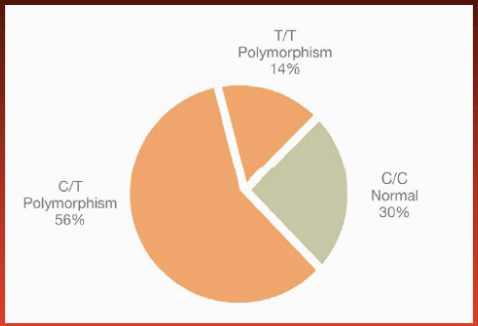
Antidepressant Augmentation

- 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

<u>* Indicated for augmentation of MDD</u>

Zajecka, John M., Goldstein, Corey & Barowski, Jeremy (2006). CHAPTER 6 - Combining Medications to Achieve Remission. Depression, 1 (1), 161-200.

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.

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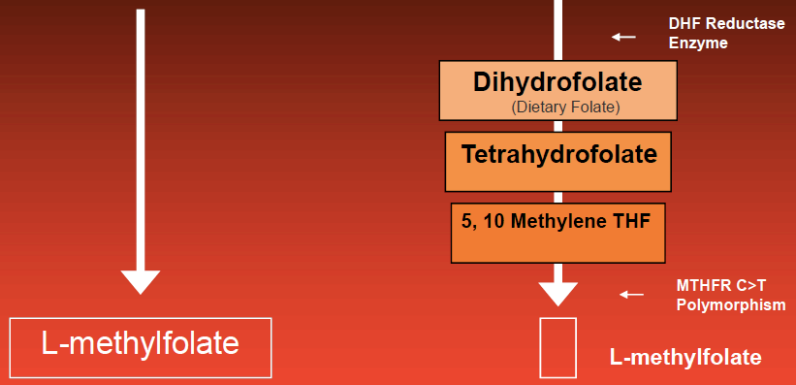
Kelly B J, et al. Psychopharmacol. 2004 ;18(4):567-71.

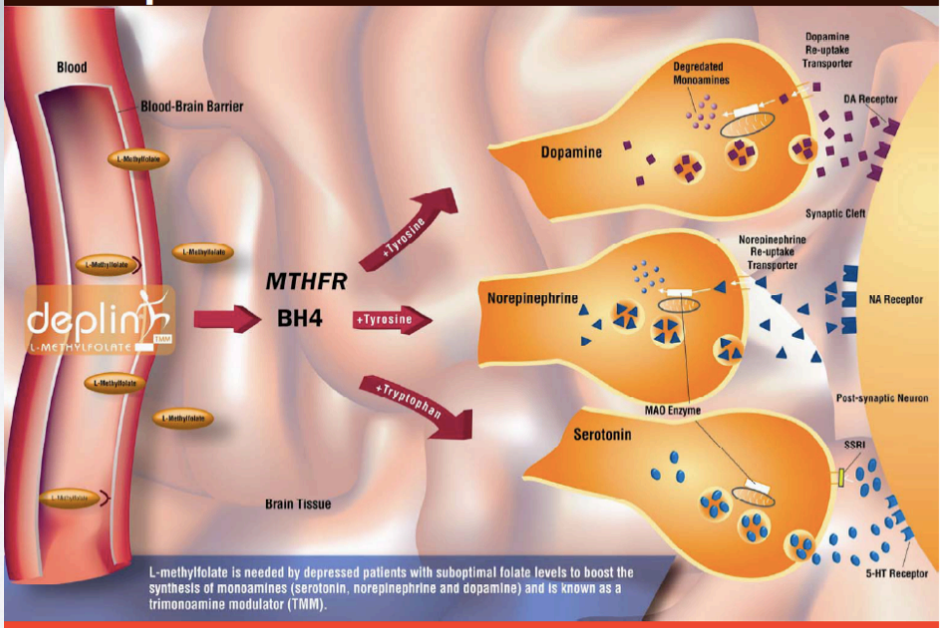
Bioavailability

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.

