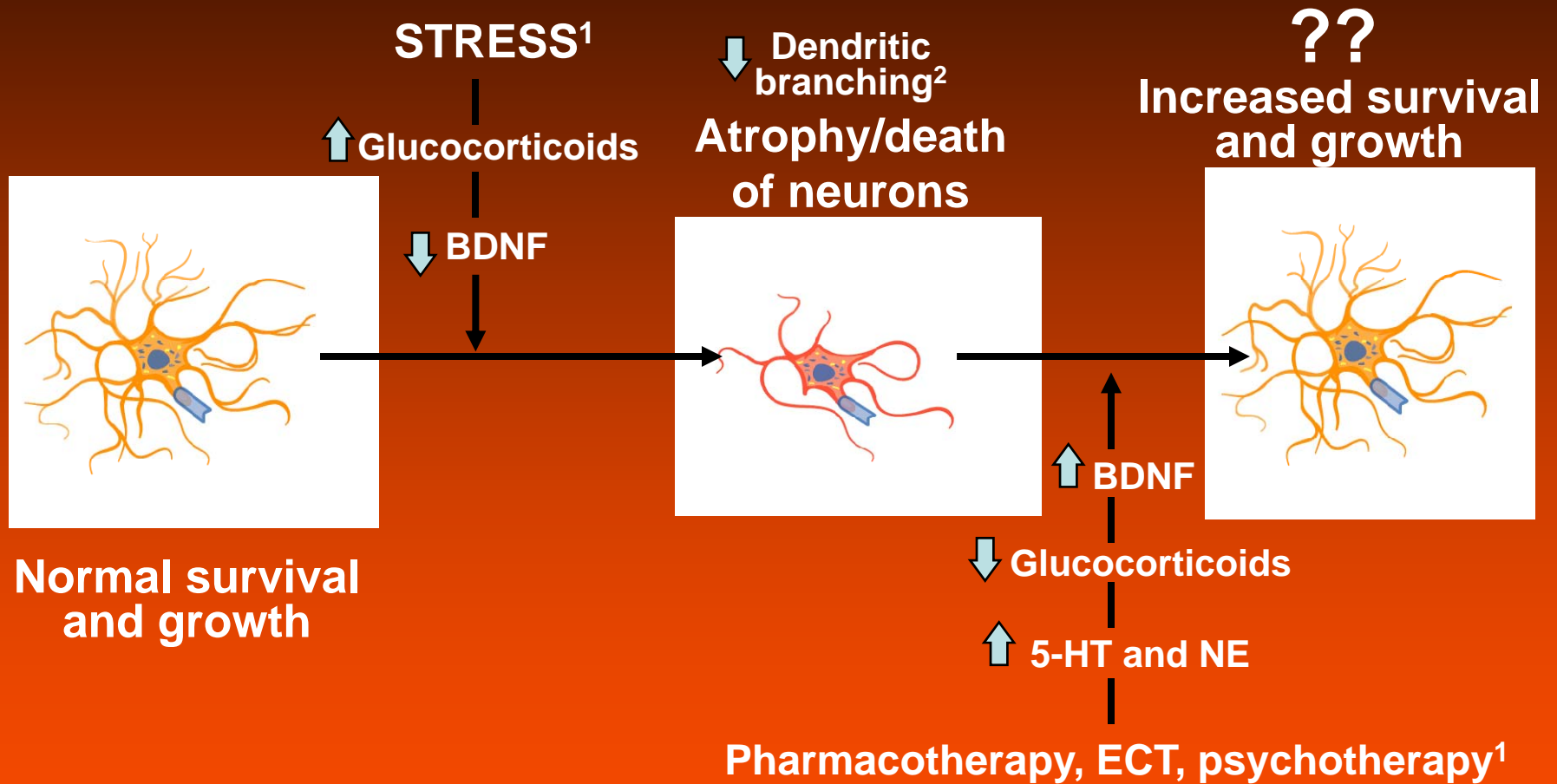


Welcome

**Evidence for Trimonoamine Modulator as
an Antidepressant Augmentation Agent**

“Major depression is among the most ‘treatable’ illnesses in medicine, but continues to have the highest morbidity and mortality.”

Can Treatment Prevent or Reverse the Damage?



5-HT=serotonin; NE=norepinephrine; ECT=electroconvulsive therapy.

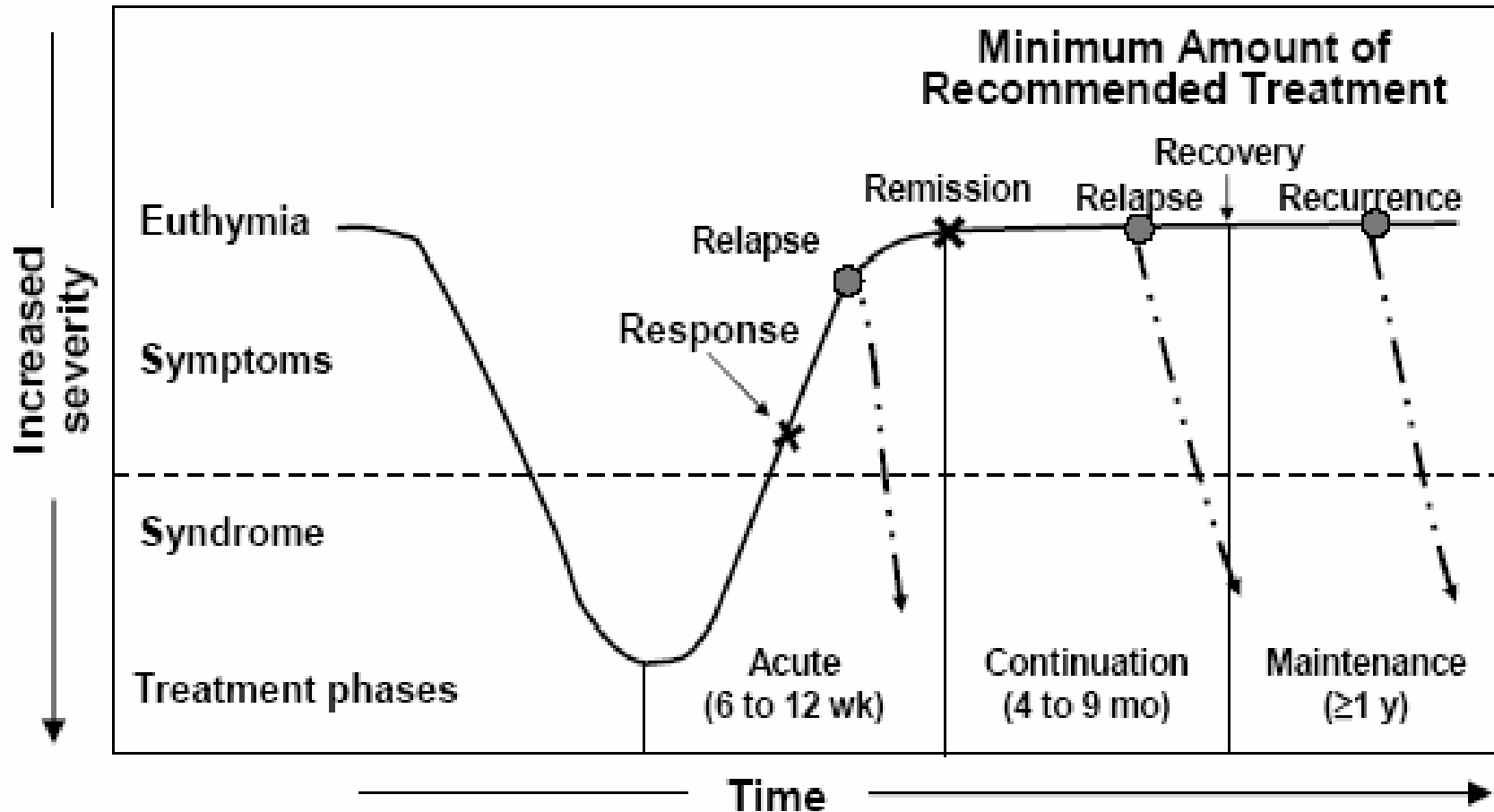
1. Duman RS, et al. Neuronal plasticity and survival in mood disorders. *Biol Psychiatry*. 2000;48(8):732-739.

