Long-term management of hepatic encephalopathy with lactulose and/or rifaximin: a review of the evidence

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A consolidated overview of evidence for the effectiveness and safety/tolerability of hepatic encephalopathy (HE) treatment over the long term is currently lacking. We identified and assessed published evidence for the long-term (≥6 months) pharmacological management of HE with lactulose and/or rifaximin. A literature search was conducted in PubMed (cutoff date 05 March 2018) using the search terms 'hepatic encephalopathy + rifaximin' and 'hepatic encephalopathy + lactulose'. All articles containing primary clinical data were manually assessed to identify studies in which long-term (≥6 months) effectiveness and/or safety/tolerability end points were reported for lactulose and/or rifaximin. Long-term effectiveness outcomes were reported in eight articles for treatment with lactulose alone and 19 articles for treatment with rifaximin, alone or in combination with lactulose. Long-term safety/tolerability outcomes were reported in six articles for treatment with lactulose alone and nine articles for treatment with rifaximin, alone or in combination with lactulose. These studies showed that lactulose is effective for the prevention of overt HE recurrence over the long term and that the addition of rifaximin to lactulose significantly reduces the risk of overt HE recurrence and HE-related hospitalization, compared with lactulose therapy alone, without compromising tolerability. Current evidence therefore supports recommendations for the use of lactulose therapy for the prevention of overt HE recurrence over the long term, and for the additional benefit of adding rifaximin to lactulose therapy. Addition of rifaximin to standard lactulose therapy may result in substantial reductions in healthcare resource utilization over the long term, by reducing overt HE recurrence and associated rehospitalization. Eur J Gastroenterol Hepatol 31:434–450

Introduction

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting, which manifests as a wide spectrum of neurological or psychiatric abnormalities, ranging from subclinical alterations to coma [1]. The primary pathophysiological mechanism underlying HE is thought to involve elevated blood levels of gut-derived neurotoxins – in particular, ammonia – entering the brain owing to the inability of the cirrhotic liver to remove them from the blood circulation [2–4]. HE increases the risk of mortality [5] and is one of the most debilitating complications of liver disease [1]. Overt HE (OHE) occurs in 30–40% of patients with cirrhosis at some time during their clinical course, with minimal HE (MHE) reported to potentially affect 20–80% of patients with cirrhosis [1].

HE has a substantial economic effect, not only owing to the direct costs of its management (particularly HE-related hospitalization) but also to the indirect costs arising from, for example, absence from work and loss of work productivity [1,6,7]. HE negatively affects the lives of both patients and caregivers [1,8] and the socioeconomic implications of HE over the longer term may be very profound, decreasing work performance, increasing the risk of vehicle accidents and severely impairing quality of life [1]. Currently available treatment options for HE include nonabsorbable disaccharides (e.g. lactulose), antibiotics (e.g. rifaximin-α 550 mg) and L-ornithine L-aspartate (LOLA) [1]. Other potential therapies include branched-chain amino acids, probiotics, metabolic ammonia scavengers and glutaminase inhibitors [1].

Nonabsorbable disaccharides not only remove nitrogen-containing substances from the gastrointestinal tract via their laxative effects but are also metabolized by the colonic microbiota to produce short-chain organic acids [2]. These acids are thought to inhibit the growth of ammonia-producing bacteria and to convert ammonia to nonabsorbable ammonium, thereby further decreasing the ammonia load [2]. Adherence to lactulose may be affected by its adverse effects, which can include severe diarrhea, hypokalemia, hyponatremia, bloating, flatulence, nausea and vomiting [9,10].

The most commonly used antibiotic, rifaximin-α 550 mg, is a locally acting oral antibiotic that is minimally absorbed

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in the gut to reduce the effects of intestinal flora, including ammonia-producing species [11,12]. Rifaximin-α 550 mg is indicated for the reduction in recurrence of episodes of OHE in patients aged ≥ 18 years [13]. *C. difficile*-associated diarrhea has been reported with the use of nearly all antibacterial agents, including rifaximin-α 550 mg [13].

Current guidelines recommend that an episode of OHE (whether spontaneous or precipitated) should be actively treated, and that secondary prophylaxis should be initiated after an episode to prevent recurrence [1]. Lactulose is recommended as the first choice for treatment of episodic HE, and for the prevention of recurrent episodes of HE after the initial episode [1]. Rifaximin is recommended as an effective add-on to lactulose for the prevention of OHE recurrence after the second episode [1]. Intravenous LOLA and oral branched-chain amino acids can be used as alternative or additional agents to treat patients who are not responsive to conventional therapy [1]. Prophylactic therapy should be continued, unless precipitating factors (e.g. infections and variceal bleeding) have been well controlled or liver function or nutritional status improved [1]. However, a consolidated overview of current evidence for the effectiveness and safety/tolerability of HE treatment in the long-term setting is currently lacking. The aims of this systematic review were therefore to identify and assess published evidence for the long-term (≥6 months) pharmacological management of HE and to discuss the implications of this evidence for everyday clinical practice.

Materials and methods

Literature searches were conducted in PubMed of titles and abstracts only, with language restricted to English and the date range unrestricted up to the cutoff date (5 March 2018), using the following search terms: 'hepatic encephalopathy + rifaximin' and 'hepatic encephalopathy + lactulose'. The abstracts of all identified articles were manually assessed to identify primary clinical data-containing manuscripts (i.e. articles containing clinical trial, clinical practice study, observational, registry, health economic and/or survey data, including journal-published congress abstracts if indexed on PubMed). These were then assessed to identify studies in which long-term effectiveness and/or safety/tolerability end points were reported for lactulose and/or rifaximin. Long-term treatment was defined as at least 6 months. The results of studies were then tabulated for further evaluation.

Similar initial searches were additionally conducted using the search terms 'hepatic encephalopathy + L-ornithine-L-aspartate, 'hepatic encephalopathy + LOLA' and 'hepatic encephalopathy + ornithine aspartate'. However, as only one study was identified that reported long-term (≥6 months) outcomes [14], the subsequent review process was restricted to evidence for lactulose and rifaximin only.

Number needed to treat (NNT) analyses were carried out for studies reporting significant between-group differences in the rate of OHE recurrence following at least 6 months of secondary prophylaxis with lactulose and/or rifaximin. Studies investigating primary prophylaxis and different dosing regimens of rifaximin were excluded from the NNT analysis.

Results

The search term 'hepatic encephalopathy + rifaximin' identified a total of 235 articles, of which 71 were assessed as containing primary clinical data (Fig. 1). The search term 'hepatic encephalopathy + lactulose' identified 355 articles, of which 130 contained primary clinical data (Fig. 1).

Effectiveness of long-term (≥ 6 months) treatment of hepatic encephalopathy with rifaximin and/or lactulose

Manual assessment of the articles containing primary clinical data identified long-term effectiveness outcomes for treatment of HE, with eight articles reporting outcomes for treatment with lactulose alone and a further 19 articles reporting outcomes for treatment with rifaximin, alone or in combination with lactulose (Table 1). NNT analyses were carried out of studies reporting at least 6 months of secondary prophylaxis with lactulose versus no lactulose ($n = 1$) [34], lactulose versus placebo ($n = 1$) [38], rifaximin + lactulose versus placebo + lactulose ($n = 2$) [16,19] and rifaximin monotherapy versus rifaximin + lactulose ($n = 1$) [31] (Fig. 2). Details of studies including more than 100 patients are summarized in more detail later.

Lactulose alone

In a single-center, retrospective, chart review of 137 patients who received lactulose for a mean duration of 27 ± 6 months after their first HE event, it was found that 75% of the patients experienced HE recurrence after 9 ± 1 months [10]. The rate of HE-related hospital readmission was 73%, and the mortality rate was 34% [10]. Thirty-nine (28.5%) patients had HE recurrence associated with lactulose nonadherence, mostly resulting from gastrointestinal adverse effects [10].

Several large single-center, open-label, randomized, controlled studies have assessed the long-term (≥6 months) effectiveness of lactulose therapy, compared with placebo, probiotics and/or no therapy. Compared with no treatment or placebo, the calculated NNT values [95% confidence intervals (CIs)] for lactulose as secondary prophylaxis for OHE recurrence were 3.28 (2.15–6.90) [34] and 3.68 (2.33–8.75) [38] (Fig. 2).

