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An Educational Review:

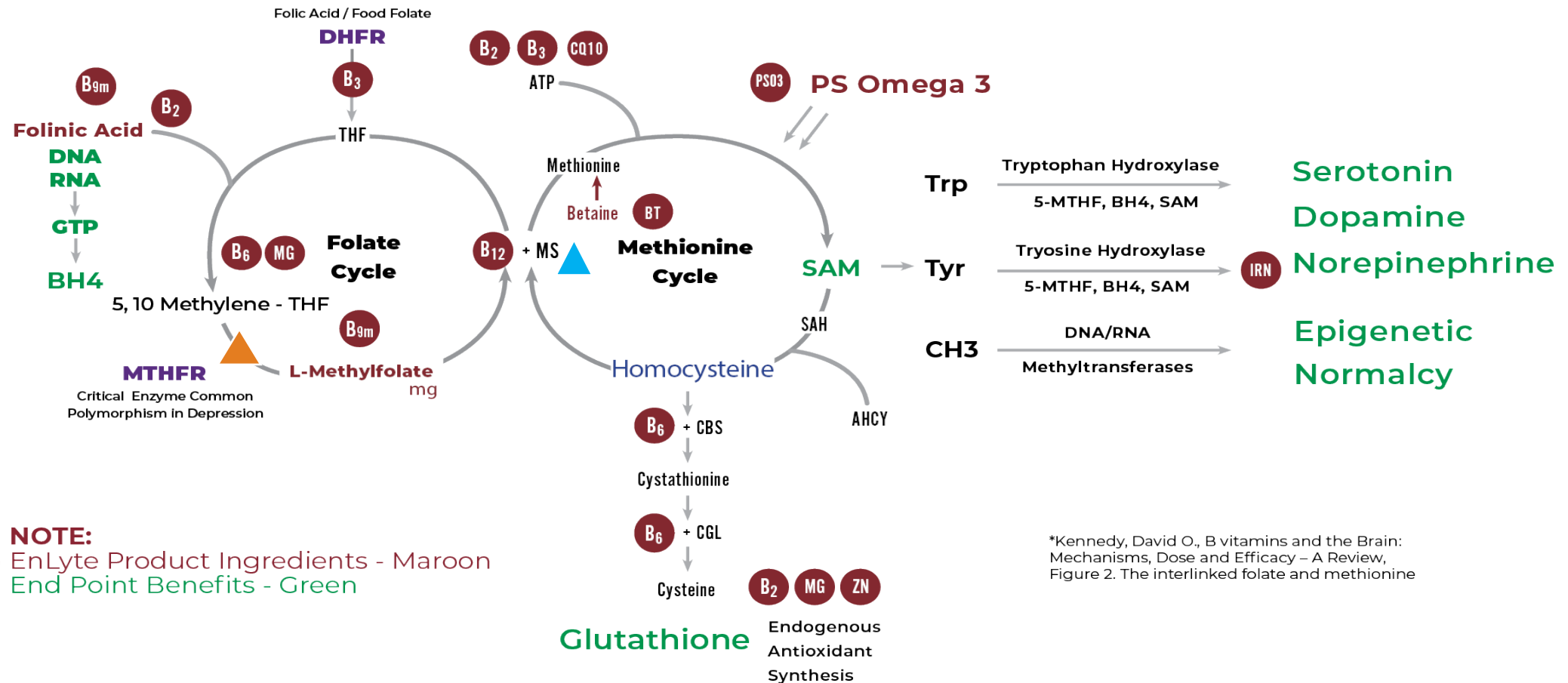
**MTHFR & Other  
Methylation Gene  
Polymorphisms in  
Psychiatric Disease  
and an Evidence-Based  
Treatment Option**

# What is MTHFR?

▲ MTHFR is Methylene tetrahydrofolate reductase, a folate cycle **ENZYME** that catalyzes/converts the folate metabolite 5,10 methylenetetrahydrofolate to 5-methyltetrahydrofolate (L-Methylfolate).