2. Sapolsky RM. Glucocorticoids and Hippocampal Atrophy in Neuropsychiatric Disorders *Arch Gen Psychiatry*. 2000;57(10):925-935.

The Importance of Achieving Remission

- Similar to any other medical illness, depression should be treated to full remission and ultimately to recovery.
- Remission has now become the standard of care in treating depression.

Phases of Treatment for Depression



Risks Associated with Failure to Achieve and Sustain Remission

- Greater risk of relapse/recurrence ¹⁻³
- More chronic depressive episodes ¹
- Shorter durations between episodes ¹
- Continued impairment in work and relationships ⁴
- Increased association with mortality,⁵ morbidity and/or mortality with stroke,⁶ diabetes complications,^{7,8} MI,⁹ CVD,¹⁰ CHF¹¹ and HIV¹²
- Ongoing risk of suicide ¹³

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2. Paykel ES et al. Psychol Med 1995;25:1171-1180.

3. Thase ME et al. Am J Psychiatry. 1992;149:1046-1052.

4. Miller IW et al. J Clin Psychiatry. 1998;59:608-619.

5. Murphy JM et al. Arch Gen Psychiatry. 1987;44:473-480.

6. Everson SA et al. Arch Intern Med. 1998;158:1133-1138.

7. Lustman PJ et al. Diabetes Care. 2000;23:934-942.

8. De Groot M et al. Psychosom Med. 2001;63:619-630.

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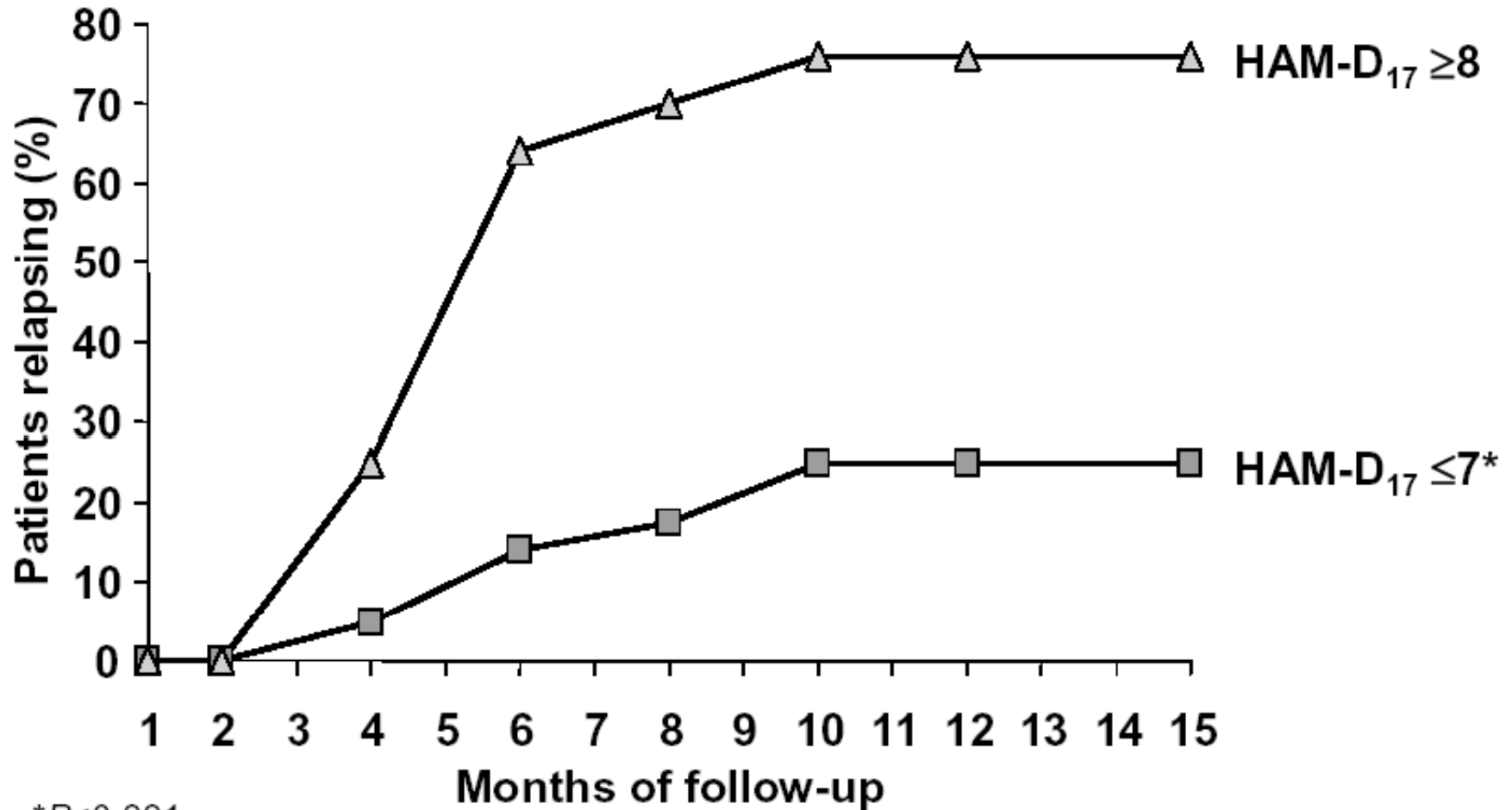
10. Penninx BWJH et al. Arch Gen Psychiatry. 2001;58:221-227.

