatigue in PBC patients has a significant impact on their physical, social, and psychological well-being. With no current licenced therapy available to treat fatigue, there is a huge unmet need which needs addressing. The current mainstay of management is largely supportive. Engaging with patients and exploring their expectations; clear communication about the available evidence and non-pharmacological interventions are cornerstones in managing these patients. Modafinil though not evidence based may be considered as non-licenced therapy in subgroup of patients with day time somnolence after obstructive sleep apnoea and other contraindications have been ruled out. Further research in developing therapies to deal with fatigue is required.

Compliance with Ethical Standards

Conflict of Interest David E. Jones has received research or speaker funding and/or has undertaken consultancy for Intercept, Falk, Pfizer, GSK, Novartis and Abbott. Amardeep Khanna and Vinod S. Hegade each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Liver EAftSot. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67(1):145–72.
2. Ali AH, Sinakos E, Silveira MG, Jorgensen RA, Angulo P, Lindor KD. Varices in early histological stage primary biliary cirrhosis. J Clin Gastroenterol. 2011;45(7):e66–71.
3. Pares A, Rodes J. Natural history of primary biliary cirrhosis. Clin Liver Dis. 2003;7(4):779–94.
4. Goldblatt J, Taylor PJ, Lipman T, et al. The true impact of fatigue in primary biliary cirrhosis: a population study. Gastroenterology. 2002;122(5):1235–41.
5. 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. 2005;54(11):1622–9.

6. Rudic JS, Poropat G, Krstic MN, Bjelakovic G, Gluud C. Ursodeoxycholic acid for primary biliary cirrhosis. Cochrane Libr. 2012.
7. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, et al. A placebo-controlled trial of Obeticholic acid in primary biliary cholangitis. N Engl J Med. 2016;375(7):631–43.
8. Poupon RE, Chretien Y, Chazouilleres O, Poupon R, Chwalow J. Quality of life in patients with primary biliary cirrhosis. Hepatology. 2004;40(2):489–94.
9. Witt-Sullivan H, Heathcote J, Cauch K, Blendis L, Ghent C, Katz A, et al. The demography of primary biliary cirrhosis in Ontario, Canada. Hepatology. 1990;12(1):98–105.
10. Cauch-Dudek K, Abbey S, Stewart DE, Heathcote EJ. Fatigue in primary biliary cirrhosis. Gut. 1998;43(5):705–10.
11. 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. 2000;95(3):760–7.
12. Puri AS, Kumar N, Gondal R, Lamba GS, Jain M. Primary biliary cirrhosis: an Indian experience. Indian J Gastroenterol. 2001;20(1): 28–9.
13.• Dyson JK, Wilkinson N, Jopson L, et al. The inter-relationship of symptom severity and quality of life in 2055 patients with primary biliary cholangitis. Aliment Pharmacol Ther. 2016;44(10):1039–50. **In this large study from the UK-PBC cohort, social dysfunction was shown to make the greatest contribution to quality of life (QoL) impairment in PBC wth younger patients more affected by QoL impairment.**
14.•• Swain MG, Jones DEJ. Fatigue in chronic liver disease: New insights and therapeutic approaches. Liver Int. 2019;39(1):6–19. **This excellent review summarises the current understanding of pathophysiology of fatigue in chronic liver disease and potential for targeting future interventions.**
15. Newton JL, Hudson M, Tachtatzis P, Sutcliffe K, Pairman J, Burt JA, et al. Population prevalence and symptom associations of autonomic dysfunction in primary biliary cirrhosis. Hepatology. 2007;45(6):1496–505.
16. Newton JL, Gibson GJ, Tomlinson M, Wilton K, Jones D. Fatigue in primary biliary cirrhosis is associated with excessive daytime somnolence. Hepatology. 2006;44(1):91–8.
17.•• Khanna A, Jopson L, Howel D, et al. Rituximab is ineffective for treatment of fatigue in primary biliary cholangitis: a phase-2 randomised controlled trial. Hepatology. 2018. **In this large clinic trial, rituximab treatment over a 12 motnh study period was shown to be safe but no evidence of effectiveness for the treatment of fatigue in PBC.**
18. Jones DE, Newton JL. An open study of modafinil for the treatment of daytime somnolence and fatigue in primary biliary cirrhosis. Aliment Pharmacol Ther. 2007;25(4):471–6.
