Psych Congress

GOOD, BETTER, BEST:

The Role of L-Methylfolate in Today's Psychiatric/Clinical Practice

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Faculty Disclosures

- **Dr. Gustavo Alva: Dr. Gus Alva:**Advisory Board, Consultant, Grant Research/Support, Speakers Bureau—AbbVie, Abbott, Acadia, Alkermes, Allergan, Amgen, Avanir, Biogen, Celgene, Cerevel Therapeutics, Cubist, Eisai, Ferring, Genentech, Janssen, Intra-Cellular Therapies, Inc., Liva Nova, Lundbeck, Merck, Myriad, Neurocrine Biosciences, Inc., Otsuka America Pharmaceutical, Inc., Sage Therapeutics, Shire, Elan, GlaxoSmithKline, Hospira, Pfizer, Bristol-Myers Squibb, Roche, Salix, Seattle Genetics, Takeda, Teva Pharmaceuticals.

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Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

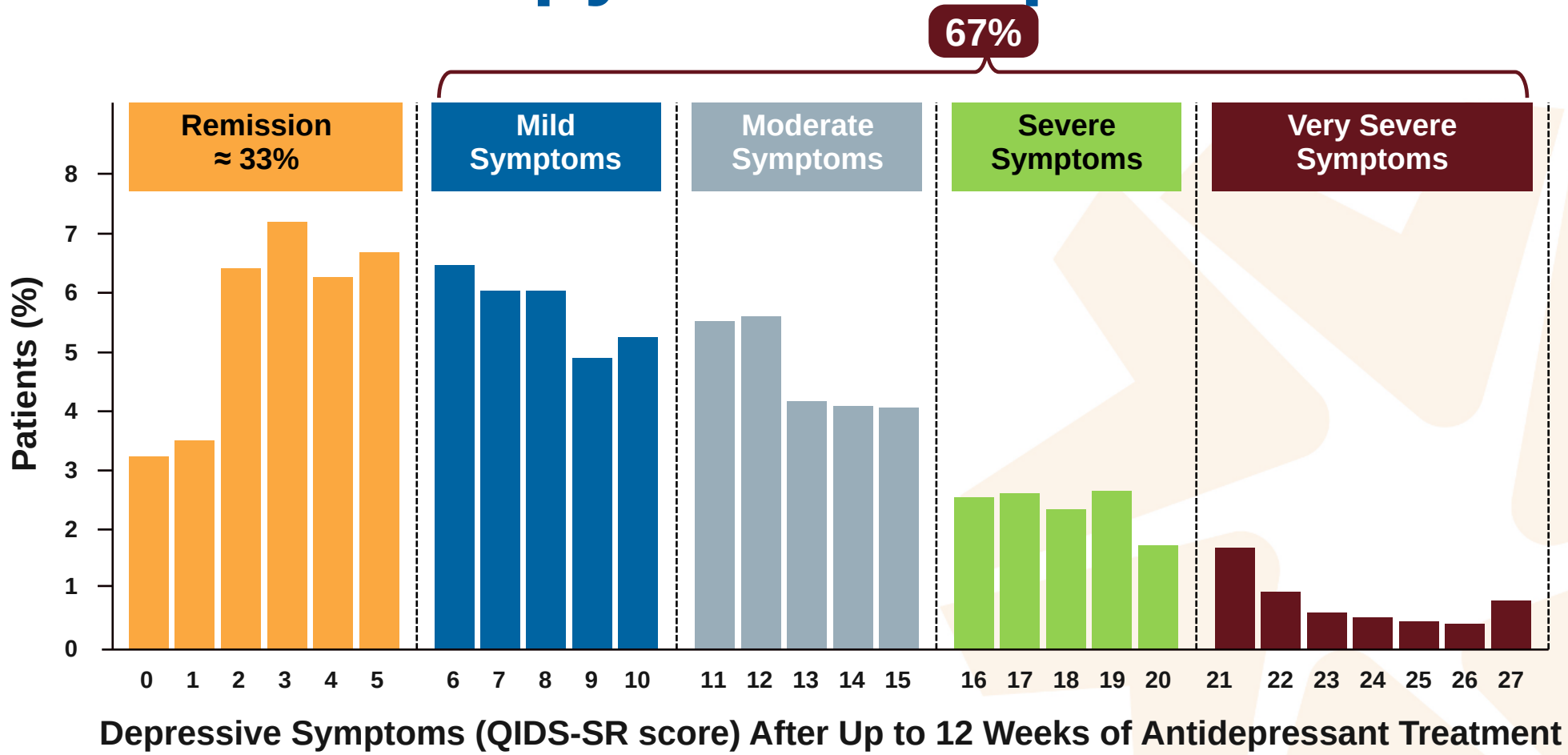
- This activity has been independently reviewed for balance.

Learning Objectives

- Describe the limitations of traditional monoaminergic antidepressants in patients with depression, including suboptimal response and remission rates
- Discuss the neurobiological role/MOA of L-methylfolate in depression and potential clinical implications
- Assess safety and efficacy data associated with the use of L-methylfolate as an adjunctive therapy to currently available antidepressant agents
- Employ treatment strategies with L-methylfolate according to specific patient profiles for improved outcomes in major depression

DISEASE STATE

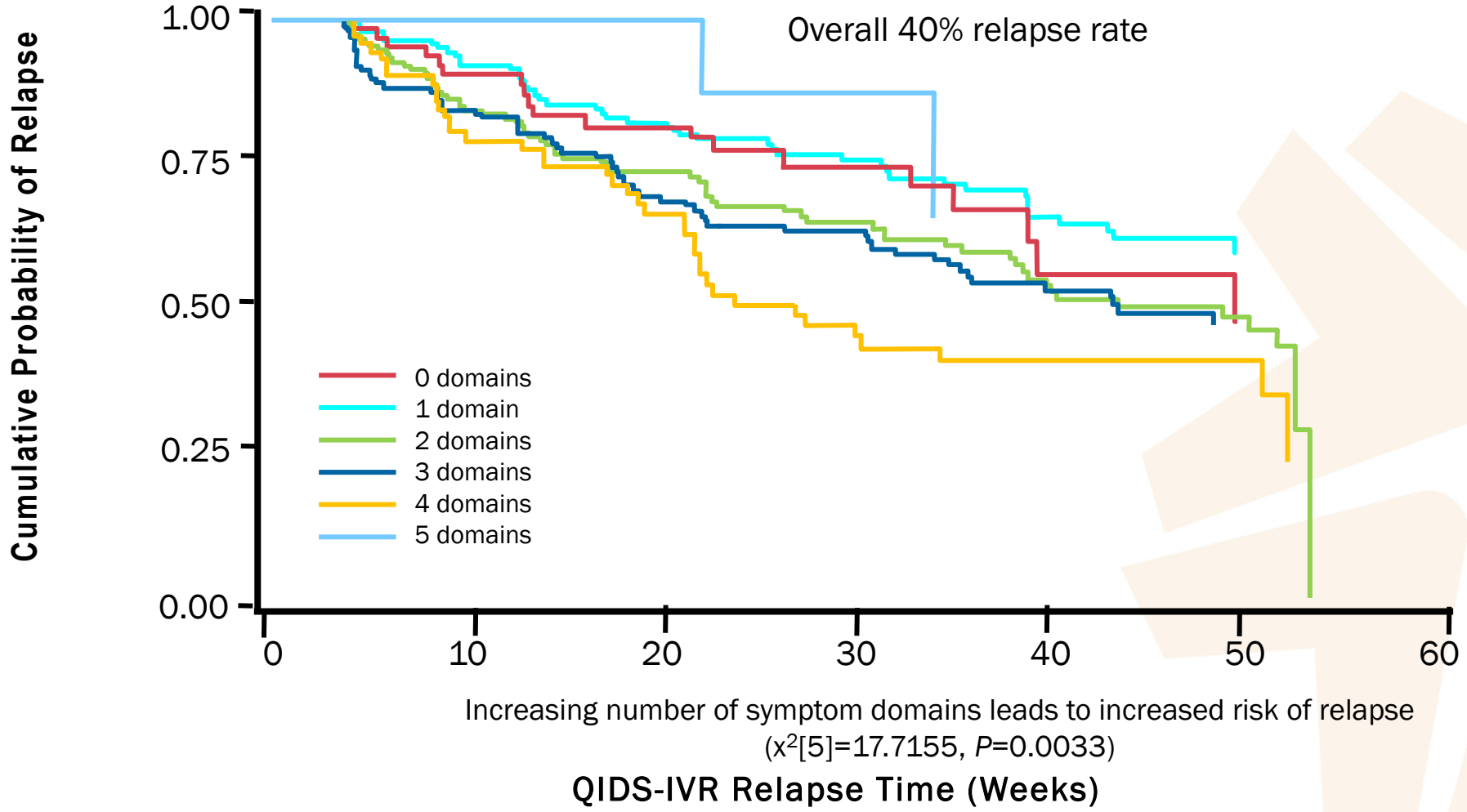
Remission Rates After Initial Antidepressant Therapy are Suboptimal



QIDS-SR=Quick Inventory of Depressive Symptomology – Self-Rated

Trivedi MH et al. *Am J Psychiatry*. 2006;163(1):28-40. Trivedi MH et al. *Am J Psychiatry*. 2006;163(1):28-40 Copyright

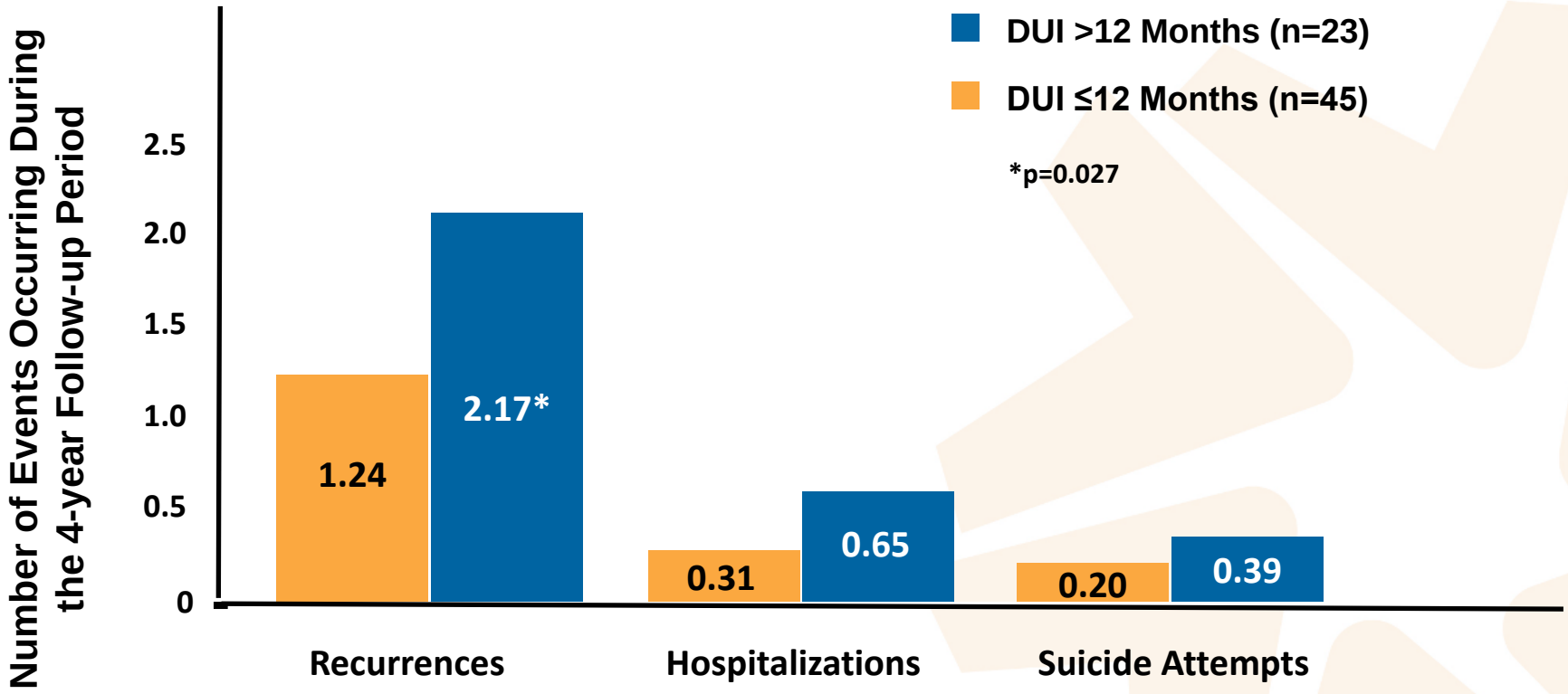
STAR-D Reveals Its Secrets – The Dangers of *Residual Symptoms & Lack of Remission*



- Sleep disturbance
- Sad mood
- Appetite/weight
- Concentration
- Outlook
- Suicidal ideation
- Involvement
- Energy/fatigue
- Psychomotor

Nierenberg AA et al. *Psychol Med.* 2010;40(1):41–50

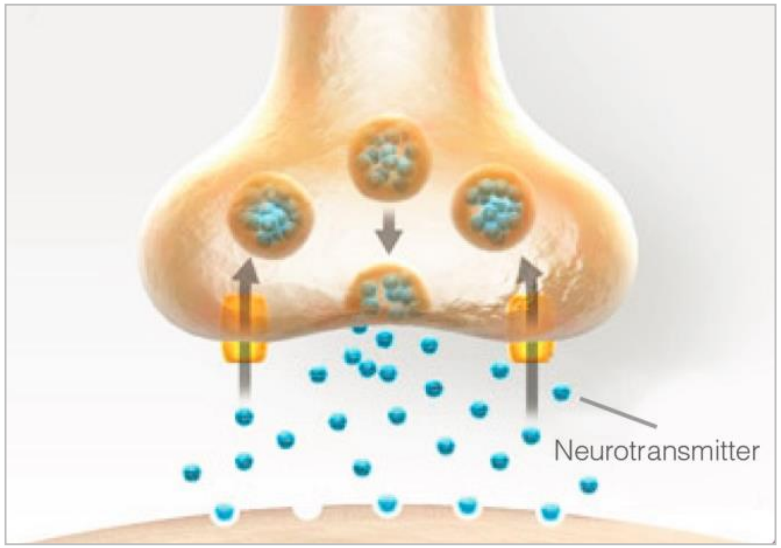
Delay of Treatment May Influence the Future Course of MDD



DUI=Duration of untreated illness, interval between the onset of the first episode and the first antidepressant treatment; MDD=Major depressive disorder.

Altamura et al. *Int J Clin Pract* 2007;61(10):1697-700

Neurotransmitters Play an Important Role in MDD Symptomatology



Norepinephrine
is linked to alertness and energy as well as attention and interest in life

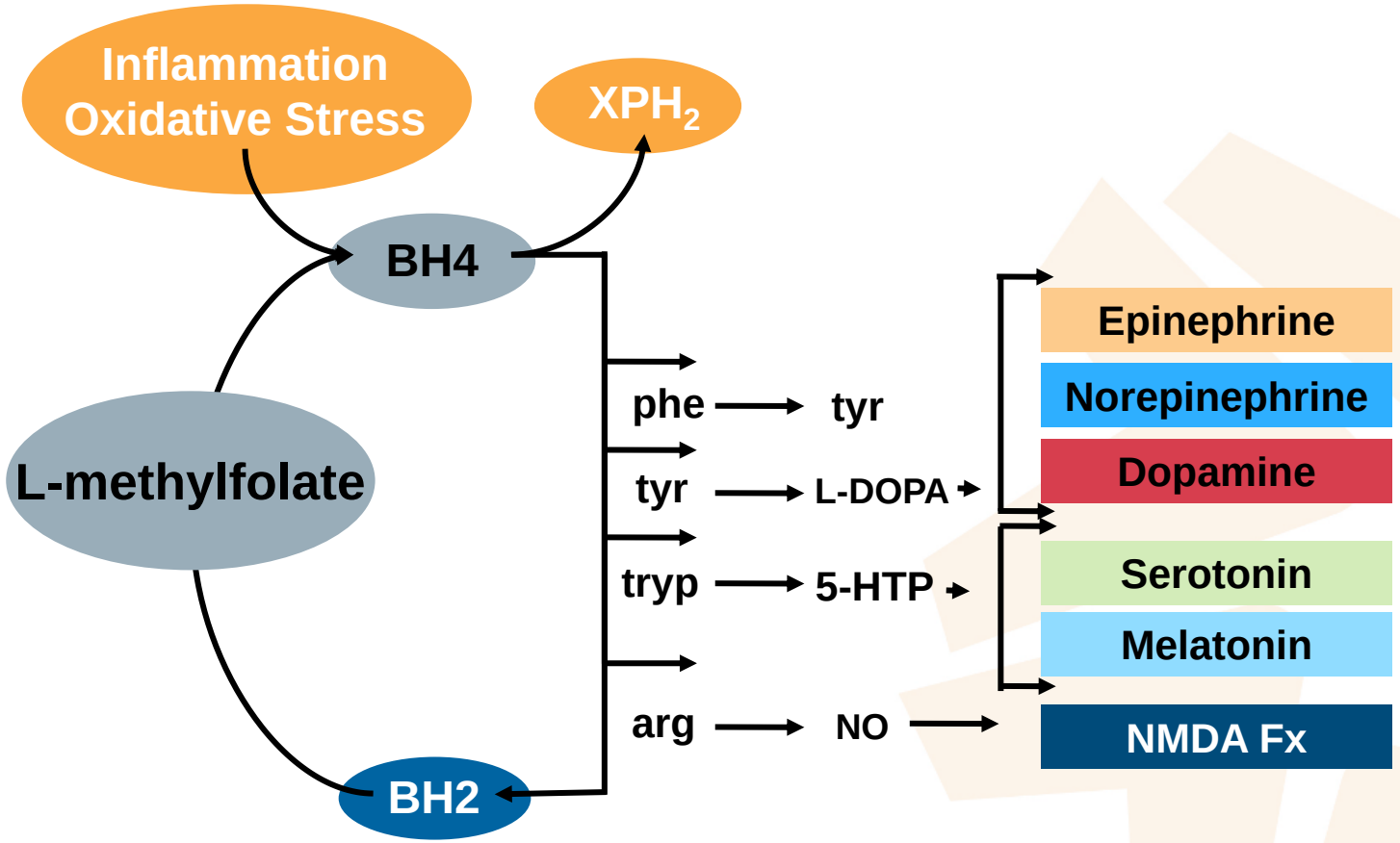
Serotonin
is linked to feelings of obsessions, anxiety, and compulsions

Dopamine
is linked to attention, motivation, pleasure, reward, and interest in life

Although every neurotransmitter is linked to different symptoms of depression, each contributes to mood

Nutt DJ. *J Clin Psychiatry*. 2008;69(suppl E1):4-7.