In a primary prophylaxis study, patients with cirrhosis but no previous history of OHE were randomized to receive lactulose therapy ($n = 60$) or no lactulose therapy ($n = 60$) for 12 months [39]. Lactulose significantly reduced the rate of OHE occurrence versus no lactulose (11 vs. 28%; $P = 0.02$) and reduced the median length of stay for HE-related hospitalization, although not significantly [39]. In a secondary prophylaxis study, patients with cirrhosis who had recovered from OHE were randomized to receive lactulose ($n = 68$), probiotics ($n = 64$) or no therapy ($n = 65$) for up to 12 months [34]. The rate of OHE recurrence was 26.5% with lactulose, 34.4% with probiotics and 56.9% with no therapy (lactulose vs. probiotics, $P =$ not significant; lactulose vs. no therapy, $P = 0.001$; and probiotics vs. no therapy, $P = 0.02$) [34]. The mortality rate was 19.1, 17.2 and 24.6% for the lactulose, probiotics and no therapy groups, respectively ($P =$ not significant between groups) [34]. In a similar secondary prophylaxis study, patients were randomized to

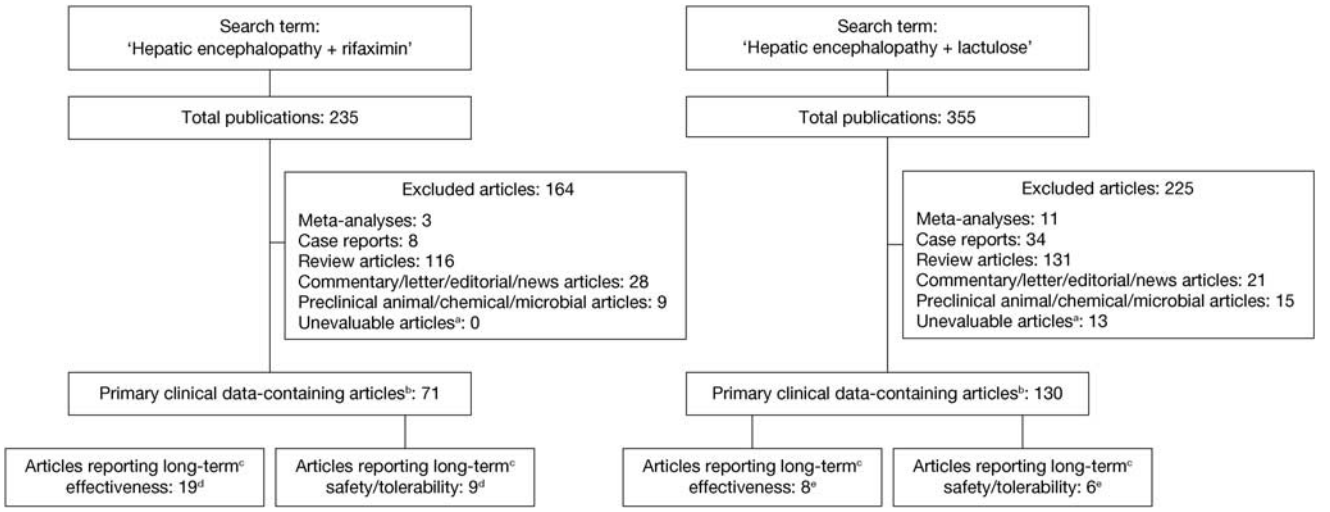

Fig. 1. Summary of numbers of journal articles indexed on PubMed, identified using the search terms 'hepatic encephalopathy + lactulose' and 'hepatic encephalopathy + rifaximin'. Searches were conducted of titles and abstracts only, with language restricted to English and the date range unrestricted up to the cutoff date (5 March 2018). [a]Articles without an abstract; [b]articles containing primary clinical trial, clinical practice study, observational, registry, health economic, or survey data, including journal-published congress abstracts, if indexed on PubMed; [c]≥6 months; [d]articles relating to rifaximin alone or in combination with lactulose; [e]articles relating to lactulose alone.

receive lactulose or placebo over a median follow-up duration of 14 months [38]. Lactulose was significantly superior to placebo in reducing the rate of OHE recurrence (19.6 vs. 46.8%; $P = 0.001$) but not in reducing the rate of hospitalization for non-HE events or mortality [38].

Rifaximin with or without lactulose

Most rifaximin studies assessed the additional benefit of rifaximin prophylaxis as an adjunct to lactulose therapy. Compared with placebo + lactulose, NNT values (95% CIs) for rifaximin + lactulose as secondary prophylaxis for OHE recurrence were calculated to be 3.28 (2.27–5.90) [16] and 4.21 (2.93–7.46) [19] (Fig. 2).

A phase III, multicenter, randomized, double-blind, placebo-controlled trial compared the effectiveness of rifaximin-α 550 mg twice daily versus placebo for the prevention of OHE recurrence over 6 months in 299 patients with cirrhosis who had experienced at least two OHE episodes in the previous 6 months but who were currently in remission [19]. More than 90% of patients in both treatment arms additionally received lactulose therapy. The rate of OHE recurrence was 22.1% with rifaximin versus 45.9% with placebo [19]. The hazard ratio for the time to a breakthrough OHE episode for rifaximin versus placebo was 0.42 (95% CI: 0.28–0.64; $P < 0.001$), reflecting a relative risk reduction of 58% with rifaximin versus placebo [19]. The rate of HE-related hospital readmission was 13.6% with rifaximin versus 22.6% with placebo, and the hazard ratio for time to first HE-related hospitalization for rifaximin versus placebo was 0.50 (95% CI: 0.29–0.87; $P = 0.01$), representing a 50% relative reduction in risk [19]. In a subanalysis of this trial ($n = 219$), conducted primarily to assess health-related quality of life, the rate of OHE recurrence was 25.7% with rifaximin versus 50.0% with placebo, and HE remission was maintained for 6 months in 74.3% of patients treated with rifaximin versus 50.0% of those treated with placebo [32].

In a similarly designed single-center, randomized, triple-blind, placebo-controlled trial, 126 patients with cirrhosis who were admitted to hospital with an index OHE event, having experienced at least one other OHE event in the previous 6 months, were treated with rifaximin-α 550 mg or placebo for 6 months, in addition to lactulose therapy [15]. In this trial, rate of HE recurrence was 44.4% with rifaximin versus 36.5% with placebo (P = not significant), and the mortality rate was 11.1% in both treatment groups [15].

When examining long-term use specifically, patients completing the trial by Bass and colleagues were eligible to enter a phase III, multicenter, open-label maintenance study, in which patients received open-label treatment with rifaximin-α 550 mg for 24 months [18]. In total, 392 patients were treated with rifaximin ('all-rifaximin' group), including 252 patients who received *de novo* treatment ('new-rifaximin' group). As in the initial trial, ~90% of patients were additionally treated with lactulose. The rates of HE-related hospitalization were 0.21 and 0.23 events/person-year of exposure (PYE) for the all-rifaximin and new-rifaximin groups, respectively [18]. In the original trial, the corresponding values were 0.30 events/PYE for rifaximin versus 0.72 events/PYE for placebo ($P < 0.0001$) [18]. A post-hoc analysis of this study was conducted for 321 patients who had been treated for mean duration of 1.5 years [17]. Data were compared between patients who had been newly recruited, having not participated in the original trial ('rifaximin-newly recruited' group), with those who received rifaximin in the original randomized controlled trial ('rifaximin-RCT' group) and those who received placebo in the original trial ('placebo-RCT' group) [17]. The rates of OHE recurrence were 772.1, 687.2 and 652.1 events/1000 person-years for the rifaximin-newly recruited, rifaximin-RCT and placebo-RCT groups, respectively (P = not significant between groups), and the corresponding mortality rates were 170.5, 134.1 and 168.5 events/1000 patient years, respectively (P = not significant between groups) [17].

Table 1. Articles reporting effectiveness outcomes over the long term (≥6 months) for patients treated with rifaximin and/or lactulose for hepatic encephalopathy. Articles reporting data for rifaximin and lactulose are presented in the rifaximin section; those reporting data for lactulose, but not rifaximin, are presented in the lactulose section.

						Efficacy outcomes						
References	Study design	Rifaximin Tx	Number of patients	Study population	Study duration[a]	Time to first breakthrough HE episode (HR or days)	Time to first HE-related hospitalization (HR)	Patients with breakthrough HE episodes (%, events/PYE, events/1000 person-years, number of HE episodes/patient)	HE-related hospital readmission (%, events/PYE, number of hospitalizations, number of bed days, number of critical care bed days, LOS)	All-cause hospital readmission (%, events/PYE, number of hospitalizations, days of hospitalization, weeks of hospitalization, LOS)	Mortality (%, events/1000 person-years)	Other end points
Rifaximin												
Ali *et al.* [15]	Single-center, randomized, triple-blind, placebo-controlled trial	550 b.i.d	63 (R) 63 (P) All patients additionally received L	Cirrhosis; ≥ 2 HE episodes in last 6 months; Conn ≥ 2; MELD ≤ 25	6 months	–	–	OHE (Conn ≥ 2): 44.4% (R) vs. 36.5% (P); $P = 0.56$	–	–	11.1% (R) vs. 11.1% (P)	–
Bajaj *et al.* [16]	Post-hoc analysis of multicenter, randomized, double-blind, placebo-controlled trial, followed by multicenter, single-arm OLM study Study compared patients who received R during OLM having switched from P at end of RCT with the same patients when treated with P during RCT	550 b.i.d	82 (P during RCT and R during OLM) L use was permitted: use was 91.2% (P during RCT) and ~ 90% (R during OLM)	Cirrhosis; history of OHE; Conn ≥ 2 within last 6 months; Conn ≤ 1 at enrolment; MELD ≤ 25	6 months (RCT) + 24 months (OLM)	HR (R during OLM vs. P during RCT) 0.21 (95% CI 0.10–0.44; $P < 0.0001$; RR 79%)	–	OHE (Conn ≥ 2): 17.1% (R during first 6 months of OLM) vs. 47.6% (P during RCT); $P < 0.0001$ 0.42 events/PYE (R during first 6 months of OLM) vs. 1.50 (P during RCT); $P < 0.0001$	0.36 Events/PYE (R during first 6 months of OLM) vs. 0.57 events/PYE (P during RCT); $P = 0.365$	0.82 Events/PYE (R during first 6 months of OLM) vs. 0.80 events/PYE (P during RCT); $P =$ NS	–	–
Bannister *et al.* [17]	Post-hoc analysis of multicenter, phase III, OLM study [18]	550 b.i.d	321 (R): 169 newly recruited (R-NR) 70 R during RCT (R-RCT) 82 P during RCT (P-RCT)	History of ≥ 1 OHE episode (Conn ≥ 2) within 12 months of screening; Conn ≤ 2 at enrolment	1.5 years	–	–	Events/1000 person-years: 687.2 (R-RCT) vs. 772.1 (R-NR) vs. 652.1 (P-RCT); $P =$ NS between groups	–	–	Events/1000 person-years: 134.1 (R-RCT) vs. 170.5 (R-NR) vs. 168.5 (P-RCT); $P =$ NS between groups	–
Bass *et al.* [19]	Multicenter, randomized, double-blind, placebo-controlled trial	550 b.i.d	140 (R) 159 (P) L use was permitted: use was 91.4% (R group) and 91.2% (P group)	Cirrhosis; ≥ 2 OHE episodes (Conn ≥ 2) in last 6 months; in remission (Conn 0 or 1); MELD ≤ 25	6 months	HR (R vs. P) 0.42 (95% CI 0.28–0.64; $P < 0.001$; RR 58%)	HR (R vs. p) 0.50 (95% CI 0.29–0.87; $P = 0.01$; RR 50%)	OHE (increase from Conn 0 or 1 at baseline to Conn ≥ 2, or increase from Conn 0 at baseline to Conn 1 + a 1-unit increase in asterixis grade): 22.1% (R) vs. 45.9% (P)	13.6% (R) vs. 22.6% (P)	–	–	–
Courson *et al.* [20]	Single-center, retrospective, cohort study	550 b.i.d	62 (R + L) 87 (L)	Admitted for HE	180 days	–	–	–	2.4% (L + R) vs. 16.2% (L); $P = 0.028$	52.4% (L + R) vs. 41.2% (L); $P = 0.252$ Median LOS: 8 days (L + R) vs. 6 days (L); $P = 0.09$	32% (L + R) vs. 22% (L); $P = 0.15$	–
Goyal *et al.* [21]	Single-center, randomized, prospective study	400 t.i.d	57 (R) 55 (L)	Cirrhosis; MHE	3 months Tx + 6 months FU (results relate to 9-month FU)	–	–	MHE: 47.6% (R) vs. 42.1% (L); $P = 0.274$ OHE: 7.1% (R) vs. 7.9% (L); $P = 0.924$	–	–	0.23% (R) vs. 0% (L); $P =$ NS	–

