

Beneficial effects of L-Ornithine L-Aspartate for prevention of overt hepatic encephalopathy in patients with cirrhosis: a systematic review with meta-analysis

BUTTERWORTH RF, University of Montreal, Montreal, Canada

INTRODUCTION

1. Presence of OHE has a negative impact on:
 - Neurocognitive function before / after OLT
 - Risk of further episodes of OHE
 - HRQOL
 - Patient survival
2. Ammonia plays a key role in the pathogenesis of OHE in cirrhosis
3. L-Ornithine L-Aspartate (LOLA) has been proven to be effective for the treatment of MHE and OHE [1,2]
4. There is currently limited information on efficacy of LOLA for OHE prevention / prophylaxis

AIMS

1. Systematic review with meta-analysis of results of RCTs
2. Efficacy of oral and iv LOLA for OHE prevention / prophylaxis

METHODS

- Electronic & manual searches of databases for results of RCTs of efficacy of LOLA for OHE prevention/prophylaxis
- Trial Quality and risk of bias assessments by Jadad score [3] and Cochrane Scoring Tool [4]
- Use of Random Effects Model (pooled risk ratio (RR) with 95% Confidence intervals)

RESULTS

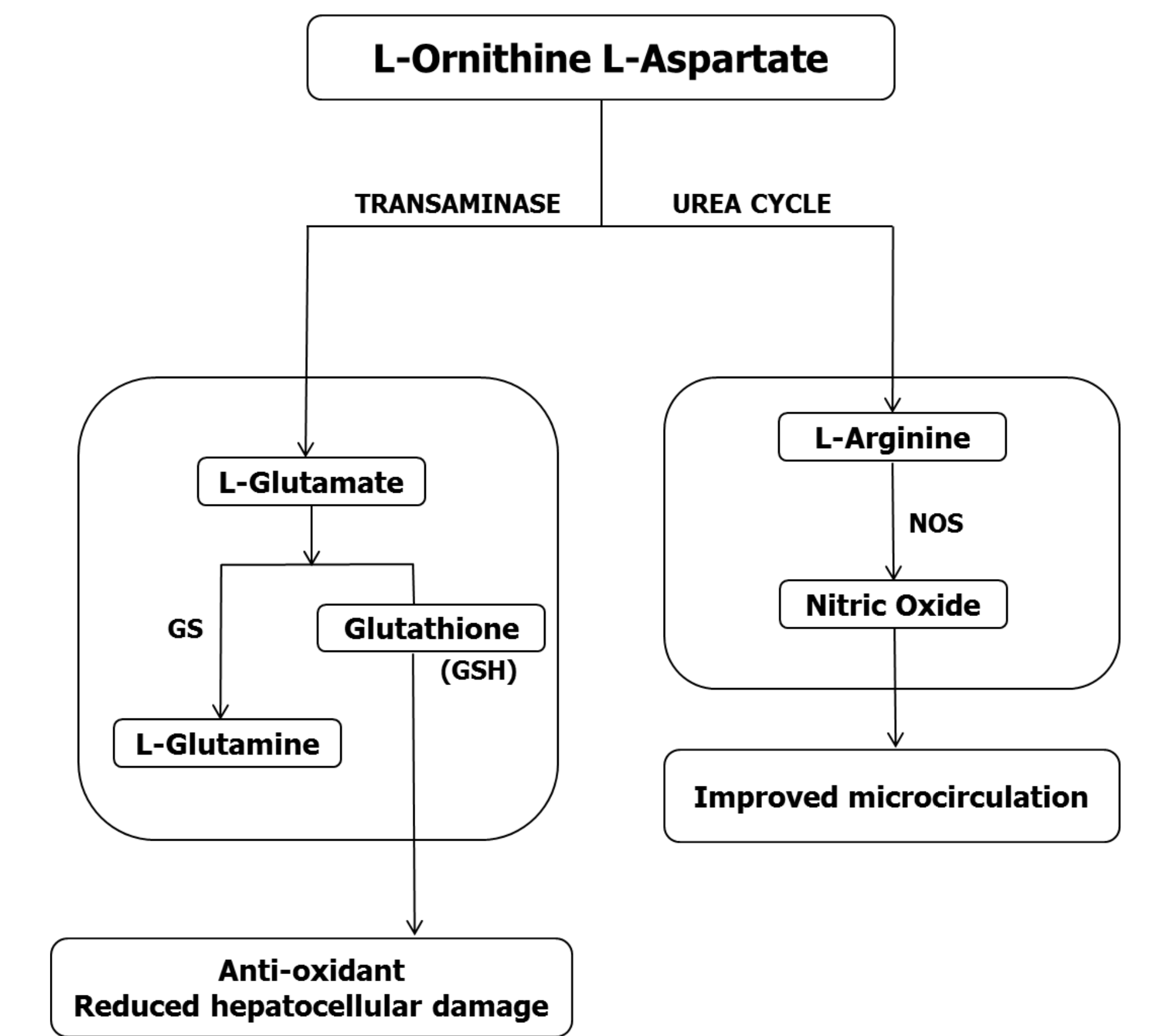
- ✓ 6 RCTs (384 patients) satisfied inclusion criteria, 5/6 having low risk of bias by Jadad/Cochrane criteria
- ✓ Treatment with LOLA (iv or oral) is effective for prevention of OHE compared to placebo / no intervention (RR: 0.38 [95% CI: 0.23, 0.62], Z score: 3.92, p<0.0001)
- ✓ Subgroup analysis revealed that treatment of MHE by oral LOLA was effective in 4/4 trials (227 patients) with RR: 2.54 [95% CI: 1.54, 4.18], Z score: 3.67, p<0.002
- ✓ Subgroup analysis revealed that oral LOLA was effective for prevention of deterioration of MHE to OHE in 3/3 trials (155 patients) with RR: 0.23 [95% CI: 0.07, 0.73], Z score: 2.50, p<0.01
- ✓ LOLA also effective for the primary OHE prophylaxis following variceal bleeding, secondary OHE prophylaxis and for post-TIPSS prophylaxis
- ✓ OHE prevention/prophylaxis by LOLA was accompanied by significant reductions of blood ammonia in 5/5 trials in which it was measured