▲ B9/Methylfolate, B12/Methylcobalamin and MS/Methionine Synthase combine to methylate **HOMOCYSTEINE** to produce SAM-E, Serotonin, Dopamine and Norepinephrine, which keeps homocysteine in check.

Brain homeostasis and mood stability requires optimal production and balance of **brain chemicals endpoints**.



# The MTHFR Gene

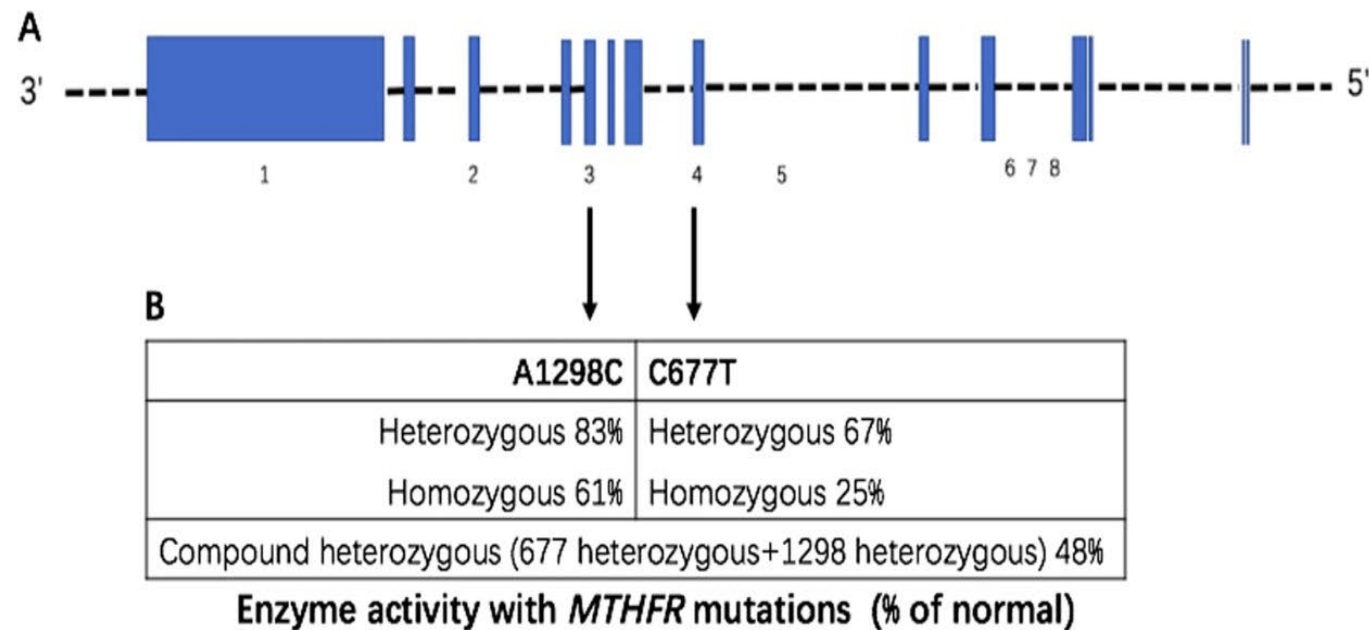
Wan et al. Methylenetetrahydrofolate reductase and psychiatric disease, Translational Psychiatry, 2018

Khan et al. MTHFR deficiency in individuals with common psychiatric comorbidities, Cureus 2024

The MTHFR gene resides on chromosome 1 and has been identified to possess 14 common or rare single nucleotide polymorphisms (SNPs) that are associated with enzymatic deficiency.

Among them, **C677T** and **A1298C** SNPs are the most reported that may reduce the MTHFR activity in various degrees.

