Supplemental Table 1. Search strategy for PubMed, Embase and Cochrane Databases

|  |  |
| --- | --- |
| PubMed | |
| Search | Query |
| #1 | ("hepatic encephalopathy"[Mesh] OR "Hepatic Encephalopathy"[tiab] OR "liver disease"[tiab] OR "Liver Cirrhosis"[mesh] OR "Liver Cirrhosis"[tiab] OR "Liver Cirrhoses"[tiab] OR "Liver Fibroses"[tiab] OR "Liver Fibrosis"[tiab] OR "Hepatic Cirrhosis"[tiab] OR "Hepatic Cirrhoses"[tiab] OR "hepatic coma"[tiab] OR "hepatic stupor"[tiab] OR "Hepatic Encephalopathies"[tiab] OR "Portal-Systemic Encephalopathy"[tiab] OR "Portosystemic Encephalopathy"[tiab] OR "Hepatocerebral Encephalopathies"[tiab] OR cirrhosis[tiab] OR "hepatoencephalopathy"[tiab] OR "ammoniac encephalopathy"[tiab] OR "hepato cerebral disease"[tiab] OR "hepatocerebral disease"[tiab] OR "hepatocerebral syndrome"[tiab] OR "hepatoencephalopathy"[tiab] OR "hepatogenous encephalopathy"[tiab] OR "liver encephalopathy"[tiab] OR "porta cava encephalopathy"[tiab] OR "portacaval encephalopathy"[tiab] OR "portal encephalopathy"[tiab] OR "portal systemic encephalopathy"[tiab] OR "portocaval encephalopathy"[tiab]) |
| #2 | (lactulose[mesh] OR lactulose[tiab] OR enulose[tiab] OR generlac[tiab] OR lactitol[tiab] OR acilac[tiab] OR actilax[tiab] OR avilac[tiab] OR bifinorma[tiab] OR bifiteral[tiab] OR cephulac[tiab] OR cholac[tiab] OR chronulac[tiab] OR colsanac[tiab] OR constilac[tiab] OR constulose[tiab] OR danilax[tiab] OR dhactulose[tiab] OR “dia-colon”[tiab] OR duphalac[tiab] OR duphulac[tiab] OR epalfen[tiab] OR evalose[tiab] OR farlac[tiab] OR gatinar[tiab] OR genlac[tiab] OR genocolan[tiab] OR hepalac[tiab] OR heptalac[tiab] OR kristalose[tiab] OR lacson[tiab] OR lactecon[tiab] OR lactocur[tiab] OR lactul[tiab] OR lactulax[tiab] OR lactulen[tiab] OR lactumed[tiab] OR lactus[tiab] OR lactuverlan[tiab] OR laevilac[tiab] OR laevolac[tiab] OR laxaron[tiab] OR laxette[tiab] OR laxilose[tiab] OR laximed[tiab] OR legendal[tiab] OR levolac[tiab] OR lipebin[tiab] OR “livo luk”[tiab] OR martulose[tiab] OR moderan[tiab] OR monilac[tiab] OR normase[tiab] OR normolax[tiab] OR portalac[tiab] OR pralax[tiab] OR regulact[tiab] OR sirolax[tiab] OR sirulax[tiab] OR tenualax[tiab] OR tulotract[tiab] OR verelait[tiab] OR flonorm[tiab] OR lepetit[tiab] OR lumenax[tiab] OR normix[tiab] OR redactiv[tiab] OR rifamycin[tiab] OR rifaxamin[tiab] OR rifaxidin[tiab] OR xifaxan[tiab] OR emportal[tiab] OR importal[tiab] OR "importan jeunes enfants"[tiab] OR lactilol[tiab] OR maltit[tiab] OR oponaf[tiab] OR portolac[tiab] OR rifaximin[tiab] OR Amivalex[tiab]) |
| #3 | #1 AND #2 |
| #4 | #3 NOT (commentary[ti] OR editorial[ti] OR editorial[pt] OR letter[pt] OR comment[pt]) |
| Embase | |
| #1 | (‘hepatic encephalopathy’/exp OR ‘liver cirrhosis’/de OR (‘Hepatic Encephalopathy’ OR ‘liver disease’ OR ‘Liver Cirrhosis’ OR ‘Liver Cirrhoses’ OR ‘Liver Fibroses’ OR ‘Liver Fibrosis’ OR ‘Hepatic Cirrhosis’ OR ‘Hepatic Cirrhoses’ OR ‘hepatic coma’ OR ‘hepatic stupor’ OR ‘Hepatic Encephalopathies’ OR ‘Portal-Systemic Encephalopathy’ OR ‘Portosystemic Encephalopathy’ OR ‘Hepatocerebral Encephalopathies’ OR cirrhosis OR ‘hepatoencephalopathy’ OR ‘ammoniac encephalopathy’ OR ‘hepato cerebral disease’ OR ‘hepatocerebral disease’ OR ‘hepatocerebral syndrome’ OR ‘hepatoencephalopathy’ OR ‘hepatogenous encephalopathy’ OR ‘liver encephalopathy’ OR ‘porta cava encephalopathy’ OR ‘portacaval encephalopathy’ OR ‘portal encephalopathy’ OR ‘portal systemic encephalopathy’ OR ‘portocaval encephalopathy’):ab,ti) |