19. Silveira MG, Gossard AA, Stahler AC, et al. A randomized, placebo-controlled clinical trial of efficacy and safety: Modafinil in the treatment of fatigue in patients with primary biliary cirrhosis. Am J Ther. 2016.
20. Talwalkar JA, Donlinger JJ, Gossard AA, Keach JC, Jorgensen RA, Petz JC, et al. Fluoxetine for the treatment of fatigue in primary biliary cirrhosis: a randomized, double-blind controlled trial. Dig Dis Sci. 2006;51(11):1985–91.
21. Prince MI, Mitchison HC, Ashley D, Burke DA, Edwards N, Bramble MG, et al. Oral antioxidant supplementation for fatigue associated with primary biliary cirrhosis: results of a multicentre, randomized, placebo-controlled, cross-over trial. Aliment Pharmacol Ther. 2003;17(1):137–43.
22. Theal JJ, Toosi MN, Girlan L, Heslegrave RJ, Huet PM, Burak KW, et al. A randomized, controlled crossover trial of ondansetron in patients with primary biliary cirrhosis and fatigue. Hepatology. 2005;41(6):1305–12.
23. Weber P, Scheurlen M, Wiedmann KH. [Methotrexate in the therapy of primary biliary cirrhosis]. Dtsch Med Wochenschr. 1991;116(36):1347–52.
24. Lindor KD, Dickson ER, Jorgensen RA, Anderson ML, Wiesner RH, Gores GJ, et al. The combination of ursodeoxycholic acid and methotrexate for patients with primary biliary cirrhosis: the results of a pilot study. Hepatology. 1995;22(4 Pt 1):1158–62.
25. Wolfhagen FH, van Buuren HR, Schalm SW. Combined treatment with ursodeoxycholic acid and prednisone in primary biliary cirrhosis. Neth J Med. 1994;44(3):84–90.
26. 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. 2004;4:13.
27. Ambinder EP, Cohen LB, Wolke AM, Field SP, Adelsberg B, Schaffner F, et al. The clinical effectiveness and safety of chronic plasmapheresis in patients with primary biliary cirrhosis. J Clin Apher. 1985;2(3):219–23.
28. Alallam A, Barth D, Heathcote EJ. Role of plasmapheresis in the treatment of severe pruritus in pregnant patients with primary biliary cirrhosis: case reports. Can J Gastroenterol. 2008;22(5):505–7.
29. Newton JL, Okonkwo O, Sutcliffe K, Seth A, Shin J, Jones DE. Symptoms of autonomic dysfunction in chronic fatigue syndrome. QJM. 2007;100(8):519–26.
30. Mells GF, Pells G, Newton JL, Bathgate AJ, Burroughs AK, Heneghan MA, et al. Impact of primary biliary cirrhosis on perceived quality of life: the UK-PBC national study. Hepatology. 2013;58(1):273–83.
31. McDonald C, Newton J, Lai HM, Baker SN, Jones DE. Central nervous system dysfunction in primary biliary cirrhosis and its relationship to symptoms. J Hepatol. 2010;53(6):1095–100.
32. Newton JL, Hollingsworth KG, Taylor R, el-Sharkawy AM, Khan ZU, Pearce R, et al. Cognitive impairment in primary biliary cirrhosis: symptom impact and potential etiology. Hepatology. 2008;48(2):541–9.
33. Hollingsworth KG, Jones DE, Aribisala BS, Thelwall PE, Taylor R, Newton JL, et al. Globus pallidus magnetization transfer ratio, T(1) and T(2) in primary biliary cirrhosis: relationship with disease stage and age. J Magn Reson Imaging. 2009;29(4):780–4.
34. Hollingsworth KG, Jones DE, Taylor R, Frith J, Blamire AM, Newton JL. Impaired cerebral autoregulation in primary biliary cirrhosis: implications for the pathogenesis of cognitive decline. Liver Int. 2010;30(6):878–85.