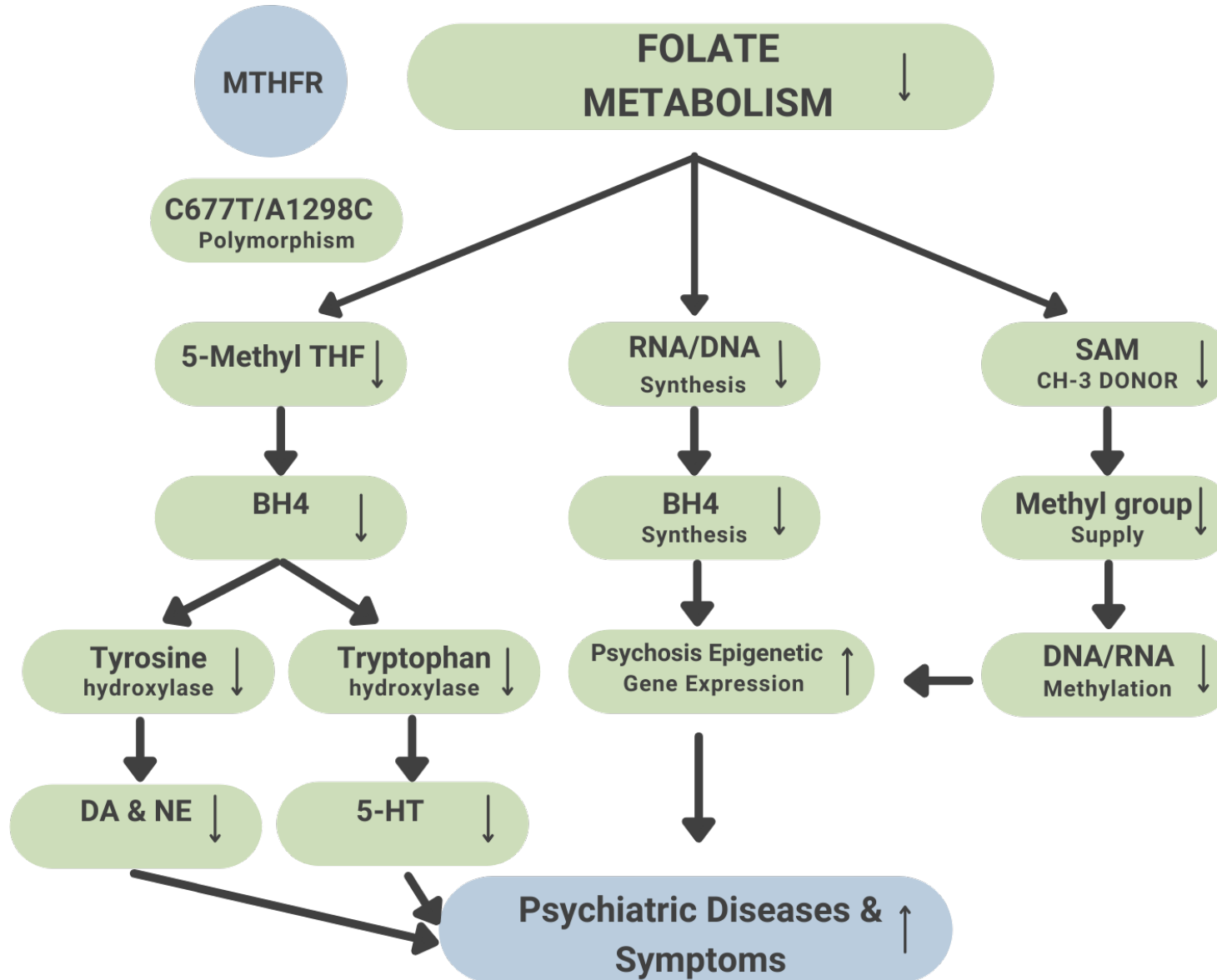
## MTHFR Enzymatic Activity with MTHFR Mutations



As DNA methylation and folate are important in mental health, reduction of MTHFR activity or folate deficiency have been associated with an onset of several psychiatric diseases: depression, schizophrenia, bipolar disorder, autism, ADHD, anorexia, anxiety, borderline personality disorder, obsessive compulsive disorder.