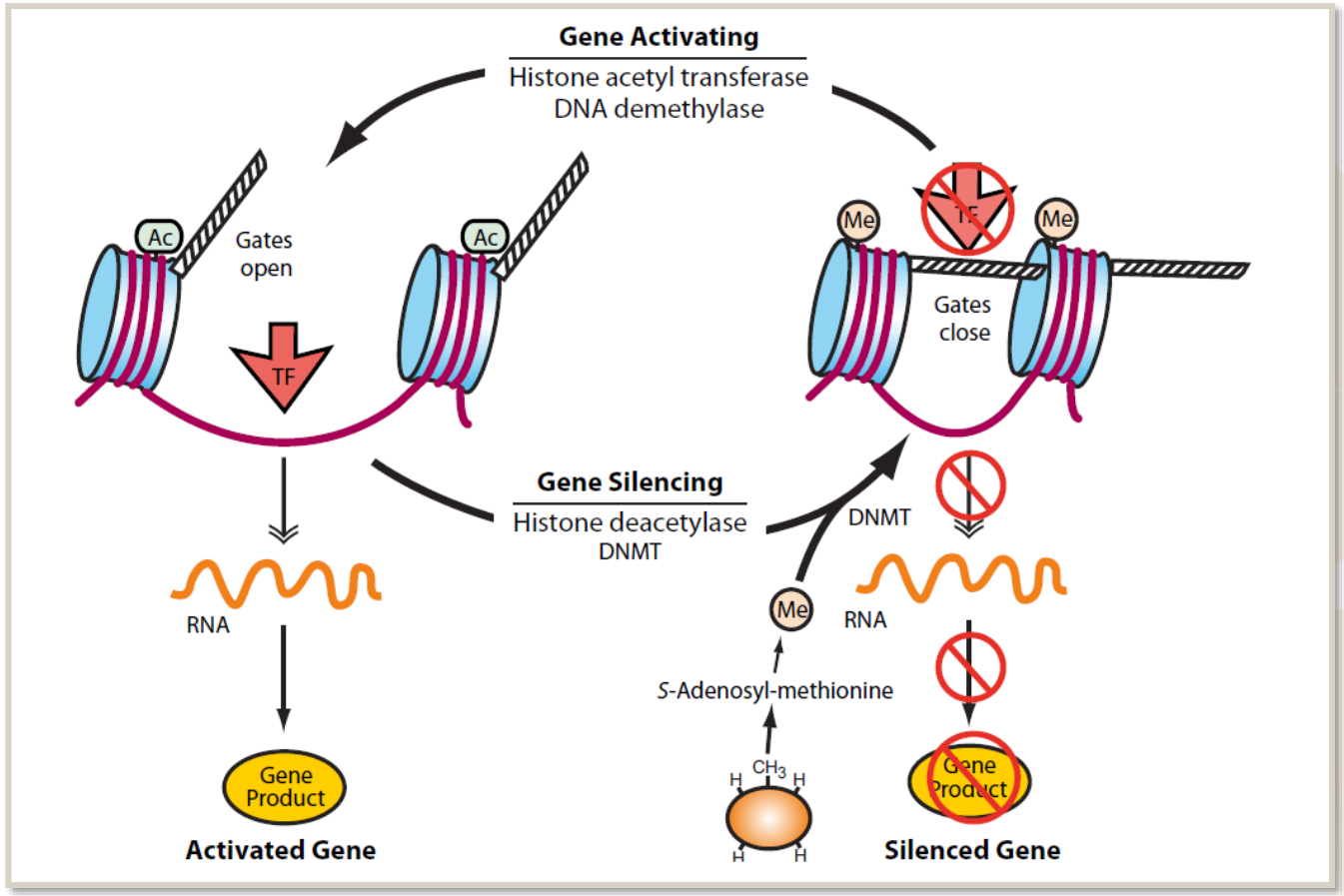
Folate–in the Form of L-methylfolate is Critical in Monoamine Synthesis



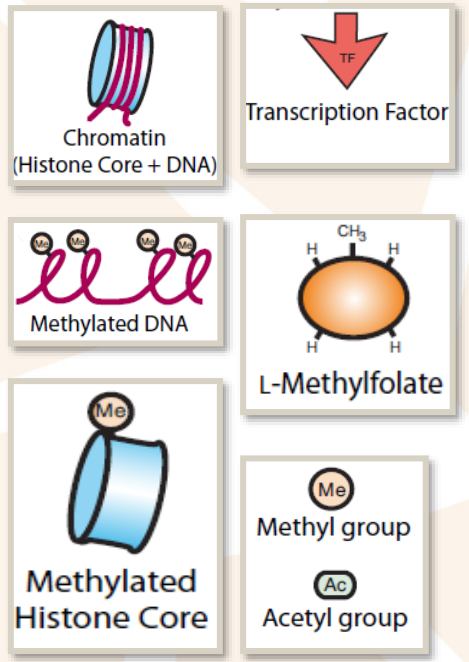
5-MTHF = 5-methyltetrahydrofolate; BH4 = tetrahydrobiopterin; XPH2 = dihydroxyanthopterin; PAH = phenylalanine hydroxylase; TH = tyrosine hydroxylase; TPH = tryptophan hydroxylase; NOS = nitric oxide synthetase; phe = phenylalanine; tyr = tyrosine; tryp= tryptophan; 5-HTP = 5-hydroxytryptophan; arg = arginine; NO = nitric oxide.

Haroon E, et al. Neuropsychopharmacology. 2012;37(1):137-162. Felger J and Miller A. Front Neuroendocrinol. 2012 August;33(3):315–327.doi:10.1016/j.yfrne.2012.09.003. Reiter R, et al. Int. J. Mol. Sci. 2013,14,7231-7272; doi:10.3390/ijms14047231.

Gene Activation and Silencing – Importance of L-Methylfolate

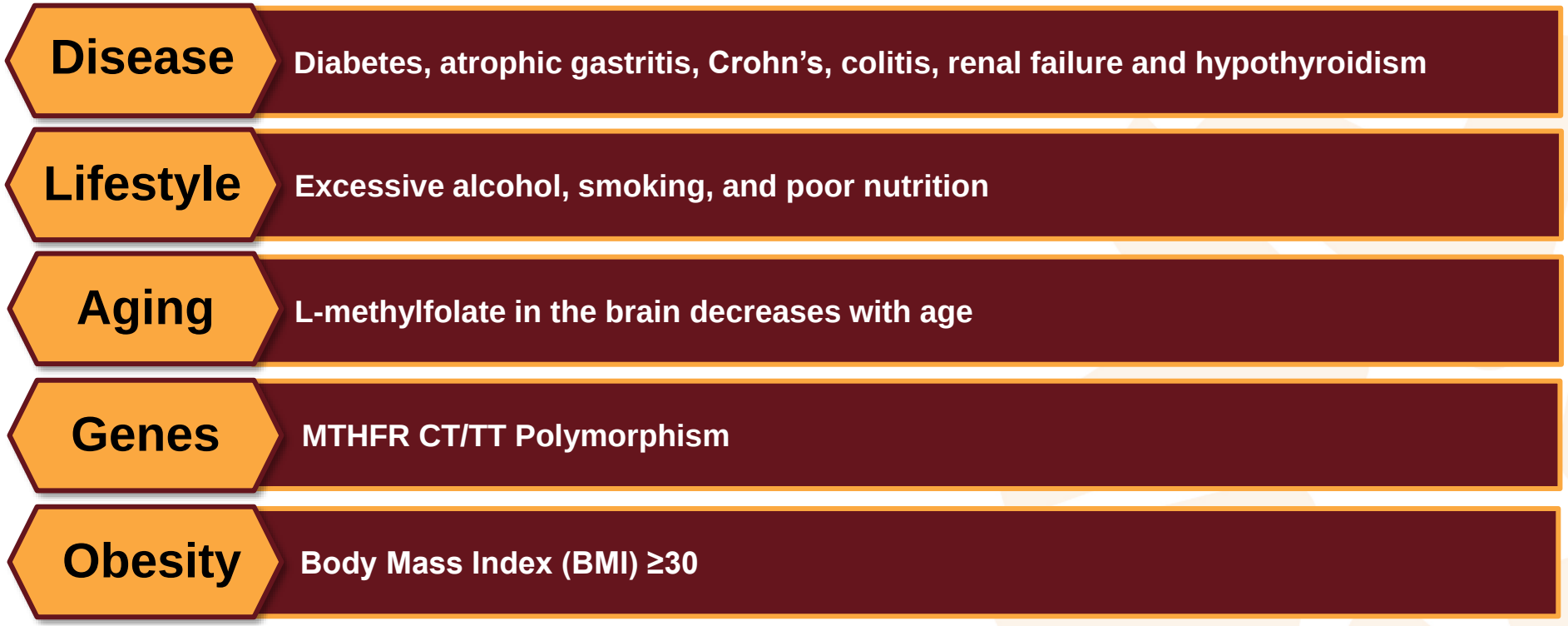


Legend:



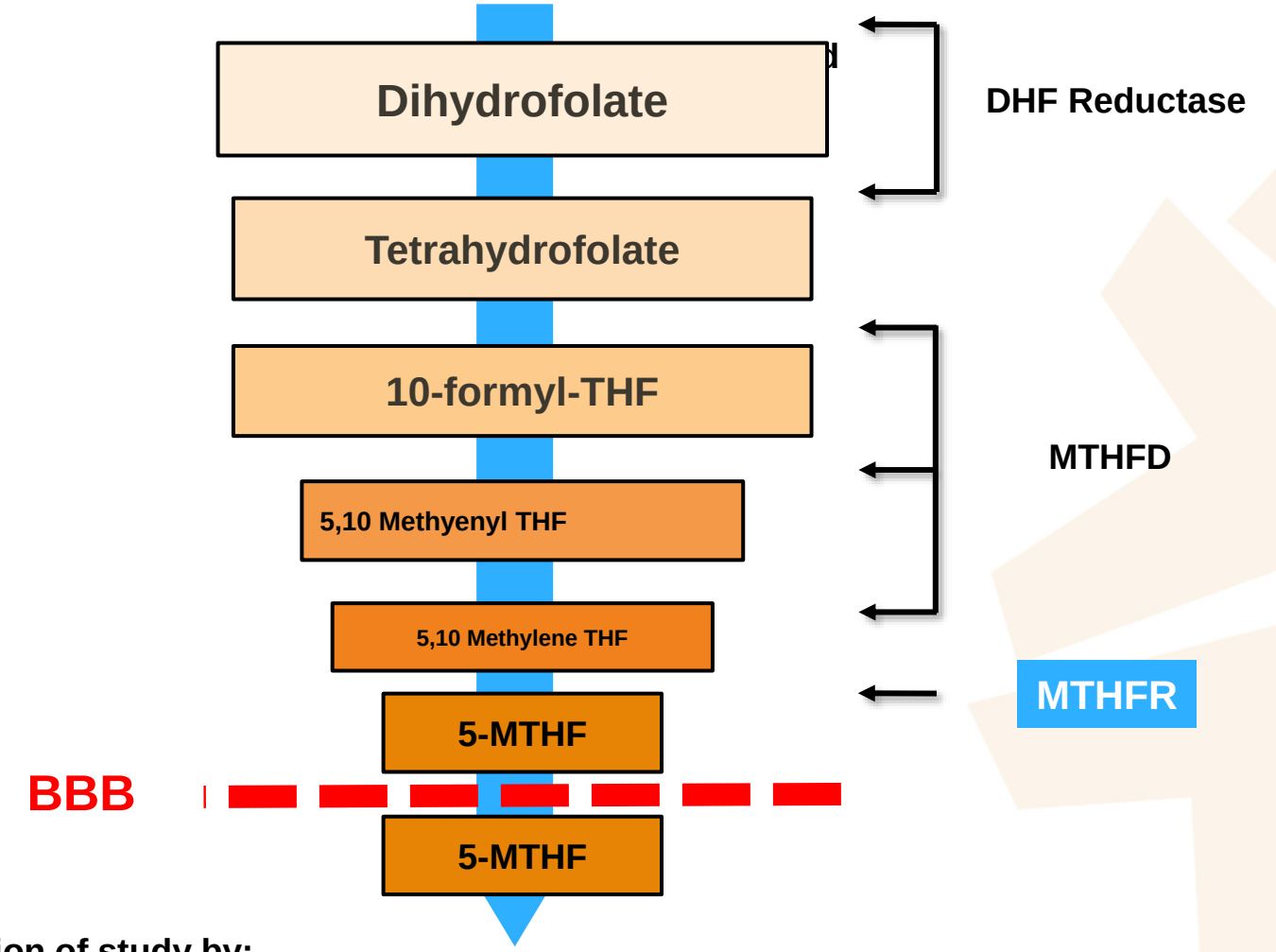
Stahl, SM. J Clin Psychiatry. 2009 Sep;70(9):1204-5.

Risk Factors for Low L-methylfolate



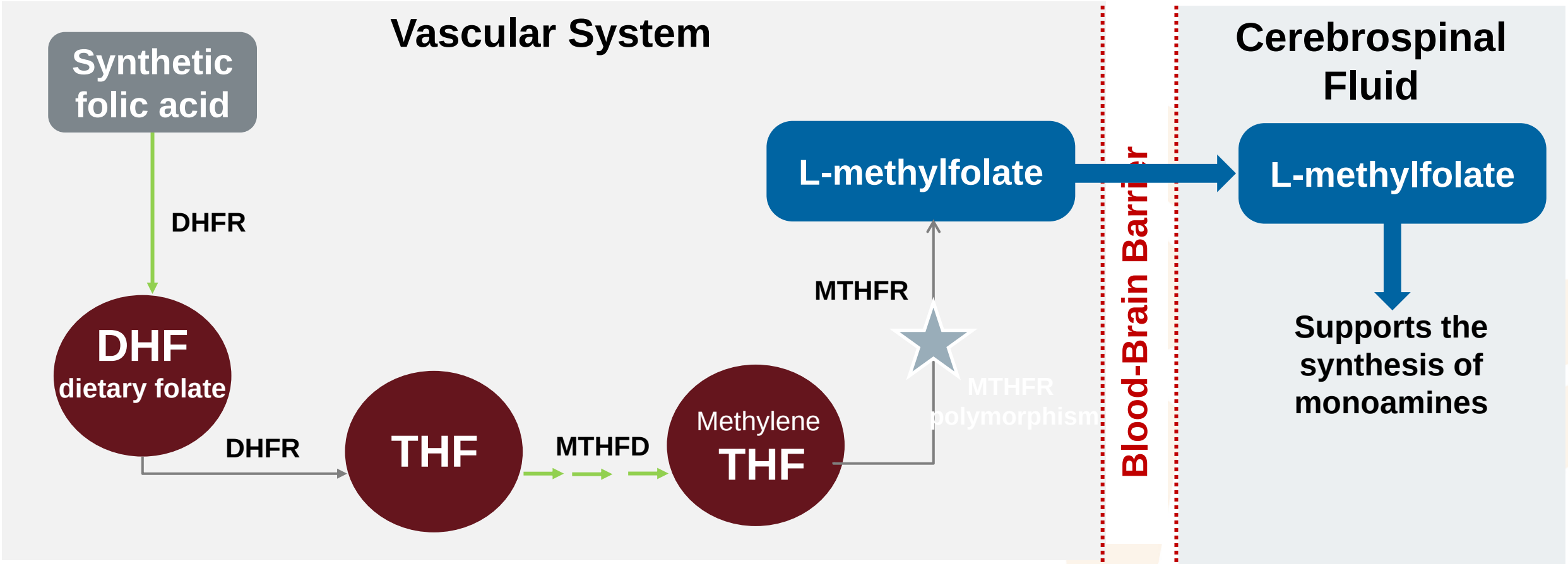
Bottiglieri T. 2005. 29:1103-12. Stahl SM. J Clin Psychiatry. 2008; 69(9):1352-53. Sobczyriska-Malefora A et al. Blood Coagula Fibrinolysis. 2009; 20(4):297-302. Amilburu A, et al. *J Physiol Biochem*. 2201;57(2):71-80. PDR® For Nutritional Supplements, 2001. ISBM: 1-56363-364-7:157-67. Garg R, et al. Am Heart J. 1999;138:1082-7. Bolander-Gouaille C, Bottigliei T. Homocystiene Related Vitamins and Neuropsychistric Disorders. France: Springer-Verlag; 2003. Oskooilar N., et al. *J Clinincal Psychiatry*. 2009. 70(11):1609-10. 9. Mahabir, S et al. *European Journal of Clinical Nutrition*. 2008;62:644-650.

Folate Metabolism



Graphical representation of study by:
Willems FF et al. *Br J Pharmacol*. 2004;141(5):825-30.
Krajinovic M. *Pharmacogenomics.* 2008; 9(7):829-832.

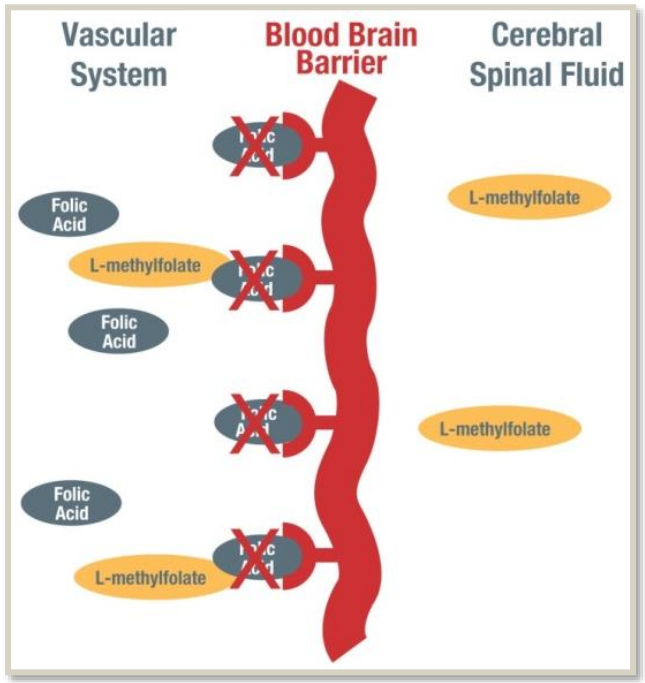
Folic Acid Metabolism Is a Multistep Enzymatic Process

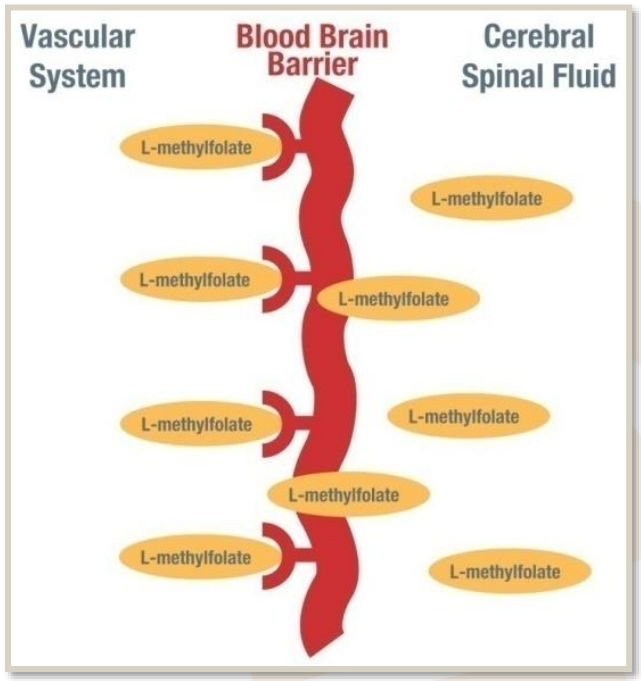


DHF=dihydrofolate; DHFR=dihydrofolate reductase; MTHFD=5,10-methylene THF dehydrogenase; THF=tetrahydrofolate

Fava M et al. *J Clin Psychiatry*. 2009;70(suppl 5):12-17

L-methylfolate Crosses the Blood Brain Barrier





Spector R & Lorenzo AV. *Am J Physiol*. 1975:229(3):777-82.
Aisen PS et al. *JAMA*. 2008;300:1774-83.
Smith I et al. *Postgrad Med J*. 1986;62(724):113-23.
Troen AM et al. *J Nutr*. 2006;136:189-94.
Botez MI et al. *Nature*. 1979;278(5700):182-3.
Stahl SM *CNS Spectrums*. 2007;12(10):739-744.