| #2 | ('rifaximin'/exp OR ‘lactulose’/exp OR (lactulose OR enulose OR generlac OR lactitol OR acilac OR actilax OR avilac OR bifinorma OR bifiteral OR cephulac OR cholac OR chronulac OR colsanac OR constilac OR constulose OR danilax OR dhactulose OR ‘dia-colon’ OR duphalac OR duphulac OR epalfen OR evalose OR farlac OR gatinar OR genlac OR genocolan OR hepalac OR heptalac OR kristalose OR lacson OR lactecon OR lactocur OR lactul OR lactulax OR lactulen OR lactumed OR lactus OR lactuverlan OR laevilac OR laevolac OR laxaron OR laxette OR laxilose OR laximed OR legendal OR levolac OR lipebin OR ‘livo luk’ OR martulose OR moderan OR monilac OR normase OR normolax OR portalac OR pralax OR regulact OR sirolax OR sirulax OR tenualax OR tulotract OR verelait OR flonorm OR lepetit OR lumenax OR normix OR redactiv OR rifamycin OR rifaxamin OR rifaxidin OR xifaxan OR emportal OR importal OR ‘importan jeunes enfants’ OR lactilol OR maltit OR oponaf OR portolac OR rifaximin OR Amivalex):ab,ti) |
| #3 | #1 AND #2 |
| #4 | #3 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) |
| Cochrane | |
| #1 | ((‘Hepatic Encephalopathy’ OR ‘liver disease’ OR ‘Liver Cirrhosis’ OR ‘Liver Cirrhoses’ OR ‘Liver Fibroses’ OR ‘Liver Fibrosis’ OR ‘Hepatic Cirrhosis’ OR ‘Hepatic Cirrhoses’ OR ‘hepatic coma’ OR ‘hepatic stupor’ OR ‘Hepatic Encephalopathies’ OR ‘Portal-Systemic Encephalopathy’ OR ‘Portosystemic Encephalopathy’ OR ‘Hepatocerebral Encephalopathies’ OR cirrhosis OR ‘hepatoencephalopathy’ OR ‘ammoniac encephalopathy’ OR ‘hepato cerebral disease’ OR ‘hepatocerebral disease’ OR ‘hepatocerebral syndrome’ OR ‘hepatoencephalopathy’ OR ‘hepatogenous encephalopathy’ OR ‘liver encephalopathy’ OR ‘porta cava encephalopathy’ OR ‘portacaval encephalopathy’ OR ‘portal encephalopathy’ OR ‘portal systemic encephalopathy’ OR ‘portocaval encephalopathy’)):ti,ab,kw  (Word variations have been searched) |
| #2 | ((lactulose OR enulose OR generlac OR lactitol OR acilac OR actilax OR avilac OR bifinorma OR bifiteral OR cephulac OR cholac OR chronulac OR colsanac OR constilac OR constulose OR danilax OR dhactulose OR ‘dia-colon’ OR duphalac OR duphulac OR epalfen OR evalose OR farlac OR gatinar OR genlac OR genocolan OR hepalac OR heptalac OR kristalose OR lacson OR lactecon OR lactocur OR lactul OR lactulax OR lactulen OR lactumed OR lactus OR lactuverlan OR laevilac OR laevolac OR laxaron OR laxette OR laxilose OR laximed OR legendal OR levolac OR lipebin OR ‘livo luk’ OR martulose OR moderan OR monilac OR normase OR normolax OR portalac OR pralax OR regulact OR sirolax OR sirulax OR tenualax OR tulotract OR verelait OR flonorm OR lepetit OR lumenax OR normix OR redactiv OR rifamycin OR rifaxamin OR rifaxidin OR xifaxan OR emportal OR importal OR ‘importan jeunes enfants’ OR lactilol OR maltit OR oponaf OR portolac OR rifaximin OR Amivalex)):ti,ab,kw  (Word variations have been searched) |
| #3 | #1 AND #2 |

