Nutritional Medicine and the Nervous System: Part 3: Mental Health Disorders

The Brain Molecules of Mental Health: A missing Link in Prevention and Treatment

- Although great advancements have been made in the area of psychotherapy for mental illness and addictions (in particular the transtheoretical model of change by Prochaska and DiClemente), this program is about the importance of NATURAL MOLECULES in the adjunctive management of mental health and brain health, including:

- Endorphins
- Neurotransmitters
- Phospholipids
- Eicosanoids
- Vitamins
- Essential Fatty Acids
- Accessory Nutrients
- Herb – medicinal ingredients
- Food Constituents

Overview of Program

1. Incidence of Mental Health Disorders
2. Success Rates of Pharmacotherapy and Psychotherapy
3. Exercise
4. Omega-3 fats
5. Vitamin D
6. Neurotransmitter Synthesis and Co-factors
7. Folic Acid, Vitamin B12 and SAMe
8. 5-Hydroxytryptophan (5-HTP)
9. CDP-choline (cytidine 5-diphosphocholine)
10. St John's Wort
11. Post-traumatic Stress Disorder (PTSD)
12. Burn Out and Rodiola
13. Sleep Disturbances
14. SPECT Scans and Mental Health
15. Adopting Wellness Habits and Proven Strategies to Stay on Track

MENTAL HEALTH INCIDENCE IN CANADA

- One in five Canadians (20%) develops an acute or chronic mental health illness or an addiction in any given year, which is among the highest in the developed world

Centre for Addiction and Mental Health (CAMH – Canada) 2014 Report

- Canadians are among the world's biggest users of antidepressants, with as much as 9% of population taking an antidepressant medication

- Consumption of **antidepressants in Canada** is the **third-highest** among 23 developed countries surveyed, with 86 doses consumed daily per 1,000 people.

- Only Australia (89 doses per 1,000 people) and Iceland (106 doses per 1,000 people) ranked higher.

Huffington Post Nov 22, 2013 http://www.huffingtonpost.ca/2013/11/22/antidepressant-use-world-canada_n_4320429.html

DEPRESSION STATS

- Approximately 3 to 7% of the North American population will suffer from a "clinically significant" episode of **major depression** in any given year.

- The **lifetime risk** for at least **one major depressive episode** among this population is approximately **16 to 24%.**

- S-adenosyl methionine as treatment for depression: A systematic review. http://works.bepress.com/cgi/viewcontent.cgi?article=1009&context=vivianmcalister&sei-redir=1&referer=http%3A%2F%2Fscholar.google.ca%2Fscholar%3Fq%3DSAMe%2Bsupplementation%2Bin%2Bmental%2Bhealth%26hl%3Den%26as_sdt%3D0%26as_vis%3D1%26oi%3Dscholart%26sa%3DX%26ei%3DB9pHVeuFLcjFggTZglHgCA%26ved%3D0CBsQgQMwAA#search=%22SAMe%20supplementation%20mental%20health%22

CAMH DATA (CENTRE FOR ADDICTION AND MENTAL HEALTH)

Prevalence:

- In any given year, 1 in 5 Canadians experiences a mental health or addiction problem.
- By the time Canadians reach 40 years of age, 1 in 2 have – or have had – a mental illness.
- 70% of mental health problems have their onset during childhood or adolescence.
- Young people aged 15 to 24 are more likely to experience mental illness and/or substance use disorders than any other age group
- Mental illness is a leading cause of disability in Canada.
- Nearly 4,000 Canadians die by suicide each year – an average of almost 11 suicides a day.
- In 2012, suicide accounted for 17% of deaths among youth aged 10 to 14, 28% among youth aged 15 to 19, and 25% among young adults aged 20-24.
- After accidents, it is the second leading cause of death for people aged 15 to 34. (1)

Economic Cost

- The cost of a disability leave for a mental illness is about double the cost of a leave due to a physical illness - $50 Billion from depression and anxiety alone (2)

- A growing body of international evidence demonstrates that promotion, prevention, and early intervention initiatives show positive returns on investment. (1)