Table 1. (*Continued*)

References	Study design	Rifaximin Tx	Number of patients	Study population	Study duration[a]	Efficacy outcomes						
						Time to first breakthrough HE episode (HR or days)	Time to first HE-related hospitalization (HR)	Patients with breakthrough HE episodes (%, events/PYE, events/1000 person-years, number of HE episodes/patient)	HE-related hospital readmission (%, events/PYE, number of hospitalizations, number of bed days, number of critical care bed days, LOS)	All-cause hospital readmission (%, events/PYE, number of hospitalizations, days of hospitalization, weeks of hospitalization, LOS)	Mortality (%, events/1000 person-years)	Other end points
Hudson *et al.* [22]	Multicenter, retrospective, observational study	1100 mg/day (34%) 1200 mg/day (61%) Other doses (5%)	207 (R) 84% of patients received concomitant L	Documented clinical diagnosis of HE; initiated on R ≥ 12 months before data collection	12 months	–	–	OHE: 57% (12 months pre-R) vs. 38% (12 months post-R) Mean number of HE episodes/patient: 1.01 (12 months pre-R) vs. 0.77 (12 months post-R) ($P=0.047$)	Mean number of liver-related hospitalizations/patient: 1.3 (6 months pre-R) vs. 0.5 (6 months post-R); $P<0.001$; 1.7 (12 months pre-R) vs. 0.8 (12 months post-R); $P<0.001$	–	19% (6 months post-R; 27% (12 months post R)	–
Irimia and Trifan [23]	Single-center, prospective study (Note: randomization not mentioned)	400 t.i.d: either intermittent (RI), that is, 14 days/month or daily (RD)	38 (RI) 28 (RD) 12 (L)	Cirrhosis; history of ≥ 1 OHE episode (West-Haven ≥ 2); in remission (West-Haven 0 or 1)	6 months Tx + 6 months FU (results relate to 12-month FU)	–	–	OHE (increase from West-Haven 0 or 1 at baseline to West-Haven ≥ 2, or increase from baseline in West-Haven score + asterixis grade by 1 point each): 26.3% (RI) vs. 25% (RD) vs. 33.3% (L); $P=$NS	31.6% (RI) vs. 28.6% (RD) vs. 50% (L); RI vs. RD, $P=$NS; RI vs. L, $P=$S; RD vs. L, $P=$S	–	–	–
Kang *et al.* [24]	Single-center, retrospective cohort study	600 b.i.d	Non-HCC: 145 (R+L) 276 (L) HCC: 173 (R+L) 448 (L)	Cirrhosis-related HE; recovered after medical treatment	Median (IQR) follow-up: 18.0 (4.3–36.3) months (non-HCC) 4.4 (1.3–16.4) months (HCC)	–	–	Recurrent HE (HE episodes that occurred within 6 months): Non-HCC: 15.9% (R+L) vs. 33.3% (L); $P<0.001$ HCC: 19.1%(R+L) vs. 29.2% (L); $P=0.03$	–	–	Overall mortality: Non-HCC: 36.6% (R+L) vs. 56.9% (L); $P=0.02$ HCC: 75.1% (R+L) vs. 82.8% (L); $P=$NS Cumulative mortality at 12, 24, 36 and 48 months: Non-HCC: 29.7, 32.4, 35.9 and 36.6% (R+L) vs. 37.0, 45.7, 52.2, and 55.1% (L) HCC: 61.8, 72.3, 74.0 and 75.1% (R+L) vs. 64.1, 75.0, 80.4% and 81.9% (L)	Rate of SBP: Non-HCC: 6.9% (R+L) vs. 42.8% (L); $P<0.001$ HCC: 12.7% (R+L) vs. 45.8% (L); $P<0.001$ Rate of variceal bleeding: Non-HCC: 7.6% (R+L) vs. 19.2% (L); $P=0.006$ HCC: 11.0% (R+L) vs. 19.2% (L); $P=0.047$ Rate of HRS: Non-HCC: 10.3% (R+L) vs. 20.3% (L); $P=0.077$ HCC: not specified; $P=$NS
Khokhar *et al.* [25]	Single-center, randomized, controlled study	550 o.d. 550 b.i.d	128 (R o.d.) 178 (R b.i.d) All patients additionally received L	Cirrhosis; CLD; history of ≥ 1 HE episode	6 months	–	–	OHE (Conn ≥ 2): 21.1% (R o.d.) vs. 30.3% (R b.i.d); $P=0.088$	–	10.9% (R o.d.) vs. 16.9% (R b.i.d)	–	–
Leevy and Phillips [26]	Single-center, retrospective, chart review	400 t.i.d	145 (R) 145 (L) All patients received L and then switched to R	HE diagnosis	6 months (last 6 months on L was compared with first 6 months on R)	–	–	–	–	Number of hospitalizations[b]: 0.5 (R) vs. 1.6 (L); $P<0.001$ Number of days of hospitalization[b]: 2.5 (R) vs. 7.3 (L); $P<0.001$ Number of weeks of hospitalization[b]: 0.4 (R) vs. 1.8 (L); $P<0.001$	–	% Patients with stage 3 or 4 HE: 6% (R) vs. 25% (L) HE grade at end of treatment significantly less severe for R vs. L; $P<0.001$% patients with asterixis: 63% (R) vs. 93% (L); $P<0.001$

Lyon *et al.* [27]	Single-center, retrospective, observational, cross-sectional, pilot study	550 b.i.d 400 t.i.d	201 (550 b.i.d) 25 (400 t.i.d)	Documented HE (ICD-9 code)	6 months	–	–	HE (ICD-9 code): 15.6% (550 b.i.d) vs. 20.0% (400 t.i.d); $P=0.566$ (OR: 0.74; 95% CI: 0.244–2.71)	–	–	–	–
Mantry and Munsaf [28]	Single-center, retrospective chart review	400–1200 mg/day	65 All received L followed by R alone (16) or with L (49) Study compared L (i.e. L alone pre-R) with R (R/R+L)	Treated for HE	6 months	–	–	–	17 Hospitalizations[c] (R) vs. 60 hospitalizations[c] (L); RR (R vs. L) 87% (OR 0.13; 95% CI 0.05–0.4; $P<0.001$) % patients with >1 hospitalization: 6% (R) vs. 23% (L); $P<0.001$ Average LOS: 1.1 days (R) vs. 1.8 days (L); $P=0.10$	36 Hospitalizations[c] (R) vs. 47 hospitalizations[c] (L); RR 16% (OR 0.84; $P=0.66$) % patients with >1 hospitalization: 5% (R) vs. 14% (L); $P=0.006$ Average LOS: 2.0 days (R) vs. 1.1 days (L); $P=$NS (Note: all of above refer to hospitalizations for non-HE events rather than all-cause)	–	% Patients with SBP: 2% (R) vs. 12% (L); $P=0.02$
Mantry *et al.* [29]	Single-center, retrospective, observational study	550 b.i.d	220 All patients additionally received L	Evaluated for liver transplant; MELD <20 or ≥20	6 months	–	–	–	2.5 Hospitalizations[b]/6 months (MELD <20) vs. 1.6 hospitalizations[b]/6 months (MELD≥20)	3.3 Hospitalizations[b]/6 months (MELD<20) vs. 3.7 hospitalizations[b]/6 months (MELD≥20) (Note: hospitalizations for non-HE events rather than all-cause)	–	–
Miglio *et al.* [30]	Multicenter, randomized, double-blind, controlled trial	400 t.i.d	25 (R) 24 (N) Both groups received treatment for 14 days/month	Cirrhosis; HE grade 1 or 2	6 months	–	–	–	–	–	–	HE grade: Significant reduction in HE grade in both groups ($P<0.001$ for each); no significant difference between groups Blood ammonia: Significant reduction in blood ammonia levels in both groups ($P<0.001$ for each); no significant difference between groups
Mullen *et al.* [18]	Multicenter, phase III, OLM study	550 b.i.d	392 (all-R)[d] 252 (new-R)[e] In original RCT: 140 (Hist-R) 159 (Hist-P) 89.8% of patients in all-R group received concomitant L	History of OHE (Conn≥2) within 12 months of screening; Conn≤2 at screening; patients from previous RCT	≥24 months	–	–	–	0.21 Events/PYE (all-R) vs. 0.23 events/PYE (new-R) [Note: in original RCT results were 0.30 events/PYE (Hist-R) vs. 0.72 events/PYE (Hist-P); $P<0.0001$; inferential stats vs. OLM results not conducted]	0.45 Events/PYE (all-R) vs. 0.44 events/PYE (new-R) [Note: in original RCT results were 0.92 events/PYE (Hist-R) vs. 1.30 events/PYE (Hist-P); inferential stats vs. OLM results not conducted]	–	–
Neff *et al.* [31]	Multicenter, retrospective chart review	400–1600 mg/day	149 (R) 54 (R+L)	Cirrhosis; treated with R for HE (Conn≥2)	1 year	Mean time to HE event: 210 (range 90–410) days (R) vs. 90 (range 30–125) days (R+L)	–	OHE (Conn≥2): 19% (R) vs. 33% (R+L)	43% (R) vs. 39% (R+L)	–	–	Maintenance of HE remission for 1 year: 81% (R) vs. 67% (R+L)