Supplemental Table 2. Additional Study Characteristics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Blinding** | **Inclusion** | **Exclusion** | **Method of CHE/MHE Diagnosis** |
| Poo  (2006) | blinded | cirrhosis, chronic persistent grade 1 or 2 OHE in the last 6 months and present at selection visit according to West Haven criteria\*, fasting plasma ammonia >60 at selection | first episode of acute HE; stage 3 or 4 HE; degenerative CNS disease or major psychiatric illness; GI bleed in last 30 days; active infection or antibiotics requirement in past 30 days; Cr >1.8 mg/dL; Na <130 mEq/L; pregnancy or breastfeeding; refusal to use contraception in women of child-bearing age; uncontrolled DM; complications or pHTN such as refractory ascites or variceal hemorrhage; medication compliance <80%; serious active infection requiring antibiotics like SBP | West Haven criteria (to ensure grade 1-2)\*, NCT (no description of cutoffs used) |
| Zeng (2006) | unblinded | patients with abnormal in the NCT, DST, and/or evoked potential examination; agreed and cooperated with the treatment. | HE now or in the past; mental, psychological, or neurological diseases; sedative or CNS inhibitor use in the latest four weeks; alcoholic cirrhosis and or active alcohol use disorder; GI bleeding; disorders of electrolytes and acid-base balance caused by diuretic use; body temperature above 37.5 deg C; diseases of heart, lung, brain, and kidney, and severe diabetic complications; illiterate or poor literacy | abnormal (>2 S.D. from “normal values”) for NCT, DST, and/or evoked potential examination |
| Prasad (2007) | unblinded | cirrhosis and MHE | current or history OHE; recent alcohol intake (<6 weeks); infection, antibiotic use or GIB within <6 weeks; use of benzodiazepines, antiepileptics or psychotropics within <6 weeks; history of shunt surgery or TIPS; electrolyte imbalance; renal impairment; HCC; severe medical problems such as congestive heart failure or pulmonary, neurological or psychiatric comorbidities that could influence QOL measurement; inability to perform neuropsychiatric tests or QOL assessments due to poor vision | two or more neuropsychiatric tests with Z score < -2 including NCT-A and NCT-B, FCT-A and FCT-B, 2 performance subsets of Wechsler Adult Intelligence Scale, picture completion test, BDT |
| Bajaj (2011) | blinded | cirrhosis and MHE | prior OHE; abuse of alcohol or illicit drugs within the past 6 months; not currently driving; MMSE < 25; current antibiotic use; allergy to rifampin/rifaximin/rifamycin | two or more neuropsychiatric tests with Z score < -2 including NCT-A, NCT-B, DST, and BDT or lures of ICT |
| Mittal (2011) | unblinded | cirrhosis and MHE | current or prior (within 6 weeks) OHE; GIB within <6 weeks; ongoing infection; Cr >1.5 mg/dL; electrolyte impairment (Na<130 or >150 mEq/L, K<3 or >5.5 mEq/L), alcohol use within <6 weeks per patient report; use of psychotropic drugs in last 6 weeks; TIPS or shunt surgery; HCC; severe medical problems such as congestive heart failure or pulmonary, neurological or psychiatric comorbidities that could influence QOL measurement; inability to perform neuropsychiatric tests or QOL assessments due to poor vision | two or more neuropsychiatric tests with Z score < -2 including NCT-A, NCT-B, FCT-A, FCT-B; if illiterate, picture completion and BDT used |
| Sanyal (2011) | blinded | age >18 years, >2 episodes of OHE (Conn score >2) associated with cirrhosis during the previous 6 months; HE remission (Conn 0 or 1) at enrollment; and MELD < 25; OHE episodes precipitated by GIB requiring transfusion of >2 units of blood, medication use, renal failure requiring dialysis, or injury to CNS were not counted as previous episodes | expected liver transplant <1 month after screening visit; presence of conditions that are known precipitants of HE (GIB, TIPS) within 3 months before screening; CKD (Cr >2 mg/dL), respiratory insufficiency; anemia (Hgb <8 g/dL), an electrolyte abnormality (Na <125 mEq/L, Ca >5 mEq/L, K<2.5 mEq/L); intercurrent infection or active SBP | N/A |
| Sidhu (2011) | blinded | age 18-65 years, liver cirrhosis, MHE | current or past history of OHE; known allergy to rifaximin / rifabutin / rifampin / rifapentine; current or recent (<6 weeks) use of alcohol; use of antibiotics within last 6 weeks; use of lactulose / lactitol, probiotics, L -ornithine- L -aspartate, zinc, metronidazole, neomycin, or rifaximin within last 6 weeks; use of interferon or psychoactive drugs such as benzodiazepines, psychotropic drugs, anti-epileptics within last 6 weeks; infection or GIB within last 6 weeks; acute superimposed liver injury; advanced medical problems such as congestive cardiac failure, advanced pulmonary disease, or renal insufficiency or electrolyte imbalance; presence of HCC; history of portosystemic shunt surgery or TIPS; pregnancy and breastfeeding; neurological or psychiatric problems that may influence QOL measurement; poor vision or motor defects that interfere with the performance of psychometric tests | two or more neuropsychiatric tests with Z score < -2 including NCT-A, FCT-A, DST, PCT, BDT |