Deplin as a Trimonoamine Modulator



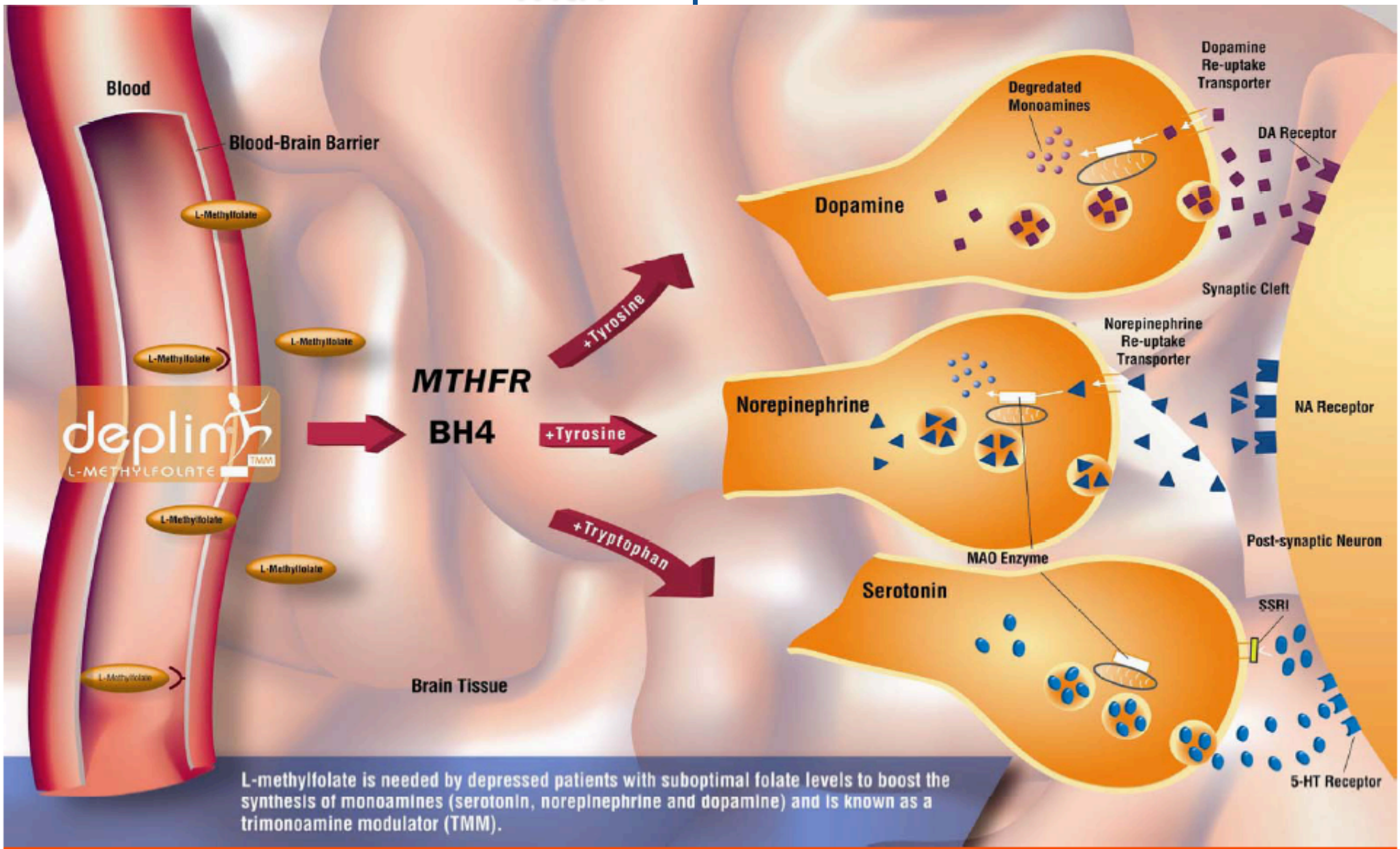
tahl S.M. Novel Therapeutics for Depression: L-methylfolate as a Trimonoamine Modulator and Antidepressant Augmenting Agent. CNS Spectrums. 2007;12(10):739-744.

