EnLyte and Reported Improvements in Sleep

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Clinical dietary management with medical prescriptive foods has emerged as an essential management tool for physicians and patients. Molecular genetic testing has made an entry into everyday clinical practice helping healthcare providers individualize treatment based not just on reducing symptoms with prescription medications but on knowing more about WHO is being treated.

50% of the general population have variant alleles for methylene teterahydrofolate reductase (MTHFR). This enzyme is crucial to the synthesis of all neurotransmitters. In fact, 70% of patients with mood symptoms have either a heterozygous or homozygous substitution leaving them less able to efficiently convert folate (vitamin B9) and other B vitamins to their methylated, reduced form necessary for use in the production of neurotransmitters. While the benefit in management of depressive symptoms has been well documented, the effect of EnLyte® on sleep has not been explored.

In an effort to assess the degree to which fatigue and resultant emotional dysregulation might be improved, EnLyte® was added in an open-label fashion to the treatment regimen of 60 patients in an outpatient neuropsychiatry clinic who had tested positive for one or two C677T allele MTHFR single nucleotide substitutions. Pre and post-EnLyte® levels of fatigue were obtained per standard clinic protocol using the Fatigue Assessment Scale (FAS) and levels of emotional dysregulation (difficulties in frustration tolerance and impulse control) with the Mech Emotional Dysregulation Inventory (MEDI).

Patients took the EnLyte® in an open label manner for 4-weeks. Most patients reported their sleep was significantly improved. This was demonstrated on the Fatigue Assessment inventories completed by patients pre- and post-EnLyte® administration where patients reported improvements in sleep quality with a 22% reduction in fatigue and a 41% reduction in related emotional dysregulation (i.e., impaired frustration tolerance and impulse control.)

Limitations of this study include the confounding variables of co-occurring diagnoses; concomitant medications and a lack of objective polysomnograhic sleep architecture data at baseline and post-EnLyte® management. Further studies are needed to better understand the benefits of EnLyte® management on crucial measures of total sleep time (TST), the percentage of total sleep time spent in N3 slow-wave sleep and in rapid eye movement (REM) sleep.

Protocol Synopsis
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Title:	An Open-Label Study of EnLyte® in a Psychiatric Outpatient Population who are MTHFR Heterozygous or Homozygous Variant with co-Occurring Disturbed Sleep
Design:	This study will be an 8 week, open-label trial using EnLyte® at a dosage of 1 capsule per day. Study agent will be dispensed to eligible subjects after completion of the baseline polysomnograms (PSGs) (performed on visit 0) are reviewed at visit 1, at visit 2 (occurring at 4 weeks) and at visit 3 (occurring at 8 weeks). A PSG will be obtained at the screening / baseline visit and visit 3 after 8 weeks of EnLyte® administration. Saliva testing of serotonin will be measured at screening / baseline and at visit 3 at 8 weeks. A Fatigue Assessment Scale (FAS), Epworth Sleepiness Scale (ESS) and Mech Emotional Dysregulation Inventory (MEDI) will be obtained at screening / baseline and at 4 and 8 weeks. A subject may withdraw from the trial at any time. **Visit Schedule:** **Screening / Baseline Visit**: within 2 weeks of screening PSG, subjects will return for: **Visit 1**: within 2 weeks of Baseline Visit. The first four weeks of EnLyte® will be dispensed after PSG data inclusion verified. **Visit 2**: 4 weeks after Visit 1. A second four weeks of EnLyte® will be dispensed after visit completion. **Visit 3**: 8 weeks after Visit 1. Following a 14 day screening period, eligible patients are seen for Visit 1 and given EnLyte® for the first 4 weeks of the total 8 week assignment to the treatment sequences, then return for visit 2 where they will receive the second of two 4-week supplies of EnLyte®.
Purpose:	The purpose of this study is to investigate the effect of 8-weeks of clinical dietary management with EnLyte® administered in an open-label fashion in children, adolescent and adult psychiatric outpatients on Sleep Architecture (REM sleep and N3 sleep percentages of total sleep time), Sleep Continuity as measured by WASO, the number of spontaneous arousals and REM latency, Fatigue as measured by use of the Fatigue Assessment Scale (FAS), Excessive Daytime Sleepiness (EDS) as measured by use of the Epworth Sleepiness Scale (ESS). and Clinical Emotional Dysregulation (CED) as measured by use of the Mech Emotional Dysregulation Inventory (MEDI).