| Elnoemany (2015) | unblinded | MHE | not reported | not reported |
| Sidhu (2016) | unblinded | age 18-65 years, liver cirrhosis, MHE | known allergy to rifaximin; current or recent (<6 weeks) use of alcohol; use of lactulose/lactitol, probiotics, metronidazole, or rifaximin within the last 6 weeks; use of interferon therapy, psychoactive drugs, or anti-epileptics within last 6 weeks; infection or GI hemorrhage within last 6 weeks; opium addiction; presence of HCC; history of portosystemic shunt surgery; prior history of OHE | two or more neuropsychiatric tests with Z score < -2 including NCT-A, FCT-A, DST, PCT, BDT |
| Bruyneel (2017) | not reported | cirrhosis, admitted to the liver unit for recurrent HE (defined as recurrent bouts of HE within 6 months, excluding other causes of AMS), maintenance therapy of 45 ml of lactulose during the 6-mo period before inclusion and at least 2 HE-related admissions since the start of lactulose treatment | age <18 years; presence of surgical shunt or TIPS; liver transplant; inability of patient to maintain regular follow-up because of failure to comply with study protocol; active alcohol use | N/A |
| Singh (2017) | unblinded | cirrhosis without OHE; cohort divided into MHE and non-MHE group | history of OHE; shunt surgery or TIPS; HCC; HRS; acute on chronic liver failure; active infection; electrolyte abnormalities; antibiotic prophylaxis for SBP, use of drugs affecting psychometric performances within 1 months; major medical comorbidities including congestive heart failure, pulmonary disease, neurological disorder or psychiatric disorder that could influence QOL measurement or performance of neuropsychological tests; alcohol intake within last one month; lactulose/rifaximin/LOLA/probiotics within the last month; GIB in the last one month | PHES score < -5 |
| Sanyal (2018) | unblinded | adults; ≥1 OHE episode during the prior 6 months, currently in HE remission (Conn score ≤1) | not reported | not reported |
| Suzuki (2018) | blinded | age 20-74 years; cirrhosis; grade I or II HE according to Inuyama Symposium in Japan; clinical, psychometric and electroencephalographic evidence of grade I-III HE of less than 2 days duration | psychiatric comorbidities; comorbidity or medical history that affected evaluation; acute hepatitis; acute liver failure; acute exacerbation of chronic hepatitis; total bilirubin ≥5.0 mg/dL, hemoglobin ≤8 g/dL, K ≤2.5 mEq/L; both blood urea nitrogen ≥25 mg/dL and Cr >2.0 mg/dL | cirrhosis; grade I or II HE according to Inuyama Symposium in Japan; other tests performed included NCT-A, NCT-B, DST (no cutoffs described) |
| Wang (2019) | unblinded | age 18–70 years, cirrhosis, MHE | unable to complete NCT and DST tests due to mental factors, nervous system diseases, intelligence or eyesight, or who are unable to complete the form for evaluating the quality of life; cirrhosis caused by chronic alcoholism who had not stopped drinking within 6 months; cirrhosis attributed to Wilson's disease or other genetic metabolic diseases affecting the nervous system; pregnant or lactating patients; galactosemia; intestinal obstruction and colic; allergy to lactulose and its components; receiving combined use of other cathartics, PPI or probiotics; patients with OHE or who also use of other blood ammonia reducing drugs (e.g. sodium glutamate, potassium glutamate, arginine and ornithine aspartate injection) or received plasma exchange treatment; antibiotic treatment within one week before the study began; acute diarrhea within one week before the study began; chronic diarrhea; current electrolyte disturbance; melena, hematemesis and other symptoms of gastrointestinal bleeding within two weeks before the study begins; other diseases that may affect the study, including severe cardiopulmonary diseases, diabetes, tumor, immune system diseases, and patients who have to receive long-term hormone treatment due to other diseases and with history of GI operation; substance abuse: excessive alcohol use (≥80 g/day), illicit IV or inhalational substances in the past two years; chronic viral hepatitis started on antiviral therapy within the past six months; any patient deemed unqualified by investigators to participate in this study | abnormal  performance on both NCT-A and DST |
| Glal (2021) | blinded | age 20-65 years, cirrhosis, HE (West Haven grade I to IV) | active GIB; major psychiatric illness; Cr >2 mg/dL; medications with high plasma protein binding capacity such as warfarin, benzodiazepines and narcotics; pregnant and breast-feeding women | N/A |
| Patel (2022) | blinded | cirrhosis, chronic HE based on the either persistent OHE (>grade 1) or >2 episodes of OHE in last 6 months | age <18 or >75 years; disseminated malignancy; celiac or inflammatory bowel disease; intestinal failure, intestinal obstruction or prior bowel resection; HIV; chronic granulomatous disease; anti-inflammatory or immunomodulatory drug use; exposure to rifaximin in past 12 weeks; concomitant antibiotic use; hypersensitivity to rifaximin-a or rifamycin-derivatives; infection with C. difficile in prior 3 months; pregnancy or breastfeeding women | N/A |