CONCLUSIONS

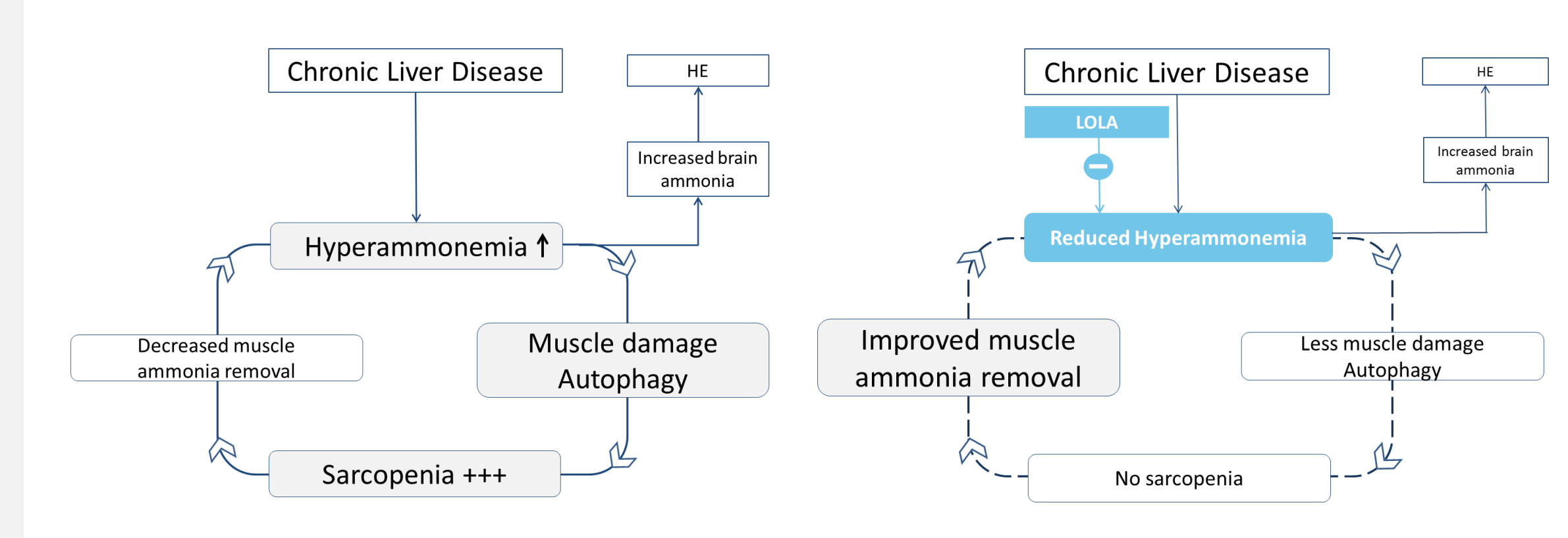
- [1] LOLA is effective for the prevention of OHE in patients with cirrhosis over a range of clinical presentations that include:
 - ✓ Decreased progression of MHE to OHE
 - ✓ Secondary prophylaxis
 - ✓ Primary prophylaxis following a GI bleed
 - ✓ Post-TIPSS
- [2] OHE prevention by LOLA in patients with cirrhosis is accompanied by reductions in hyperammonemia
- [3] Both oral and iv formulations of LOLA appear to be effective for reducing the progression of MHE to OHE in patients with cirrhosis.