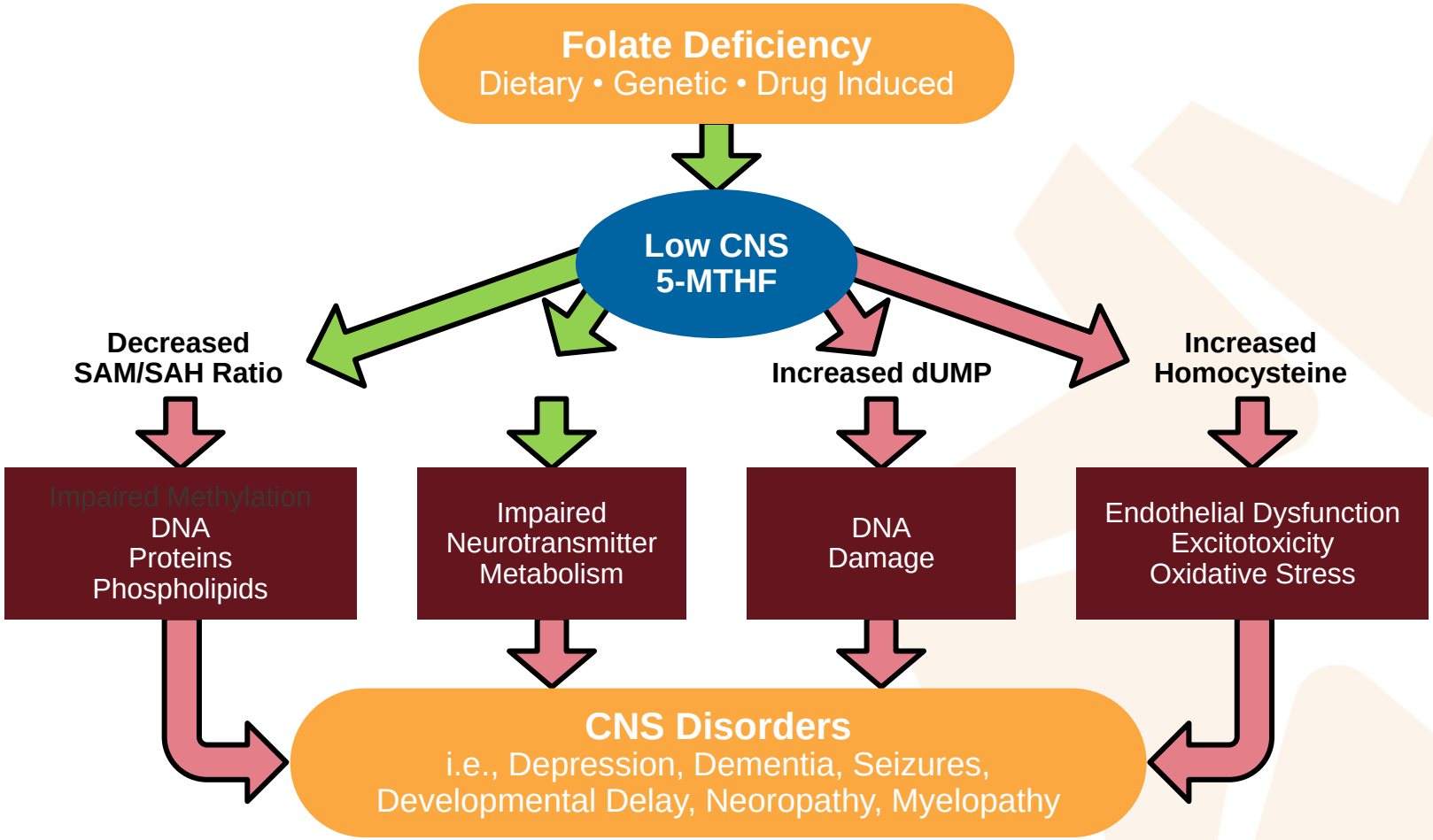
Synthetic folic acid blocks L-methylfolate from crossing the blood brain barrier (BBB).[1]

High dose synthetic folic acid has led to an increase in depression,[2] neurological complications,[3] suppression of the immune system[4] and a decrease in monoamines.[5]

L-methylfolate, in the absence of synthetic folic acid, passes more readily into the CNS[1] to regulate neurotransmitter synthesis in depressed individuals.[6]

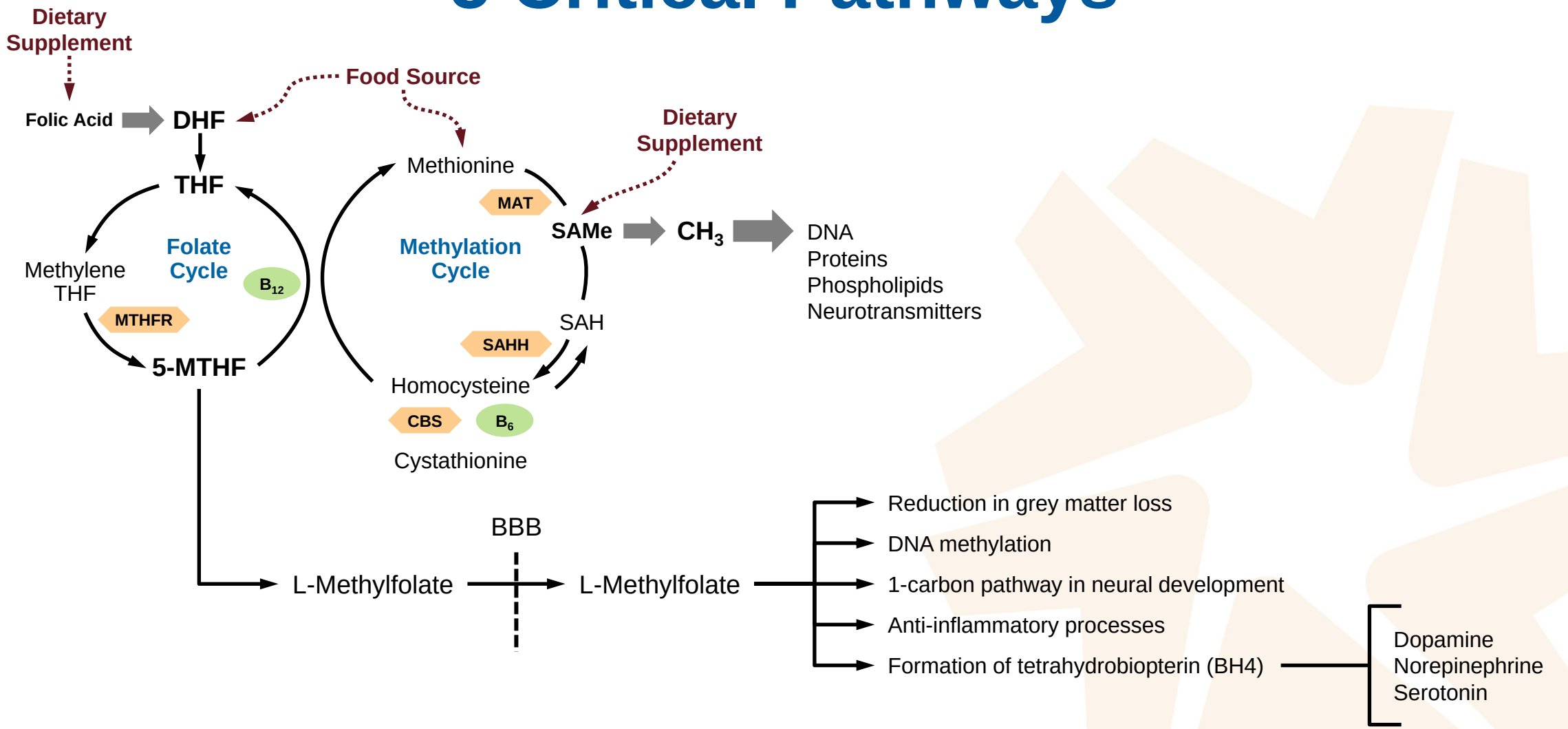
Spector R & Lorenzo AV. *Am J Physiol*. 1975:229(3):777-82. Aisen PS et al. *JAMA*. 2008;300:1774-83. Smith I et al. *Postgrad Med J.* 1986;62(724):113-23. Troen AM et al. *J Nutr*. 2006;136:189-94. Botez MI et al. *Nature.* 1979;278(5700):182-3. Stahl SM *CNS Spectrums.* 2007;12(10):739-744.

Consequences of Folate Deficiency Impact Both Brain and Body



Bottiglieri T, Reynolds E. In: Bailey LB, ed. Folate in Health and Disease, Second Edition. Boca Raton, FL: Taylor & Francis Group; 2009:355-380

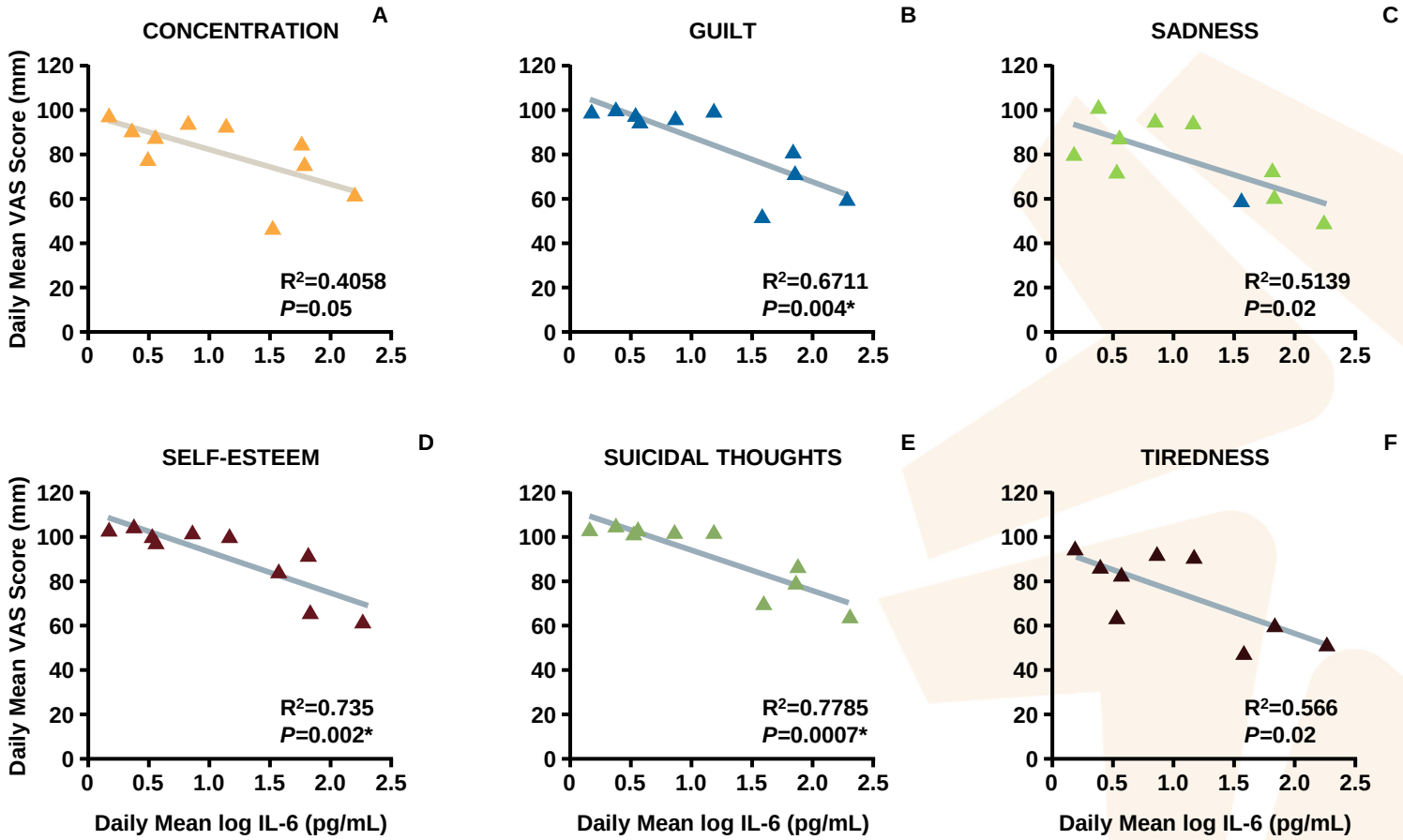
The Critical Role of L-methylfolate in 5 Critical Pathways



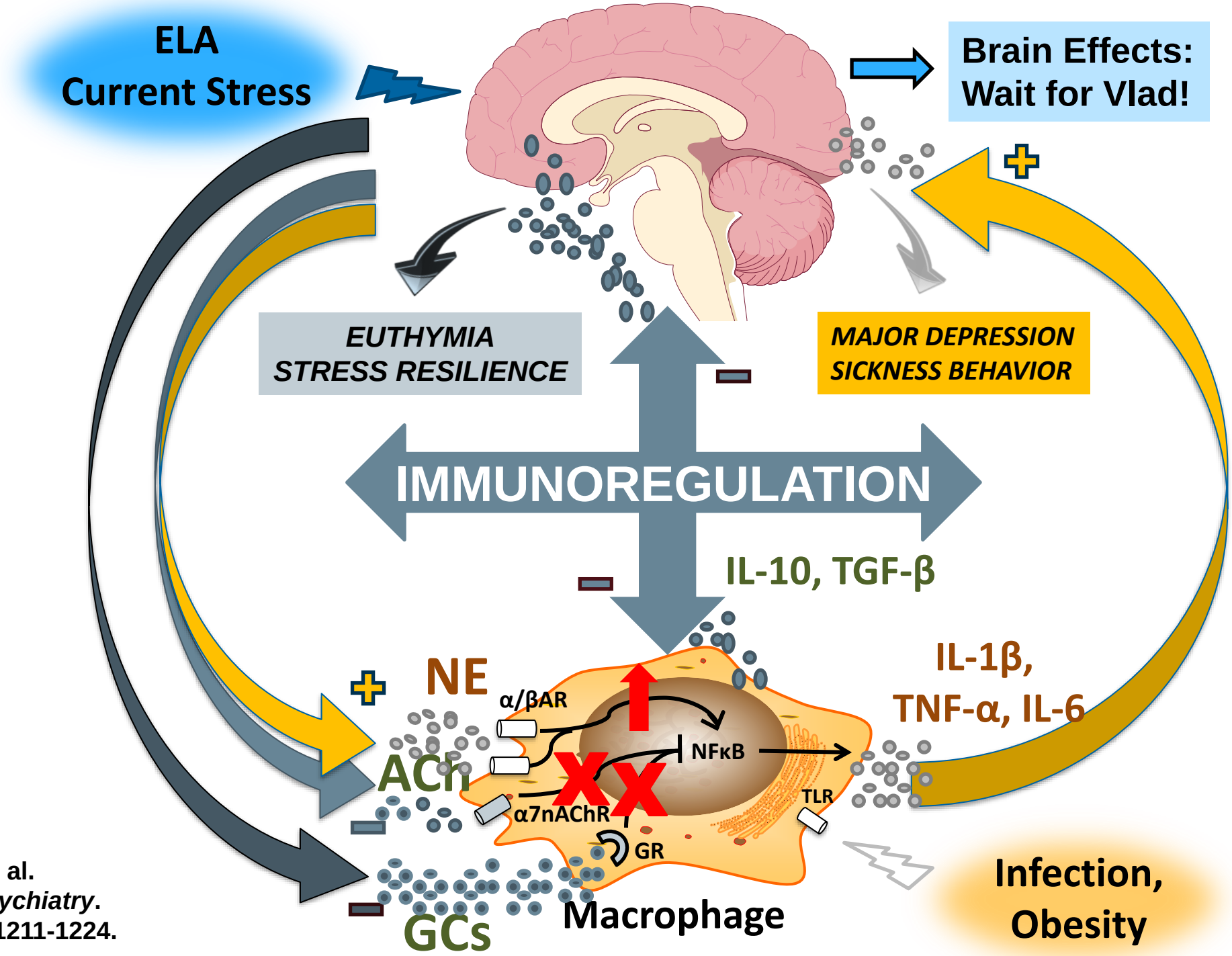
Jain R, et al. Good, better, best: clinical scenarios for the use of L-methylfolate in patients with MDD. *CNS Spectrums*. https://doi.org/10.1017/S1092852919001469

Inflammatory Markers Predict Symptom Severity in Depression

Comparison of 9 MDD Patients With 9 Matched Healthy Controls

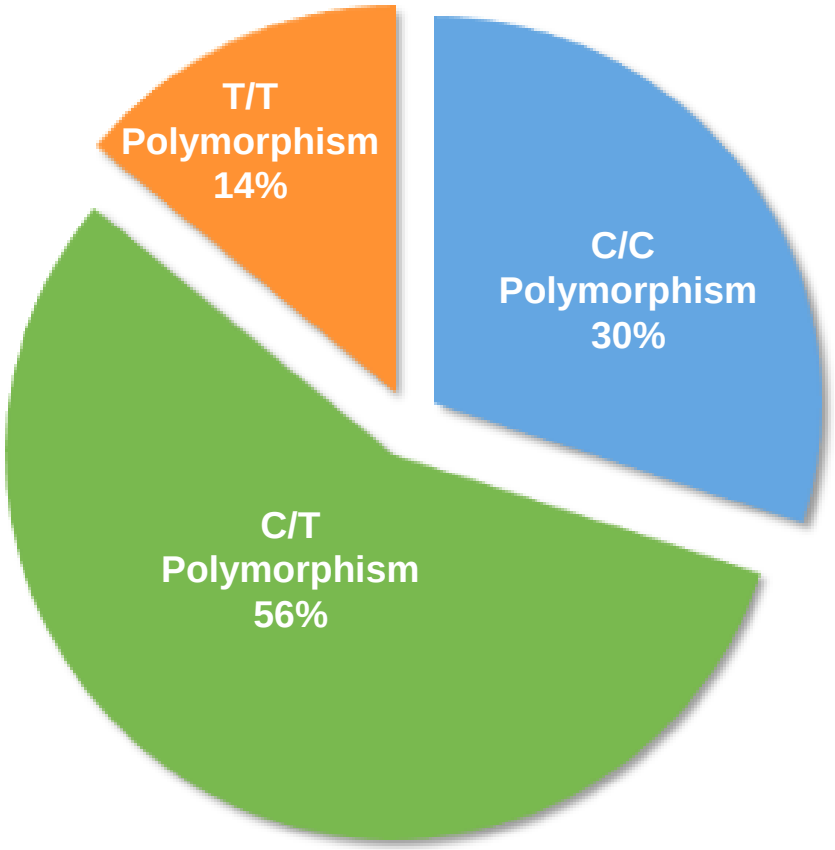


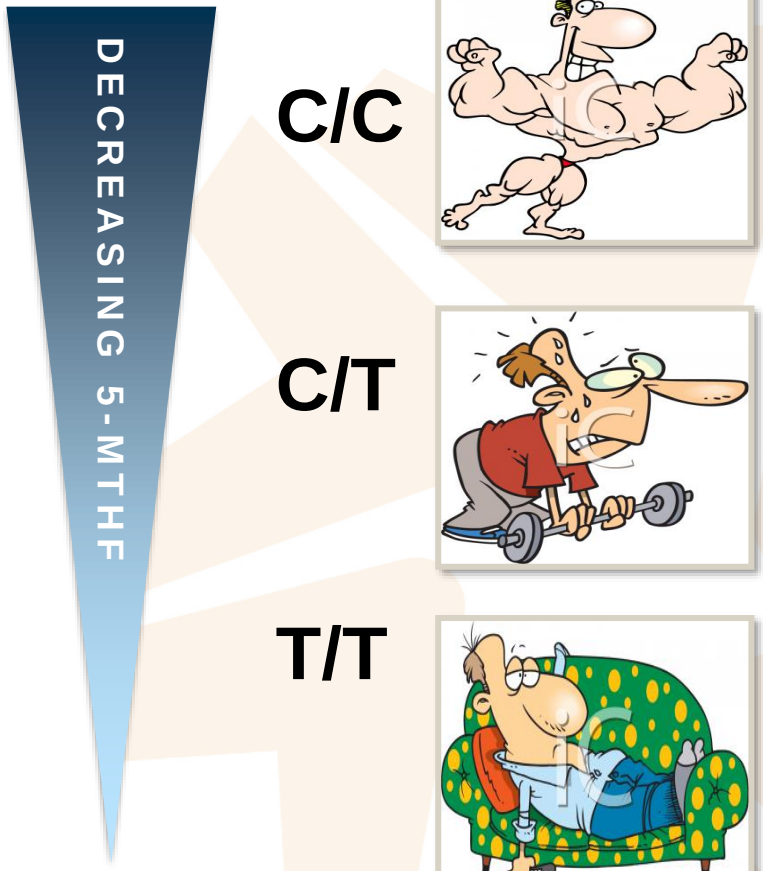
Alesci et al. *J Clin Endocrinol Metab.* 2005;90(5):2522-30.



Raison CL et al.
Arch Gen Psychiatry.
2010;67(12):1211-1224.