Enrollment:	150 subjects
Clinical Sites:	1 Site
Timeline	Enrollment for this study is expected to be completed in 10 months from start-up and last patient / last visit completed in 12 months. Enrollment can begin within 2 weeks from JayMac approval and Central IRB approval (Western IRB) with also an estimated two (2) week period of time. Data collection will begin with patient screening and execution of the informed consent/ assent for the first potential subject. Initial enrollment (expected): April, 2014 Last enrollment (expected): February, 2015 Last anticipated follow-up contact: April 1, 2015
Patient Population:	Male and Female psychiatric outpatients, 6-65 (inclusive) with any Psychiatric diagnosis as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), with an MTHFR heterozygous or homozygous mutation (one or both WT alleles substituted by a C677T or other thermolabile T variant of the MTHFR genotype, with poor sleep quality as defined by a slow-wave (N3) sleep percentage of Total Sleep Time (TST) < 20%, or a Rapid Eye Movement (REM) sleep percentage of Total Sleep Time (TST) < 25% who meet all study inclusion criteria and no study exclusion criteria.
Primary Endpoints:	Change (increase) in PSG data (N3 and / or REM percentage of Total Sleep Time) from baseline to endpoint among patients treated for 8 weeks with EnLyte® comparing post-treatment PSG to PSG data at Baseline.
Secondary Endpoints:	Compare the effect of EnLyte® for 8 weeks with that of placebo, using the Fatigue Assessment Scale (FAS); the Epworth Sleepiness Scale (ESS); the Mech Emotional Dysregulation Inventory (MEDI) and saliva testing assessments of serotonin all assessed at baseline and after 8 weeks of study agent. Secondary PSG data objectives will also be the number of spontaneous arousals; wake time after sleep onset (WASO) and the REM latency as measured during PSGs at baseline and after 8 weeks of study agent. Characterize adverse events that occur following EnLyte® administration using vital signs and spontaneous adverse events.

Inclusion Criteria:	1. Must be 6-65 years of age, inclusive. 2. Both male and female subjects 3. Meets Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V™) criteria for a psychiatric diagnosis and have symptoms of poor sleep quality. 4. Has either a MTHFR heterozygous or homozygous mutation (one or both WT alleles substituted by a C677T or other thermolabile T variant of the MTHFR genotype on molecular genetic testing. 5. Has evidence of <20% N3 sleep and / or <25% REM sleep as a percentage of Total Sleep Time (TST) on baseline polysomnogram (PSG). 6. Understands and is able, willing, and likely to fully comply with the study Has given written informed consent to participate in the study in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines and applicable regulations before completing any study procedures. 7. If a minor children <18- parent or legal guardian able to give an inform consent.
Exclusion Criteria:	1. Subjects unable to swallow or effectively orally administer the study agent. 2. Has any concurrent chronic or unstable medical condition that could confound the results of safety assessments, increase risk to the subject or lead to difficulty complying with the protocol. 3. Subjects experiencing suicidal or homicidal ideation will be excluded from participation. 4. Pregnant women. 5. Currently has (or had) a history within the last 6 months of an alcohol or drug abuse or dependence according to DSM-V™ criteria (excluding nicotine) as established by the clinical assessment at the screening visit. 6. Currently has (or had) a history any serious systemic (e.g., diabetes, hyper/hypothyroidism of neurological condition (e.g., epilepsy, brain tumor). 7. Has taken an investigational drug or taken part in a clinical trial within 30 days prior to Screening. 8. Has history of allergic reactions or sensitivity to EnLyte® as well as any illness that could jeopardize the participant's health or limit their successful completion of the trail. 9. Any other reason that, in the opinion of the investigator, prevents the subject from participating in the study or compromise the patient safety

Statistical Methodology	TBD

Study Schema

Procedure	Screening/ Baseline Visit (Day -0)	Visit 1 (Day 1)	Visit 2 (Day 28-30)	Visit 2 (Day 60) Endpoint
Informed Consent	X			
Inclusion/Exclusion Criteria	X	X		
Medical History	X			
Psychiatric History	X			
Safety Assessments				
Physical Exam	X			
Vital Signs & Weight	X	X	X	X
Collect AEs		X	X	X
Safety Labs	X			X
Efficacy Assessments				
PSG	X			X
Fatigue Assessment Scale (FAS)	X	X	X	X
Epworth Sleepiness Scale (ESS)	X	X	X	X
Mech Emotional Dysregulation Inventory (MRDI)	X	X	X	X
Saliva testing of Serotonin	X			X

	Primary endpoint	Secondary endpoint
PSG [REM Sleep or N3 Sleep-as a fraction of total sleep time]	X	
Fatigue Assessment Scale (FAS)		X
Epworth Sleepiness Scale (ESS)		X
Mech Emotional Dysregulation Inventory (MRDI)		X
PSG (Number of spontaneous arousals)		X
PSG [Wake time after sleep onset (WASO)]		X
PSG- [REM Latency)		X
Serotonin as measured by saliva testing		X