NOVEL MULTIMODAL MECHANISMS OF ACTION OF LOLA

- [1] Established metabolic processes (urea cycle, glutamine synthetase) involved in ammonia removal
- [2] Direct hepatoprotective properties of LOLA mediated via metabolites of LOLA (GSH, NO)

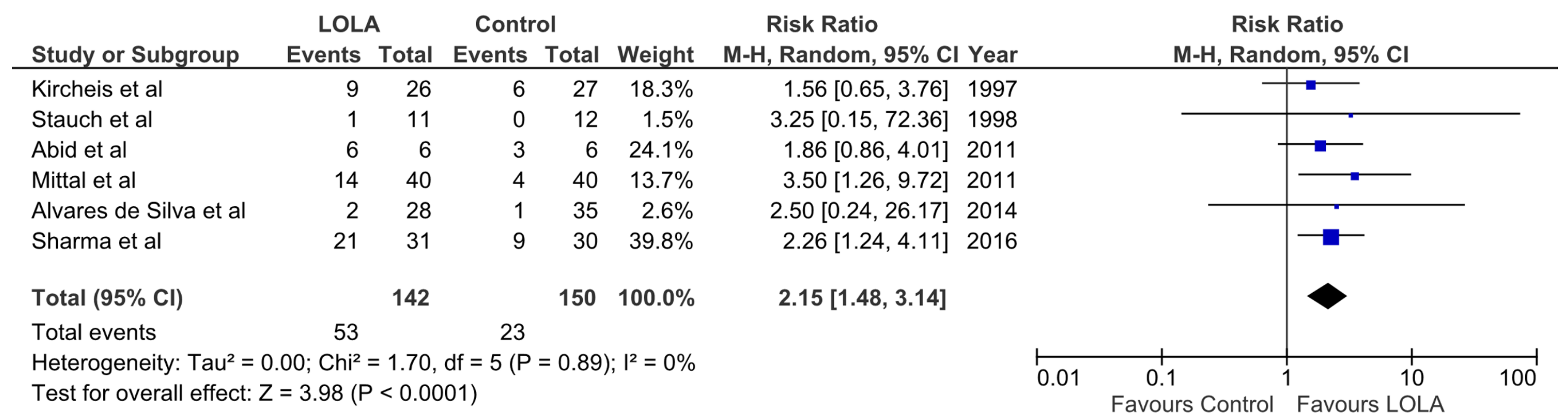


- [3] Prevention of muscle damage (sarcopenia) leading to improved muscle ammonia detoxification