# Biochemical Mechanisms of MTHFR in Psychiatric Disease

Fig 3. Wan et al. Methylenetetrahydrofolate reductase and psychiatric disease, Translational Psychiatry, 2018



# Association between variants of MTHFR genes and psychiatric disorders: A meta-analysis

## Frontiers in Psychiatry, A Systemic Review

Yu-Zin Zhang et al August 18, 2022  
81 screened studies out of 893 found

**49,755** subjects

**20,981** patients

**28,794** controls

## Meta-analysis Findings

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- MTHFR C677T and A1298C both heterozygous and homozygous play a significant role in the common pathogenesis of Major Depressive Disorder, Schizophrenia, Bipolar Disease, and others
  - These mental disorders are more likely to occur in families suggesting that they are related to genetic factors
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# COMMON YET MOSTLY UNTESTED GENETIC METHYLATION POLYMORPHISMS AFFECTING YOUR PATIENTS

- **FOLH1**- Catalyzes early folate conversion
- **MTR**- Provides for Methionine Synthase
- **FUT2**- B12 Absorption
- **DHFR**- Provides Dihydrofolate Reductase
- **MTHFD1**- Catalyzes late folate conversion
- **CBS**- With B6(P-5-P) converts Hcy to Cystathionine
- **MTTR**- Converts SAH into SAM with B12(MC)
- **TCN1/2**- B12 absorption and transport
- **FOLR1**- Folate Receptor 1, signaling cascade
- **COMT**- Dopamine maintenance in the PFC
- **TPHI**- Tryptophan serotonin conversion

Mitchell et al. B vitamin polymorphisms and behavior: Evidence of associations with neurodevelopment, depression, schizophrenia, bipolar disorder and cognitive decline, Neuroscience and Behavioral Reviews, 2014

“ The homocysteine theory of psychiatric disorders argues that, for each patient, a unique cluster of genetic vulnerabilities will result in not only low neurotransmitters, but a baseline of elevated CNS homocysteine, impaired methylation of DNA, RNA and histones, suboptimal antioxidant production and impaired hormonal signaling. ”

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“ A unique set of polymorphisms may not be clinically significant at baseline, yet disease may manifest in times of psychosocial or environmental stress prompting major psychiatric disorders. ”

Andrew Farah, MD DFAPA  
Adjunct Professor for Psychiatric Research High Point Univ.  
Attending Psychiatrist at Novant Health  
Medical Director at Strategic Interventions

EnLyte/EnBrace HR Small Gel Cap

# INGREDIENTS

Rx | All Natural | Unique | Bioactive Coenzyme Vitamin Gel Cap

EnLyte/EnBrace HR/ENL contains all the natural coenzymes and mineral cofactors to circumvent/nullify the negative effects of methylation polymorphisms to normalize methylation biochemical end points that correlate to clinical wellness.

L-Methylfolate Magnesium	7mg
Folinic Acid	2.5mg
DHF	1mg
B12 (Adenosylcobalamin)	50mcg
B6 (Pyridoxal-5-Phosphate)	25mcg
B1 (Thiamine Pyrophosphate)	25mcg
B2 (Flavin Adenine Dinucleotide)	25mcg
B3 (Nicotinamide Adenine Dinucleotide)	25mcg
PS-Omega-3 (Phosphatidylserine, EPA, DHA)	20mg
Magnesium Ascorbate	24mg
Magnesium L-Threonate	1mg
Iron	1.5mg
Zinc Ascorbate	1mg
Betaine	500mcg
Citric Acid Monohydrate	1.83mg
Sodium Citrate	3.67mg
CoQ10	500mcg
Piperine (B Vitamin Bioenhancer)	500mcg