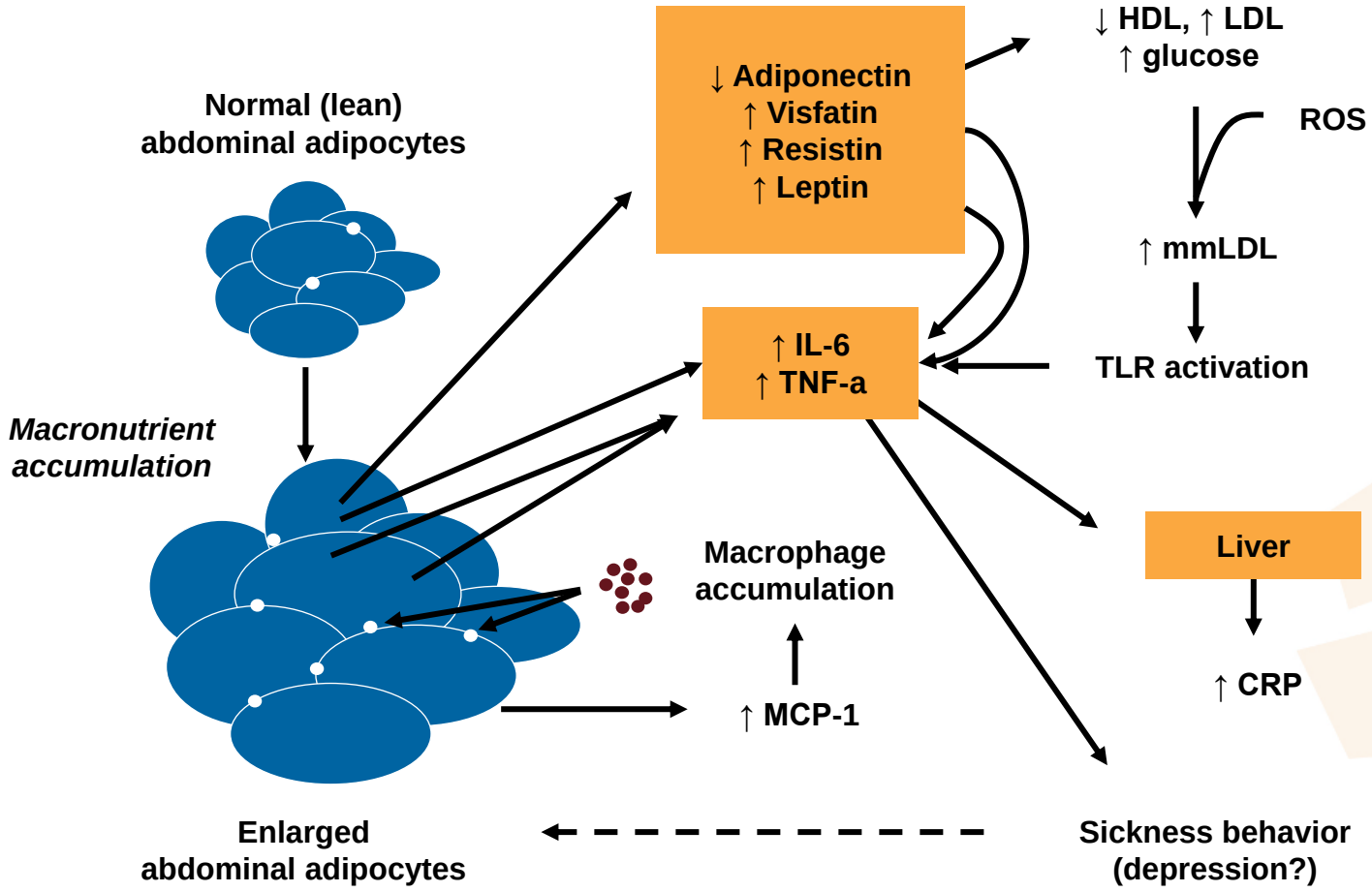
Up to 70% of MDD Patients Have a Genetic Mutation Reducing Conversion Folic Acid to L-methylfolate





Kelly CB et al. *J Psychopharmacol*. 2004;18(4):567-71.
Bottiglieri T et al. *J Neurol Neurosurg Psychiatry*. 2000;69:228-32.
Surtees R, Heales S, & Bowron. *Clinical Science*. 1994;86:697-702

Adiposity, Inflammation, and Depression



High caloric intake in the diet leads to increased accumulations

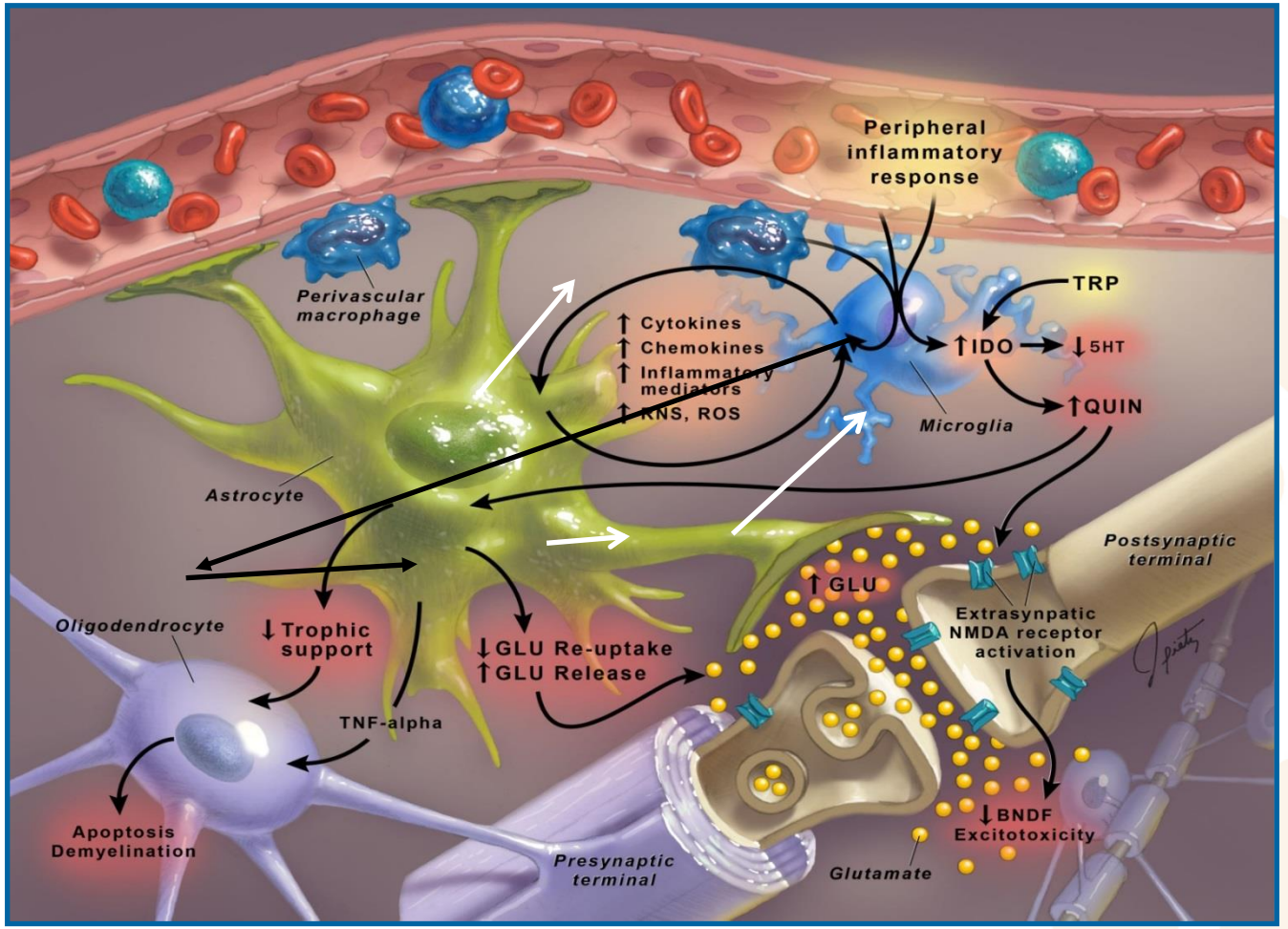
of lipids
in adipocytes.

Increased lipid content results in an increased release of MCP-1 (CCL2), a chemoattractant that increases the infiltration of macrophages into adipose tissue.

Both adipocytes and macrophages release inflammatory mediators such
as IL-6 and TNF-α into the peripheral circulation.

Shelton RC, Miller AH. *Prog Neurbiol*. 2010;91(4):275-299.

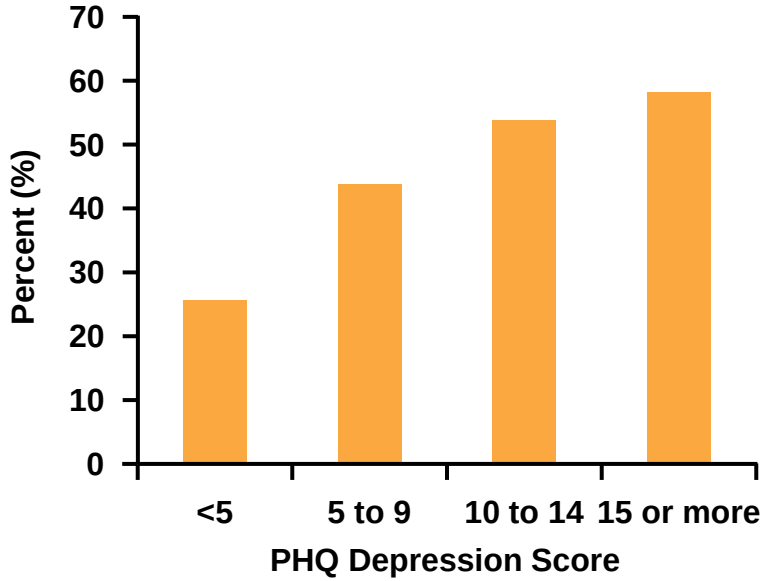
Glia–Microglia-Neuron Interactions: Role of Neuro-inflammation in Major Depression



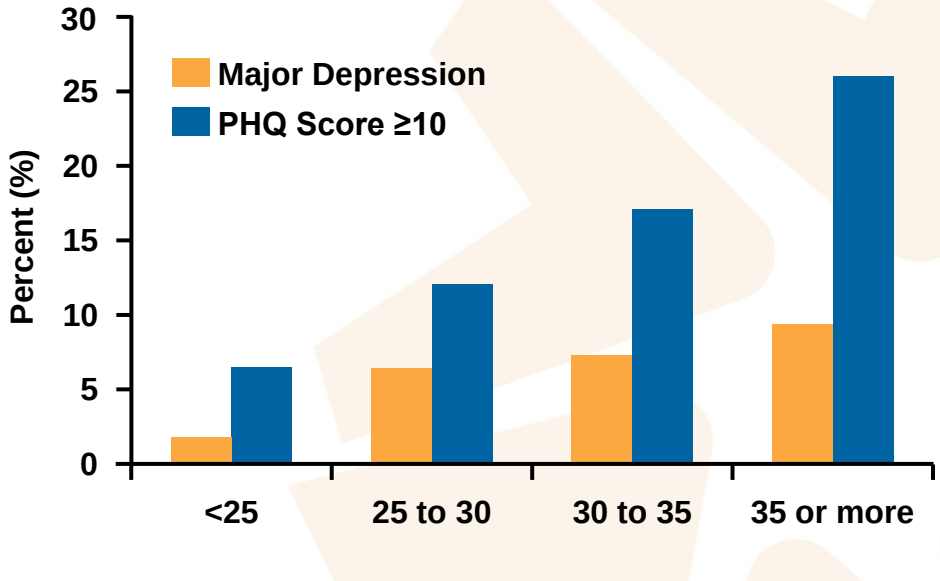
Miller AH, et al. *Biol Psychiatry*. 2009;65(9):732-741. Rocha SM, et al. *Neurobiol Dis*. 2012;47(3):407-415. Boscia F, et al. *PLoS One*. 2009;4(8):e6486. Lee M, et al. *Glia*. 2011;59(1):152-165.

Deleterious Bidirectional Association Between Obesity and Depression

Depression Associated with Obesity



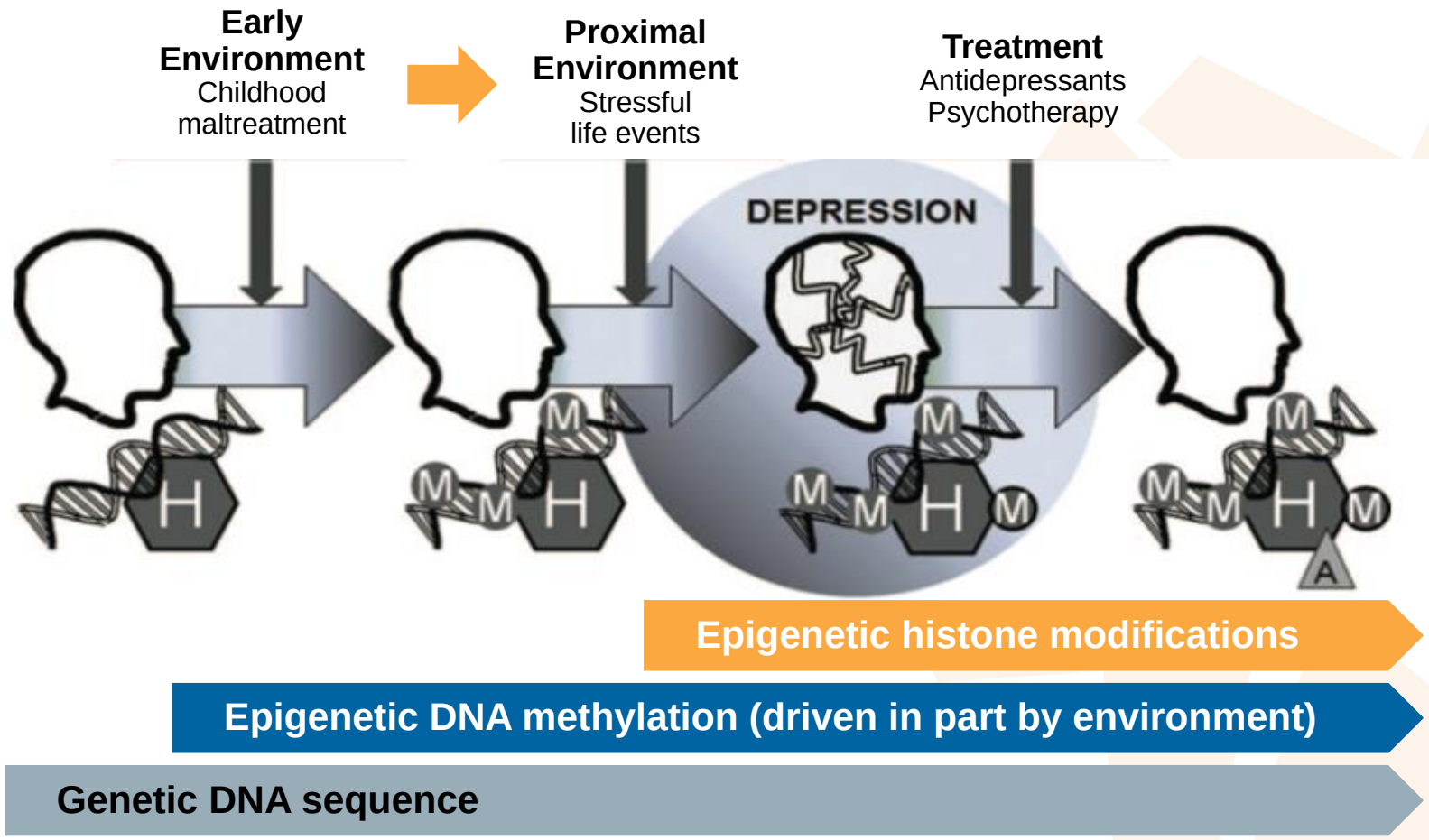
Obesity Associated with Depression



BMI = body mass index; PHQ = Patient Health Questionnaire.

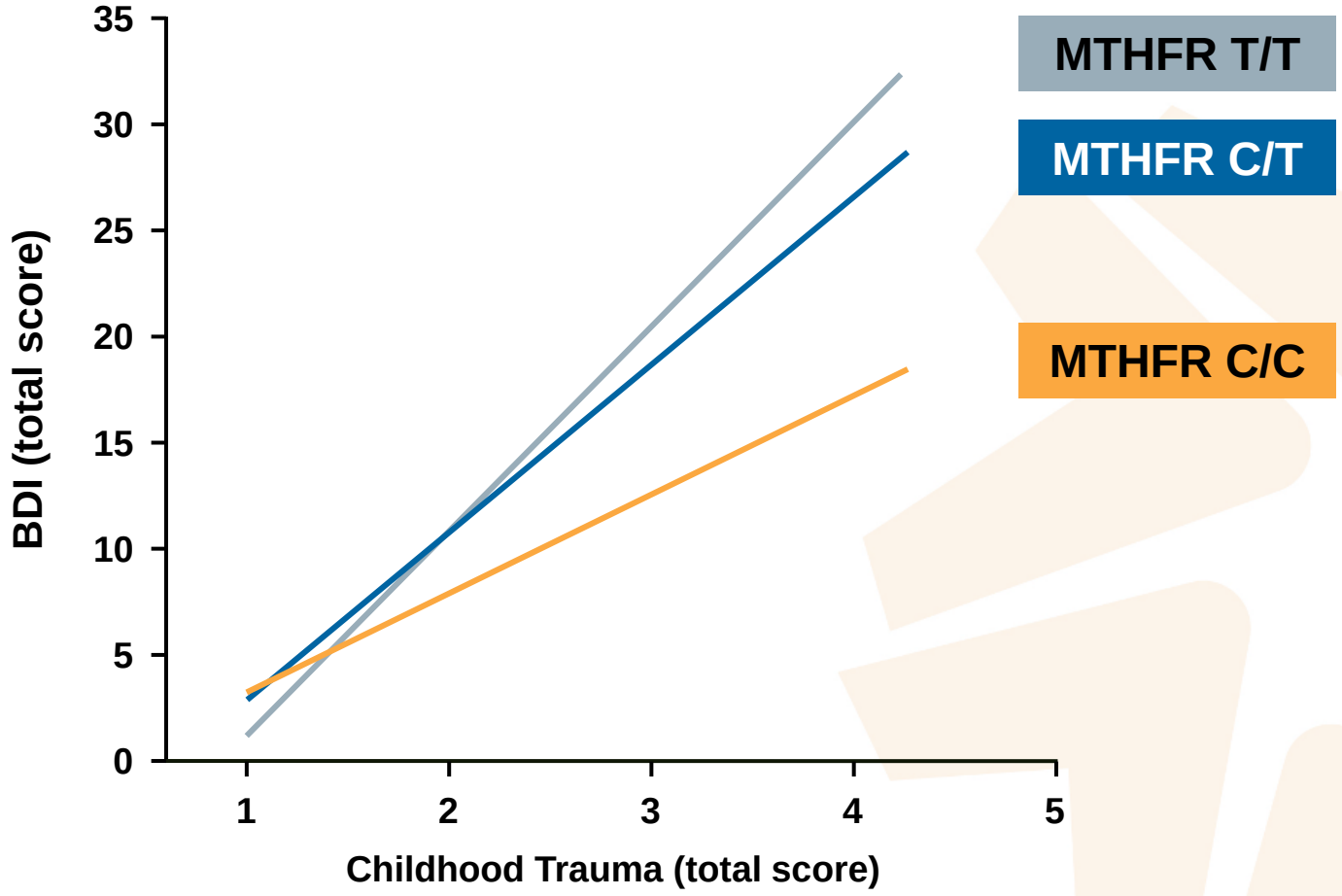
Simon GE, et al. *Gen Hosp Psychiatry*. 2008;30(1):32-39. Pan A, et al. *Int J Obes*. 2012:36(4):595-602.

Interaction of Genetics, Epigenetics and Environment in MDD



Uher R. *Harv Rev Psychiatry*. 2011;19(3):109-124.