\* grade I-II patients were allowed in the study but mean (S.D.) of West-Haven grade was 1.1 (0.10) in lactulose group and 1.0 (0.14) in LOLA group

HE: hepatic encephalopathy; OHE: overt hepatic encephalopathy; NCT: number connection test; FCT: figure connection test; BDT: block design test; ICT: inhibitory control test; DST: digital symbol test; PHES: psychometric hepatic encephalopathy score; CNS: central nervous system, GI: gastrointestinal; GIB: gastrointestinal bleeding Cr: creatinine; Na: sodium; K: potassium; Ca: calcium; DM: diabetes mellitus; pHTN: portal hypertension; TIPS: transjugular intrahepatic portosystemic shunt; HCC: hepatocellular carcinoma; SBP: spontaneous bacterial peritonitis; QOL: quality of life; MMSE: mini mental status exam; AMS: altered mental status; HRS: hepatorenal syndrome; HIV: human immunodeficiency virus

Supplemental Table 3. Bias assessments of included non-RCTs using Newcastle-Ottawa Scale (NOS)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Representativeness of exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Precision of Exposure Dose Ascertainment | Ascertainment of exposure done prospectively or retrospectively | Demonstration that outcome of interest was not present at start of study, or baseline assessment |
| Bruyneel (2017) | 1 | N/A | 0 | 0 | N/A | 1 |
| Singh (2017) | 1 | N/A | 1 | 0 | 1 | 1 |

Supplemental Table 3 (continued). Bias assessments of included non-RCTs using Newcastle-Ottawa Scale (NOS)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Adjustment for confounding | Assessment of outcome | Was follow-up long enough for outcomes to occur? | Adequacy of follow-up of cohorts | Risk of Bias (low, medium, high) | Notes on Generalizability |
| Bruyneel (2017) | 0 | 1 | 1 | 1 | low | Inpatient sample from Brussels, Belgium |
| Singh (2017) | 0 | 1 | 1 | 1 | low | Patients recruited from New Delhi, India |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author (year)** | **Treatment/**  **Comparator** | **Total SIP**  **(95% CI)** | **Total Psychosocial (95% CI)** | **Total Physical (95% CI)** | **Social Interactions (95% CI)** | **Alertness (95% CI)** | **Emotional Behavior (95% CI)** | **Communication (95% CI)** |
| Prasad (2007) | Lactulose (n=25) | 6.8†  (5.2, 8.4) | 8.5 †  (6.6, 10.4) | 3.0†  (1.9, 4.1) | 8.5  (5.9, 11.1) | 10.4  (7.0, 13.8) | 9.0†  (5.9, 12.0) | 2.7  (0.3, 5.1) |
| No treatment (n=20) | 0.0  (-0.3, 0.6) | 0.8  (-0.0, 1.6) | 0.0  (-1.0, 1.0) | 0.5  (-0.8, 1.8) | -0.8  (-3.0, 1.5) | 2.8  (-0.8, 6.3) | 0.8  (-1.6, 3.1) |
| Mittal (2011) | Lactulose  (n=35) | 7.0†  (5.6, 8.4) | 5.2†  (4.2, 6.2) | 3.6†  (2.9, 4.3) | 3.9†  (2.9, 4.8) | 3.6†  (2.9, 4.4) | 9.8†  (8.2, 11.5) | 2.1  (0.3, 3.8) |
| No treatment  (n=31) | 1.1  (0.2, 2.0) | 1.1  (0.2, 2.0) | -0.0  (-0.8, 0.7) | 1.6  (0.5, 2.8) | 0.2  (-0.7, 1.1) | 0.4  (-1.1, 1.9) | 0.8  (-0.4, 2.0) |
|  |  |  |  |  |  |  |  |  |
| Sidhu (2011) | Rifaximin  (n=37) | 4.6\*†  (3.8, 5.5) | 1.2\*†  (0.7, 1.8) | 2.0\*†  (1.5, 2.4) | 5.3\*†  (1.7, 9.0) | 1.3  (-0.2, 2.2) | 5.3\*†  (2.7, 8.0) | 0.4†  (-0.2, 1.0) |
| Placebo  (n=30) | 0.9  (0.5, 1.3) | 0.2  (-0.0, 0.4) | 0.5  (0.2, 0.9) | 0.7  (-1.0, 2.5) | 0.1  (-0.4, 0.6) | 1.9  (0.6, 3.2) | -0.7  (-1.4, 0.0) |
| Bajaj (2011) | Rifaximin  (n=21) | 1  (-0.2, 2.2) | 5\*  (3.4, 6.6) | 0  (-1.2, 1.2) | NR | NR | NR | NR |
| Placebo  (n=21) | 2  (0.1, 3.9) | 2  (-0.2, 4.2) | 1  (-0.2, 2.2) | NR | NR | NR | NR |
|  |  |  |  |  |  |  |  |  |
| Elnoemany (2015) | Lactulose  (n=31) | 7.8  (5.6, 9.9) | NR | NR | NR | NR | NR | NR |
| Rifaximin  (n=32) | 7.2  (4.9, 9.6) | NR | NR | NR | NR | NR | NR |
| Sidhu (2016) | Lactulose  (n=37) | 7.0  (4.8, 9.2) | NR | NR | 7.9  (3.8, 12.0) | 8.3  (3.8, 12.8) | 6.3  (2.1, 10.5) | 2.3  (0.0, 4.6) |
| Rifaximin  (n=41) | 8.2  (6.3, 10.1) | NR | NR | 10.3  (5.9, 14.7) | 9.9  (5.2, 14.6) | 8.1  (3.6, 12.6) | 2.8  (0.9, 4.7) |

Supplemental Table 4. Changes in Sickness Impact Profile (SIP)

Positive values indicate improvement

\* Intragroup difference (i.e. before vs after) significant at p<0.05; † Intergroup difference (i.e. treatment vs comparator) significant at p<0.05