Table 1. (*Continued*)

References	Study design	Rifaximin Tx	Number of patients	Study population	Study duration[a]	Efficacy outcomes: Time to first breakthrough HE episode (HR or days)	Time to first HE-related hospitalization (HR)	Patients with breakthrough HE episodes (%, events/PYE, events/1000 person-years, number of HE episodes/patient)	HE-related hospital readmission (%, events/PYE, number of hospitalizations, number of bed days, number of critical care bed days, LOS)	All-cause hospital readmission (%, events/PYE, number of hospitalizations, days of hospitalization, weeks of hospitalization, LOS)	Mortality (%, events/1000 person-years)	Other end points
Sanyal *et al.* [32]	Multicenter, randomized, double-blind, placebo-controlled trial (Note: subanalysis of Bass *et al.* 2010 RCT – the primary focus of this paper is HRQOL)	550 b.i.d	101 (R) 118 (P) Patients were allowed to take L: use was 93% (R group) and 95% (P group)	Cirrhosis; ≥2 OHE episodes (Conn ≥2) in last 6 months; in remission (Conn 0 or 1); MELD ≤25	6 months	–	–	OHE (increase from Conn 0 or 1 at baseline to Conn ≥2, or increase from Conn 0 at baseline to Conn 1+a 1-unit increase in asterixis grade): 25.7% (R) vs. 50.0% (P)	–	–	–	Maintenance of HE remission for 6 months: 74.3% (R) vs. 50.0% (P)
Vlachogiannakos *et al.* [33]	Single-center, prospective study	400 t.i.d	23 (R) 46 (C) (Note: each R patient was matched by age, sex and Child–Pugh grade to two C)	Alcohol-related decompensated cirrhosis (Child–Pugh > 7); ascites; abstinent from alcohol for last 6 months; responded to R in previous prospective study	Up to 5 years (median FU 36 months; range 5–60 months)	–	–	–	–	–	–	Maintenance of HE remission: 68.5% (R) vs. 53% (C); $P=0.034$ Survival: 61% (R) vs. 13.5% (C); $P=0.012$ % patients with variceal bleeding: 35% (R) vs. 59.5% (C); $P=0.011$ % patients with SBP: 4.5% (R) vs. 46% (C); $P=0.027$ % patients with HS: 4.5% (R) vs. 51% (C); $P=0.037$

References	Study design	Lactulose Tx	Number of patients	Study population	Study duration[a]	Efficacy outcomes: Time to first breakthrough HE episode (HR or days)	Time to first HE-related hospitalization (HR)	Patients with breakthrough HE episodes (%, episodes/patient)	HE-related hospital readmission (%, LOS)	All-cause hospital readmission (%)	Mortality (%)	Other end points
Lactulose												
Agrawal *et al.* [34]	Single-center, open-label, randomized, controlled trial	30–60 ml/day (in 2/3 divided doses)	68 (L) 64 (PB) 65 (NT)	Cirrhosis; previous history of HE; no OHE	Up to 12 months	–	–	OHE: 26.5% (L) vs. 34.4% (PB) vs. 56.9% (NT); L vs. NT $P=0.001$; PB vs. NT $P=0.02$; L vs. PB $P=0.349$	–	27.9% (L) vs. 32.8% (PB) vs. 43.0% (NT); $P=$ NS between groups (Note: hospitalizations for non-HE events rather than all-cause)	19.1% (L) vs. 17.2% (PB) vs. 24.6% (NT); $P=$ NS between groups	–
Bajaj *et al.* [10]	Single-center, retrospective chart review	30 ml b.i.d	137 (L)	Cirrhosis; first episode HE	Mean 27±6 months	9±1 months	–	75% (L)	73% (L)	–	34% (L)	–
Moratalla *et al.* [35]	Two-center, prospective, observational study	30–60 ml/day	First cohort: 26 (L) 46 (no L) Second cohort: 40 (L)	MHE	6 months	–	–	OHE: First cohort: 4.3% (L) vs. 23.5% (no-L); $P=0.01$ Second cohort: 2.5% (L)	–	–	–	% patients with variceal bleeding: 11.5% (L) vs. 4.3% (no-L) % patients with SBP: 0% (L) vs. 4.3% (no-L)

Riggio *et al.* [36]	Single-center, randomized, controlled study	Initial 30 ml/day (in 2 divided doses)	15 (L) 16 (La)	Cirrhosis; surgical portal-systemic anastomosis	6 months	–	–	40% (L) vs. 28.6% (La); P = NS	–	–	–	–
Riggio *et al.* [37]	Single-center, randomized, crossover study	38.2 ± 19 g/day (range 30–78 g/day)	12 (L/La)	Cirrhosis; surgical nonselective portosystemic shunt	2 × 6 months Tx (mean FU: 57 ± 49 months)	–	–	60% (L) vs. 25% (La); P = 0.21	–	–	–	–
Sharma *et al.* [38]	Single-center, open-label, randomized, controlled trial	30–60 ml/day (in 2/3 divided doses)	70 (L) 70 (P)	Cirrhosis; recovered from HE	Median FU: 14 months (range: 1–20 months)	–	–	OHE (West-Haven ≥ 2): 19.6% (L) vs. 46.8% (P); P = 0.001	–	14.7% (L) vs. 9.3% (P); P = NS (Note: hospitalizations for non-HE events rather than all-cause)	8% (L) vs. 17% (P); P = 0.18	–
Sharma *et al.* [39]	Single-center, open-label, randomized, controlled trial	30–60 ml/day (in 2/3 divided doses)	60 (L) 60 (no L)	Cirrhosis; no previous OHE	12 months	–	–	OHE (West-Haven ≥ 2): 11% (L) vs. 28% (no L); P = 0.02	Median (range) LOS for HE: 6 (4–16) (L) vs. 7 (3–20) (no L); P = 0.07	18% (L) vs. 14% (no L) (P = value not specified) (Note: hospitalizations for non-HE events rather than all-cause)	9% (L) vs. 20% (no L); P = 0.16	–
Takuma *et al.* [40]	Single-center, prospective, randomized, controlled study	30–60 ml/day	39 (ZS) 40 (no ZS) All patients received L	Cirrhosis; hyperammonaemia; grade 1 or 2 recurrent episodic HE unresponsive to standard therapies (lactulose and protein-restricted diet) for ≥ 4 weeks	6 months	–	–	Average number of HE episodes/patient at baseline and 6 months: 3.8 ± 1.2 and 1.8 ± 1.8 (ZS) vs. 3.7 ± 1.2 and 3.6 ± 2.3 (no ZS), respectively; P < 0.05 for ZS vs. no ZS; P < 0.05 for ZS baseline vs. ZS 6 months	–	–	–	Average HE grade at baseline and 6 months: 1.4 ± 0.5 and 0.9 ± 0.9 (ZS) vs. 1.4 ± 0.5 and 1.3 ± 0.9 (no ZS), respectively; P < 0.05 for ZS vs. no ZS; P < 0.05 for ZS baseline vs. ZS 6 months

b.i.d, twice daily; C, control; CI, confidence interval; CLD, chronic liver disease; FU, follow-up; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; Hist-P, historical placebo; Hist-R, historical rifaximin; HR, hazard ratio; HRQOL, health-related quality of life; HS, hepatorenal syndrome; ICD, International Classification of Diseases; L, lactulose; La, lactitol; LOS, length of stay; MELD, model for end-stage liver disease; MHE, minimal hepatic encephalopathy; N, neomycin; NR, not reported; NT, no therapy; o.d., once-daily; OHE, overt hepatic encephalopathy; OLM, open-label maintenance; OR, odds ratio; P, placebo; PB, probiotics; P-RCT, placebo during randomized controlled trial; PYE, person-years of exposure; R, rifaximin; RCT, randomized controlled trial; RD, rifaximin daily; RI, rifaximin intermittent (14 days/month); R-NR, rifaximin-newly recruited; RR, relative reduction; R-RCT, rifaximin during randomized controlled trial; S, statistically significant; SBP, spontaneous bacterial peritonitis; t.i.d, three times daily; Tx, treatment; ZS, zinc supplementation.

[a]Only time points ≥ 6 months are shown.

[b]Per patient.

[c]Total number.