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.
5. Bottigleri T. Prog Neuro-Psychopharm & Biol Psychiatry. 2005; 29:1103-12.
6. Levitt A, & Joffe R. Biol Psychiatry. 1989;25:867-72.
7. Wesson VA, et al. Psychiatry Res. 1994;53(3):313-22.
8. Abou Saleh MT & Coppen A. Acta Psychiatr Scand. 1989;80(1):78-82.

L-MethylFolate and Monamine Synthesis in Patients with Depression



Stahl S.M. Novel Therapeutics for Depression: L-methylfolate as a Trimonoamine Modulator and Antidepressant Augmenting Agent. CNS Spectrums. 2007;12(10):739-744.

•Recommendations for Other Treatment Options

Sleep deprivation:

- Effective transient treatment for depressive disorders
- Response may be maintained using medications (for example, antidepressants, lithium, or pindolol) or bright light
- May be most useful as an adjunctive treatment in hospitalized patients

Light Therapy

- Effective in treating mild seasonal depression
- Not effective in summertime depression
- Not effective for more severe depression
- Compact LED Units available

Glutathione and the Role of NAC

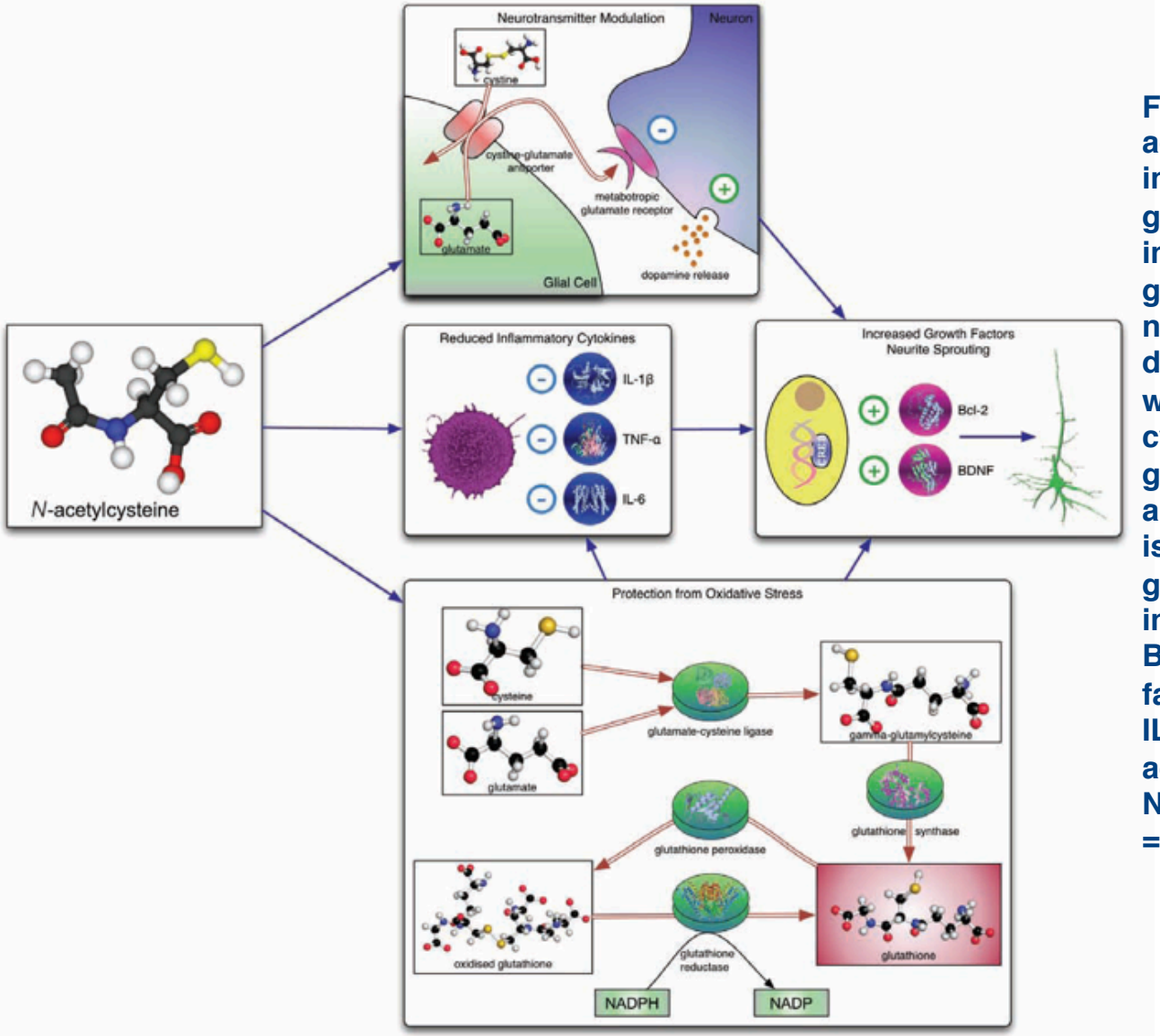
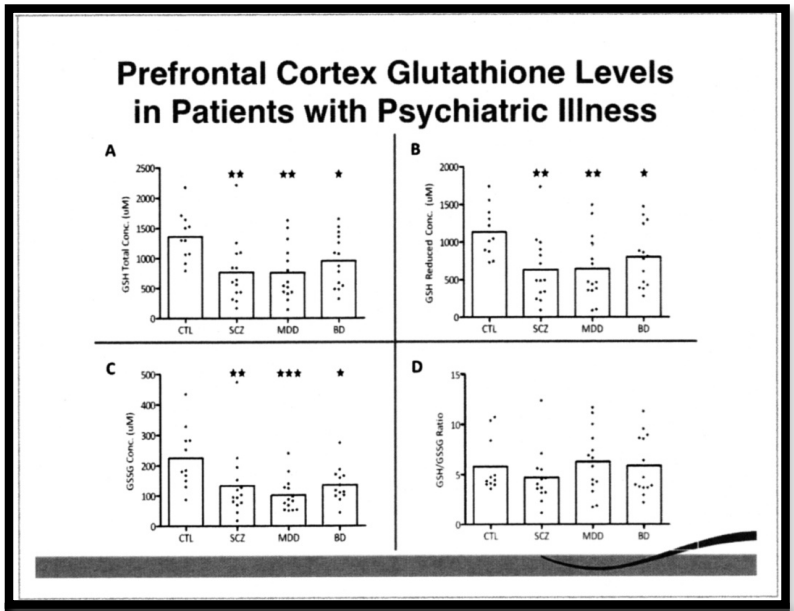
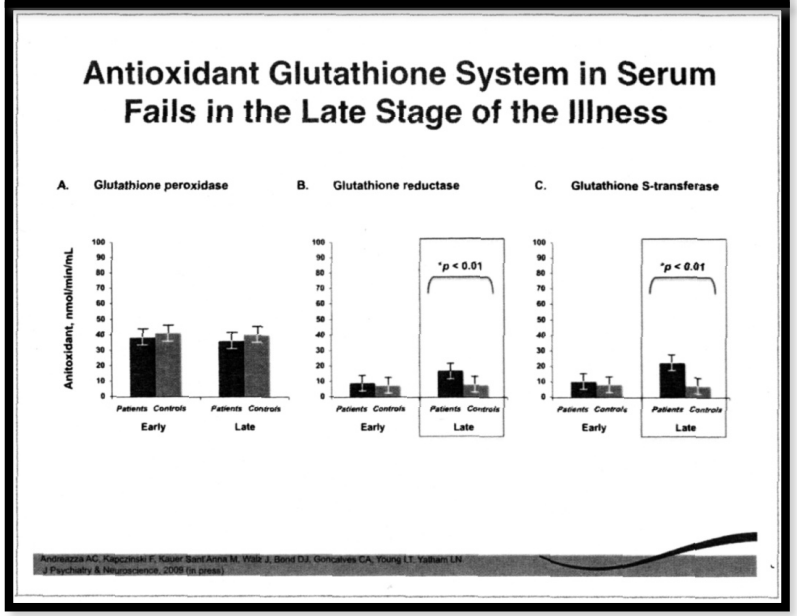