References

1. CAMH - http://www.camh.ca/en/hospital/about_camh/newsroom/for_reporters/Pages/addictionmentalhealthstatistics.aspx

2. Conference Board of Canada Data 2016 - http://www.cbc.ca/news/business/canada-economy-depression-anixety-1.3744300

MENTAL HEALTH AND WELLNESS

Wellness Programs for College Students Should Address Mental Health in 5 Ways:

1. **Prevention Strategies** – via multi-faceted messaging to reach entire student population (digital notification ability)

2. **Early Detection** – prompting student to take printed form to their physician

3. **Alternative Access to Care – Telemedicine** – many Canadians and temporary visitors don't have a family doctor. Telemedicine enables them to seek help from a psychiatrist. Some individuals prefer Telemedicine to face-to-face Doctor experience and are more inclined to seek help it this avenue of care is easily available

4. **Peer- Support** – to help manage interpersonal and environmental factors that trigger and aggravate mental health disorders

5. **Pharmacogenetic Testing** – to ensure the first drug used is the one best suited to the patient's need.

PHARMACOTHERAPY SUCCESS RATES

- **65%** of patients with major depression **fail to respond to the initial medication trial**, and 75% of those fail to respond to subsequent trials
- These “non-responders” account for 2.5 times greater healthcare costs

($10, 358 more per year) than responders.

- “Non-responders” also have 6-times higher employment absenteeism costs and 4 times more disability claims cost

- Preliminary evidence shows that **pharmacogenetic-guided treatments** have a 42.3% rate of improvement in medication response, versus without pharmacogenetic guidance (24.7%)

- CAMH Pharmacogenetics Program: Individualized Medicine: Pharmacogenetics Assessment & Clinical Treatment

- Overall – only 30-40% of patients with major depression have only a partial response to available pharmacotherapy and psychotherapeutic interventions, when factor in relapse rates.

- Quershi, NA, Al-Bedah AM. Mood disorders and complementary and alternative medicine: A literature review. Neuropsychiatric disease and treatment. 2013. 9:639-658

- The economic burden of mental illness in Canada is estimated at $51 billion per year. This includes health care costs, lost productivity, and reductions in health-related quality of life.

- CAMH website: http://www.camh.ca/en/hospital/about_camh/newsroom/for_reporters/Pages/addictionmentalhealthstatistics.aspx

MENTAL HEALTH DISORDERS

Lifestyle and Natural Therapies Are Shown To Be An Important Adjunct To:

1. Prevention
2. Treatment
3. Preventing Relapse
4. Treating Pregnant and Postpartum Women Who Can't Take Many Medications

And Preserving Brain Health Throughout Your Lifetime

Unfortunately, this area is often completely ignored by mental health professionals.

EXERCISE

Prevention

- Some studies show that physically active people have **lower rates of anxiety and depression** than sedentary people.

- In one study, researchers found that those who got regular vigorous exercise were **25% less likely** to develop **depression or an anxiety disorder** over the next **five years.**

Exercise as Part of Therapy

- Exercise has a positive effect for most patients with depression, but not all patients report a benefit
- The mood-elevating effect of exercise is **temporary**, thus, regular exercise sessions are required to achieve and maintain mood elevation
- Exercise releases **endorphins**, and may increase synthesis of **serotonin and nor-epinephrine (animal research),** which trigger a positive feeling of wellbeing, often resulting in a positive and energizing outlook on life

Regular exercise has been shown to:

- Reduce stress
- Ward off anxiety and feelings of depression
- Boost self-esteem
- Improve sleep

- WebMD: http://www.webmd.com/depression/guide/exercise-depression

J CLIN PSYCHIATRY - 2007

Exercise as Important Adjunct to Pharmacotherapy

- Remission rates with selective serotonin reuptake inhibitors and other commonly used antidepressants are approximately 30%

- For these patients, adding exercise to pharmacotherapy or vice versa, or starting both in combination are worthwhile clinical approaches

- At the very least exercise should be considered as an augmentation to standard pharmacotherapy.