[d]All patients who received rifaximin (i.e. those who received rifaximin in RCT, those who received rifaximin or placebo in RCT and continued into OLM, and those who were newly enrolled in OLM).

[e]Patients who received placebo in RCT and switched to rifaximin in OLM + those newly enroled in OLM.

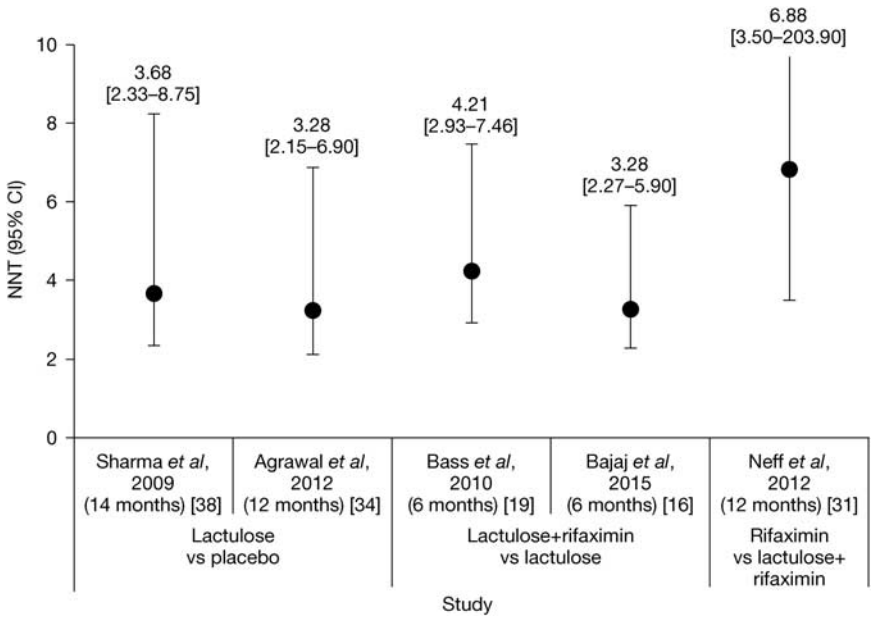

Fig. 2. NNTs with 95% CIs for lactulose versus no lactulose/placebo [34,38], rifaximin + lactulose versus placebo + lactulose [16,19], and rifaximin monotherapy versus rifaximin + lactulose [31]. CI, confidence interval; NNT, number needed to treat.

In addition to these prospective data, several large retrospective studies have assessed the effectiveness of rifaximin + lactulose in comparison with lactulose alone. The IMPRESS study was a multicenter, retrospective, observational study of 207 patients with HE, 84% of whom received concomitant lactulose, designed to assess the effect of rifaximin-α 550 mg on hospital resource use [22]. Outcomes were compared for the 6 months before starting rifaximin ('pre-rifaximin') versus the 6 months following rifaximin initiation ('post-rifaximin'), and for 12 months pre-rifaximin versus 12 months post-rifaximin. OHE episodes were experienced by 57% of patients in the 12 months pre-rifaximin versus 38% in the 12 months post-rifaximin [22]. The mean number of HE episodes per patient decreased significantly from the 12 months pre-rifaximin to the 12 months post-rifaximin ($P = 0.047$) [22].

A single-center, retrospective, cohort study compared the effectiveness of rifaximin (600 mg, twice daily) + lactulose versus lactulose alone in patients with cirrhosis-related HE who either did or did not have hepatocellular carcinoma (HCC) [24]. Median follow-up was 18.0 months in the non-HCC population ($n = 421$) and 4.4 months in the HCC population ($n = 621$) [24]. In the non-HCC population, the rate of HE recurrence was 15.9% for rifaximin-+ lactulose versus 33.3% for lactulose alone ($P < 0.001$), and the overall mortality rate was 36.6% for rifaximin-+ lactulose versus 56.9% for lactulose alone ($P = 0.02$) [24]. Furthermore, NNT analysis showed that 9.6 patients without HCC would need to be treated with rifaximin to increase the survival rate of one patient each year [24]. In the HCC population, the rate of HE recurrence was 19.1% for rifaximin + lactulose versus 29.2% for lactulose alone ($P = 0.03$), and the overall mortality rate was 75.1% for rifaximin + lactulose versus 82.8% for lactulose alone ($P =$ not significant) [24]. In both the non-HCC and HCC populations, rates of spontaneous bacterial peritonitis and variceal bleeding were significantly lower for rifaximin + lactulose versus lactulose alone [24]. Finally, a single-center, retrospective, cohort study of patients admitted for HE compared the effectiveness of rifaximin-α 550 mg + lactulose ($n = 62$) versus lactulose alone ($n = 87$) over 180 days [20]. The rate of HE-related hospital readmission was significantly lower with rifaximin + lactulose versus lactulose alone (2.4 vs. 16.2%; $P = 0.028$), but the rate of all-cause hospital readmission was not significantly different between groups, and neither were the median length of hospital stay or the rate of mortality [20].

Studies have also assessed the effectiveness of different rifaximin treatment regimens when used in addition to lactulose therapy. No significant differences were observed between patients treated with rifaximin-α 550 mg once-daily versus twice daily [25], or between patients treated with rifaximin-α 550 mg twice daily versus rifaximin 400 mg, three times daily; although rifaximin-α 550 mg twice daily was shown to be more cost-effective than the three times daily regimen [27].

Direct head-to-head evidence of the long-term effectiveness of rifaximin versus lactulose is scarce. In a single-center, retrospective chart review, 145 patients diagnosed with HE received at least 6 months of treatment with lactulose before receiving at least 6 months of treatment with rifaximin (400 mg, three times daily), and outcomes were compared for the last 6 months of lactulose treatment versus the first 6 months of rifaximin treatment [26]. The number of hospitalizations per patient was significantly lower with rifaximin versus lactulose (0.5 vs. 1.6; $P < 0.001$), as was the number of days of hospitalization per patient (2.5 vs. 7.3; $P < 0.001$) and number of weeks of hospitalization per patient (0.4 vs. 1.8; $P < 0.001$) [26]. Rifaximin was also compared with lactulose in a single-center, prospective study, designed to investigate for how long patients with MHE should be treated [21]. Patients with cirrhosis with MHE were randomized to receive primary prophylaxis treatment with either rifaximin (400 mg, three times daily) or lactulose for 3 months, and

Table 2. Articles reporting safety/tolerability outcomes over the long term (≥6 months) for patients treated with rifaximin and/or lactulose for hepatic encephalopathy. Articles reporting data for rifaximin and lactulose are presented in the rifaximin section; those reporting data for lactulose, but not rifaximin, are presented in the lactulose section

						Safety outcomes						
References	Study design	Rifaximin Tx	Number of patients	Study population	Study duration[a]	Incidence of AEs (%, rate/PYE until AE)	Type of AEs (%, rate/PYE until AE)	Serious AEs (%)	Infection-related AEs (rate/PYE until AE)	Death (%, deaths/PYE)	Discontinuation due to AEs (%)	Other safety results
Rifaximin												
Ali *et al.* [15]	Single-center, randomized, triple-blind, placebo-controlled trial	550 b.i.d	63 (R) 63 (P) All patients additionally received L	Cirrhosis; ≥2 HE episodes in last 6 months; Conn ≥2; MELD ≤25	6 months	–	Abdominal pain: 1.6% (R) vs. 0% (P) Nausea and vomiting: 4.8% (R) vs. 3.2% (P) Sore throat/fatigue: 0% (R) vs. 1.6% (P) General weakness: 1.6% (R) vs. 0% (P)	–	–	11.1% (R) vs. 11.1% (P)	–	–
Bajaj *et al.* [16]	*Post-hoc* analysis of multicenter, randomized, double-blind, placebo-controlled trial, followed by single-arm OLM study Study compared patients who received R during OLM having switched from P at end of RCT with the same patients when treated with P during RCT	550 b.i.d	82 (P during RCT and R during OLM) L use was permitted: use was 91.2% (P during RCT) and ~90% (R during OLM)	Cirrhosis; history of OHE; Conn ≥2 within last 6 months; Conn ≤1 at enrolment; MELD ≤25	6 months (RCT) + 24 months (OLM)	–	Rate/PYE until AE (R during OLM vs. P during RCT)[a]: Ascites: 0.27 vs. 0.19 Headache: 0.0 vs. 0.38 Nausea: 0.26 vs. 0.47 Peripheral oedema: 0.29 vs. 0.36	R during OLM[b] anaemia (3.7%), ascites (3.7%), cellulitis (3.7%), hyponatraemia (3.7%), acute renal failure (2.4%), chest pain (2.4%), hepatic cirrhosis (2.4%), hypoglycaemia (2.4%), hyperkalaemia (2.4%), pneumonia (2.4%), UTI (2.4%) P during RCT[b]: Atrial fibrillation (2.4%), bacterial peritonitis (2.4%), cellulitis (2.4%)	Rate/PYE until AE (R during OLM vs. P during RCT)[b]: Cellulitis: 0.17 vs. 0.08 Peritonitis: 0.06 vs. 0.11 Pneumonia: 0.08 vs. 0.0 Sepsis/septic shock: 0.08 vs. 0.08 UTI/kidney infection: 0.14 vs. 0.29	–	–	Change from baseline in PT: 0.42 s (R during OLM) vs. -0.04 s (P during RCT) Change from baseline in INR: −0.01 (R during OLM) vs. −0.04 (P during RCT) No clinically significant changes in laboratory values from baseline to Month 6 for R during OLM
Bass *et al.* [19]	Multicenter, randomized, double-blind, placebo-controlled trial	550 b.i.d	140 (R) 159 (P) L use was permitted: use was 91.4% (R group) and 91.2% (P group)	Cirrhosis; ≥2 OHE episodes (Conn ≥2) in last 6 months; in remission (Conn 0 or 1); MELD ≤25	6 months	80.0% (R) vs. 79.9% (P)	AEs[a]: Nausea: 14.3% (R) vs. 13.2% (P) Diarrhoea: 10.7% (R) vs. 13.2% (P) Fatigue: 12.1% (R) vs. 11.3% (P) Peripheral oedema: 15.0% (R) vs. 8.2% (P) Ascites: 11.4% (R) vs. 9.4% (P) Dizziness: 12.9% (R) vs. 8.2% (P) Headache: 10.0% (R) vs. 10.7% (P) Note: $P > 0.05$ for all comparisons	Serious AEs[c]: Anaemia: 2.9% (R) vs. 0% (P) Ascites: 2.9% (R) vs. 2.5% (P) Oesophageal varices: 2.9% (R) vs. 1.3% (P) Pneumonia: 2.9% (R) vs. 0.6% (P) Vomiting: 2.1% (R) vs. 0% (P) Generalized oedema: 2.1% (R) vs. 1.3% (P) Hepatic cirrhosis: 2.1% (R) vs. 3.8% (P) Cellulitis: 2.1% (R) vs. 1.3% (P) Acute renal failure: 1.4% (R) vs. 2.5% (P) Note: $P > 0.05$ for all comparisons	AEs possibly related to infection[b]: Bacterial peritonitis: 1.4% (R) vs. 2.5% (P) Pneumonia: 2.9% (R) vs. 0.6% (P) GI haemorrhage: 0.7% (R) vs. 1.9% (P) Haematochezia: 1.4% (R) vs. 0.6% (P) Bacteraemia: 0.7% (R) vs. 1.3% (P) Gastritis: 1.4% (R) vs. 0% (P) *C. difficile* infection: 1.4% (R) vs. 0% (P) Sepsis: 0% (R) vs. 1.3% (P) Note: $P > 0.05$ for all comparisons	6.4% (R) vs. 6.9% (P)	–	–