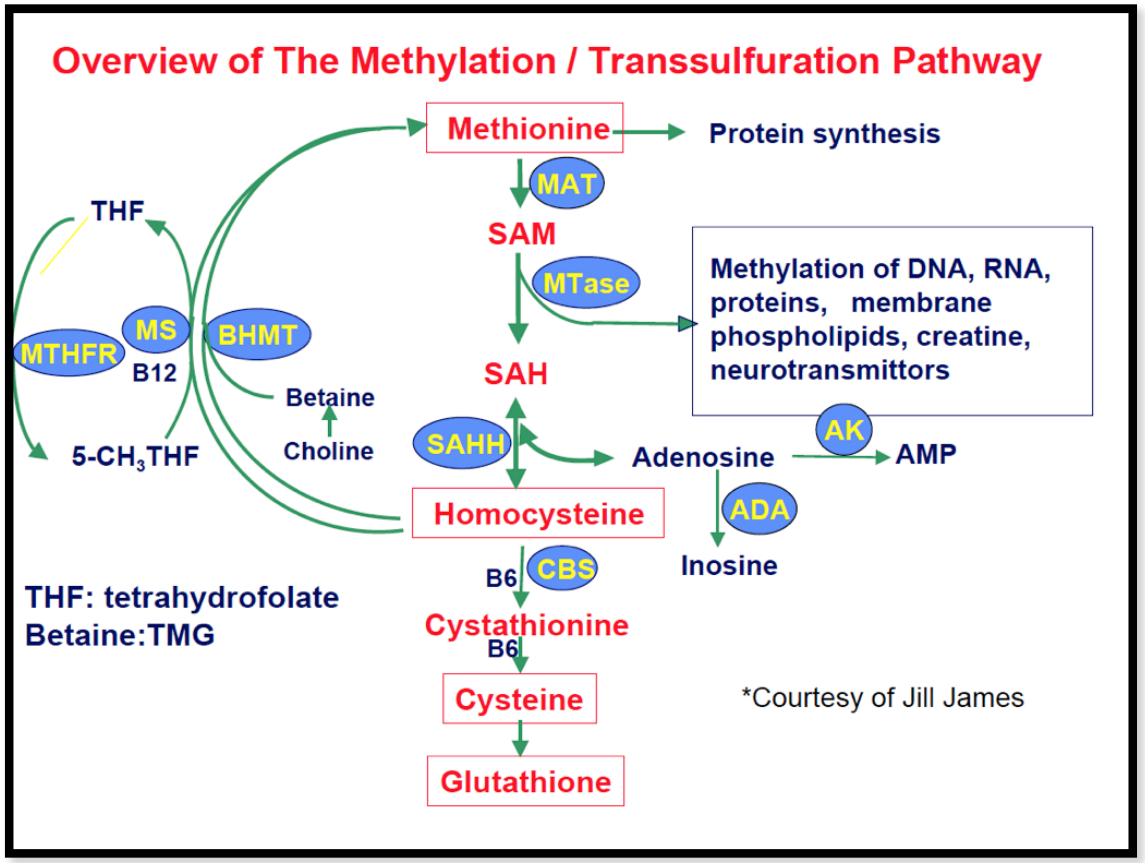
Fig. 1: Mechanisms of action of *N*-acetylcysteine (NAC). Top to bottom: increased activity of cystine–glutamate antiporter results in increased activation of metabotropic glutamate receptors on inhibitory neurons and facilitates vesicular dopamine release; NAC is associated with reduced levels of inflammatory cytokines and acts as a substrate for glutathione synthesis. These actions are believed to converge upon mechan isms promoting cell survival and growth factor synthesis, leading to increased neurite sprouting.
BDNF = brain-derived neurotrophic factor;
IL = interleukin; NADP = nicotinamide adenine dinucleotide phosphate; NADPH = reduced form of NADP; TNF = tumour necrosis factor.