11. Vaccarino V et al. J Am Coll Cardiol. 2001;38(1):199-205.

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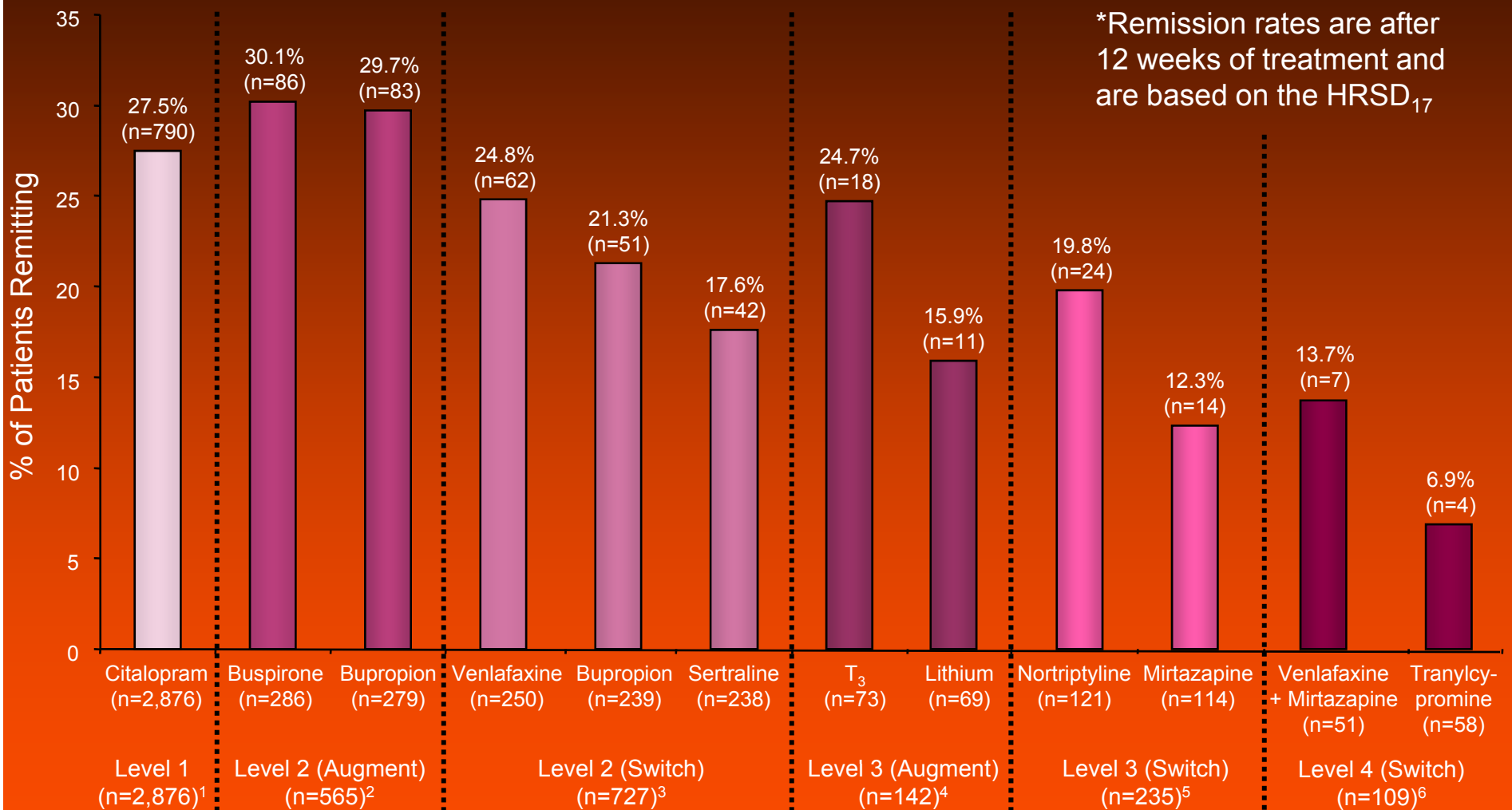
13. Judd LL et al. J Affect Disord. 1997;45:5-18.

Full Remission Decreases Risk of Relapse



* $P < 0.001$

STAR*D Results Demonstrate Diminishing Effectiveness of TRD Treatments



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

2. Trivedi MH, et al. *N Engl J Med* 2006;354(12):1243-1252.

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4. Nierenberg AA, et al. *Am J Psychiatry* 2006;163(9):1519-1530.

5. Fava M, et al. *Am J Psychiatry* 2006;163(7):1161-1172.

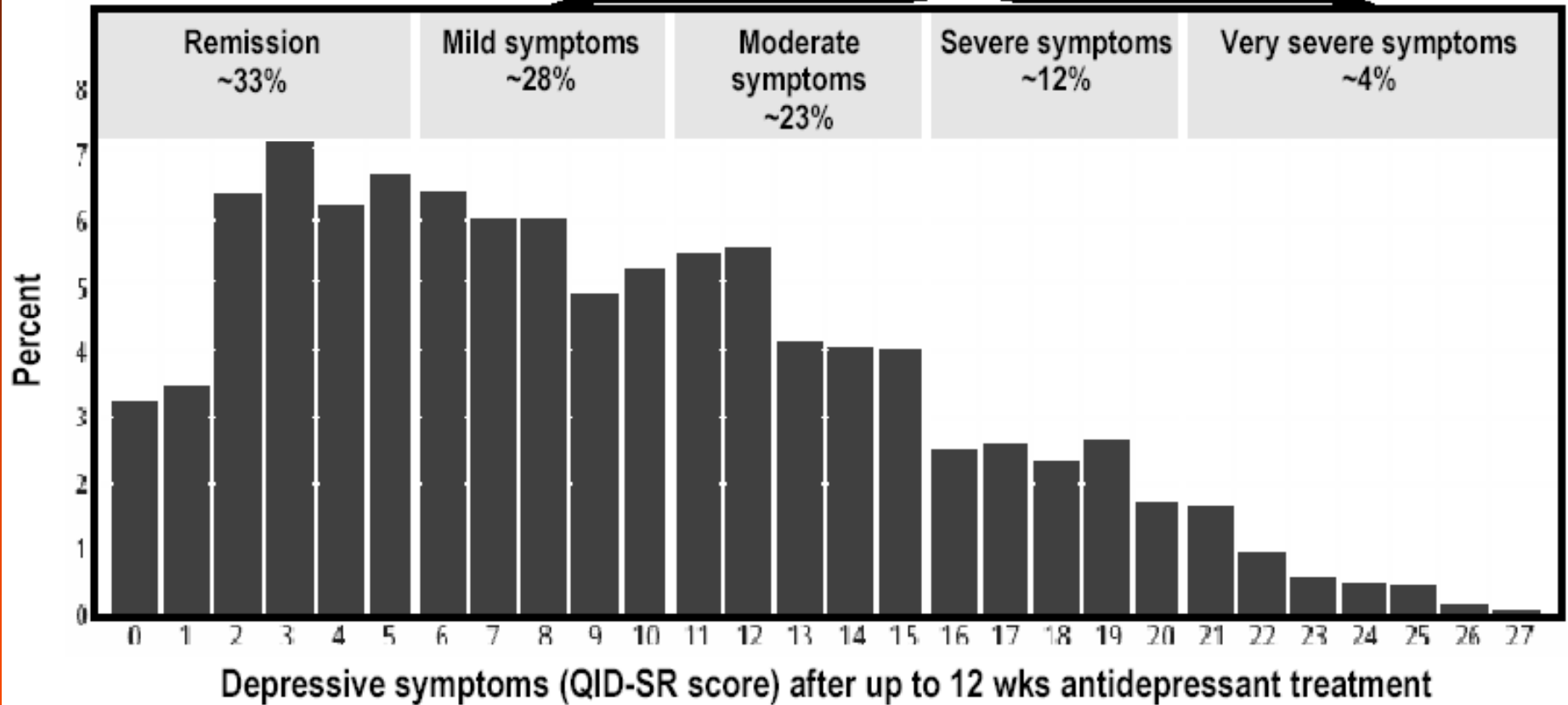
6. McGrath PJ, et al. *Am J Psychiatry* 2006;163(9):1531-1541.