Table 2. (*Continued*)

References	Study design	Rifaximin Tx	Number of patients	Study population	Study duration[a]	Safety outcomes						
						Incidence of AEs (%, rate/PYE until AE)	Type of AEs (%, rate/PYE until AE)	Serious AEs (%)	Infection-related AEs (rate/PYE until AE)	Death (%, deaths/PYE)	Discontinuation due to AEs (%)	Other safety results
Hudson *et al.* [22]	Multicenter, retrospective, observational study	1100 mg/day (34%) 1200 mg/day (61%) Other doses (5%)	207 (R) 84% of patients received concomitant L	Documented clinical diagnosis of HE; initiated on R ≥ 12 months before data collection	12 months	4.3% (R)	AEs: *C. difficile* infection: 1.9% (R) Rash: 1.0% (R) Abdominal pain: 0.5% (R) Teeth discoloration: 0.5% (R)	None	*C. difficile* infection: 1.9% (R)	19% (6 months post-R); 27% (12 months post-R)	None	–
Kang *et al.* [24]	Single-center, retrospective cohort study	600 b.i.d	318 (R + L) 724 (L)	Cirrhosis-related HE; recovered after medical treatment	Median (IQR) follow-up: 18.0 (4.3–36.3) months (non-HCC) 4.4 (1.3–16.4) months (HCC)	–	–	–	*C. difficile*-associated diarrhoea: 0.3% (R + L) vs. 1.0% (L); P = NS	–	–	–
Leevy and Phillips [26]	Single-center, retrospective, chart review	400 t.i.d	145 (R) 145 (L) All patients received L and then switched to R	HE diagnosis	6 months (last 6 months on L was compared with first 6 months on R)	–	Diarrhoea* Mild: 93% (R) vs. 8% (L) Moderate: 6% (R) vs. 59% (L) Severe: <1% (R) vs. 22% (L) Very severe: 0% (R) vs. 10% (L) Flatulence* Mild: 97% (R) vs. 26% (L) Moderate: 3% (R) vs. 54% (L) Severe: 0% (R) vs. 11% (L) Very severe: 0% (R) vs. 9% (L) Abdominal pain* Mild: 86% (R) vs. 38% (L) Moderate: 11% (R) vs. 46% (L) Severe: 2% (R) vs. 10% (L) Very severe: <1% (R) vs. 6% (L) Headache Mild: 86% (R) vs. 82% (L) Moderate: 10% (R) vs. 12% (L) Severe: 3% (R) vs. 5% (L) Very severe: 0% (R) vs. <1% (L) *P < 0.001, R vs. L	–	–	–	–	% Patients with grade 3 or 4 HE: 6% (R) vs. 25% (L); P < 0.001 (for overall difference in HE grade) % patients with asterixis: 63% (R) vs. 93% (L); P < 0.001
Mantry and Munsaf [28]	Single-center, retrospective chart review	400–1200 mg/day	65 All received L followed by R alone (16) or with L (49) Study compared L (i.e. L alone pre-R) with R (R/R + L)	Treated for HE	6 months	2% (R) vs. 86% (L); P < 0.001	Abdominal pain: 2% (R) vs. 29% (L) Excessive diarrhoea: 0% (R) vs. 83% (L) Cramping: 0% (R) vs. 32% (L) Bloating: 0% (R) vs. 12% (L)	Severe dehydration: 0% (R) vs. 1.5% (L)	–	–	2% (R) vs. 37% (L); P < 0.001	% Patients with SBP: 2% (R) vs. 12% (L); P = 0.02

Mullen *et al.* [18]	Multicenter, phase III, OLM study	550 b.i.d	392 (all-R)[d] 252 (new-R)[e] In all-R ($N=392$): 352 (R+L) 40 (R alone) In original RCT: 140 (Hist-R) 159 (Hist-P)	History of OHE (Conn ≥ 2) within 12 months of screening; Conn ≤ 2 at screening; patients from previous RCT	24 months	Rate/PYE until AE: 0.71 (all-R) vs. 0.69 (new-R) vs. 2.24 (Hist-R) vs. 2.76 (Hist-P)	Rate/PYE until AE: Complications of portal hypertension All AEs: 0.57 (all-R) vs. 0.96 (Hist-R) vs. 0.89 (Hist-P) Acute kidney injury/HS: 0.15 (all-R) vs. 0.04 (Hist-R) vs. 0.20 (Hist-P) Ascites and oedema: 0.39 (all-R) vs. 0.81 (Hist-R) vs. 0.69 (Hist-P) Varices and variceal/GI bleed: 0.12 (all-R) vs. 0.12 (Hist-R) vs. 0.15 (Hist-P) Haematological complications All AEs: 0.18 (all-R) vs. 0.27 (Hist-R) vs. 0.16 (Hist-P) Anaemia: 0.14 (all-R) vs. 0.23 (Hist-R) vs. 0.13 (Hist-P) Thrombocytopenia/coagulation: 0.07 (all-R) vs. 0.06 (Hist-R) vs. 0.02 (Hist-P) Other Electrolyte imbalance: 0.11 (all-R) vs. 0.12 (Hist-R) vs. 0.07 (Hist-P) Fatigue/sleep disorders: 0.2 (all-R) vs. 0.58 (Hist-R) vs. 0.70 (Hist-P) Muscular atrophy: 0.02 (all-R) vs. 0 (Hist-R) vs. 0.04 (Hist-P)	Rate/PYE until AE: 0.48 (all-R) vs. 0.46 (new-R) vs. 1.02 (Hist-R) vs. 1.37 (Hist-P)	Rate/PYE until AE: All infections: 0.73 (all-R) vs. 1.12 (Hist-R) vs. 1.33 (Hist-P) Cellulitis: 0.07 (all-R) vs. 0.06 (Hist-R) vs. 0.07 (Hist-P) *C. difficile* infection: 0.01 (all-R) vs. 0.04 (Hist-R) vs. 0 (Hist-P) Peritonitis: 0.04 (all-R) vs. 0.06 (Hist-R) vs. 0.13 (Hist-P) Pneumonia: 0.08 (all-R) vs. 0.08 (Hist-R) vs. 0.02 (Hist-P) Sepsis/septic shock: 0.06 (all-R) vs. 0.04 (Hist-R) vs. 0.11 (Hist-P) UTI/kidney infection: 0.19 (all-R) vs. 0.19 (Hist-R) vs. 0.32 (Hist-P)	19.4% (All-R); no deaths attributed to R Deaths/PYE: 0.15 (all-R) vs. 0.24 (Hist-P)	Rate/PYE until AE: 0.25 (all-R) vs. 0.22 (new-R) vs. 0.60 (Hist-R) vs. 0.98 (Hist-P)	GI AEs in all-R population based on lactulose use (Rate/PYE until AE): All AEs: 0.51 (R) vs. 1.19 (R+L) Abdominal pain: 0.09 (R) vs. 0.20 (R+L) Ascites: 0.09 (R) vs. 0.15 (R+L) GI bleeding event: 0.08 (R) vs. 0.14 (R+L) Nausea: 0.05 (R) vs. 0.23 (R+L) Constipation: 0.06 (R) vs. 0.11 (R+L) Vomiting: 0.04 (R) vs. 0.13 (R+L) Diarrhoea: 0.04 (R) vs. 0.12 (R+L) Oesophageal varices: 0.04 (R) vs. 0.05 (R+L) Diverticulum: 0.04 (R) vs. 0.01 (R+L) Abdominal distension: 0.02 (R) vs. 0.05 (R+L)
Neff *et al.* [41]	Multicenter, retrospective chart review	Mean (range) 1055 (600–1600) mg/day	211 (R) All patients additionally received lactulose	Cirrhosis; treated with R for HE	Mean (range) 250 (180–385) days	–	Diarrhoea: 8% No patients had *C. difficile* infection	–	–	–	–	–
Lactulose												
Agrawal *et al.* [34]	Single-center, open-label, randomized, controlled trial	30–60 ml/day (in 2/3 divided doses)	64 (L) 64 (PB) 65 (NT)	Cirrhosis; previous history of HE; no OHE	Up to 12 months	–	L: diarrhoea (26.4%), abdominal bloating (16.2%), distaste to L (17.6%) PB: constipation (21.8%), abdominal distension (14%) NT: constipation (21.5%)	–	–	–	–	–