J Psychiatry Neurosci 2011;36(2)

Glutathione Reduced in Psychiatric Illness: the Role of NAC







NAC N-Acetyl Cysteine or Cysteine, is a precursor of glutathione, an antioxidant. It is thought to reduce glutamate over activity.
It is used in treatment of Tylenol OD, Mercury Poisoning, Interstitial Lung disease, Renal Failure.
It is under investigation for adjunctive treatment of schizophrenia, Bipolar Disorder, OCD, Memory impairment.

Effects of Yoga on Depressive Symptoms and QOL in Unipolar and Bipolar Depression

Patients are increasing turning to alternative and complementary treatments, including yoga, to treat depressive symptoms (Kessler et al., 2001).

Advantages of yoga:

- **Low-cost**
- **Non-invasive**
- **High patient acceptance**
- **Improves physical health**

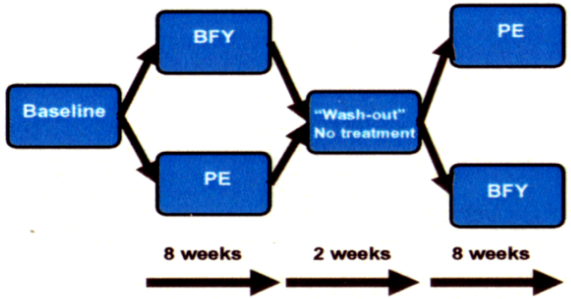
We developed a manualized integrative yoga program, referred to as Breathing-Focussed Yoga (BFY) that emphasizes breath control, and includes postures and guided meditation.

Three components of breath control:

1) Ujjaji – slow inhalation, exhalation and holding of breath
2) Kapalabhati – vigourous breathing with forced exhalation
3) Cyclical breathing – repeated pattern of slow, moderate and fast breathing

Study design

- 16-week pilot RCT comparing the efficacy of BFY versus psychoeducation (discussion group) (PE) in cross-over design
- Included patients with residual symptoms of both unipolar and bipolar depression
- Patients were randomized to 2 groups: 8 weeks of BFY followed by 8 weeks of PE, or the reverse.



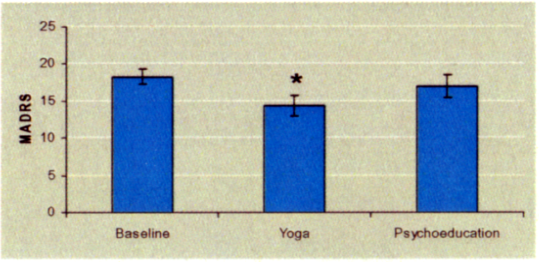
Materials and methods

- Primary efficacy measure: Montgomery-Asberg Depression Rating Scale (MADRS)
- Secondary efficacy measures: Clinical Global Impression Severity and Improvement Scales (CGI-S and CGI-I), Beck Depression Inventory (BDI) and the Quality of Life Satisfaction and Enjoyment Scale (Q-LES-Q)
- All efficacy measures were completed at Baseline, Week 8 and Week 16 by raters blind to treatment intervention

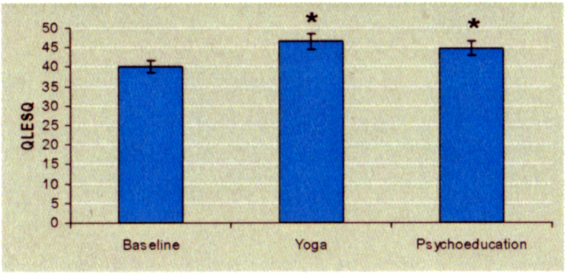
Results

A repeated measures cross-over analysis yielded significant differences between baseline and the BFY and PE groups in depressive symptoms (MADRS and BDI), clinical global impression (CGI), and quality of life (Q-LES-Q) over the 16 weeks.