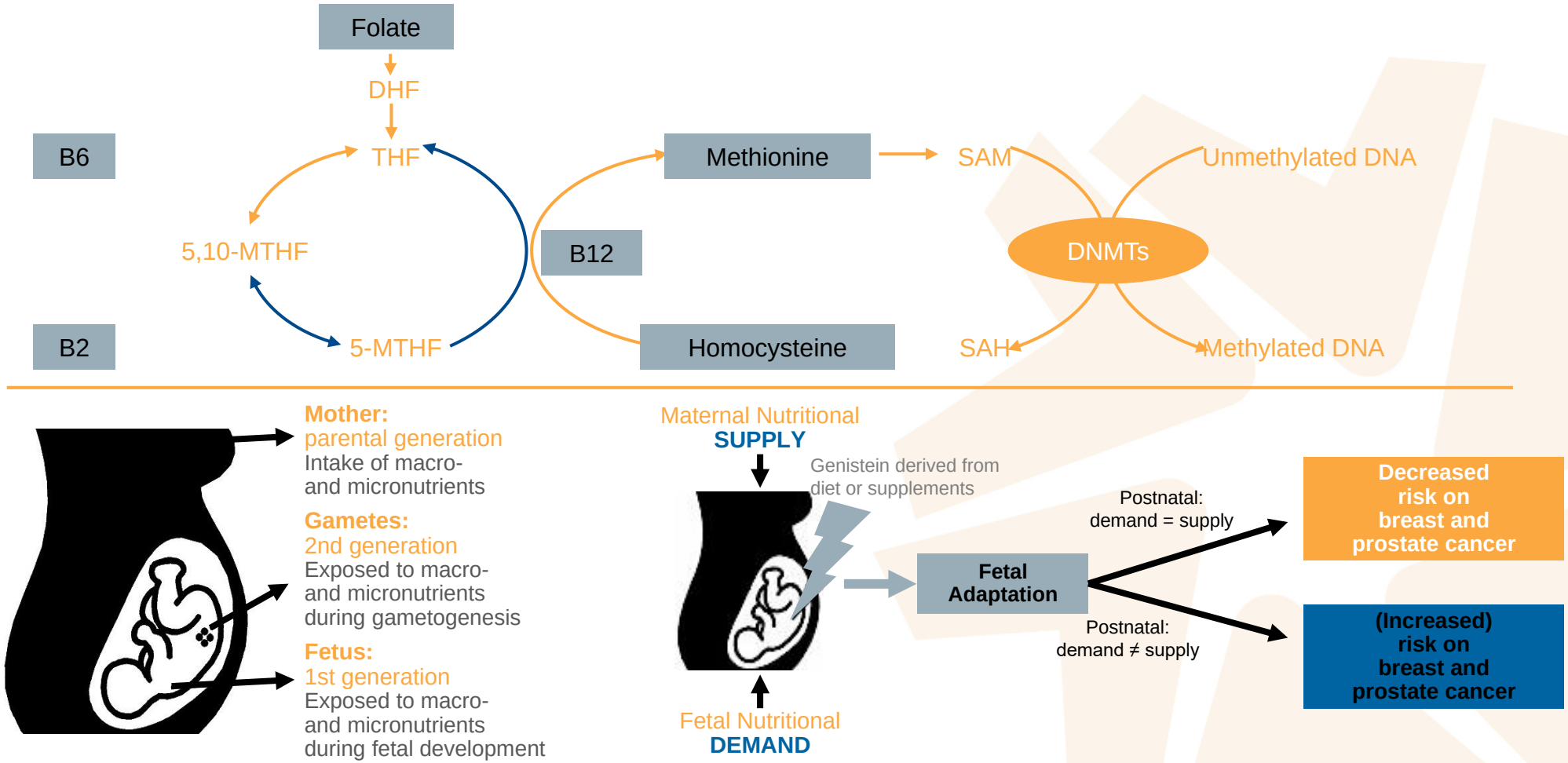
Environmental Conditions Can Enhance or Expose Depressogenic Potential of Genes



P=.0027.
BDI = Beck Depression Inventory; MTHFR = methylenetetrahydrofolate reductase.

Lok A, et al. *Transl Psychiatry*. 2013;3:e288.

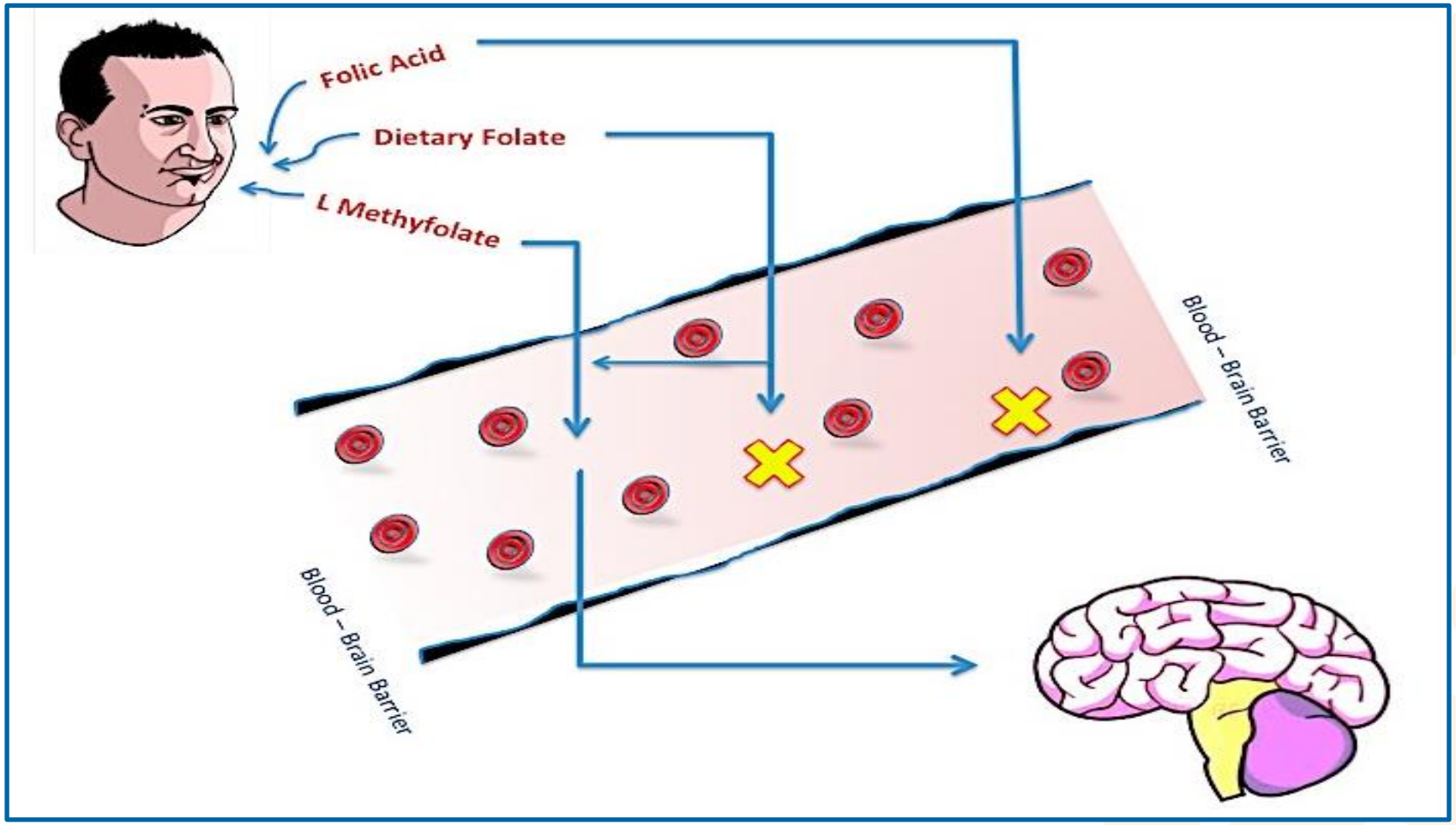
Methylation of DNA Occurs via the Folate Pathway – Implications for Epigenetics



Vanhees K, et al. *Cell Mol Life Sci*. 2013 Jul 27;[Epub ahead of print].

Understanding Blood Brain Barrier And Folate Issues

The only active folate that crosses the blood brain barrier is L-methylfolate



Spector R & Lorenzo AV. *AM J Physiol*. 1975; 229(3):777-82.

L-METHYLFOLATE

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ATP Clinical Research
Assistant Professor,
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Riverside Private Practice Psychiatrist, Pacific Neuropsychiatric Specialists
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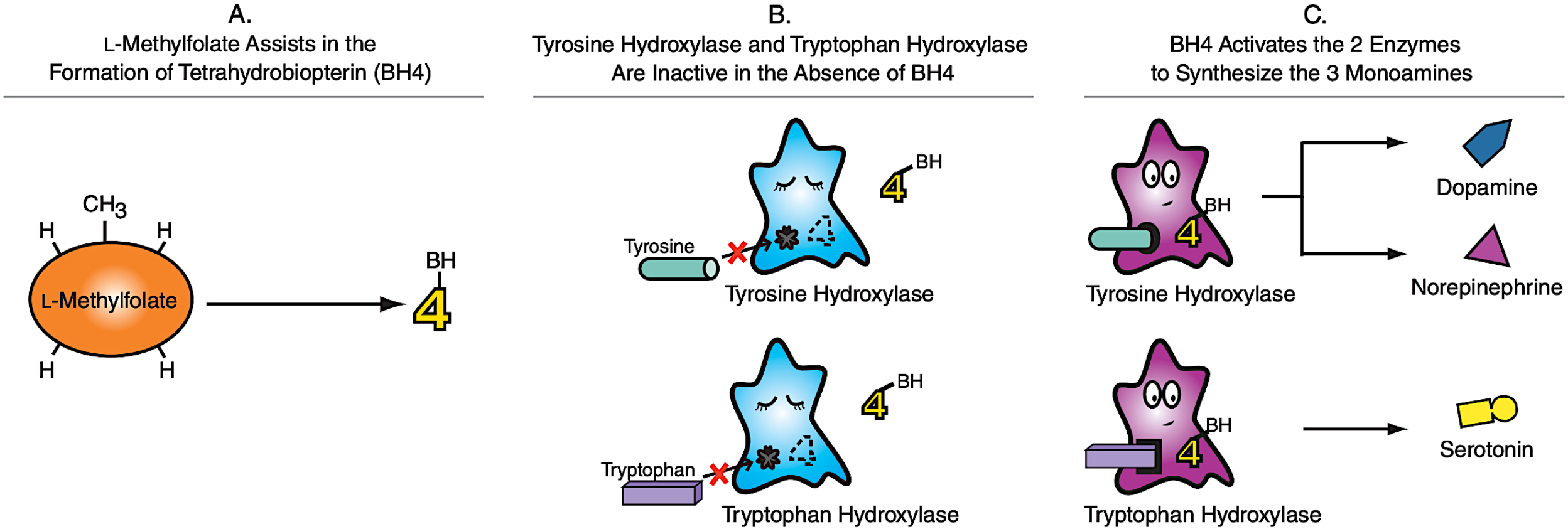
LMF Augmentation: Conceptually, It's an Intriguing Augmentation Agent with SSRIs/SNRIs



Stahl SM. *J Clin Psychiatry*. 2008.69(9).

Overview of LMF Clinical Trials in MDD

Study	Design	Patients	Treatment Arms	Primary Endpoint
Trial 1[1]	Multicenter, randomized, double-blind, sequential parallel (two 30-day phases) trial in SSRI-resistant MDD	N=148; ≥12 QIDS-SR, tx with SSRI ≥8 weeks (stable for ≥4 weeks)	• PBO → PBO • PBO → 7.5 mg • 7.5 mg → 15 mg	• Improvement in HAM-D17 • Response[a] rates according to HAM-D17
Trial 2[1]	Multicenter, randomized, double-blind, sequential parallel (two 30-day phases) trial in SSRI-resistant MDD	N=75; ≥12 QIDS-SR, tx with SSRI ≥8 weeks (stable for ≥4 weeks)	• PBO → PBO • PBO → 15 mg • 15 mg → 15 mg	• Improvement in HAM-D17 • Response[a] rates according to HAM-D17
Post hoc analyses[2,3]	Exploratory analyses evaluating effects of biological, inflammatory, and/or genetic markers on treatment response	N=74	—	Effect of biomarkers on response to HAM-D28
Open-label extension[4]	12-month, open-label, extension trial of Trials 1 and 2	N=68	15 mg	Reduction in HAM-D17 score at 12 months
Real-world study[5]	Retrospective cohort study evaluating patients previously prescribed DEPLIN®	N=502	7.5 mg or 15 mg	Reduction in PHQ-9 from baseline

1. Papakostas GI et al. *Am J Psychiatry.* 2012;169(12):1267-1274. 2. Papakostas GI et al. *J Clin Psychiatry.* 2014;75(8):855-863. 3. Shelton RC et al. *J Clin Psychiatry.* 2015;76(12):1635-1641. 4. Zajecka JM et al. *J Clin Psychiatry.* 2016;77(5):654-660. 5. Shelton RC et al. *Prim Care Companion CNS Disord.* 2013;15(4):doi:10.4088/PCC.13m01520.

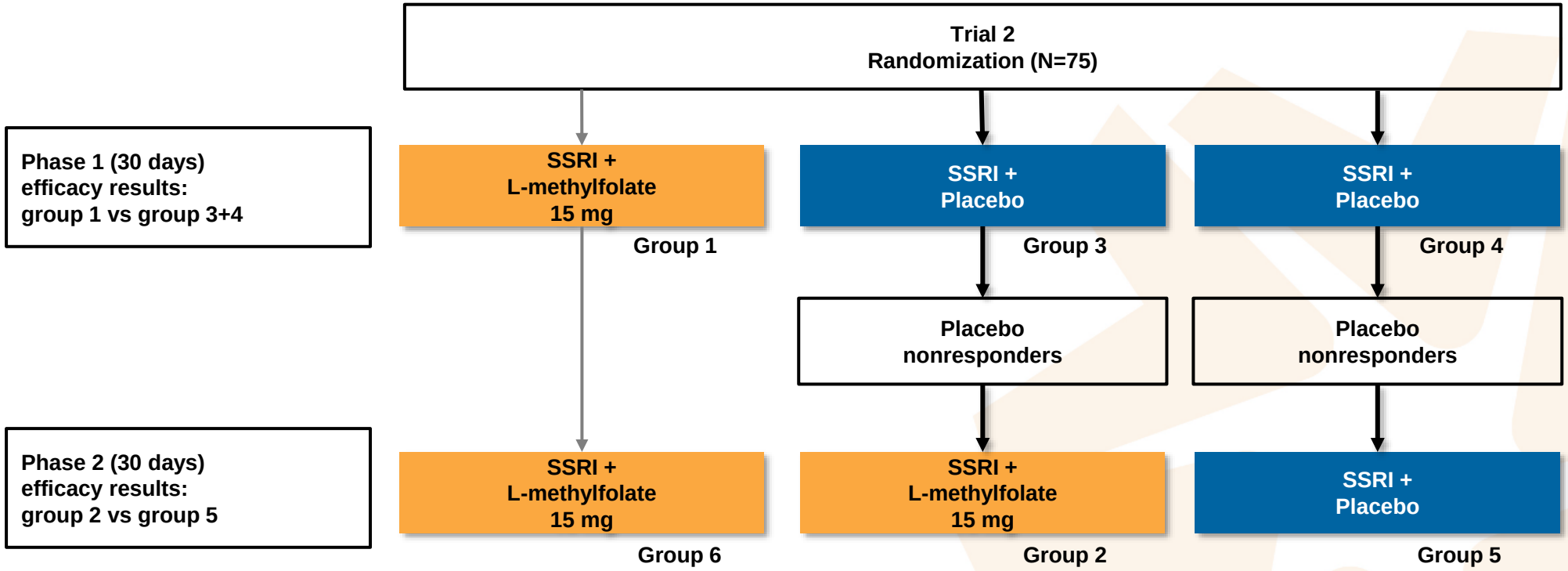
Two High Quality Studies Examined LMF in MDD

Patient Selection

- Adults aged 18-65 years and meeting DSM-IV criteria for a current episode of MDD
- QIDS-SR ≥12 at screening and baseline visits
- SSRI given current episode for ≥8 weeks at adequate doses
- Must have been on a stable SSRI dose for the past 4 weeks
- Excluded if failed >2 adequate antidepressant trials during current episode Study Design
- Multi-center, randomized, double-blind study
- Two 30-day treatment phases using a sequential parallel comparison design (SPCD)
- Markers were evaluated as moderators of L-methylfolate response on HDRS-28 :
  - Plasma L-methylfolate levels > or < the median for the study population
  - Plasma Hcy levels > or < the median for the study population
  - BMI ≥30 kg/m^2 or <30 kg/m^2
  - SAM/SAH ratio (methylation)
  - CRP (inflammation)
  - 4HNE (oxidative stress)
  - Whole blood MTHFR C677T and MTR A2756G genotypes

Papakostas G, et al. *Am J Psychiatry*. 2012;69(12):267-1274.

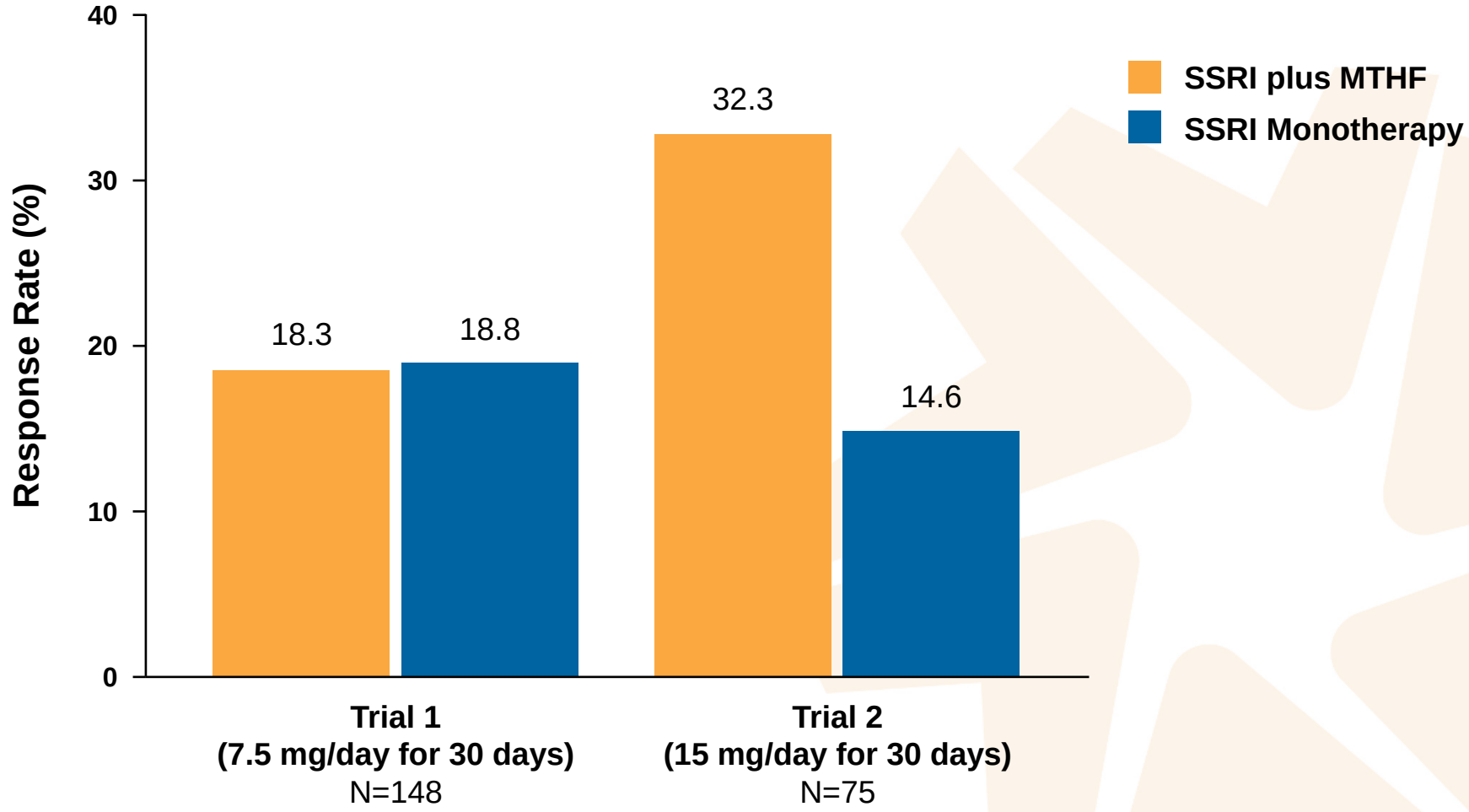
Sequential Parallel Comparison Design Trial 2: Adjunctive 15 mg L-methylfolate



Pooled (combined and averaged) efficacy results: 30-day results from groups 1+2 vs 30-day results from groups 3+4+5. Group 6 not included in efficacy results analyses. SSRI doses remained constant.