NR: not reported

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author (year)** | **Treatment/**  **Comparator** | **Ambulation (95% CI)** | **Mobility**  **(95% CI)** | **Body Care (95% CI)** | **Sleep/Rest (95% CI)** | **Work**  **(95 CI)** | **Home Management (95% CI)** | **Recreation/**  **Past times (95% CI)** | **Eating**  **(95% CI)** |
| Prasad (2007) | Lactulose (n=25) | 3.7†  (2.1, 5.2) | 5.4  (2.7, 8.0)† | 1.6  (0.5, 2.7) | 9.0  (5.2, 12.9)† | 15.8  (7.1, 24.6) | 12.6  (7.3, 18.0) | 11.6  (7.7, 15.5)† | 3.9  (2.5, 6.3) |
| No treatment (n=20) | -1.9  (-4.1, 0.3) | 1.2  (-1.1, 3.5) | 0.7  (-0.1, 1.6) | 2.3  (-0.3, 4.9) | -0.0  (-2.9, 2.7) | 0.9  (-1.4, 3.3) | -0.3  (-2.5, 1.9) | -0.6  (-3.1, 2.0) |
| Mittal (2011) | Lactulose  (n=35) | 5.1†  (3.7, 6.5) | 4.6†  (3.2, 6.1) | 3.2†  (2.4, 4.0) | 11.6†  (9.8, 13.5) | 9.5†  (4.1, 14.9) | 6.3†  (4.6, 8.1) | 7.7†  (5.8, 9.7) | 2.5  (1.4, 3.5) |
| No treatment  (n=31) | -0.2  (-0.7, 1.1) | 0.6  (-1.4, 2.6) | -0.4  (-1.1, 0.3) | 2.9  (0.5, 5.3) | 0.6  (-0.3, 1.6) | -0.3  (-2.3, 1.8) | 3.1  (1.4, 4.7) | 1.1  (0.0, 2.3) |
|  |  |  |  |  |  |  |  |  |  |
| Sidhu (2011) | Rifaximin  (n=37) | 2.0\*†  (0.9, 3.1) | 13.6\*†  (9.7, 17.4) | 4.2\*†  (2.4, 6.1) | 9.8\*†  (7.6, 12.1) | 1.4  (0.4, 2.3) | 0.7  (-1.4, 2.8) | 1.2  (-0.2, 2.7) | 0.8\*  (0.2, 1.5) |
| Placebo  (n=30) | 1.0  (-0.6, 2.5) | 5.2  (2.4, 7.9) | -0.9  (-2.9, 1.1) | -0.4  (-1.9, 1.1) | 0.6  (0.3, 1.4) | 2.0  (0.5, 3.4) | 0.2  (-0.6, 1.1) | 0.1  (-0.5, 0.6) |
| Bajaj (2011) | Rifaximin  (n=21) | NR | NR | NR | -4  (-8.4, 0.4) | 4  (-0.4, 8.4) | 1  (-0.9, 2.9) | 7  (4.2, 9.8) | 0  (-0.6, 0.6) |
| Placebo  (n=21) | NR | NR | NR | 1  (-3.1, 5.1) | 2  (-2.1, 6.1) | 4  (1.8, 6.2) | 2  (-0.8, 4.8) | 1  (0.0, 2.0) |
|  |  |  |  |  |  |  |  |  |  |
| Elnoemany (2015) | Lactulose  (n=31) | NR | NR | NR | NR | NR | NR | NR | NR |
| Rifaximin  (n=32) | NR | NR | NR | NR | NR | NR | NR | NR |
| Sidhu (2016) | Lactulose  (n=37) | 1.7  (-1.6, 5.0) | 19.5  (12.8, 26.2) | 6.3  (3.0, 9.6) | 6.8  (3.4, 10.2) | 5.3  (-0.7, 11.3) | 10.0  (5.8, 14.3) | 9.3  (4.4, 14.2) | 0.2  (-1.9, 2.3) |
| Rifaximin  (n=41) | 5.3  (2.5, 8.1) | 15.8  (10.6, 21.0) | 6.4  (2.4, 8.8) | 5.8  (2.9, 8.7) | 11.2  (6.1, 16.3) | 11.3  (7.5, 15.1) | 10.8  (6.9, 14.7) | 1.1  (-0.6, 2.8) |

Supplemental Table 4 (continued). Changes in Sickness Impact Profile (SIP)

Positive values indicate improvement

\* Intragroup difference (i.e. before vs after) significant at p<0.05; † Intergroup difference (i.e. treatment vs comparator) significant at p<0.05

NR: not reported

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author (year)** | **Treatment/**  **Comparator** | **Physiological**  **(95% CI)** | **Psychological**  **(95% CI)** | **Social Relationship**  **(95% CI)** | **Environmental**  **(95% CI)** |
| Zeng (2006) | Lactulose (short-term)  (n=19) | -12.4  (-24.0, -0.8) | -13.2  (-24.0, -2.4) | -13.0  (-24.1, -1.9) | -1.6  (-11.4, 8.2) |
| Lactulose (long-term)  (n=18) | 7.0†  (-7.2, 21.2) | 6.0†  (-4.9, 16.9) | 3.5†  (-9.7, 16.7) | -2.0  (-10.8, 6.8) |
| Vitamin B  (n=19) | -14.5  (-26.3, -2.7) | -13.7  (-22.3, -5.1) | -14.2  (-25.1, -3.3) | -4.1  (-15.2, 7.0) |