Unresolved Symptoms of Depression

More than 2/3 of patients had unresolved symptoms

67%

STAR*D Study (N=2876)



Remission should be the “standard of care” in every patient with depression

- Clinical trials may not always represent “real world” patients with MDD (e.g. comorbidity).
- Look for “modifiable factors” that may improve outcomes in all stages of treatment (e.g. “new” diagnoses, drug interactions, folate deficiency, adherence, SUDs).
- Keep expectations reasonable.
- Ask patient to identify “target symptoms” or a “wish list.”
 - all stages of treatment
 - can uncover significant “residual symptoms” when patient looks/feels better
 - “when was the last time you belly-laughed?”

The Ideal Treatment for MDD: Broad-Spectrum Approach

- Optimize effect on all potential biological systems early in treatment.
 - Trimonoamine modulation (5HT, NE, DA)
 - selective serotonin increase → compensatory decrease of NE and DA → fatigue, amotivation, blunted affect, cognitive impairment, sexual side effects, or “tachyphylaxis”
 - use broad-spectrum AD early
 - augmentation over switching
 - consider possible role of folate-related dysfunction on 5HT, NE, DA (from genetic polymorphism, illness, medication)
 - Consider other neurotransmitter/modulator dysfunction (glutamate, GABA, HPA axis)
- Consider psychotherapeutic interventions.

Differential Diagnosis

- Neurological disorders
- Endocrine disorders
- Other medical illness
- Medications
- Other psychiatric illness

Risk Factors Associated with Low Folate

- Genetic polymorphism MTHFR C677T
 - 7 out of 10 depressed patients
 - 56% - C/T polymorphism
 - 4 X more likely to have depression than general population
 - 14% - T/T polymorphism
- Lifestyle
 - ETOH
 - smoking
 - poor nutrition
- Medications
 - anticonvulsants
 - oral contraceptives
 - lithium
 - fenofibrates, niacin
 - sulphasalazine
 - methotrexate
 - metformin
- Illness
 - diabetes
 - atrophic gastritis
 - Crohn's disease
 - hypothyroid
 - renal failure

Alpert M, et al. Jnl Clin Psychopharmacology. 2003;23(3):309-13.

Fava M, et al. Am J Psychiatry. 1997;154(3):426-28.

Popakostas G, et al. Psychiatry Research, 2005;140(3):301-7.

Bottiglieri T. Prog Neuro-Psychopharmacology & Biol Psychiatry. 2005; 29:1103-12.

Arinami T, et al. Am J Genetics. 1997;74:526-28.

Procopciuc L.M., Poster Pres. P86 presented at Biol Psych. 2005.

Bjelland I. et al. Arch Gen Psychiatry. 2003;60(6):618-26.

Kelly B J, et al. Psychopharmacol. 2004 ;18(4):567-71.

Association of Low Folate Levels with Depression

- Depressed patients with low RBC folate are 6 times more likely not to respond to antidepressant therapy and less likely to achieve remission.^{1,2}
- Low serum or low red blood cell folate levels have been reported in 15%-56% of depressed patients.^{3,4}
- The severity of a depressive episode, length of an episode, and later onset of clinical improvement are inversely correlated with RBC folate levels.⁵⁻⁸
- Depressed patients with low RBC folate are associated with impairment in the synthesis and release of monoamine neurotransmitters: serotonin, norepinephrine, and dopamine.⁵
- Higher folate levels in patients taking SSRIs and TCAs predicted a better response, but the trend was stronger with SSRIs.¹

1. Alpert M, et al. *Jrnl Clin Psychopharmacology*. 2003;23(3):309-13.

2. Popakostas G, et al. *Psychiatry Research*, 2005;140(3):301-7.

3. Alpert, JE & Fava, M. *Nutrition Reviews*. 1997;55(5):145-49

4. Coppen A, & Bolander-Gouaille C. *Journal of Psychopharm*. 2005;19(1):59-65.

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6. Levitt A, & Joffe R. *Biol Psychiatry*. 1989;25:867-72.

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Switch? Combine? Augment?