35.• Mosher VAL, Swain MG, Pang JXQ, et al. Magnetic resonance imaging evidence of hippocampal structural changes in patients with primary biliary cholangitis. Clin Transl Gastroenterol. 2018;9(7):169. **In this elegant study, hippocampal changes were shown to occur early in the disease course of PBC, similar in magnitude to those observed in major depressive disorder and neurodegenerative diseases.**
36.• Grover VP, Southern L, Dyson JK, et al. Early primary biliary cholangitis is characterised by brain abnormalities on cerebral magnetic resonance imaging. Aliment Pharmacol Ther. 2016;44(9): 936–45. **In the pre-cirrhotic PBC patients neuroimaging abnormalities were shown, suggesting that the brain changes seen in PBC occur early in the pathological process, even before significant liver damage has occurred.**
37. Goldblatt J, James OF, Jones DE. Grip strength and subjective fatigue in patients with primary biliary cirrhosis. JAMA. 2001;285(17):2196–7.
38. Allen DG, Lannergren J, Westerblad H. Muscle cell function during prolonged activity: cellular mechanisms of fatigue. Exp Physiol. 1995;80(4):497–527.
39. Rico-Sanz J. Progressive decrease of intramyocellular accumulation of H+ and pi in human skeletal muscle during repeated isotonic exercise. Am J Physiol Cell Physiol. 2003;284(6):C1490–6.

40. Prentis J, Jones D, Trenell M, Snowden C. P75 impaired cardiorespiratory reserve in primary biliary cirrhosis patients undergoing liver transplant assessment. Gut. 2011;60(Suppl 2):A34–5.
41. Teoh KL, Mackay IR, Rowley MJ, Fussey SP. Enzyme inhibitory autoantibodies to pyruvate dehydrogenase complex in primary biliary cirrhosis differ for mammalian, yeast and bacterial enzymes: implications for molecular mimicry. Hepatology. 1994;19(4):1029–33.
42. Yeaman SJ, Kirby JA, Jones DE. Autoreactive responses to pyruvate dehydrogenase complex in the pathogenesis of primary biliary cirrhosis. Immunol Rev. 2000;174:238–49.
43. ter Borg PC, Fekkes D, Vrolijk JM, van Buuren HR. The relation between plasma tyrosine concentration and fatigue in primary biliary cirrhosis and primary sclerosing cholangitis. BMC Gastroenterol. 2005;5(1):11.
44. Watt FE, James OF, Jones DE. Patterns of autoimmunity in primary biliary cirrhosis patients and their families: a population-based cohort study. QJM. 2004;97(7):397–406.
45. Elta GH, Sepersky RA, Goldberg MJ, Connors CM, Miller KB, Kaplan MM. Increased incidence of hypothyroidism in primary biliary cirrhosis. Dig Dis Sci. 1983;28(11):971–5.
46. Jones DE, Sutcliffe K, Pairman J, Wilton K, Newton JL. An integrated care pathway improves quality of life in primary biliary cirrhosis. QJM. 2008;101(7):535–43.
47. Myers RP, Swain MG, Lee SS, Shaheen AA, Burak KW. B-cell depletion with rituximab in patients with primary biliary cirrhosis refractory to ursodeoxycholic acid. Am J Gastroenterol. 2013;108(6):933–41.
48. Tsuda M, Moritoki Y, Lian ZX, Zhang W, Yoshida K, Wakabayashi K, et al. Biochemical and immunologic effects of rituximab in patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid. Hepatology. 2012;55(2):512–21.
49. Watson JP, Jones DE, James OF, Cann PA, Bramble MG. Case report: oral antioxidant therapy for the treatment of primary biliary cirrhosis: a pilot study. J Gastroenterol Hepatol. 1999;14(10):1034–40.
50. Surrenti C, Pozzi M, Biagini MR, Franco C, Lombardo R, Avanzi G. Effects of plasma exchange (PE) in primary biliary cirrhosis (PBC). A pilot study. Hepatogastroenterology. 1990;37(1):128–30.
51. Gross CR, Malinchoc M, Kim WR, Evans RW, Wiesner RH, Petz JL, et al. Quality of life before and after liver transplantation for cholestatic liver disease. Hepatology. 1999;29(2):356–64.
52. Carbone M, Bufton S, Monaco A, Griffiths L, Jones DE, Neuberger JM. The effect of liver transplantation on fatigue in patients with primary biliary cirrhosis: a prospective study. J Hepatol. 2013;59(3):490–4.
53. Talwalkar JA, Lindor KD. Primary biliary cirrhosis. Lancet. 2003;362(9377):53–61.