Exercise Dosage:

- Exercise 3 to 5 days a week seems to be the most effective dose
- Must have at least moderate intensity (stretching ineffective therapy)
- While 150 minutes of physical activity per week is the ultimate goal of treatment, for depressed individuals, 3 to 5 periods of exercise a week for 30 minutes per period is overwhelming at first.
- When starting a depressed individual on an exercise program, a reasonable and attainable goal can be as minimal as 10, 15, or 20 minutes of physical activity at a time, at least 3 times per week.
- On average, it takes 3 weeks to see significant improvements in mood elevation scores in depressed patients

Exercise Adherence: the importance of tracking tools

- **Self-monitoring** exercise behavior and addressing key psychosocial issues, such as barriers to exercise, exercise self-efficacy, and social support for exercise, as well as providing brief and supportive follow-up contact, **can improve exercise adherence by up to 25%** in the general population.

- Otto M.W. **Exercise for Mood and Anxiety Disorders.** Prim Care Companion J Clin Psychiatry. 2007; 9(4): 287–294. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2018853

Final Note: Best to **exercise outside during the day,** as sunlight and vitamin D also help to reverse depression (of course risk of skin cancer also increases, so precautionary measures should be in place)

Penckofer S et al. Vitamin D and depression: Where is the sunshine? Issuess Ment Health Nurs. 2010. 31(6): 385-393

OMEGA-3 FATS

Omega-3 fats from fish oil shown to be helpful in treatment of:

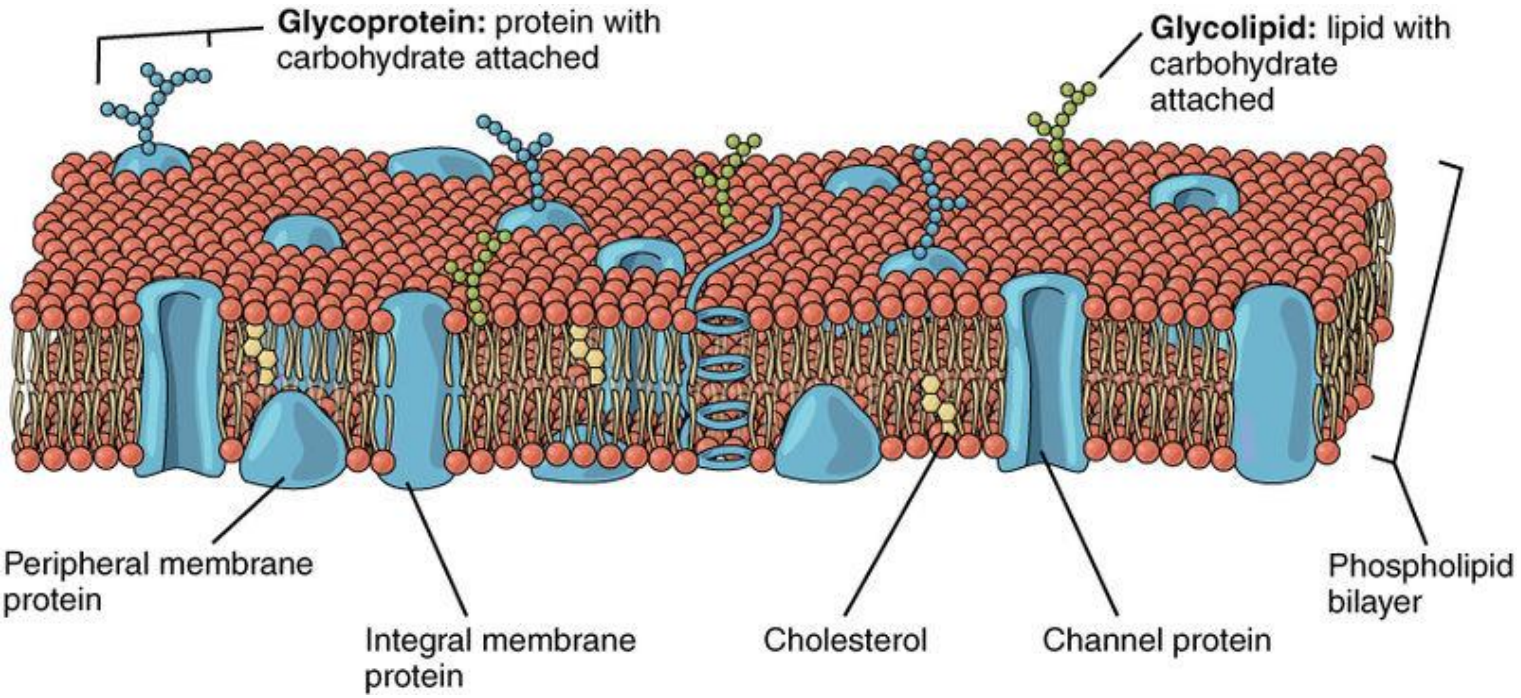
- Unipolar Depression
- Bipolar Depression
- Management of Depression in pregnant women – who cannot take prescription medications
- Postpartum Depression – during breast feeding medications are also not recommended