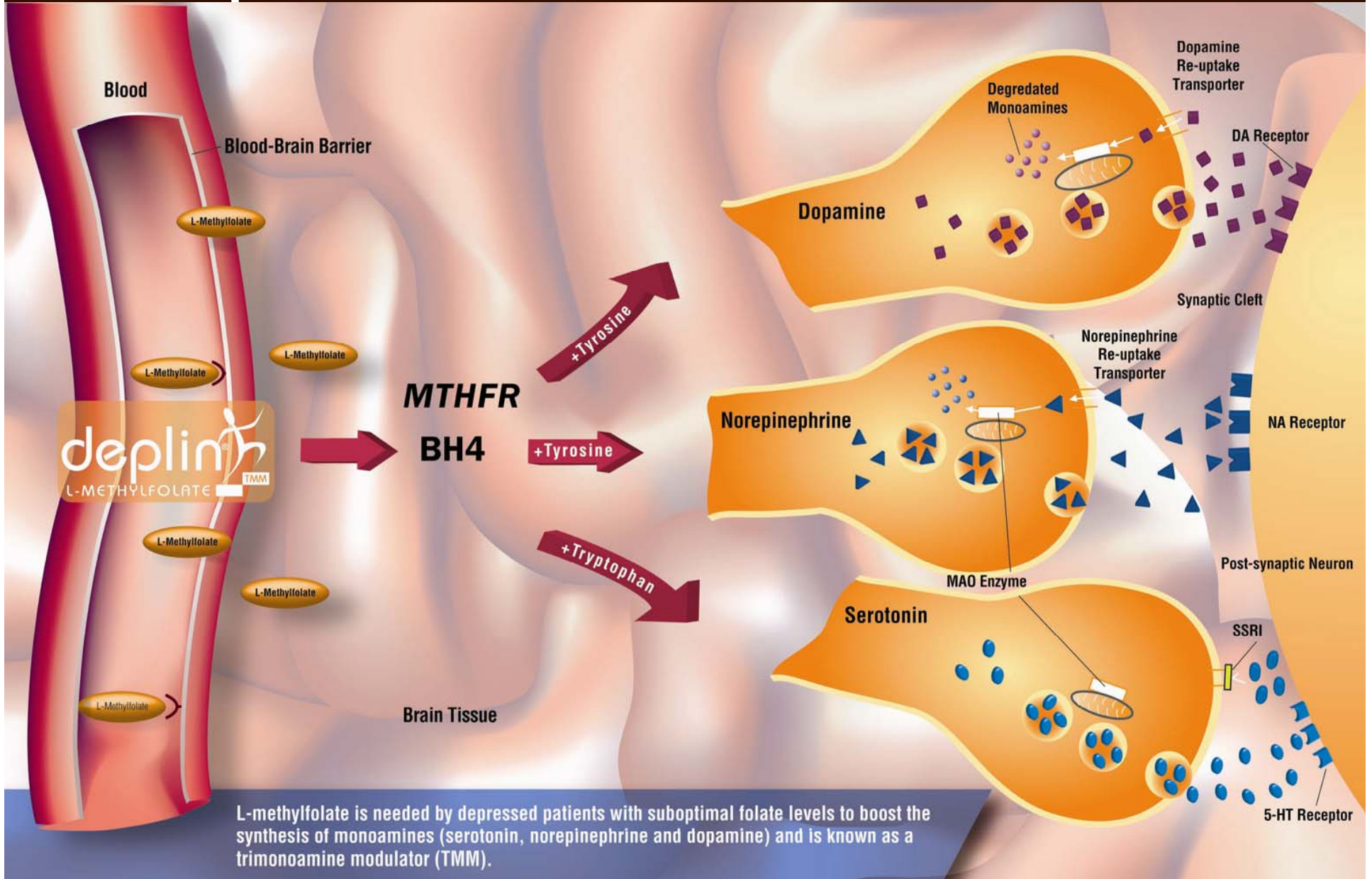
- General guidelines
 - <25% efficacy: SWITCH vs. augment
(COMBINE during SWITCH?)
 - 25-50% efficacy: SWITCH vs AUGMENT
 - >50% efficacy: AUGMENT vs switch

Antidepressant Augmentation

- Vagus Nerve Stimulation*
- L-methylfolate*
- Aripiprazole*
- Atypical antipsychotics
- Lithium
- Thyroid hormone (T3)
- Stimulants
- Modafinil
- Buspirone
- Lamotrigine
- Carbamazepine
- Divalproex sodium
- Dopamine agonists
- Estrogen (as replacement)
- Buprenorphine
- SAMe
- Phototherapy (for SAD)
- Psychotherapy
 - CBT
 - CBASP
 - ITP
- Electroconvulsive therapy

* Indicated for augmentation of MDD

Deplin as a Trimonoamine Modulator



L-methylfolate (5-MTHF) vs. Folic Acid

	L-methylfolate	Folic Acid
Bioequivalent Dose¹	7.5mg	52.5 mg
Unlikely to mask pernicious anemia from a B-12 deficiency²	Yes	No
Unlikely to impair immune system³	Yes	No
Unaffected by MTHFR C>T Polymorphism⁵ (~70% depressed population)	Yes	No
Able to Cross Blood Brain Barrier & aid in the synthesis of neurotransmitters^{6,7}	Yes	No
Does not Bind to BBB Receptors Inhibiting L-methylfolate absorption into the CNS^{4,8}	Yes	No*

* Unmetabolized folic acid (especially doses $\geq 1.0\text{mg}$) binds to the "folate receptor" transport mechanism with a greater affinity than 5-MTHF resulting in a reduction in the transfer of MTHF across the BBB, which may lead to a lowering of the CNS MTHF level.⁴

1. Willems F et al. British Jnl of Pharmacology. 2004;141(5):825-30.

2. Scott J.M. & Weir D. The Lancet. 1981 2:337-40.

3. Troen AM et al, J. Nutrition. 2006;136:189-94,

4. Bailey S. College of Medicine, University of South Alabama (data file)

5. Papakostas G et al. J. Clinical Psychiatry. 2004;65(8):1090-95.

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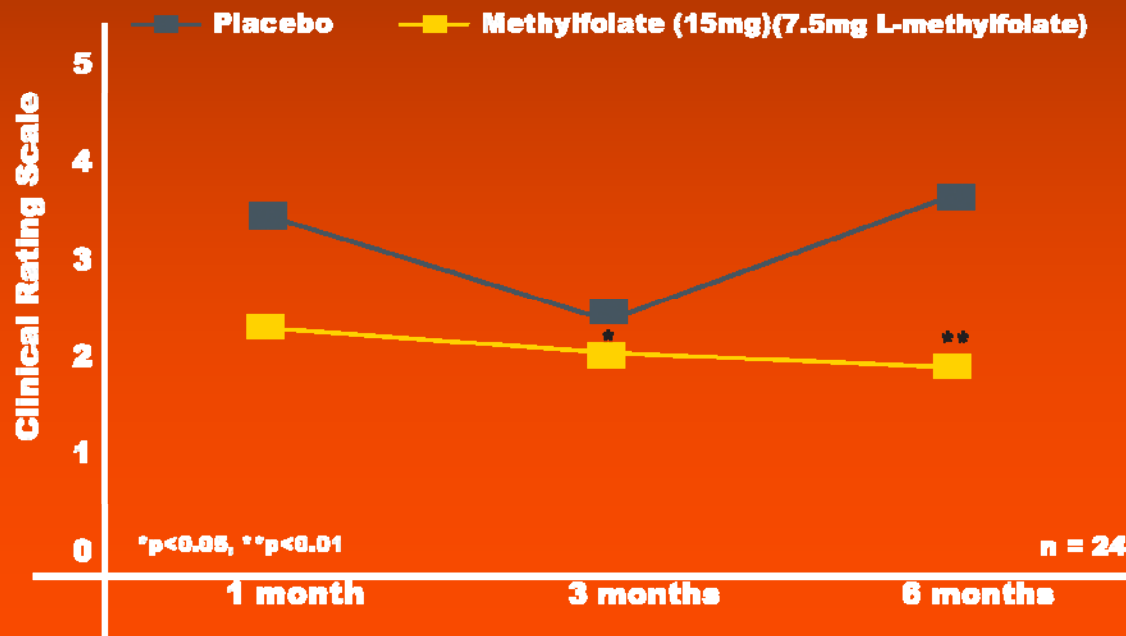
7. Wu D & Pardridge WM, Pharmaceutical Research, 1999;16(3):415-419.