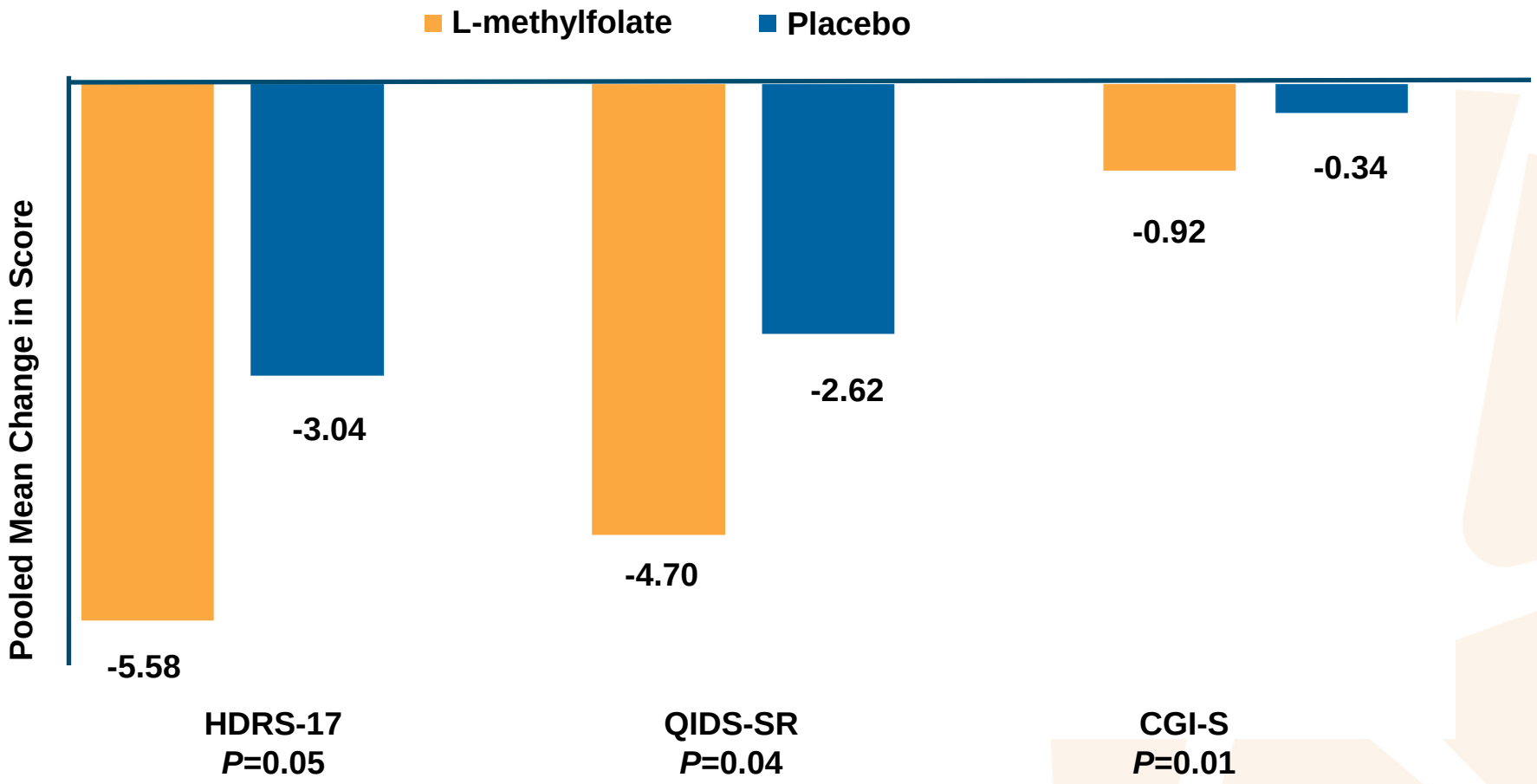
Papakostas G, et al. *Am J Psychiatry*. 2012;69(12):267-1274.

LMF and Treatment Resistant Depression TRD: Results from Two Well Conducted Trials



Papakostas G et al. *Am J Psych*. 2012. 169(12):1267-1274

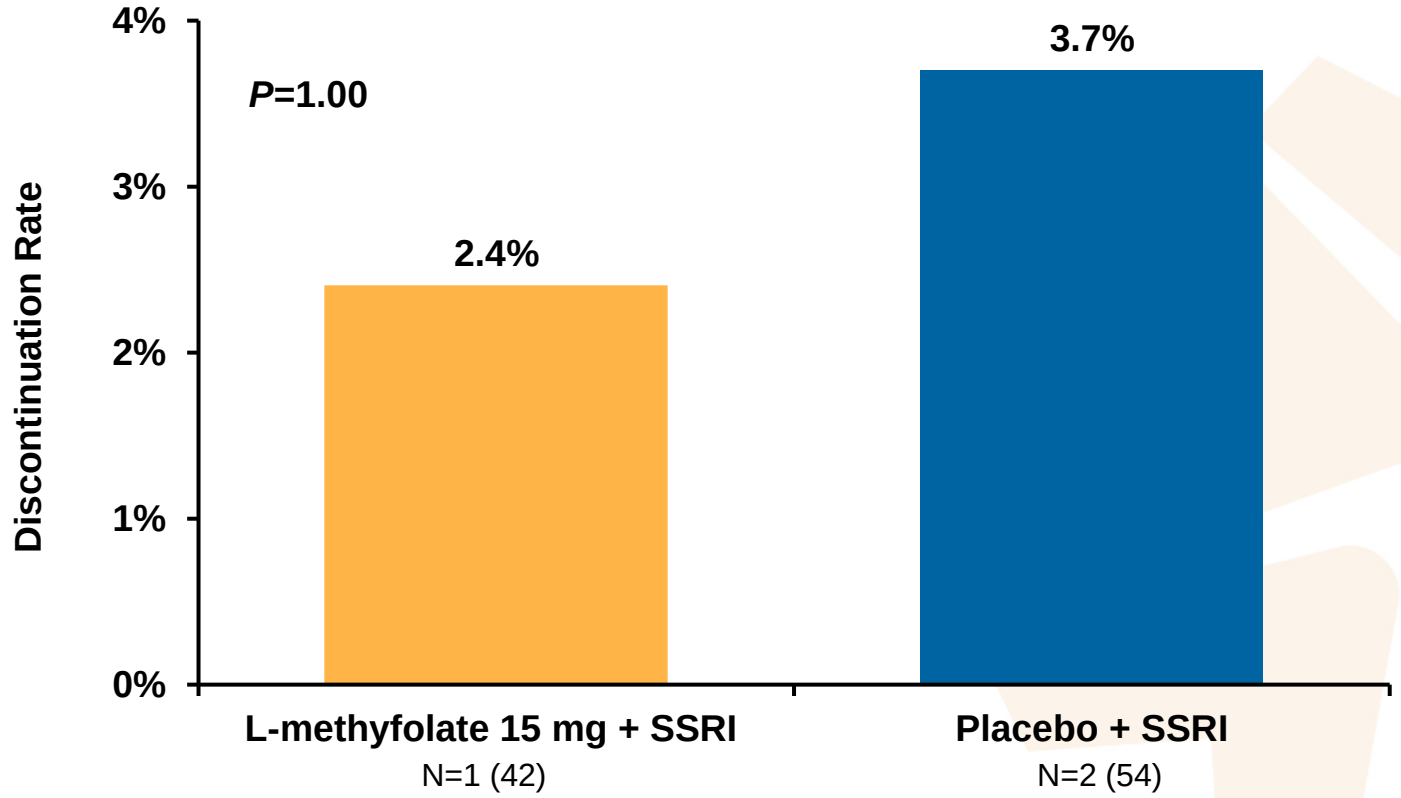
Adjunctive 15 mg L-methylfolate Pooled Mean Score Reduction – 30 Days



HDRS = Hamilton Depressive Rate Scale.
QIDS = Quick Inventory of Depressive Symptomatology.
CGI = Clinical Global Impression.
Papakostas G, et al. *Am J Psychiatry*. 2012;69(12):267-1274.

Adjunctive 15 mg L-methylfolate Tolerability

No Difference in Discontinuation Due to Adverse Events



n=75: Phase I & 2 L-methylfolate 19; Placebo Phase 1=28; Placebo Phase 2=28

Papakostas G, et al. (2011, March). Poster Presentation at European Psychiatric Association, Vienna, Austria

L-methyfolate Adverse Event

Adverse Event	Placebo[a] (n=54)	L-methylfolate 15 mg/day[a] (n=42)
Gastrointestinal	8 (14.8)	7 (16.7)
Sleep	3 (5.5)	1 (2.4)
Psychological	9 (16.7)	4 (9.5)
Somatic	16 (29.6)	6 (14.3)
Infectious	7 (13.0)	5 (11.9)
Cardiovascular	0 (0)	0 (0)
Sexual	0 (0)	1 (2.4)
Miscellaneous	5 (9.3)	1 (2.4)

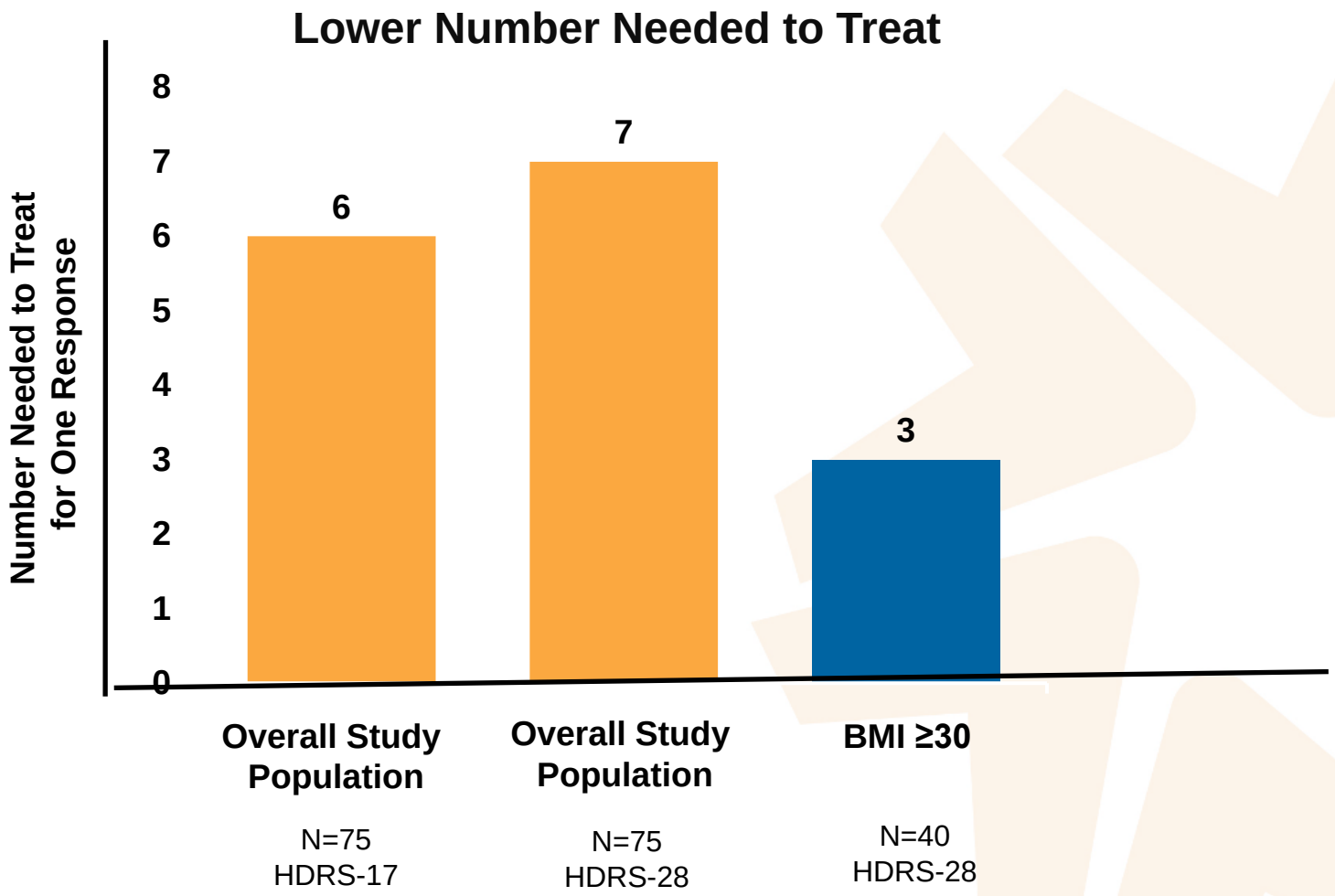
Data are n (%)
[a] Ns are based on the total numbers of patients who received placebo or 15 mg of L-methylfolate, respectively, at some point during the trial.
Jain R, et al. Good, better, best: clinical scenarios for the use of L-methylfolate in patients with MDD. *CNS Spectrums*. https://doi.org/10.1017/S1092852919001469

Adverse Events from these Two MDD Studies – LMF Appears to Be Well Tolerated

Side Effect Category	Placebo (N=112) [a]		MTHF 7.5 mg/day (N=94)[a]		MTHF 15 mg/day (N=30)[a]		*P*
	N	%	N	%	N	%	
Gastrointestinal	23	20.1	9	9.6	3	10.0	.06
Sleep	12	10.7	3	3.2	2	6.7	.11
Psychological	12	10.7	3	3.2	2	6.7	.05
Somatic	22	19.6	9	9.6	3	10.0	.09
Infectious	13	11.6	6	6.4	2	6.7	.38
Cardiovascular	4	3.6	0	0.0	2	6.7	.08
Sexual	0	0.0	0	0.0	0	0.0	.99
Miscellaneous	3	2.7	1	1.1	2	6.7	.24

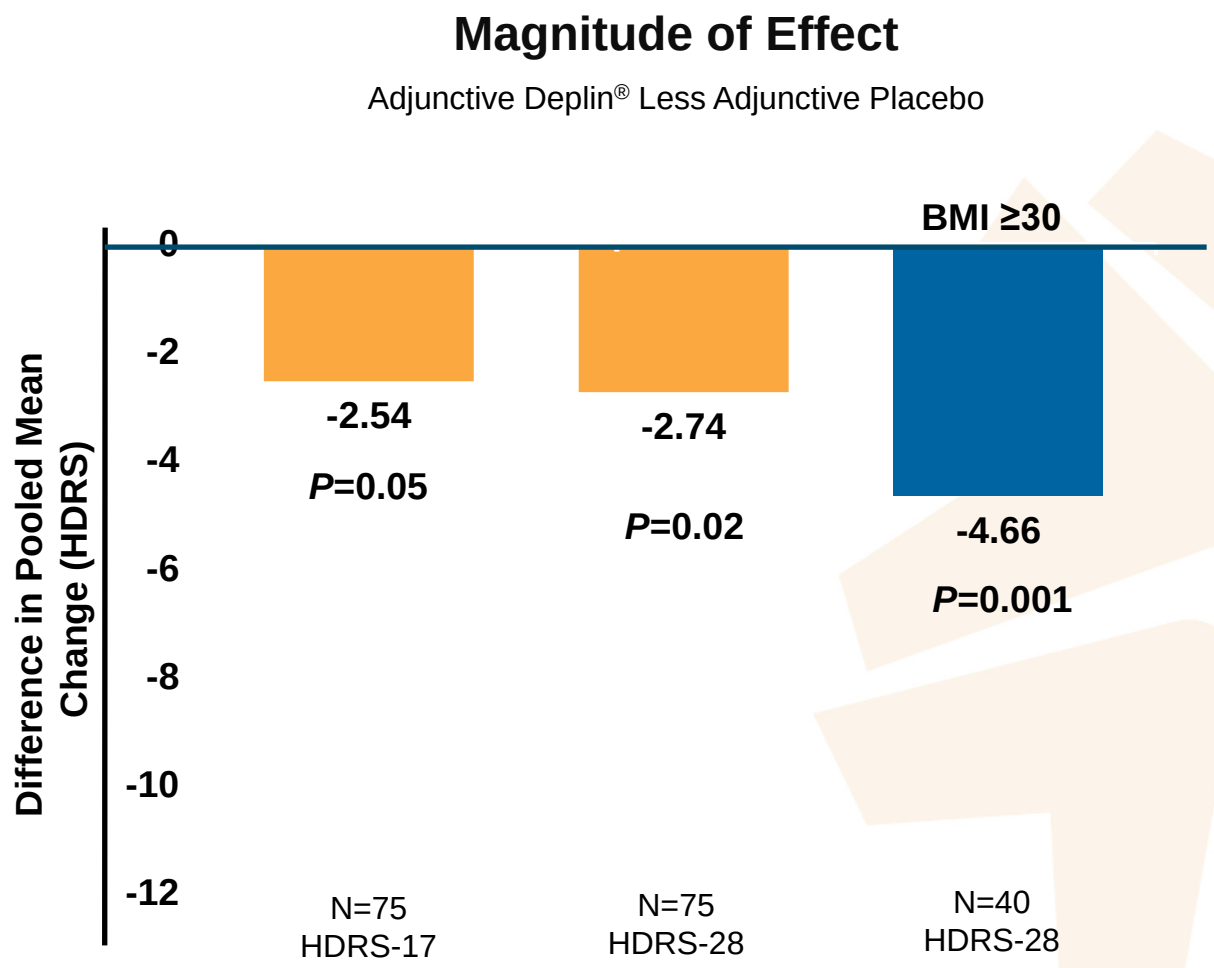
Papakostas G et al. *Am J Psych*. 2012. 169(12):1267-1274.

Number Needed to Treat for Response Adjunctive LMF in MDD



Papakostas G, et al. *Am J Psychiatry*, 2012;169(12):1267-74.

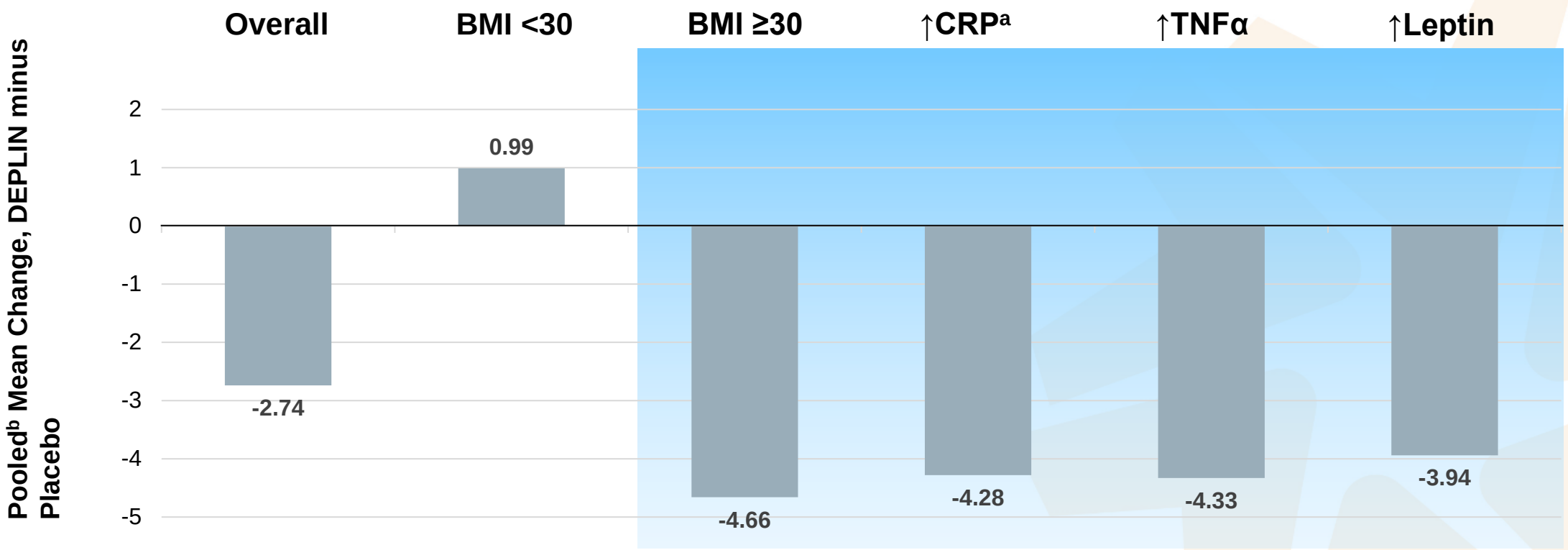
Baseline Mean Change Treatment Effect Stratified by BMI ≥30 Compared to General Study Population



Papakostas G, et al. *Am J Psychiatry*, 2012;169(12):1267-74.