Table 2. (*Continued*)

References	Study design	Rifaximin Tx	Number of patients	Study population	Study duration[a]	Safety outcomes						
						Incidence of AEs (%, rate/PYE until AE)	Type of AEs (%, rate/PYE until AE)	Serious AEs (%)	Infection-related AEs (rate/PYE until AE)	Death (%, deaths/PYE)	Discontinuation due to AEs (%)	Other safety results
Moratalla *et al.* [35]	Two-center, prospective, observational study	30–60 ml/day	First cohort: 26 (L) 46 (no L) Second cohort: 40 (L)	MHE	6 months	–	First cohort: no AEs Second cohort: L: transient diarrhoea (12.5%), flatulence (7.5%)	–	–	–	–	–
Riggio *et al.* [36]	Single-center, randomized, controlled study	Initial 30 ml/day (in 2 divided doses)	15 (L) 16 (La)	Cirrhosis; surgical portal-systemic anastomosis	6 months	–	L: meteorism (40%), flatulence (40%), nausea (6.7%) La: nausea (6.3%), asthenia (6.3%), epigastric pain (6.3%; treatment stopped)	–	–	–	–	–
Riggio *et al.* [37]	Single-center, randomized, crossover study	38.2 ± 19 g/day (range 30–78 g/day)	12 (L/La)	Cirrhosis; surgical non-selective portosystemic shunt	2 × 6 months Tx (mean FU 57 ± 49 months)	–	L: meteorism (58.3%), flatulence (58.3%) La: flatulence (16.7%), nausea (8.3%)	–	–	–	–	–
Sharma *et al.* [38]	Single-center, open-label, randomized, controlled trial	30–60 ml/day (in 2/3 divided doses)	70 (L) 70 (P)	Cirrhosis; recovered from HE	Median FU 14 months (range 1–20 months)	–	L: diarrhoea (23%), abdominal bloating (10%), distaste to L (13%) P: constipation (16%)	–	–	–	–	–
Sharma *et al.* [39]	Single-center, open-label, randomized, controlled trial	30–60 ml/day (in 2/3 divided doses)	60 (L) 60 (no L)	Cirrhosis; no previous OHE	12 months	–	L: diarrhoea (24%), distaste to L (20%), abdominal bloating (8%)	–	–	–	–	–

AE, adverse event; b.i.d, twice daily; C, control; FU, follow-up; GI, gastrointestinal; HE, hepatic encephalopathy; Hist-P, historical placebo; Hist-R, historical rifaximin; HS, hepatorenal syndrome; INR, international normalized ratio; L, lactulose; La, lactitol; MELD, Model for End-stage Liver Disease; MHE, minimal hepatic encephalopathy; NT, no therapy; OHE, overt hepatic encephalopathy; OLM, open-label maintenance; P, placebo; PB, probiotics; PYE, person-years of exposure; R, rifaximin; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis; t.i.d, three times daily; Tx, treatment; UTI, urinary tract infection.

[a]Reported in ≥ 10% patients.

[b]Reported in ≥ 2 patients.

[c]Reported in ≥ 2% patients.

[d]All patients who received rifaximin (i.e. those who received rifaximin in RCT, those who received rifaximin or placebo in RCT and continued into OLM, and those who were newly enrolled in OLM).

[e]Patients who received placebo in RCT and switched to rifaximin in OLM + those newly enroled in OLM.

then followed up for a further 6 months [21]. After 9 months, the rate of MHE recurrence was 47.6% for rifaximin versus 42.1% for lactulose (P = not significant), and the rate of OHE occurrence was 7.1% for rifaximin versus 7.9% with lactulose (P = not significant) [21].

Only one long-term study has assessed the effectiveness of rifaximin monotherapy with that of rifaximin + lactulose therapy [31]. Compared with rifaximin + lactulose, the calculated NNT value (95% CI) for rifaximin monotherapy as secondary prophylaxis for OHE recurrence was 6.88 (3.50–203.90) (Fig. 2). This was a multicenter, retrospective, chart review comparing 1-year outcomes of 149 patients with cirrhosis treated with rifaximin (400–1600 mg/day) with those of 54 patients treated with rifaximin + lactulose [31]. The rate of maintenance of HE remission for 1 year was 81% with rifaximin monotherapy versus 67% with rifaximin + lactulose [31]. Mean time to a breakthrough OHE event was 210 days with rifaximin monotherapy versus 90 days with rifaximin + lactulose [31]. HE-related hospitalization rates were similar with rifaximin (43%) and rifaximin + lactulose (39%) [31]. In both groups, response to rifaximin appeared to be enhanced in patients with a mean baseline model for end-stage liver disease score of less than or equal to 20 [31]. These findings appear to contrast with those of a single-center, retrospective, observational study of 225 patients evaluated for liver transplantation, all of whom were treated with rifaximin-α 550 mg + lactulose for 6 months, which showed a lower rate of HE-related hospitalization in patients with a model for end-stage liver disease score of at least 20 versus less than 20 (1.6 vs. 2.5 per 6 months) [29].

Safety/tolerability of long-term (≥ 6 months) treatment of hepatic encephalopathy with rifaximin and/or lactulose

Manual assessment of the articles containing primary clinical data identified six articles reporting long-term safety/tolerability outcomes for treatment with lactulose alone and a further nine articles reporting long-term safety/tolerability outcomes for treatment of HE with rifaximin, alone or in combination with lactulose (Table 2). Details of studies including more than 100 patients are summarized in more detail later.

Lactulose alone

Three large single-center, open-label, randomized, controlled studies have assessed the long-term (≥6 months) safety/tolerability of lactulose therapy, compared with placebo, probiotics and/or no therapy [34,38,39]. In a primary prophylaxis study, in which patients with cirrhosis but no previous history of OHE were randomized to receive lactulose therapy (n = 60) or no lactulose therapy (n = 60) for 12 months, all patients treated with lactulose remained adherent to treatment [39]. The most commonly reported adverse events (AEs) with lactulose were diarrhea, distaste to lactulose and abdominal bloating, which improved following reduction of lactulose dosing [39]. In a secondary prophylaxis study, in which patients with cirrhosis who had recovered from OHE were randomized to receive lactulose (n = 68), probiotics (n = 64) or no therapy (n = 65) for up to 12 months, all lactulose patients remained adherent to treatment [34]. AEs in the lactulose group again comprised diarrhea, distaste to lactulose and abdominal bloating [34]. Lactulose dosing was reduced in these patients but not stopped. In the probiotics group, AEs comprised constipation and abdominal distension, which were managed with dietary advice and on-and-off use of proton pump inhibitors [34]. In the no therapy group, only constipation was reported, which was managed with dietary modifications [34]. Similar results were observed in another secondary prophylaxis study, in which patients were randomized to receive lactulose or placebo over a median follow-up duration of 14 months [38]. All patients remained adherent to lactulose therapy, and AEs in the lactulose group comprised diarrhea, distaste to lactulose and abdominal bloating [38]. Lactulose dosing was decreased in these patients but not stopped. In the placebo group, the only AE was constipation, which was managed with dietary modifications [38].

Rifaximin with or without lactulose

In the phase III, multicenter, randomized, double-blind, placebo-controlled trial, carried out by Bass *et al.* [19], which compared rifaximin-α 550 mg (n = 140) versus placebo (n = 159) for the prevention of OHE recurrence over 6 months (concomitant lactulose use > 90% in both groups), the overall incidence of AEs was 80.0% with rifaximin versus 79.9% with placebo. The most commonly reported AEs (≥10% of patients in either group) were nausea, diarrhea, fatigue, peripheral edema, ascites, dizziness and headache, but there were no significant differences between treatment groups [19]. There were also no significant differences between groups in the incidences of serious AEs and AEs related to infection, including *Clostridium difficile* infection [19]. Deaths occurred in 6.4 and 6.9% of rifaximin-treated and placebo-treated patients, respectively [19].

In the similarly designed single-center, randomized, triple-blind, placebo-controlled trial carried out by Ali *et al.* [15], the incidence of AEs was low and similar in patients treated with rifaximin-α 550 mg (n = 63) or placebo (n = 63) for 6 months, in addition to lactulose therapy. Deaths occurred in 11.1% of patients in both treatment groups [15].

In the 24-month, open-label maintenance study that followed the trial by Bass and colleagues, a total 392 patients were treated with rifaximin-α 550 mg ('all-rifaximin' group), including 252 patients who received *de novo* treatment (82 patients who received placebo in the original trial and 170 newly recruited patients; 'new-rifaximin' group) [18]. Approximately 90% of the patients in the all-rifaximin group additionally received treatment with lactulose. Safety/tolerability results were compared with those for patients who received rifaximin and placebo in the original phase III trial ['historical-rifaximin' (n = 140) and 'historical-placebo' (n = 159) groups, respectively]. The overall rates of AEs/PYE were lower in the all-rifaximin (0.71) and new-rifaximin (0.69) groups than in the historical-rifaximin (2.24) and historical-placebo (2.76) groups [18], as were the rates of serious AEs/PYE and discontinuation owing to AEs (rate/PTE) [18]. The rate of death/PYE was 0.15 in the all-rifaximin group compared with 0.24 in the historical-placebo group [18]. The rate of *C. difficile* infection remained stable with long-term

rifaximin treatment [18]. When comparing patients who received rifaximin in combination with lactulose ($n = 352$) with those who received rifaximin alone ($n = 40$), the incidence of gastrointestinal-related AEs was significantly higher in the combination therapy group than in the monotherapy group (69.6 vs. 47.5%; $P < 0.001$), including the incidences of nausea and abdominal pain [18].