- A significant reduction in depressive symptoms was noted, as measured by the MADRS; however, the degree of improvement differed between the two study interventions ($F(2,54)=3.55$, $p=0.04$, $\eta 2=0.12$). The most improvement from baseline seen in the BFY group (1.50, $p=0.008$).



- There was a significant improvement in quality of life from baseline ($F(2,52)=6.50$, $p=0.003$, $\eta 2=0.20$), with both the BFY group (-6.40, $p=0.004$) and the PE group (-5.33, $p=0.004$) reporting a similar increase from baseline.

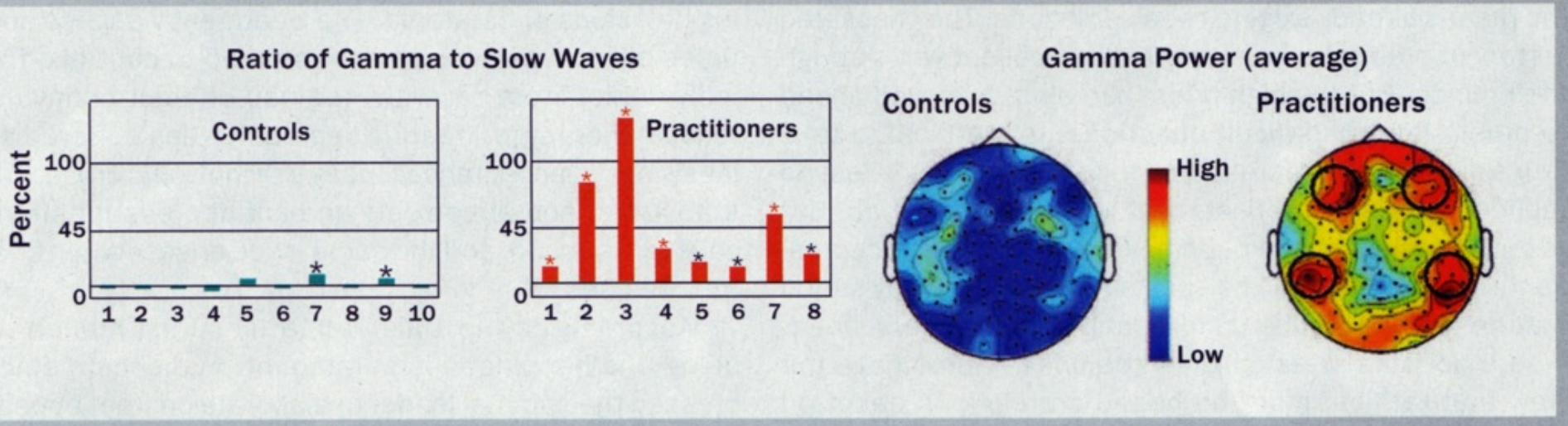


Conclusions

- Both BFY and PE improve symptoms and quality of life
- BFY may be superior in reducing depressive symptoms
- Analysis of larger sample data may produce stronger results in favour of BFY

Meditation Controls Negative Emotion

People can diffuse ill feelings by mastering emotions such as anger. Tibetan monks who are experts in meditation rid themselves of negativity by augmenting the brain's gamma waves, which can be measured in a lab (*right*). Richard Davidson of the University of Wisconsin–Madison tested eight monks (*right graph*) during meditation. They boosted their gamma waves to twice (*black stars*) or three times (*orange stars*) the resting level. A composite head diagram (*right*) shows regions of greatest gamma activity. Eight volunteers who had just been taught how to meditate and acted as controls (*left graph*) showed little gamma-wave gain.