# THE JOURNAL OF CLINICAL PSYCHIATRY

## 330 ADULT PATIENT RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED STUDY

### OBJECTIVE:

This 8-week study was designed to evaluate the efficacy and safety of EnLyte/EnBrace HR as monotherapy in adults with major depressive disorder (MDD) who were also positive for at least 1 methylenetetrahydrofolate reductase (MTHFR) polymorphism associated with depression and further test the hypothesis that EnLyte/EnBrace HR will lower homocysteine in a majority of clinical responding patients.

MAY 2016

Correlation of Clinical Response With Homocysteine Reduction During Therapy With EnLyte/EnBrace HR in Patients With MDD Who Are Positive for MTHFR C677T or A 1298C Polymorphism - Andrew Farah, MD

### 1) Mean MADRS Symptom Score of EnBrace HR Versus Placebo



### 2) 30% Reduction in Homocysteine Levels (Compared to Placebo)

**NO SIDE EFFECT WAS REPORTED AT GREATER RATE  
THAN PLACEBO**

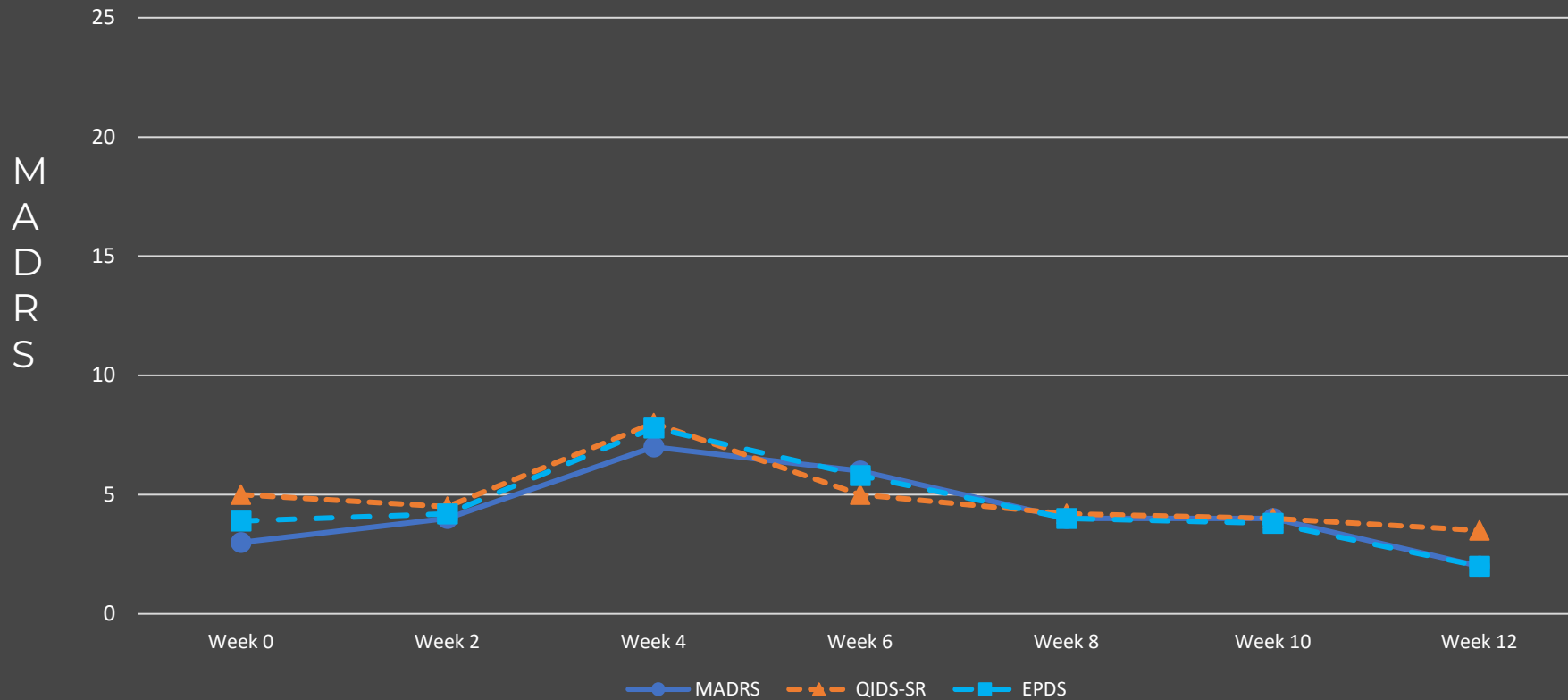
**ONSET OF ACTION: 2 WEEKS**



# EnBrace HR For The Treatment and Prevention of Depression in Women Trying to Conceive and During Pregnancy

Marlene P. Freeman, MD et al, Annals of Clinical Psychiatry February 2019 | FDA APPROVED

Relapse Prevention Group: MDD, But Well at Baseline Due to SSRIs/SNRIs - Drug ADs Replaced with EnBrace HR at Pregnancy



## RESULTS:

Patients did not relapse to a major depressive episode or state compared to 63% that did in the Cohen comparator

## Conclusion:

Study results suggest EnBrace HR is a novel and well-tolerated intervention with efficacy for the prevention and treatment of depression among women planning pregnancy and who are pregnant

