

# Hepatic Encephalopathy Management: Reviewing Alternatives to Rifaximin

## OVERVIEW OF HEPATIC ENCEPHALOPATHY MANAGEMENT IN HOSPICE

Hepatic encephalopathy, a complex neuropsychiatric syndrome, arises from the accumulation of toxic substances, primarily ammonia, due to impaired liver function. Elevated ammonia levels in the blood lead to astrocyte swelling and dysfunction, contributing to cognitive and neurological disturbances in patients with advanced liver disease. Rifaximin, an antibiotic, is commonly used to reduce the production of ammonia-forming gut bacteria. However, in certain hospice settings, alternatives to rifaximin might be considered due to various factors, including patient preferences, contraindications, unavailability of the drug, or comparative cost-effectiveness. This resource was developed to review possible rifaximin alternative treatments.

## REVIEWING HEPATIC ENCEPHALOPATHY CLASSIFICATION

WEST HAVEN CLASSIFICATION SYSTEM	
<b>GRADE 0</b>	Minimal hepatic encephalopathy; lack of detectable changes in personality or behavior; minimal changes in memory, concentration, intellectual function, and coordination; asterixis is absent.
<b>GRADE 1</b>	Trivial lack of awareness; shortened attention span; impaired addition or subtraction; hypersomnia, insomnia, or inversion of sleep pattern; euphoria, depression, or irritability; mild confusion; slowing of ability to perform mental tasks.
<b>GRADE 2</b>	Lethargy or apathy; disorientation; inappropriate behavior; slurred speech; obvious asterixis; drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behavior, and intermittent disorientation, usually regarding time.
<b>GRADE 3</b>	Somnolent but can be aroused; unable to perform mental tasks; disorientation about time and place; marked confusion; amnesia; occasional fits of rage; present but incomprehensible speech.
<b>GRADE 4</b>	Coma with or without response to painful stimuli.

Use of medication for the management of HE is reserved for patients classified as Grade II-IV, presenting with altered mentation secondary to accumulation of ammonia and other neuroactive substances in the setting of end stage liver disease.

## PHARMACOLOGIC TREATMENT OPTIONS

RIFAXIMIN ALTERNATIVES FOR HEPATIC ENCEPHALOPATHY MANAGEMENT			
<b>LACTULOSE</b>			
<b>Mechanism of Action</b>	Metabolism produces lactic, acetic and formic acid, and decreasing colonic pH resulting in: <ul style="list-style-type: none"> <li>▪ Decreased growth of ammonia producing bacteria and growth of beneficial microorganisms</li> <li>▪ Decreased ammonia load by changing ammonia to ammonium, which is not absorbed</li> </ul>		
<b>Dosing</b>	<b>Clinical Comparison</b>	<b>Additional Notes</b>	<b>Cost/Day</b>
15-45ml/dose 2-3 doses/day	1 <sup>st</sup> line agent, superior to placebo	<ul style="list-style-type: none"> <li>▪ Titrate dose to achieve 2-3 bowel movements/day</li> <li>▪ Diarrhea, nausea, bloating and flatulence most common SE</li> </ul>	15ml TID: \$1.29 45ml TID: \$3.87
<b>NEOMYCIN</b>			
<b>Mechanism of Action</b>	Approximately 97% of orally administered neomycin remains in the GI tract, where it interferes with bacterial protein synthesis, resulting in decreased growth of ammonia producing bacteria		
<b>Dosing</b>	<b>Clinical Comparison</b>	<b>Additional Notes</b>	<b>Cost/Day</b>
500mg BID-QID	Equivalent to lactulose	<ul style="list-style-type: none"> <li>▪ Absorbed neomycin accumulates in inner ear, renal cortex</li> <li>▪ Oto- and renal toxicity risk limit long-term use</li> </ul>	500mg QID: \$8
<b>METRONIDAZOLE</b>			
<b>Mechanism of Action</b>	Interacts with bacterial DNA resulting in inhibition of protein synthesis and cell death, resulting in a decrease of ammonia-producing organisms		
<b>Dosing</b>	<b>Clinical Comparison</b>	<b>Additional Notes</b>	<b>Cost/Day</b>
250-500mg BID	Equivalent to lactulose	<ul style="list-style-type: none"> <li>▪ May be considered for short-term trial for tx of HE</li> <li>▪ Avoid long-term use due to renal and neurotoxicity risk</li> </ul>	\$1.80-\$2.00

## SUMMARY

While alternatives to rifaximin exist, it is important to consider the risk vs. benefit of using one of the available alternative agents. If lactulose has not been properly trialed, it should be considered first line for treatment of symptoms secondary to HE due to anticipated efficacy, favorable side effect profile and significantly lower therapy cost. Working closely with the patient and caregivers to maintain 1-2 bowel movements/day will promote efficacy as well as tolerability by limiting number of stools/day. Neomycin and/or metronidazole may be considered if the patient is unable to tolerate lactulose, but due to undesirable side effect profile, recommend limiting use to 7-14 days.

Thus if patient not able to tolerate, or achieve desired effect with options above, use of rifaximin may be necessary to help manage HE. Due to significant cost associated with use, and challenge of differentiating between HE vs. altered mental status vs. terminal delirium near the end of life, it is important to trial and closely monitor efficacy of rifaximin if used. Recommend only continuing therapy with rifaximin if clinically significant, meaningful improvement experienced with use.

Please reach out to the BetterRX Clinical Pharmacy Team with any questions or issues.

## References:

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