LMF & MDD: Inflammation and Obesity-Related Factors

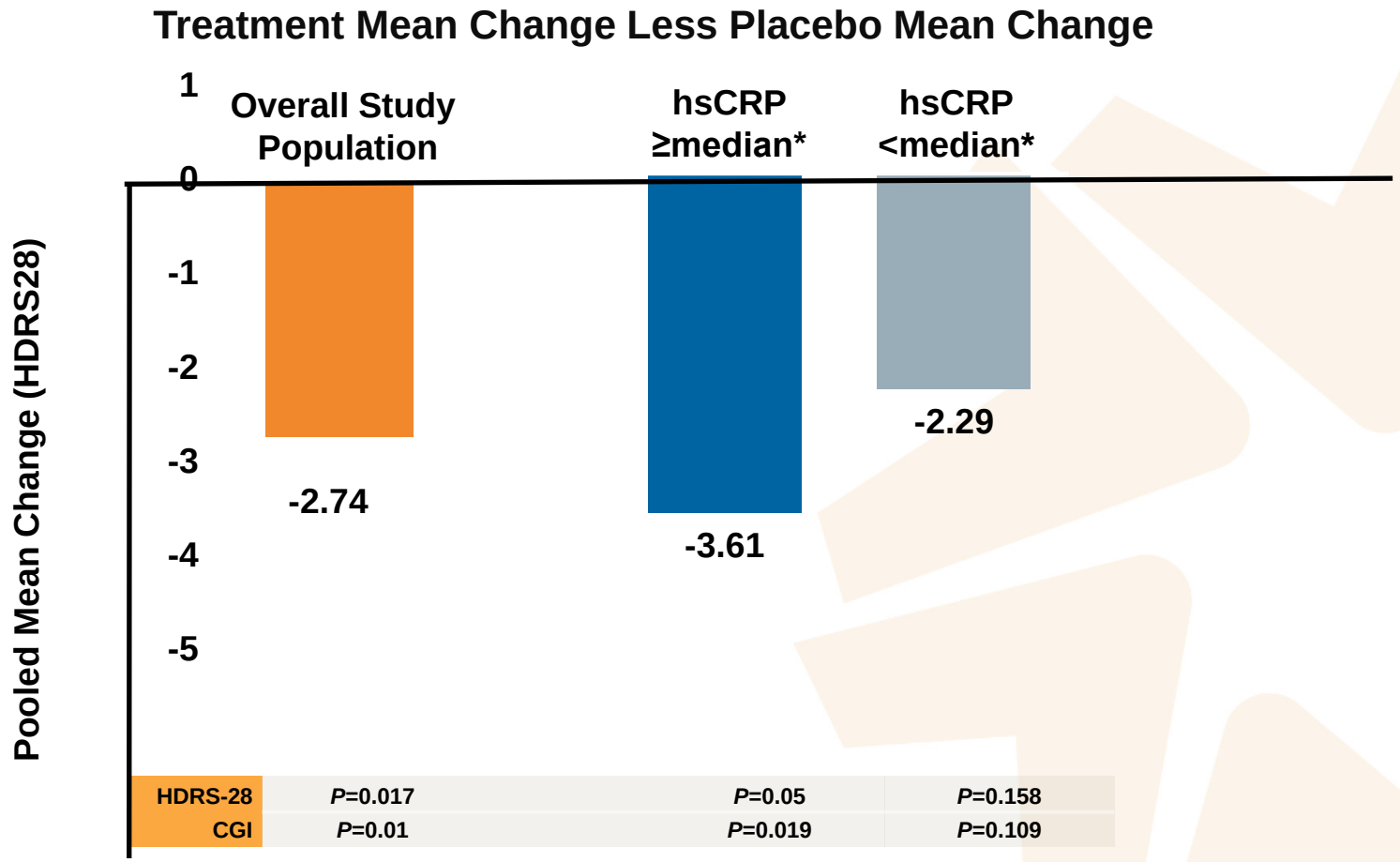
Post Hoc Analysis: DEPLIN 15 mg/d vs Placebo on Pooled Mean Change From Baseline for HAM-D17 Stratified by Inflammatory Biomarkers and Obesity (N=69)



[a]hsCRP levels above the median value of (log) 5.01 were considered to be associated with systemic inflammation. [b]Pooled across study groups from 2 randomized clinical trials. BMI=body mass index; CRP=C-reactive protein; HAM-D17=Hamilton Depression Rating Scale-17 item; hsCRP=high-sensitivity C-reactive protein; TNFα=tumor necrosis factor alpha.

Shelton RC et al. *J Clin Psychiatry*. 2015;76(12):1635-1641.

Baseline Mean Change Treatment Effect Stratified by hsCRP



*median = 2.25 mg/L

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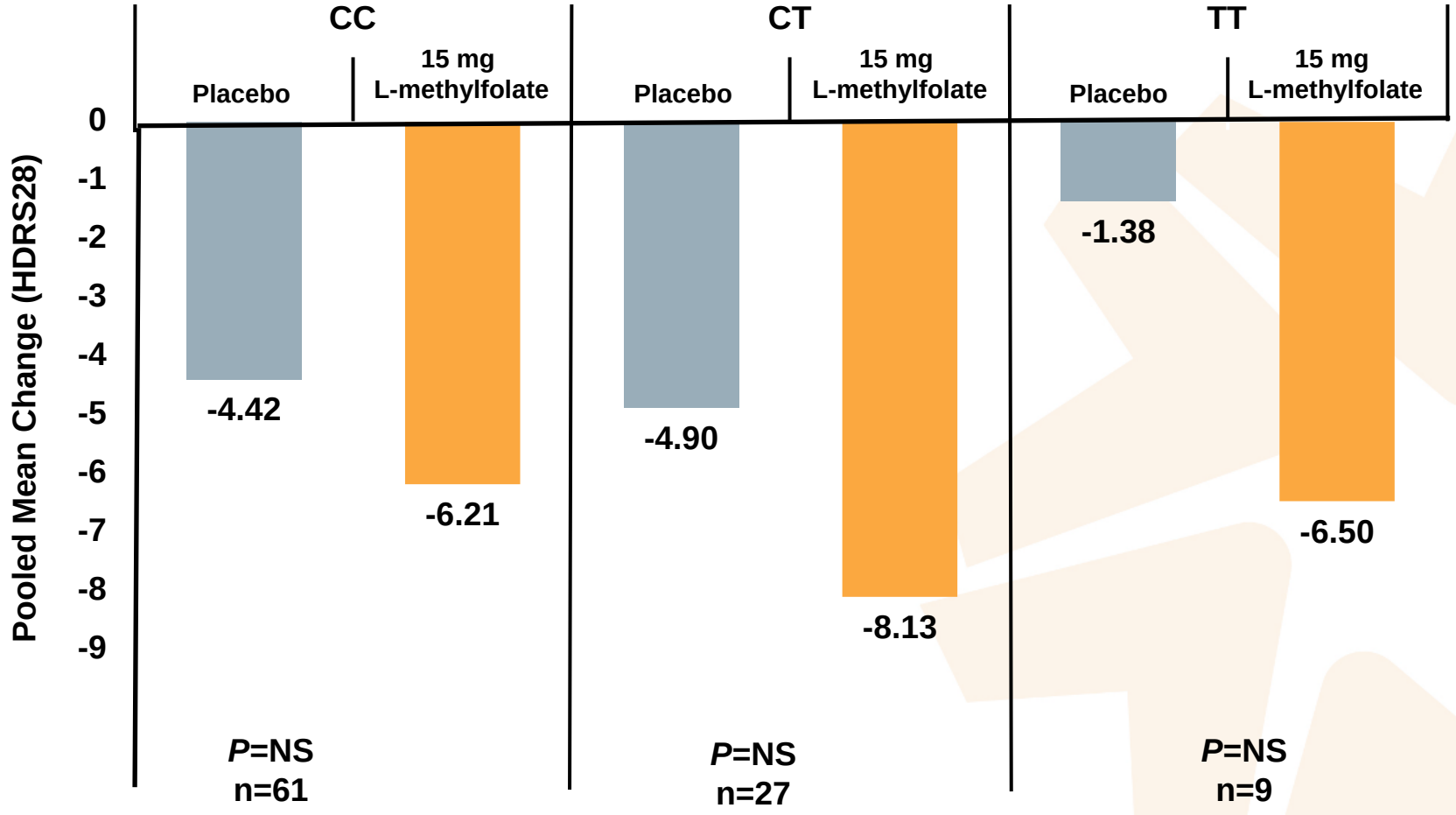
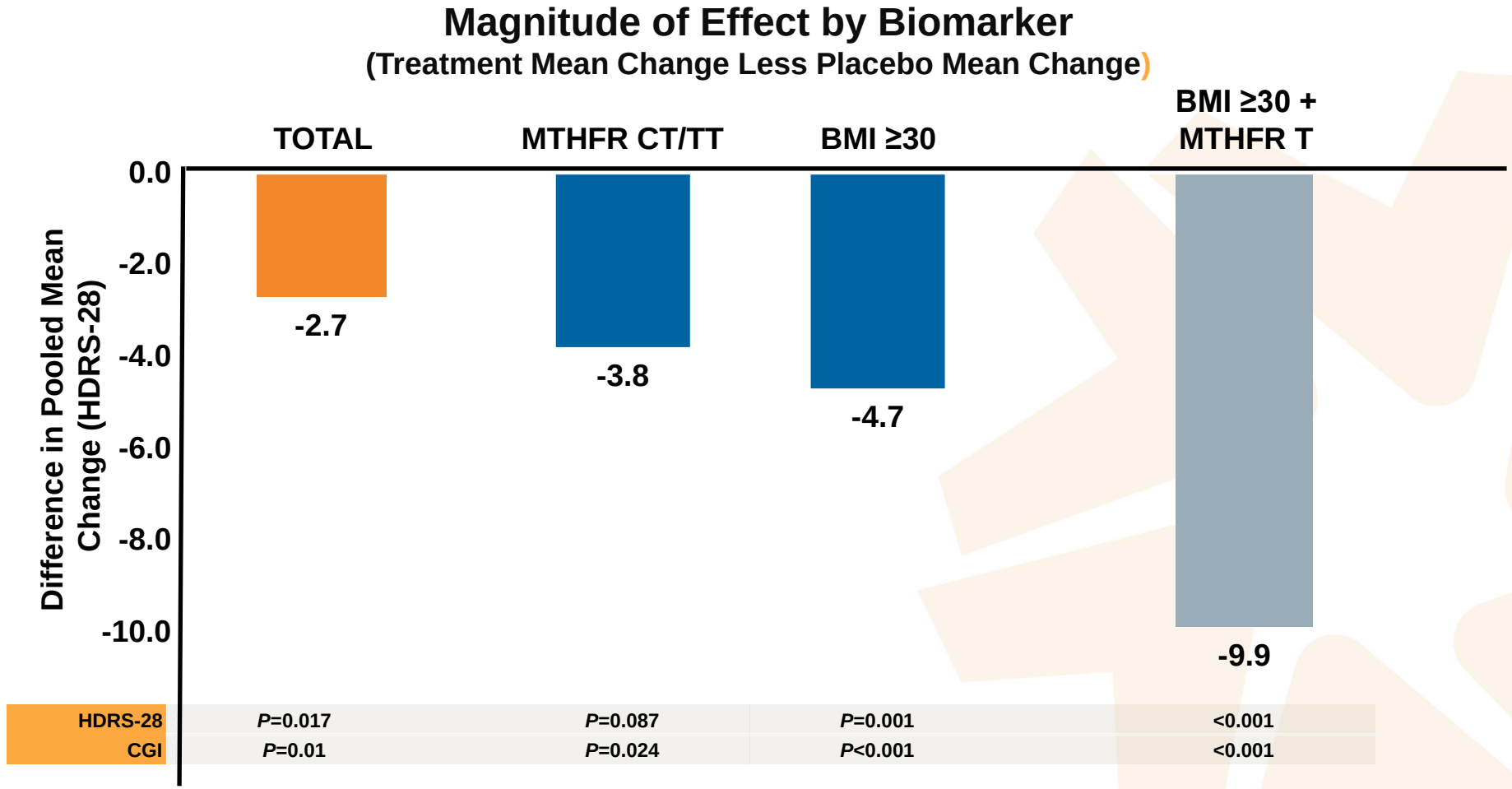
Raison C., et al. (2013, October) Poster Presented at the 26th Annual U.S. Psychiatric and Mental Health Congress. Las Vegas, NV

Treatment Effect by MTHFR Genotype Augmentation of SSRIs



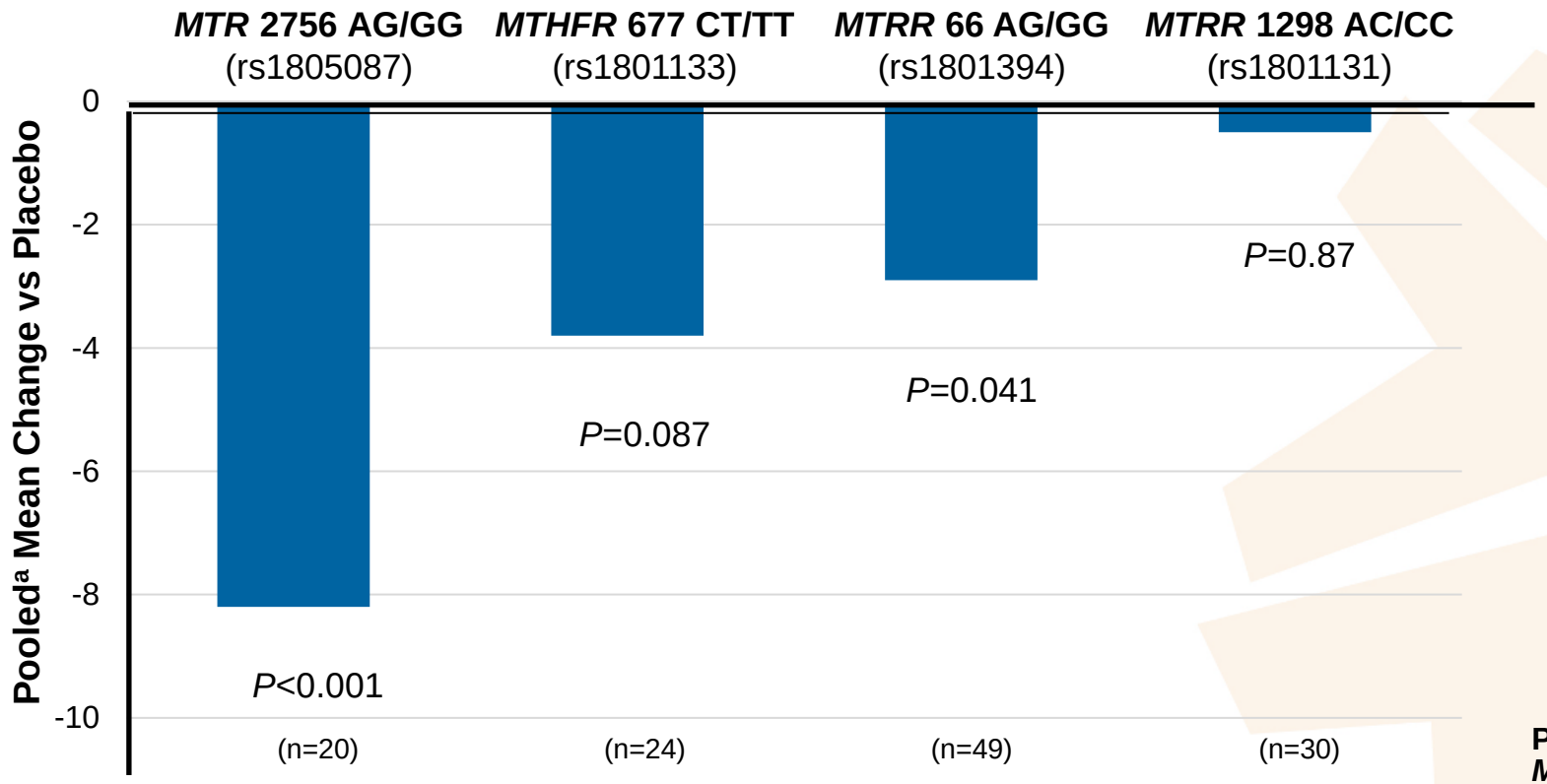
Papakostas G, et al. Poster presented at the Society for Biological Psychiatry Annual Meeting, May 3, 2012, Philadelphia, PA.

Synergistic Effect of MTHFR & BMI
Adjunctive 15 mg L-methylfolate vs Adjunctive Placebo



Papakostas G., et al. Poster presented at the American Psychiatric Association Annual Meeting, May 8, 2012, Philadelphia, PA.

Genetic Variants in MDD and LMF Augmentation



[a]Change from baseline on HAM-D28. All *P* values vs placebo.
HAM-D28=Hamilton Depression Rating Scale-28 item.

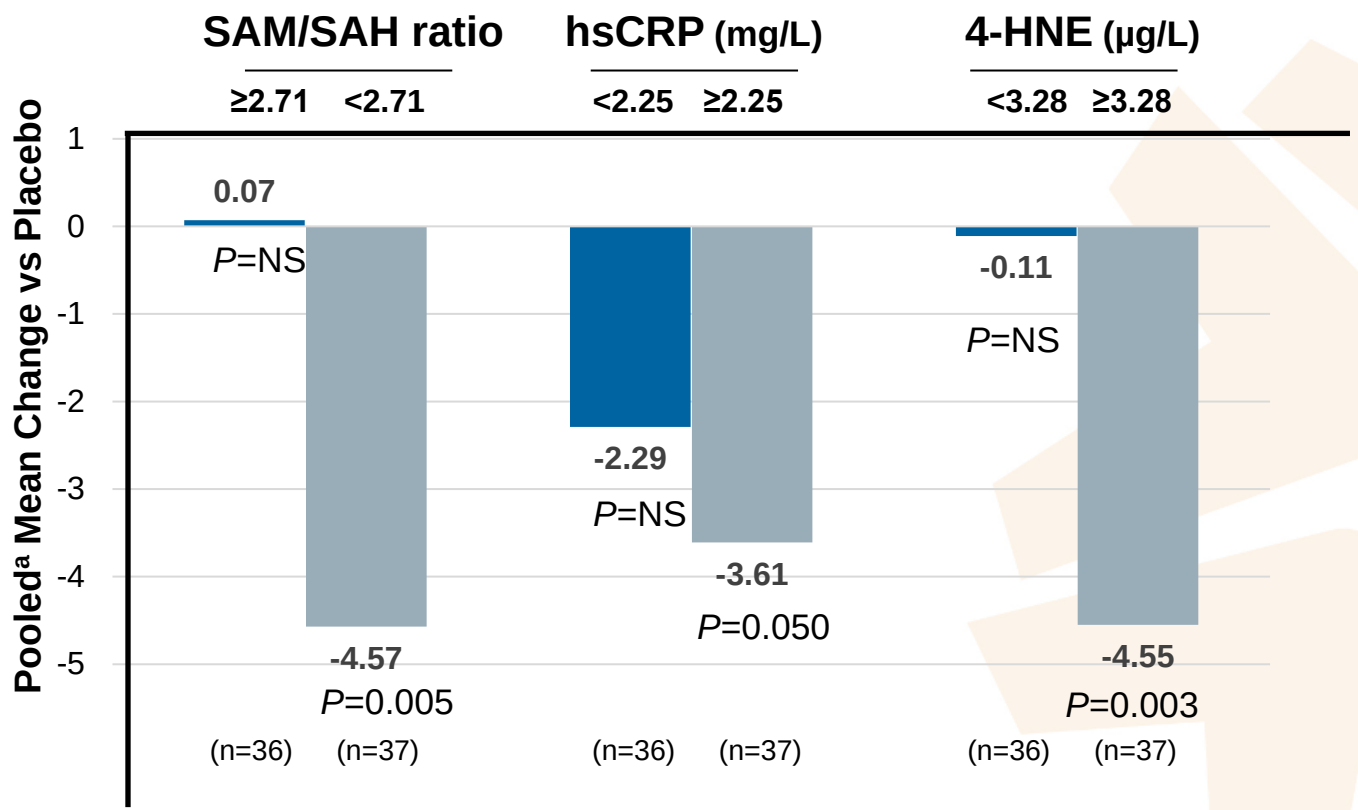
Post Hoc Analysis: LMF 15 mg/d vs Placebo on Pooled Mean Change From Baseline for HAM-D28 Stratified by Select Genetic Markers

Patients with the *MTR* 2756 AG/GG or the *MTRR* 66 AG/GG genotypes demonstrated a significantly greater response in HAM-D28

The *MTHFR* 677 CT/TT and *MTHFR* 1298 AC/CC genotypes was not associated with a statistically significant difference compared with controls

Papakostas GI et al. *J Clin Psychiatry*. 2014;75(8):855-863.