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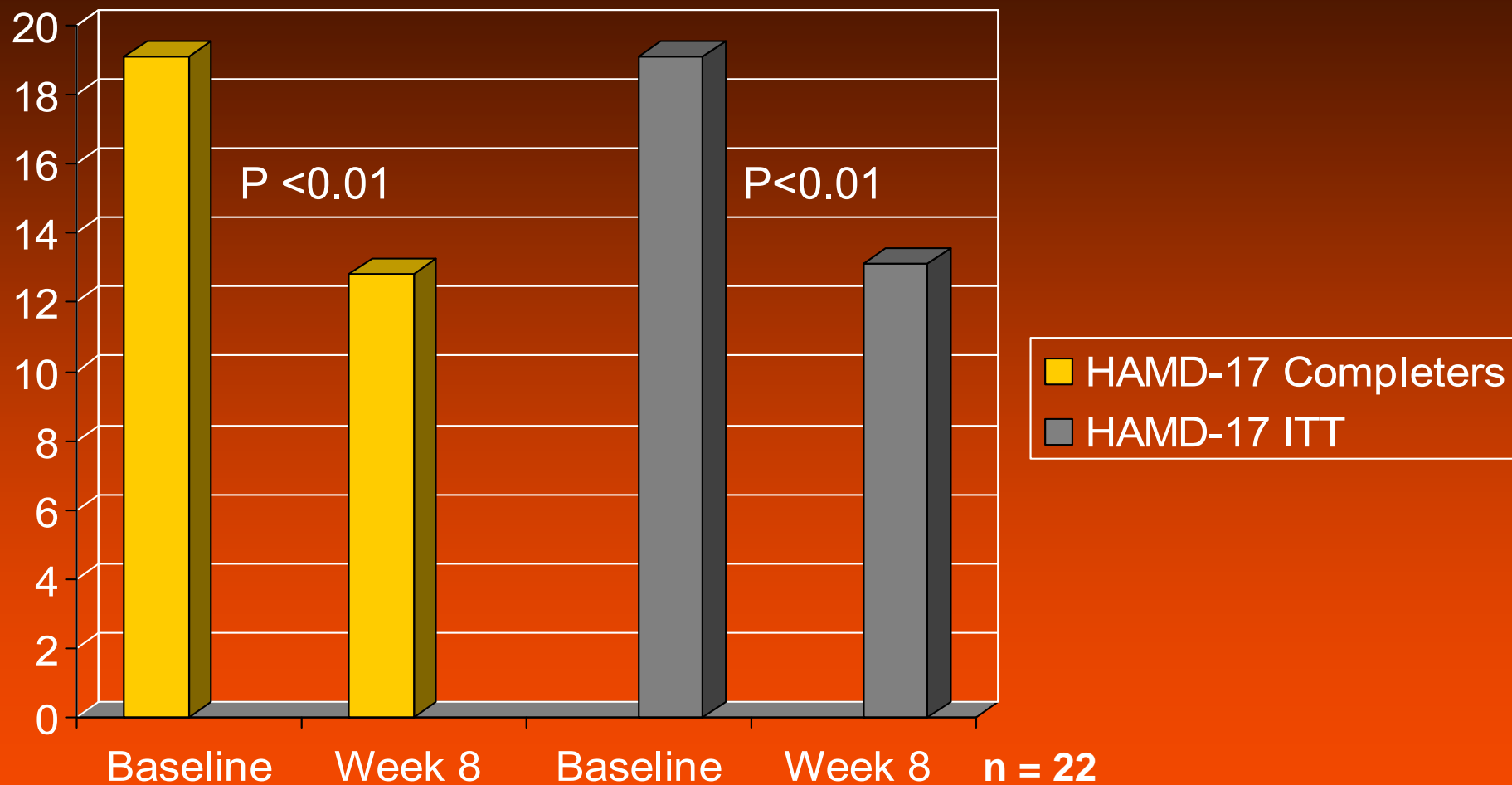
Depressed Patients on an Antidepressant Demonstrate Enhanced Response with Methylfolate

- Methylfolate augmented patients experienced significantly greater clinical improvement ($p < 0.05$) and social improvement ($p < 0.01$) at 3 and 6 months compared to patients treated with placebo.
- Methylfolate augmented patients continued to improve compared to placebo-augmented patients who began to decompensate by the end of 6 months.
- No additional adverse events were reported with the addition of methylfolate.

Methylfolate Augmentation of TCAs & MAOIs



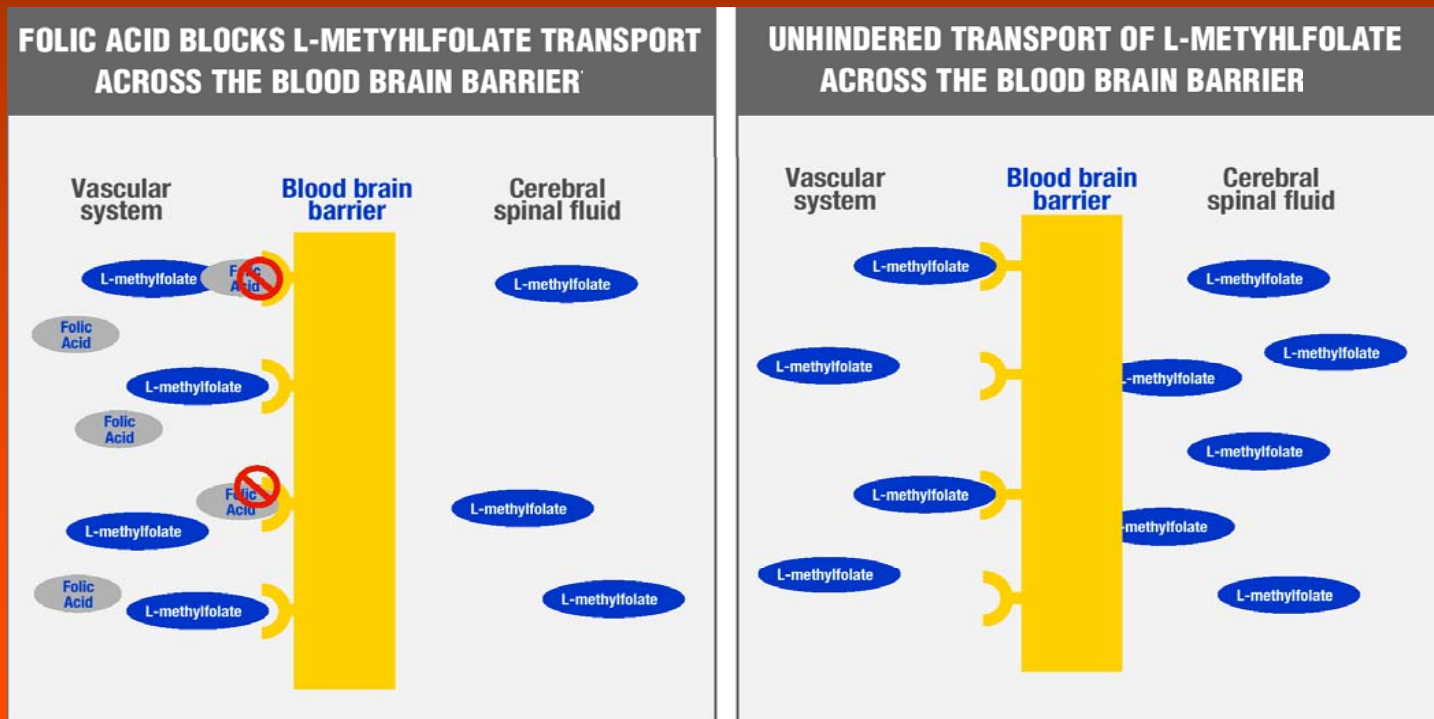
Open Study of 5-Formyl Tetrahydrofolate Augmentation in SSRI-Resistant Depressed Patients



No additional adverse events were reported with the addition of 5-formal tetrahydrofolate.
L-methylfolate is the predominant circulating form of reduced folate and the active metabolite of 5-formal tetrahydrofolate.