Supplemental Table 5. Changes in WHOQOL-BREF

Positive values indicate improvement

\* Intragroup difference (i.e. before vs after) significant at p<0.05; † Intergroup difference (i.e. long-term vs short-term and placebo) significant at p<0.05

Supplemental Table 6. Changes in SF-36

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Treatment/**  **Comparator** | **Physical Component Summary**  **(95% CI)** | **Mental Component Summary**  **(95% CI)** | **Physical Function**  **(95% CI)** | **Role-limitation Physical**  **(95% CI)** | **Bodily pain**  **(95% CI)** | **Vitality**  **(95% CI)** |
| Singh (2017)‡ | Lactulose (n=47) | 13  (NR) | 11  (NR) | 10  (NR) | 15  (NR) | 13  (NR) | 10  (NR) |
| None | NA | NA | NA | NA | NA | NA |
| Poo (2006) | Lactulose (n=10) | 0  (-15.8, 15.8) | -2  (-19.0, 15.0) | NR | NR | NR | NR |
|  |  |  |  |  |  |  |  |
| Bruyneel (2017) | Rifaximin (n=12) | -1  (NR) | 4  (NR) | NR | NR | NR | NR |
| None | NA | NA | NA | NA | NA | NA |

Positive values indicate improvement

\* Intragroup difference (i.e. before vs after) significant at p<0.05; † Intergroup difference (i.e. treatment vs comparator) significant at p<0.05

‡ SF-36 (version 2)

LOLA: L-Ornithine L-Aspartate

Supplemental Table 6 (continued). Changes in SF-36

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Treatment/**  **Comparator** | **General Health**  **(95% CI)** | **Social Functioning**  **(95% CI)** | **Role-limitation Emotional**  **(95% CI)** | **Mental Health**  **(95% CI)** |
| Singh (2017)\* | Lactulose (n=47) | 14  (NR) | 10  (NR) | 11  (NR) | 11  (NR) |
| None | NA | NA | NA | NA |
|  |  |  |  |  |  |
| Poo (2006) | Lactulose (n=10) | NR | NR | NR | NR |
|  |  |  |  |  |  |
| Bruyneel (2017) | Rifaximin (n=15) | NR | NR | NR | NR |
| None | NA | NA | NA | NA |

Positive values indicate improvement

\* Intragroup difference (i.e. before vs after) significant at p<0.05; † Intergroup difference (i.e. treatment vs comparator) significant at p<0.05

‡ SF-36 (version 2)

Supplemental Table 7. Changes in SF-8

|  |  |  |  |
| --- | --- | --- | --- |
| **Author**  **(year)** | **Treatment/**  **Comparator** | **Physical Component Summary**  **(95% CI)** | **Mental Component Summary**  **(95% CI)** |
| Suzuki (2018) | Lactitol (n=83) | 3.2\*  (0.7, 5.7) | 0.1  (-2.0, 2.2) |
| Rifaximin (n=80) | 3.4\*  (0.9, 5.9) | 1.6\*  (-0.7, 3.9) |

Positive values indicate improvement

\* Intragroup difference (i.e. before vs after) significant at p<0.05

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Treatment/**  **Comparator** | **Total CLDQ**  **(95% CI)** | **Fatigue**  **(95% CI)** | **Abdominal Symptoms**  **(95% CI)** | **Systemic Symptoms**  **(95% CI)** | **Activity**  **(95% CI)** | **Emotional Function**  **(95% CI)** | **Worry**  **(95% CI)** |
| Sanyal (2011) | Rifaximin (n=101) | NR\* | NR\* | NR\* | NR\* | NR\* | NR\* | NR\* |
| Placebo (n=118) | NR | NR | NR | NR | NR | NR | NR |
| Glal (2021) | Rifaximin (n=30) | 0.1  (-0.1, 0.3) | 0.2\*  (0.0, 0.4) | 0.1  (-0.3, 0.4) | -0.2  (-0.4, 0.0) | 0.2\*  (0.0, 0.4) | -0.1  (-0.6, 0.4) | 0.1  (-0.1, 0.3) |
|  |  |  |  |  |  |  |  |  |
| Sanyal (2018) | Rifaximin (n=113) | 0.44  (0.40, 0.48) | 0.44  (0.01, 0.87) | 0.36  (-0.11, 0.83) | 0.26  (-0.12, 0.64) | 0.58  (0.16, 1.0) | 0.44  (0.18, 0.80) | 0.51  (-0.063, 1.08) |
| Rifaximin + Lactulose (n=108) | 0.18  (0.14, 0.22) | 0.34  (-0.12, 0.77) | 0.04  (-0.44, 0.52) | 0.12  (-0.28, 0.52) | 0.25  (-0.22, 0.72) | 0.17  (-0.24, 0.58) | 0.13  (-0.36, 0.62) |