Biomarkers Associated with Inflammation Predict Positive Response to LMF



Post Hoc Analysis: DEPLIN 15 mg/d vs Placebo on Pooled Mean Change From Baseline for HAM-D28 Stratified by Baseline Level of Plasma Marker

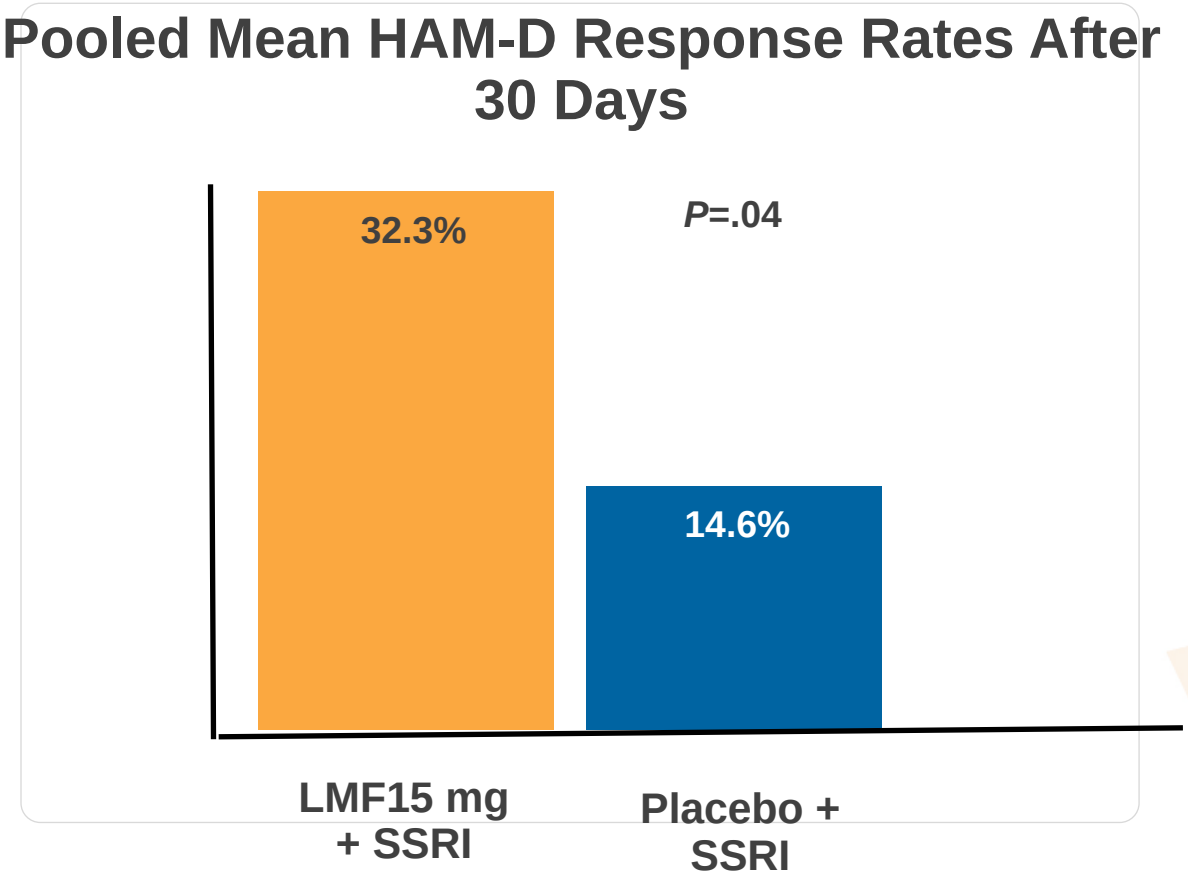
Patients with increased levels of inflammatory markers demonstrated significantly greater response in HAM-D28

[a]Pooled across study phases with equal weights.

4-HNE=4-hydroxy-2-nonenal; HAM-D28=Hamilton Depression Rating Scale-28 item; hsCRP=high-sensitvity C-reactive protein; NS=not significant; SAH=S-adenosylhomocysteine; SAM=S-adenosylmethionine.

Papakostas GI et al. *J Clin Psychiatry*. 2014;75(8):855-863.

LMF Augmentation for SSRI-Resistant MDD Significantly Improved Treatment Response Rates



HAM-D = Hamilton Depression Rating Scale

2X THE RESPONSE

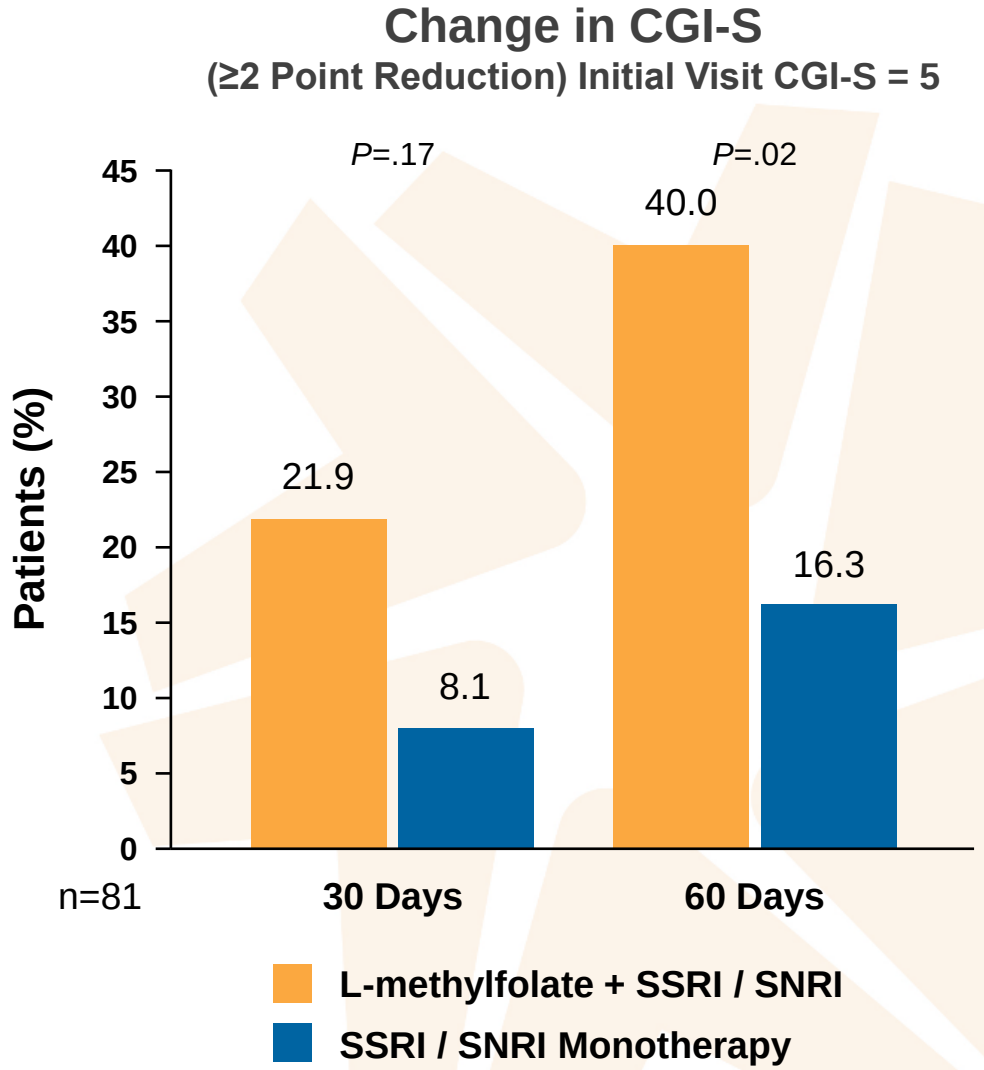
Papakostas GI et al. *Am J Psychiatry*. 2012;169(12):1267-1274.

’Real Life’ Data on LMF: A Retrospective Study Reveals Significant Positive Effect of LMF

A retrospective analysis of L-methylfolate plus SSRI/SNRI at treatment initiation (n=95) and SSRI/SNRI monotherapy (n=147) from patient charts.

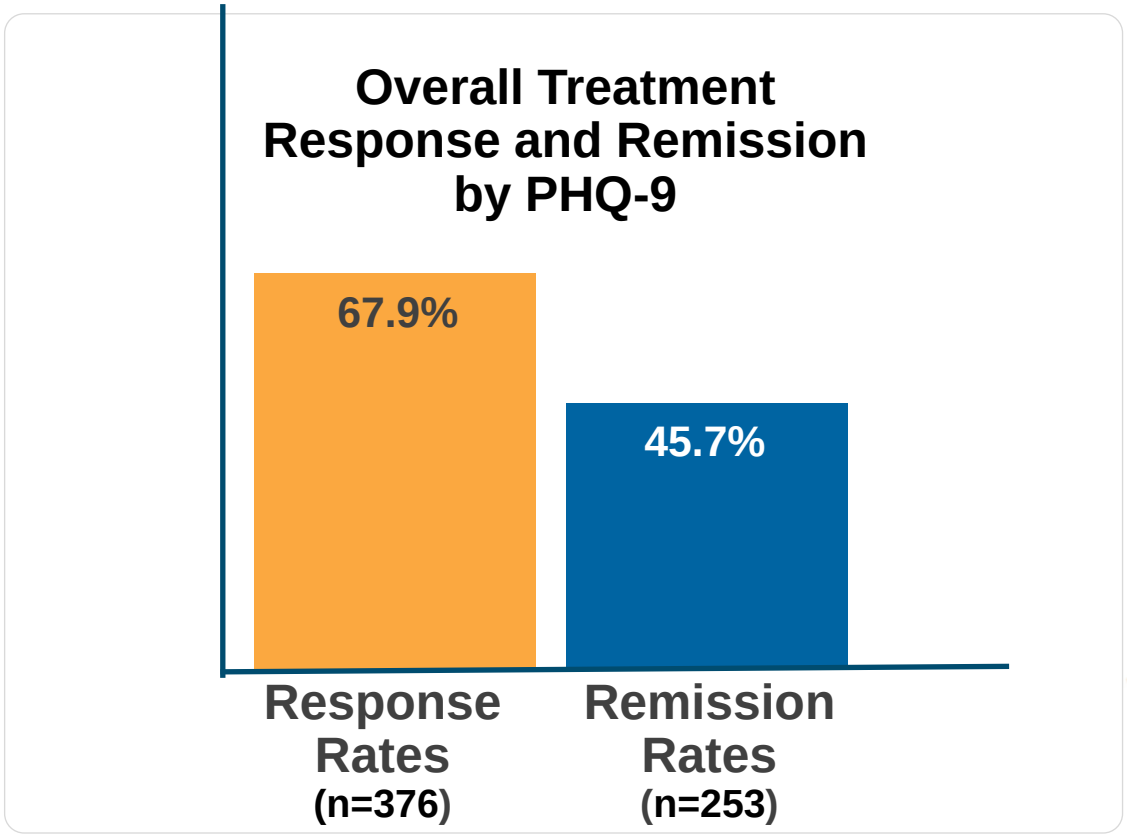
Setting: Outpatient, private psychiatric clinic/practice.

Participants: Adults 18 to 70 with major depressive episode (single or recurrent).



Ginsburg LD et al. *Innov Clin Neurosci*. 2011;8(1):19–28.

L-methylfolate was Shown to Improve Response and Remission Rates in a 12-Week Real-world Study



Patient compliance was very high:

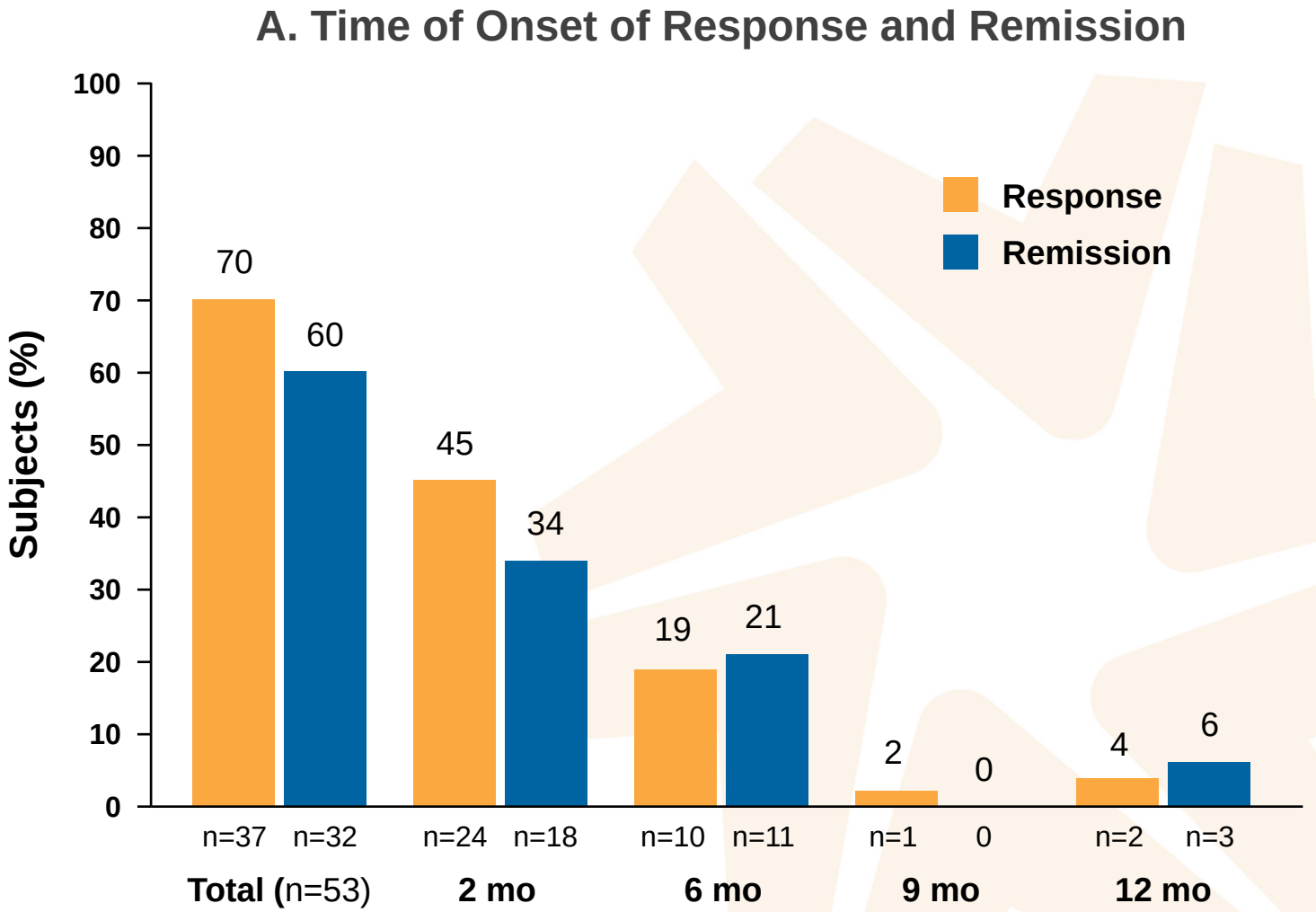
>90%

of patients reported on LMF

Shelton RC et al. *Prim Care Companion CNS Disord*. 2013;15(4):1-9.

Does LMF Have Long Term Benefit?
1 Year Open Label Study Looks Promising

- 12 month open label study (n=68)
- L methylfolate 15 mg was added to SSRI and SNRI



Zajecka JM ,et al. *J Clin Psychiatry*. 2016.77(5):654-660.

L-Methylfolate with SSRI Shows Significant and Long-term Response and Remission Rates

Patients achieve response

92%

of patients achieved response within the first 3 to 6 months of the long-term maintenance phase

Patients achieve remission

75%

of patients (3 of 4) met the remission criteria,

REMISSION

was achieved within 3 to 6 months

60%

of patients who failed to show a response at the end of acute therapy achieved remission during the long-term maintenance phase of the trial

Patients achieve relapse and recurrence

91%

of patients (10 of 11) met the recovery criteria, having ≥6 months of remission from the start of the open-label phase

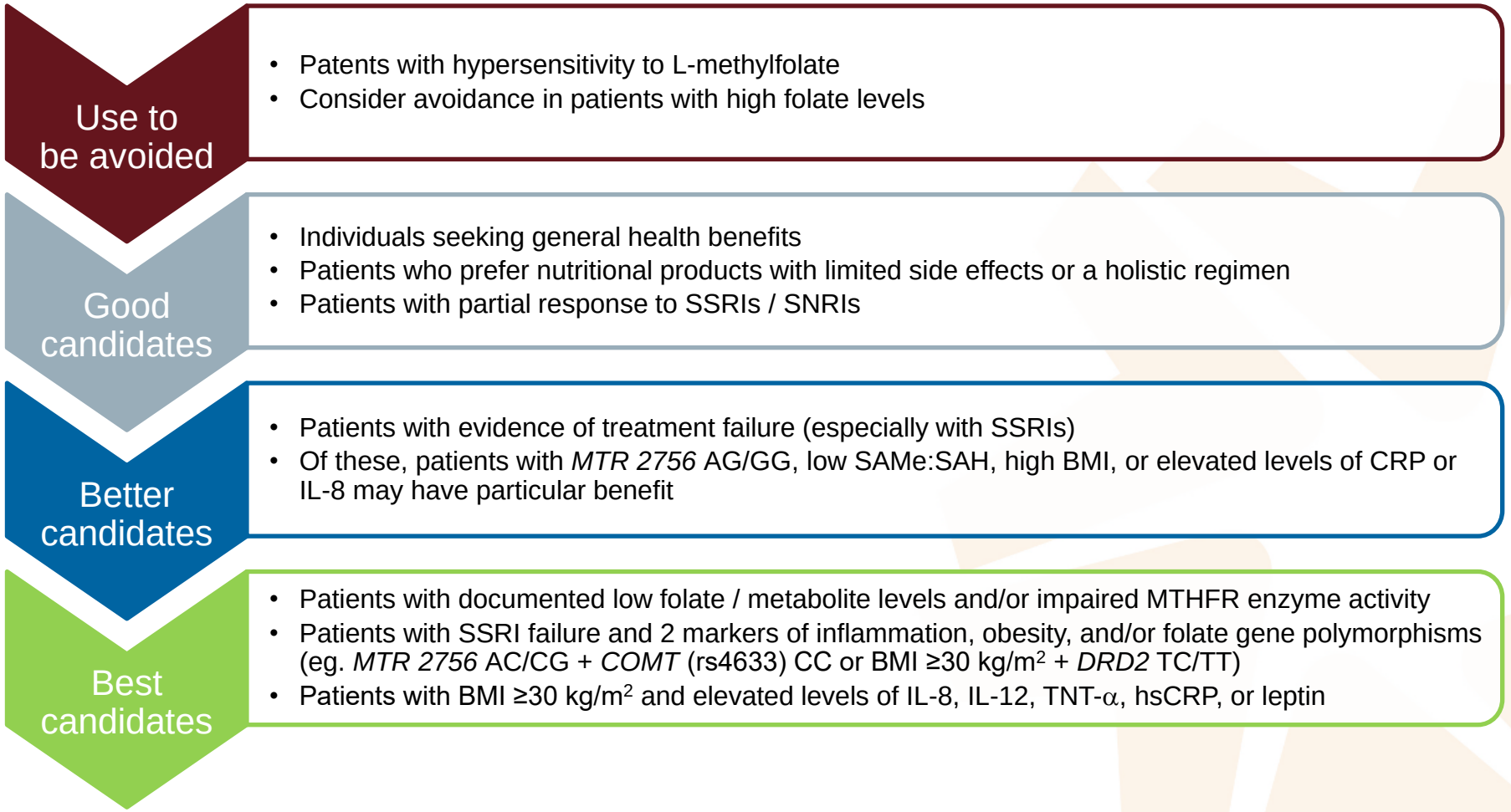
NONE

of these patients experienced a relapse or recurrence

Zajecka JM et al. *J Clin Psychiatry*. **2016;77(5):654-660.**

In Summary

Good, Better, Best Clinical Situations for Potential Use of LMF



Jain R, et al. Good, better, best: clinical scenarios for the use of L-methylfolate in patients with MDD. *CNS Spectrums.* https://doi.org/10.1017/S1092852919001469

Questions?