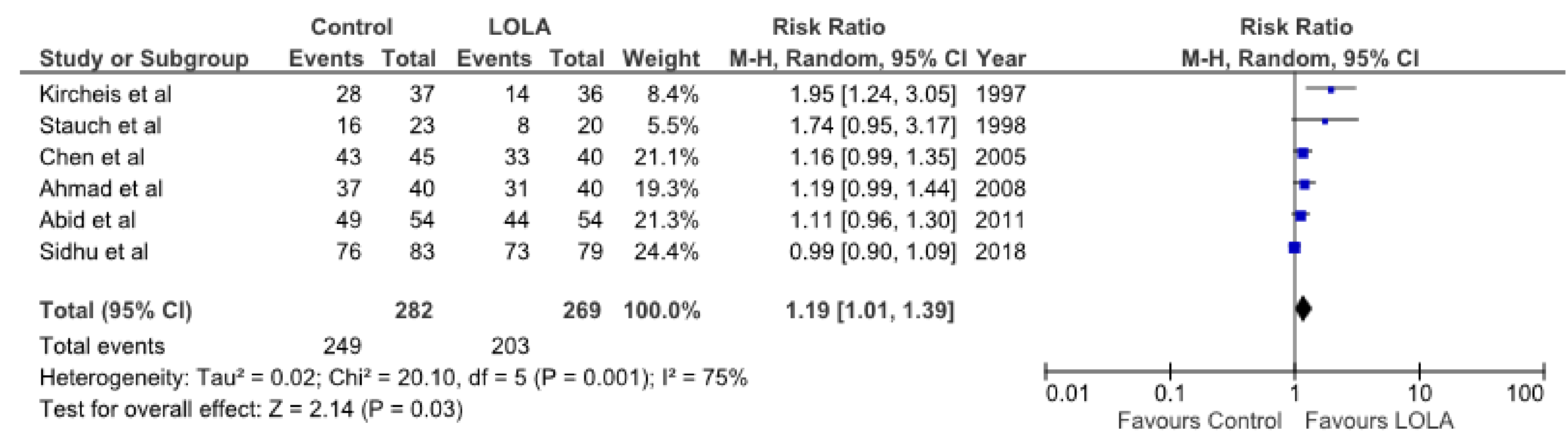


EFFICACY OF LOLA FOR THE PREVENTION AND TREATMENT OF HE IN CIRRHOSIS

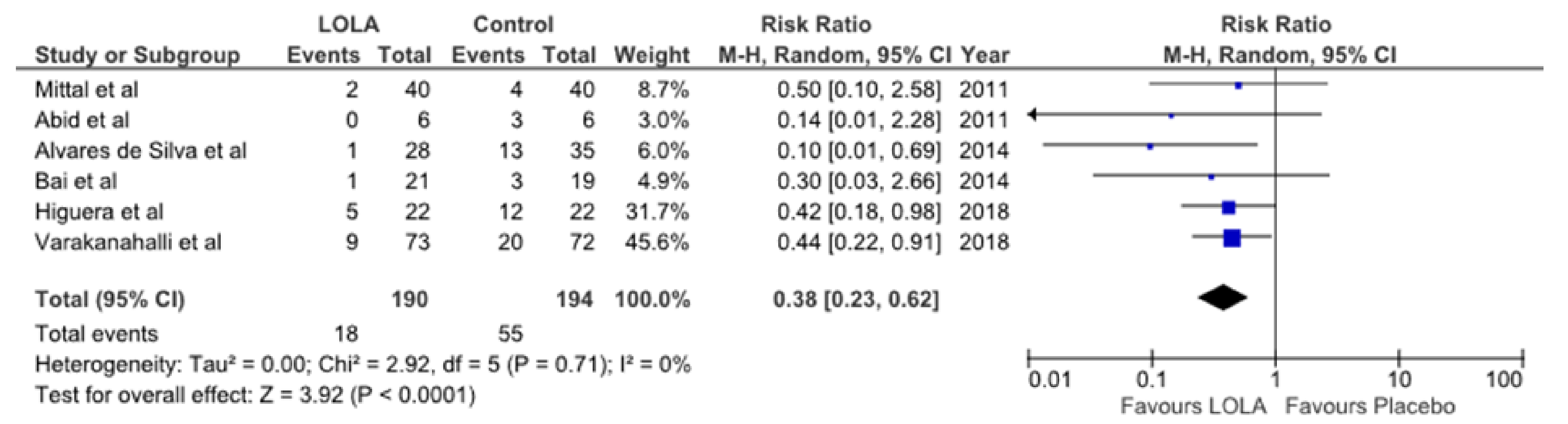
A. LOLA improves mental state in patients with MHE



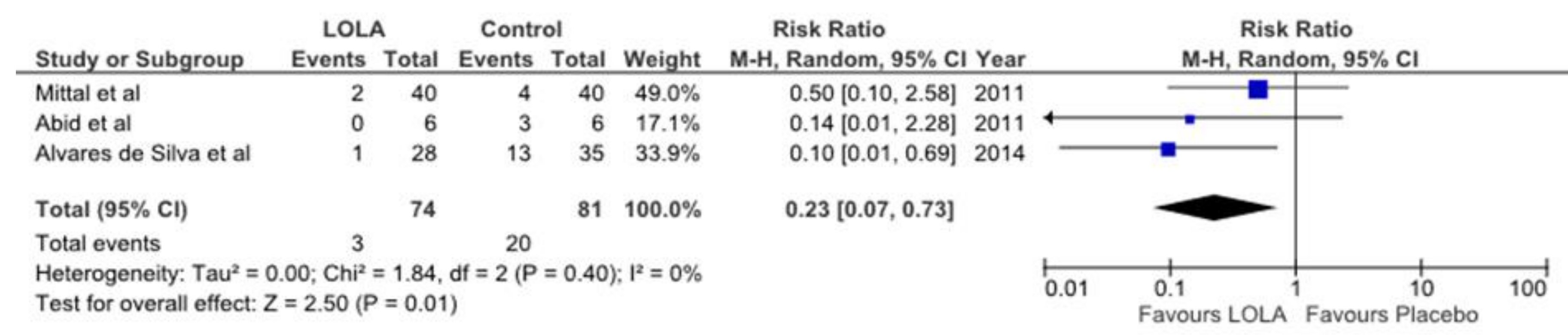
B. LOLA improves mental state in patients with OHE