Supplemental Table 8. Changes in Chronic Liver Disease Questionnaire

\* Intragroup difference (i.e. before vs after) significant at p<0.05; † Intergroup difference (i.e. treatment vs comparator) significant at p<0.05

Statistical significance not reported in Sanyal (2018)

Supplemental Table 9. Changes in Modified Chinese QoL Questionnaire

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Treatment/**  **Comparator** | **Total QoL**  **(95% CI)** | **Physical functioning**  **(95% CI)** | **Psychological well-being**  **(95% CI)** | **Symptom/side effects**  **(95% CI)** | **Social functioning**  **(95% CI)** | **Self-evaluation**  **(95% CI)** |
| Wang (2019) | Lactulose (n=59) | 12.6\*†  (8.7, 16.5) | 4.6\*†  (3.0, 6.2) | 3.0\*  (1.8, 4.2) | 2.1\*  (1.1, 3.2) | 1.1\*  (0.5, 1.7) | 2.0\*  (1.3, 2.6) |
| No treatment (n=28) | 6.4  (1.6, 11.1) | 1.5  (-0.6, 3.6) | 1.4  (-0.1, 3.0) | 0.9  (-0.9, 2.6) | 0.6  (-0.2, 1.3) | 2.2  (1.4, 3.0) |

Positive values indicate improvement

\* Intragroup difference (i.e. before vs after) significant at p<0.05; † Intergroup difference (i.e. treatment vs comparator) significant at p<0.05

Supplemental Table 10. Changes in Sleep Patient Reported Outcomes

|  |  |  |  |
| --- | --- | --- | --- |
| **Author**  **(year)** | **Treatment/**  **Comparator** | **Epworth Sleepiness Scale**  **(95% CI)** | **Pittsburgh Sleep Quality Index**  **(95% CI)** |
| Singh (2017) | Lactulose (n=47) | 3.3  (2.2, 4.4)\* | 3.4  (2.3, 4.5)\* |
| None | NA | NA |
|  |  |  |  |
| Bruyneel (2017) | Rifaximin (n=14) | 6.0  (NR) | 1.4  (-1.9, 4.7) |
| None | NA | NA |

Positive values indicate improvement

\* Intragroup difference (i.e. before vs after) significant at p<0.05; † Intergroup difference (i.e. treatment vs comparator) significant at p<0.05

Supplemental Table 11. Changes in Caregiver Burden Inventory (CBI)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author**  **(year)** | **Treatment/**  **Comparator** | **Total CBI**  **(95% CI)** | **CBI - Physical**  **(95% CI)** | **CBI - Social**  **(95% CI)** | **CBI - Emotional**  **(95% CI)** | **CBI - Developmental**  **(95% CI)** |
| Sanyal (2018) | Rifaximin (n=113) | 1.14  (0.083, 2.2) | 1.24  (-0.042, 2.5) | 0.5  (-0.66, 1.7) | 0.6  (-0.24, 1.4) | 1.2  (-0.24, 2.6) |
| Rifaximin + Lactulose (n=108) | -0.16  (-1.1, 0.78) | -0.25  (-1.5, 1.0) | -0.9  (-2.0, 0.16) | -0.7  (-1.5, 0.08) | -0.2  (-1.4, 1.0) |

Positive values indicate improvement

\* Intragroup difference (i.e. before vs after) significant at p<0.05; † Intergroup difference (i.e. treatment vs comparator) significant at p<0.05

|  |  |  |
| --- | --- | --- |
| **Author**  **(year)** | **Treatment/Comparator** | **Euro-QOL Index**  **(95% CI)** |
| Poo (2006) | Lactulose (n=10) | 10.4\*  (-8.7, 29.5) |

Supplemental Table 12. Changes in Euro-QOL Index

Positive values indicate improvement

\* Intragroup difference (i.e. before vs after) significant at p<0.05; Between group difference not assessed

Supplemental Table 13. Changes in Hospital Anxiety and Depression Score (HADS)

|  |  |  |  |
| --- | --- | --- | --- |
| **Author**  **(year)** | **Treatment/Comparator** | **HADS-A**  **(95% CI)** | **HADS-D**  **(95% CI)** |
| Bruyneel (2017) | Rifaximin (n=15) | -0.4  (-4.1, 3.3) | 1.5  (-2.2, 5.2) |
| None | NA | NA |

Positive values indicate improvement

\* Intragroup difference (i.e. before vs after) significant at p<0.05; Between group difference not assessed

HADS: Hospital Anxiety and Depression Score

Supplemental Table 14. Changes in EQ-5D

|  |  |  |  |
| --- | --- | --- | --- |
| Author (year) | **Treatment/Comparator** | **EQ-5D Descriptive System** | **EQ VAS** |
| Patel  (2021) | Rifaximin (n=16) | -0.8  (-1.6, 0.9) | 10.0  (-3.9, 23.9) |
| Placebo (n=16) | -0.1  (-0.6, 0.3) | -5.1  (-16.3, 6.1) |

EQ-5D descriptive system: mobility, self-care, usual activities, pain/discomfort, anxiety/depression

EQ VAS: visual analogue scale of health state score

Note: 3 observations each in rifaximin and placebo groups removed due to having only baseline measurements