Ellen Frank Ph.D.: Social Rhythms Therapy

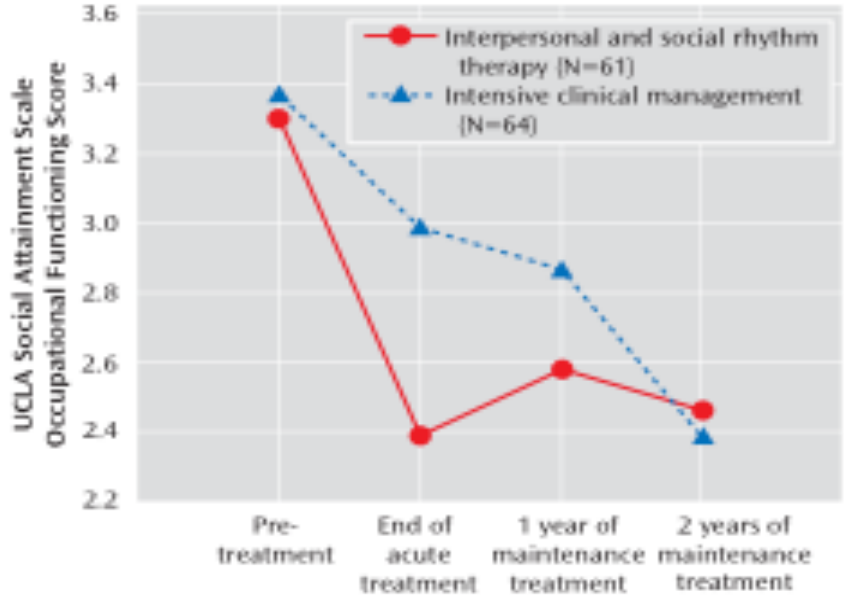
Ellen Frank, Ph.D. Isabella Soreca, M.D. Holly A. Swartz, M.D. Andrea M. Fagiolini, M.D. Alan G. Mallinger, M.D. Michael E. Thase, M.D. Victoria J. Grochocinski, Ph.D. Patricia R. Houck, M.S.H. David J. Kupfer, M.D.

Objective: Recent studies demonstrate the poor psychosocial outcomes associated with bipolar disorder. Occupational functioning, a key indicator of psychosocial disability, is often severely affected by the disorder. The authors describe the effect of acute treatment with interpersonal and social rhythm therapy on occupational functioning over a period of approximately 2.5 years.
Method: Patients with bipolar I disorder were randomly assigned to receive either acute and maintenance interpersonal and social rhythm therapy, acute and maintenance intensive clinical management, acute interpersonal and social rhythm therapy and maintenance intensive clinical management, or acute intensive clinical management and maintenance interpersonal and social rhythm therapy, all with appropriate pharmacotherapy. Occupational functioning was measured with the UCLA Social Attainment Scale at baseline, at the end of acute treatment, and after 1 and 2 years of maintenance treatment.
Results: The main effect of treatment did not reach conventional levels of statistical significance; however, the authors observed a significant time by initial treatment interaction. Participants initially as- signed to interpersonal and social rhythm therapy showed more rapid improvement in occupational functioning than those initially assigned to intensive clinical management, primarily accounted for by greater improvement in occupational functioning during the acute treatment phase. At the end of 2 years of maintenance treatment, there were no differences between the treatment groups. A gender effect was also observed, with women who initially received interpersonal and social rhythm therapy showing more marked and rapid improvement. There was no effect of maintenance treatment assignment on occupational functioning outcomes.
Conclusions: In this study, interpersonal and social rhythm therapy, with its emphasis on amelioration of interpersonal and role functioning, improved occupational functioning significantly more rap- idly than did a psycho educational and supportive approach with no such emphasis on functional capacities.

Essential Elements of Social Rhythms Therapy
1. Regularize daily routines
2. Emphasize link between daily routines and moods
3. Use social rhythm metric to monitor routines

Essential Elements of Interpersonal Therapy
1. Emphasize link between life events, role satisfaction and moods
2. Focus on interpersonal problem areas: grief, role transition, role disputes, interpersonal deficits
3. Grieve loss of healthy self.

FIGURE 1. Change in Occupational Functioning Over Course of Acute and Maintenance Treatment in Patients Assigned to Acute Phase Interpersonal and Social Rhythm Therapy Versus Intensive Clinical Management[a]



Frank,Ellen, Am J Psychiatry 2008; 165:1559–1565