# Patient History Pointing to MTHFR SNP

Poor response to SSRI or SNRIs

Treatment Resistant Depression

Hispanic ethnicity, average 60-85% incidence

Mental illness in the family

Miscarriages, infertility, poor pregnancy outcomes or neurodevelopmental issues in children in the family - ASD, ADHD, etc.

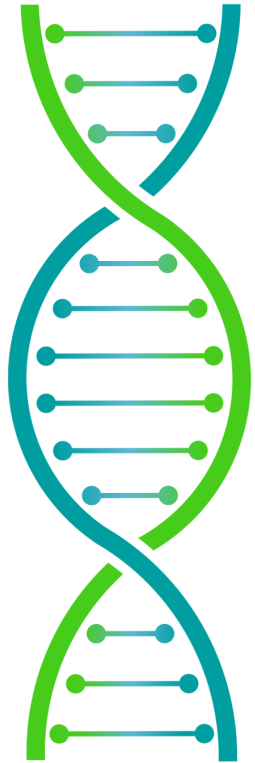
Addiction in the family, 90% incidence

Cardiovascular issues at a relatively young age in the family

Diabetes in the family

ASD and/or ADHD, 90% genetic components

# Genetic Test Kits



Genetic  
Test  
**MTHFR**  
**\$99**

[CLICK HERE](#)

## Process:

1. Order Test - Genetic tests are mailed directly to the patient
2. Swab your mouth
3. Mail to the Certified Lab in a prepaid envelope

## Results:

Once a patient's buccal swabs have been received by our accredited 3rd party lab, results are normally available in 1 week. Results will be emailed or faxed to the medical provider and/or patient.

# HOW TO PRESCRIBE

## STEP 1

### USE OUR ONLINE PRESCRIBER FORM

Fill in prescriber and patient information and then hit “submit”

[CLICK HERE](#)

## STEP 2

### WE WILL OFFER YOUR PATIENT THEIR FIRST 60 DAYS FOR \$60

We will also provide them with the insurance steps and help determine the most cost-effective option moving forward

## STEP 3

### IF IT'S COVERED ON INSURANCE, WE WILL CONTACT YOUR OFFICE WITH PRESCRIBING INFO

If your patient does not have coverage or has a high co-pay, we will offer our discounted cash-pay option for EnLyte/EnBrace HR. No further action is needed for your office.