C. Efficacy of LOLA for the prevention of OHE

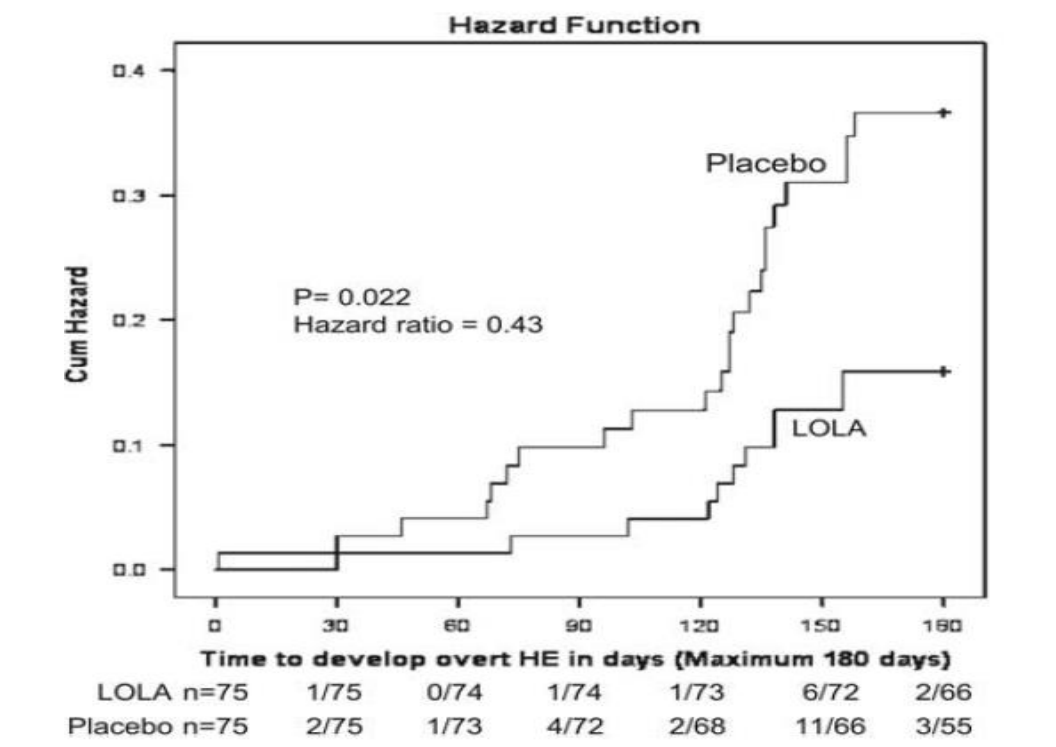


D. Efficacy of LOLA for the prevention of progression from MHE to OHE



E. Secondary prophylaxis of OHE in patients with cirrhosis

Time for breakthrough of OHE is indicated from randomization to six month follow-up in LOLA treatment group compared to placebo by the Cox proportional hazard model resulting in HR of 0.431 [95% CI: 0.210-0.885], p<0.022; from Varakanahalli et al. 2018 with permission



REFERENCES & CONTACT

REFERENCES

- [1] Butterworth RF et al. 2018; J Clin Exp Hepatol 8(3), 301-313.
- [2] Butterworth RF, McPhail MJW 2019; Drugs 79(Suppl 1): 31.
- [3] Jadad AR et al. 1996; Contr Clin Trials 17(1), 1-12.
- [4] Higgins JPT and Green S [Eds] 2011; Cochrane Handbook, version 5.1.0
- [5] Butterworth RF 2019; Metab Brain Dis. Jul 23. doi:10.1007/s11011-019-00463-8
- [6] Butterworth RF 2019, J Pharmacol Pharmaceut Res 2(3),1-9
- [7] Butterworth RF Gruengreiff K 2019; JSM Liver Clin Res 3,5.
- [8] Butterworth RF 2019; Can J Gastroenterol Hepatol. doi: 10.1155/2019/8182195.

CONTACT INFORMATION
 Roger F Butterworth
 rb@enceph.com