In the multicenter, retrospective, observational IMPRESS study of 207 patients with HE (all of whom were treated with rifaximin-α 550 mg and 84% of whom received concomitant lactulose), 4.3% of patients had documented AEs, most commonly *C. difficile* infection ($n = 4$) and rash ($n = 2$) [22]. No serious AEs were reported. Of the four patients who developed *C. difficile* infection, none had a history of *C. difficile* and none was on concomitant antibiotics. All patients continued rifaximin therapy [22]. In a single-center, retrospective, cohort study that compared the effectiveness of rifaximin (600 mg, twice daily) + lactulose ($n = 318$) versus lactulose alone ($n = 724$) in patients with cirrhosis-related HE who either did or did not have HCC, *C. difficile* infection rates were 0.3% with rifaximin + lactulose versus 1.0% with lactulose alone, over a median follow-up duration of 18.0 months in patients without HCC and 4.4 months in patients with HCC [24]. In a multicenter, retrospective chart review of 211 patients treated with rifaximin (mean: 1055 mg/day; range: 600–1600 mg/day), in addition to lactulose, over a mean follow-up duration of 250 days, 8% of patients experienced diarrhea but none experienced *C. difficile* infection [41]. All cases of diarrhea were resolved with standard antidiarrheal therapy, which was administered after stool analysis excluded *C. difficile* infection [41].

Direct head-to-head evidence of the long-term safety/tolerability of rifaximin versus lactulose is limited to a single-center, retrospective chart review, in which 145 patients diagnosed with HE received at least 6 months of treatment with lactulose before receiving at least 6 months of treatment with rifaximin (400 mg, three times daily) [26]. Outcomes were compared for the last 6 months of lactulose treatment versus the first 6 months of rifaximin treatment [26]. The percentages of patients with diarrhea, flatulence and abdominal pain were significantly higher during the lactulose period than the rifaximin period ($P < 0.001$ for all) [26]. There was no significant difference in the percentage of patients with headache, which was the only other AE reported [26].

Discussion

This systematic review shows an increasing body of evidence for the use of rifaximin in addition to lactulose, and for lactulose therapy alone, in the long-term management of patients with HE. In line with the current guidelines [1], this evidence supports the use of lactulose therapy as secondary prophylaxis for the prevention of recurrence of OHE events over the long term [34,35,38]. In addition, one study has showed the effectiveness of lactulose as primary prophylaxis in the prevention of long-term OHE occurrence [39]. Although there is very little direct head-to-head evidence of rifaximin versus lactulose over the long term, there is considerable evidence to support recommendations for the use of rifaximin as an add-on treatment to standard lactulose therapy in the secondary prophylaxis setting [1].

In terms of effectiveness, several long-term, open-label clinical trials and clinical practice studies have showed that, when added to lactulose therapy, rifaximin significantly reduces the recurrence of OHE events and rate of HE-related hospitalization, in comparison with lactulose therapy alone [16,19,20,22,24,28]. An exception to this was a single-center, randomized, placebo-controlled trial, carried out by Ali *et al.*, in which rifaximin was found to be no better than placebo when combined with lactulose therapy as secondary prophylaxis against OHE recurrence [15]. In discussing the potential reasons for the discrepancy in the findings of this trial, compared with those of the phase III trial by Bass *et al.* [19], the authors point out that the study populations differed in terms of primary etiology of cirrhosis, geographical and dietary background [15]. The authors therefore speculated that the gut flora [42–44] of the two study populations might have differed. Nevertheless, the majority of current evidence supports an enhanced therapeutic benefit in adding rifaximin to lactulose therapy for the prevention of OHE recurrence and HE-related hospitalization.

Historically, the NNT measure was designed to quantify treatment benefit directly in terms of the number of patients who would need to be treated before benefit is observed, thereby providing a means of expressing absolute, as opposed to relative, risk in a clinically meaningful way [45–47]. Although the number of studies eligible for inclusion in the current NNT analyses was limited, the results showed that, in terms of long-term secondary prophylaxis for the prevention of OHE recurrence, approximately four patients would need to be treated with lactulose before clinical benefit is observed, compared with no treatment or placebo. This must be considered within the clinical context showing a very high rate of OHE recurrence with no prophylaxis or with poor adherence to lactulose therapy. Importantly, to show the add-on benefit of rifaximin to lactulose, the NNT is approximately four patients to prevent the recurrence of OHE. The relatively low NNT value for adding rifaximin to lactulose therapy provides further support for the clinical benefit of these treatments for the prevention of OHE recurrence over the long term. Only one study compared rifaximin monotherapy versus rifaximin + lactulose, and NNT analysis showed that approximately seven patients would need to be treated with rifaximin monotherapy before clinical benefit is observed (in comparison with rifaximin + lactulose). However, the results of this single study should be viewed with caution, not only because the 95% CI was very wide but also because the study design was such that patients who received rifaximin monotherapy may have had less severe HE than those who received combination therapy, which may have affected their likelihood of long-term remission [31].

For chronic conditions such as HE, the success of treatment is dependent on its tolerability, as patients will only adhere to treatment if they are able to tolerate it over the long term. Long-term tolerability problems, such as adverse gastrointestinal symptoms, also have a major effect on health-related quality of life [48]. In the case of lactulose, tolerability is a major clinical consideration. In a study of 137 patients who received long-term secondary

prophylaxis with lactulose, 75% experienced OHE recurrence, and this was associated with lactulose nonadherence in 38% of these patients, mainly because of gastrointestinal adverse effects, such as unpredictable diarrhea, abdominal pain and bloating [10]. Crucially, all patients who were nonadherent on lactulose therapy, and nearly two-thirds of those who were adherent, experienced OHE recurrence [10]. There is evidence to suggest that patient acceptance of lactulose is influenced by sociocultural factors; for example, in a recent survey of 100 outpatients with cirrhosis from India and the USA, who did not have previous or current experience with lactulose but who underwent dedicated education about its use for HE prevention, a significantly higher proportion of Indian versus US patients agreed to accept lactulose treatment [49]. In this context, it is perhaps noteworthy that a substantial number of the lactulose studies identified in this review were carried out in patients from the Indian subcontinent. Taken together, such findings highlight the need for additional, effective and better tolerated therapeutic options in the long-term management of HE, across all sociocultural patient groups.

In the 6-month phase III trial that compared rifaximin-α 550 mg with placebo for the prevention of OHE recurrence in patients in HE remission, more than 90% of whom were additionally treated with lactulose, the overall incidence of AEs was the same in both groups, and there were no significant between-group differences in the incidence of the most commonly reported AEs and serious AEs [19]. In the 24-month open-label maintenance study that followed this trial, the incidences of total AEs, serious AEs and AEs leading to discontinuation were lower than those observed in the rifaximin and placebo arms of the original 6-month trial [18]. In addition, long-term retrospective studies have showed a low incidence of AEs when rifaximin is added to lactulose therapy in clinical practice [22,41]. As with nearly all antibacterial agents, *C. difficile*-associated diarrhea has been reported with rifaximin treatment [13]. However, this has not emerged as a major safety concern following long-term treatment in clinical trials [18,19] and in clinical practice studies [22,24,41].

HE is associated with a substantial economic burden, primarily because of the direct costs of hospitalization and rehospitalization following recurrence, and secondarily because of the indirect costs associated with outpatient care, disability, lost productivity and the wider negative effect on the lives of patients' caregivers [1,50,51]. As previously discussed, current evidence for the long-term treatment of HE with rifaximin as an add-on to lactulose therapy demonstrates that it not only significantly decreases OHE recurrence, in comparison with lactulose therapy alone, but also significantly reduces the rate of HE-associated hospitalization and length of hospital stay [16,19,20,22,24,28,52]. There is therefore a substantial body of evidence showing that the addition of rifaximin to standard lactulose therapy results in significant reductions in healthcare resource utilization over the long term.

A limitation of this systematic review was that, following a thorough assessment of the available data, meta-analysis of outcome measures was found to be unfeasible and inappropriate, because of the heterogeneity of the designs, treatment settings and patient populations of the studies that were identified. NNT analysis was also limited by the low number of studies that could be assessed in this way.

Conclusion

Current evidence supports recommendations for the use of lactulose therapy for the prevention of OHE recurrence over the long term, and for the additional benefit of adding rifaximin to lactulose therapy. The addition of rifaximin to lactulose significantly further reduces the risk of OHE recurrence and HE-related hospitalization, compared with lactulose therapy alone, with a demonstrably low NNT to achieve these further benefits. There is also emerging evidence to indicate that a switch to rifaximin monotherapy may be appropriate for those for whom lactulose is ineffective and/or poorly tolerated, and/or when adherence to lactulose therapy is problematic, although this requires further research.

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Conflicts of interest

M.H.: Speaker fees and travel expenses from Norgine, Astellas, Janssen and AbbVie; in addition, advisory board honoraria from Norgine and Novartis. M.S.: Lecture and travel fees from AbbVie, Gilead, Falk and Norgine; in addition, advisory board honoraria from AbbVie and Norgine.

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