Crossing the Blood Brain Barrier

- Unmetabolized folic acid is unable to cross the blood brain barrier (BBB) and may become bound to receptors (folate binding protein) on the membrane, thereby blocking the absorption of L-methylfolate*.
- Consequently, the amount of L-methylfolate crossing the BBB into cerebral spinal fluid (CSF) is reduced.
- L-methylfolate, in the absence of unmetabolized folic acid, passes more readily into the CSF which aids in neurotransmitter synthesis.



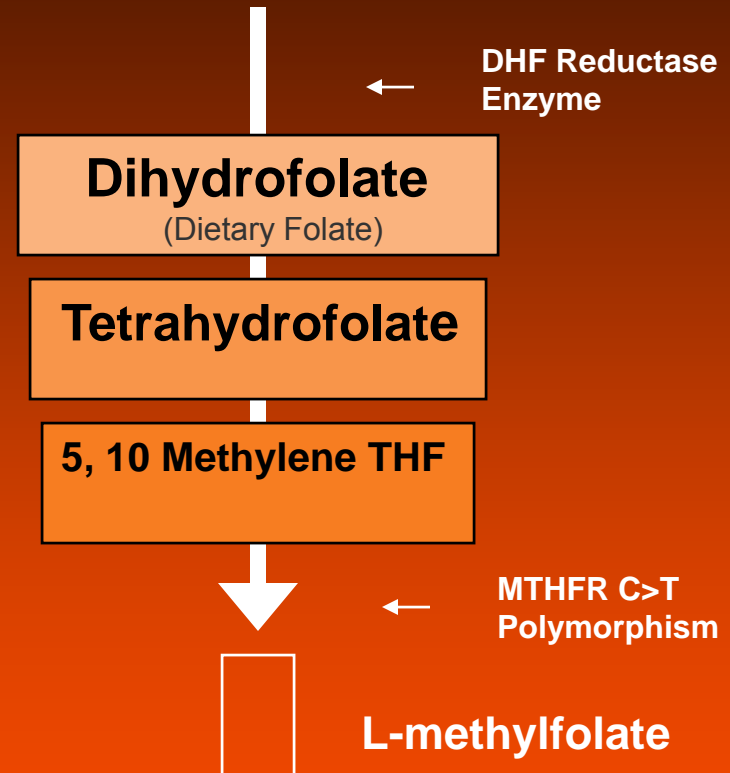
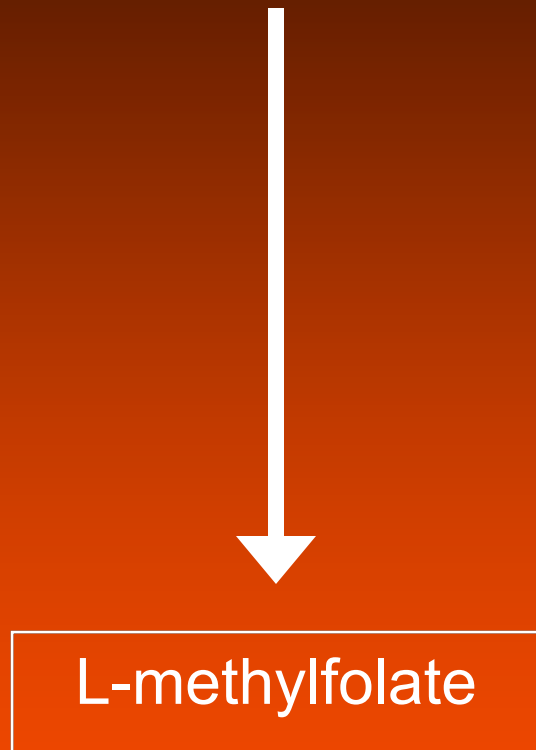
* Bailey S. College of Medicine, University of South Alabama (data file)

Bioavailability

L-methylfolate

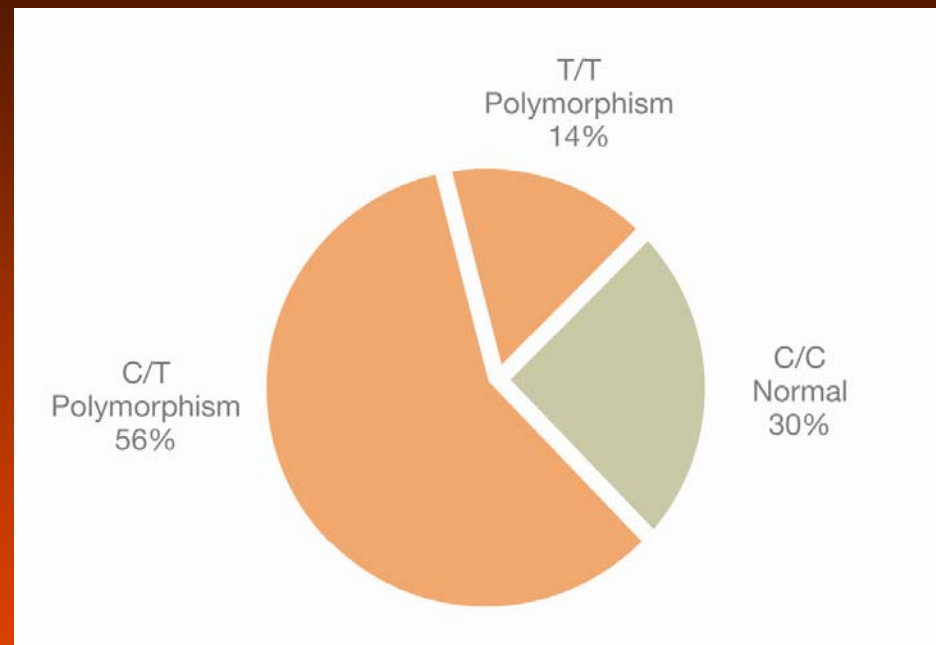
Vs.

Folic Acid



- Folic acid requires a 4 step transformation process to be converted to the active form of folate, L-methylfolate (5-MTHF).
- L-methylfolate is unaffected by the MTHFR C→T polymorphism.

70% Prevalence of MTHFR Polymorphism in Depression



- Patients who have the MTHFR C→T genotypes have a **1.36 times** greater chance of developing depression (and reported to be as high as 4X the general population)^{1,2}
- The odds of having the T/T genotype is almost **3X** as great in depressed patients verses the normal population.^{3,4}

1. Bjelland I. et al. Arch Gen Psychiatry. 2003;60(6):618-26
2. Procopciuc L.M., Poster Pres. P86 presented at Biol Psych. 2005.

3. Arinami T, et al. Am J Genetics. 1997;74:526-28.
4. Kelly B J, et al. Psychopharmacol. 2004 ;18(4):567-71.

DEPLIN® (L-methylfolate) Safety Profile

Well tolerated in both acute and chronic therapy

- Folate augmentation to standard psychotropic medication was well tolerated in acute and maintenance trials(12 months).^{1,2,6,7}
- DEPLIN® is not contraindicated with any medications.⁸
- Does not appear to be associated with weight gain, sexual dysfunction, or sleep disturbances.¹⁻⁷

Suicide/Overdose

- No suicidal ideation or suicides were reported with folate.¹⁻⁷

No titration required

- No need for initial titration or tapering when discontinuing treatment. ⁸
- **Dose:** one 7.5mg tablet a day with or without food.⁸

1. Coppen A. et al. J. Affective Disorders, 1986;10:9-13.

2. Godfrey PSA et al. The Lancet. 1990;18:392-95.

3. Guaraldi et al. Annals Clin Psych. 1993;5(2):101-5.

4. Passeri M et al. Aging Clin Exp Res. 1993;5: 63-71.

5. Di Palma C et al. Curr Therapeutic Research. 1994;55(5):559-68.

6. Coppen A & Bailey J. J Affective Disorders, 2000;60:121-30.

7. Alpert JE et al. Annals of Clin Psych. 2002;14(1): 33-38.

8. Deplin Full Prescribing Information.

DEPLIN[®] Overview

- DEPLIN[®] tablets contains 7.5 mg of L-methylfolate. DEPLIN[®] is available by prescription.
- L-methylfolate is needed to boost the synthesis of monoamine neurotransmitters (serotonin, norepinephrine, dopamine) and is known as a trimonoamine modulator (TMM).¹
- Indication: DEPLIN[®] is indicated for the distinct nutritional requirements of depressed individuals who present with suboptimal folate levels in the cerebrospinal fluid, plasma, and/or red blood cells, with particular emphasis, as an adjunctive treatment (augmentation) for individuals experiencing an episode of major depressive disorder that has not fully remitted following an adequate trial of an antidepressant. DEPLIN[®] is indicated regardless of MTHFR C677T polymorphism genotype.²

DEPLIN[®] should always occur under the care of a physician.

1. Stahl S. Essentials of Psychopharmacology. 3rd ed. New York, NY:Cambridge University Press; In press.

2. Deplin Full Prescribing Information.

Summary

- A partial response in clinical depression is common and associated with a poorer outcome.
- Augmentation strategies can build-off a partial antidepressant response and may accelerate onset of action.
- Despite available strategies, many MDD patients fail to achieve remission.
- L-methylfolate acts as a TMM boosting the synthesis of serotonin, norepinephrine and dopamine which, if deficient, may enhance an antidepressant response.
- DEPLIN[®] (7.5mg L-methylfolate) is well tolerated and has a low potential for drug interactions.^{1,2}

1. Deplin Full Prescribing Information

2. Deplin clinical Evaluation Patient Response Survey

Thank you

Folate Clinical Trials in Depression

Reference	Design	Folate &/or Comparator	Sample characteristics	Outcome
Coppen, A. et al; J. Affective Disorders, 1986; 10:9-13.	Double-blind, controlled 12 months	Folic acid (200 mcg) or placebo in combination with lithium	75 patients on lithium therapy.	Patients with highest plasma folate had a greater reduction in affective morbidity ⁷
Godfrey, et al., The Lancet, 1990; 18:392-395.	Double blind controlled 6 months	MTHF (15mg) or placebo. Other psychotropic medication allowed	24 depressed and 17 schizophrenic subjects with low RBC folate (<200 ng/ml). DSM-III diagnosis.	Significant decrease in mean outcome scores in MTHF group at 3 and 6 months ⁸
Crellin R, Bottiglieri T et al. Drugs 45(5):623-636, 1993.	Double-blind randomized trial for 6 wks. Nonresponders crossed over for an additional 6 wks. Responders were followed for 6 months.	MTHF @ 50mgs or amitriptyline @ 150mgs. No other psychotropic medications allowed	31 mild to moderately depressed subjects enrolled in the study. Investigators blinded to plasma data collected. DSM-III-R and MADS >or=14.	Of 19 subjects randomized (n=16) or crossed over (n=3) to treatment (MTHF) 8 responded (MADS < by 25% or more). Of 20 subjects (n=15) or crossed over (n=5) to treatment (amitriptyline) 7 responded. Only 3 patients (10%) had low or borderline RBC folate values at randomization. ⁹
Guaraldi, Gian Paolo, et al. 1993; 5:101-105	Open trial 6 weeks	MTHF (50 mg), no other psychotropic medication	20 Elderly depressed subjects. DSM-III-R, HAM-D-21 > or = 18	16 completed at least 4 weeks, 81% response rate (decrease in HAM-D >50%) ¹⁰
Passeri, M., et al. Aging Clin. Exp. Res., 1993; 5:63-71.	Double blind, controlled 8 weeks	MTHF (50mg) or Trazodone (100 mg). Psychotropic medication allowed but not AD	96 patients with dementia, MMSE 12-23, and depression, HAM-D score >18.	Significant decrease in HAM-D scores at 4 and 8 weeks in the MTHF and TRZ groups. Response rate: 45% MTHF, 29% TRZ (NS) ¹¹
DiPalma, C., et al. Therapeutic Research, 1994; 55:5559-568.	Open trial 4 weeks. One week run-in placebo period	MTHF @ 90mgs/day (30mg TID) as monotherapy.	36 chronic alcoholics with major depression then treated with 90mg/day of MTHF for 4 weeks.	All 36 subjects completed. The HSRD, ZSRD, face scale and VAS showed a statistical significance of P<0.01 Folate deficiency may be primary or secondary to the depressive disorder but in either case it improves mental function. ¹²
Coppen A, et al. Journal of Affective Disorders, 2000; 60:121-130.	Double blind controlled 10 weeks	Folic acid (500 mcg) or placebo in combination with fluoxetine (20mg)	127 depressed subjects. DSM-III-R, HAM-D-17 score > or = 20.	Significantly greater improvement in Folic acid + fluoxetine group in females only. Effect linked to higher plasma folate and lower tHcy levels ¹³
Alpert, JE, et al. Annals Clin Psychiatry, 2002;14:33-38.	Open trial 8 weeks	Folinic acid in combination with an SSRI	22 depressed subjects. DSM-IV, HAM-D-17 score > or = 12. Partial or no response to an SSRI	16 subjects completed. 31% achieved a response (decrease in HAM-D >50%), 19% achieved remission. ¹⁴