Mechanism of Action

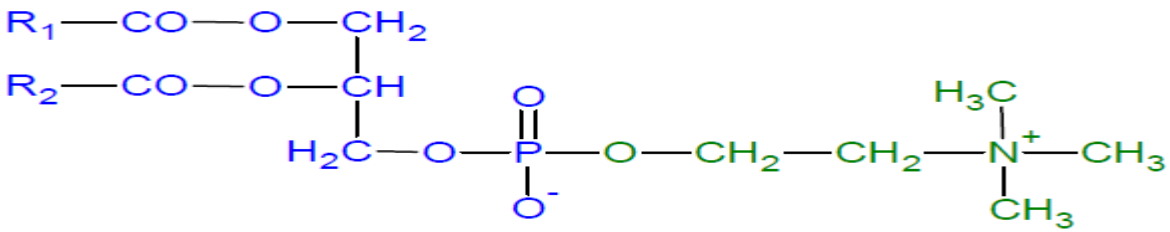
Omega-3 fats shown to:

1. Increase **"fluidity"** of nerve cell membrane – loss of membrane fluidity and flexibility results in disturbances of membrane proteins (including enzymes), ion channels and neurotransmitters - all common features in unipolar and bipolar depression
2. **Reduce synthesis of inflammatory eicosanoids** – inflammatory eicosanoids are a common finding in depression
3. **Prevent release of inflammatory cytokines** – inflammatory eicosanoids are a common finding in depression

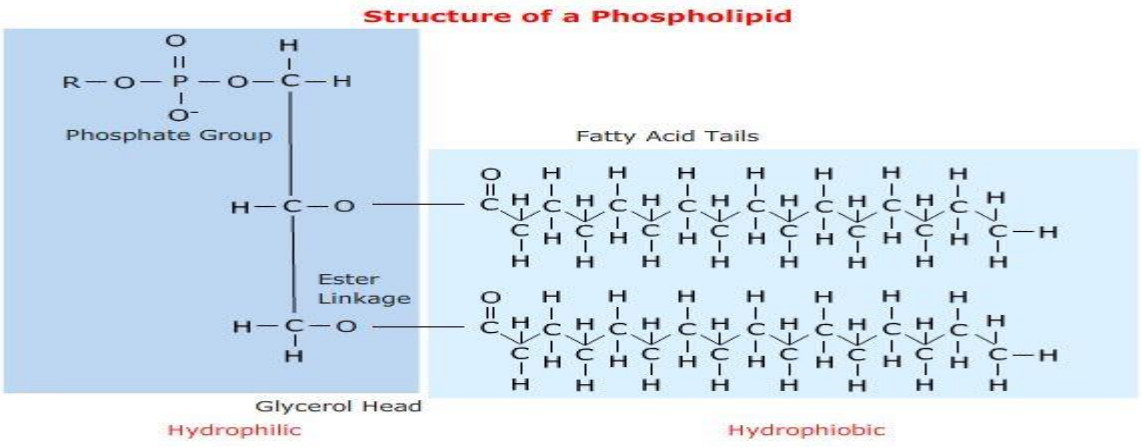
CELL MEMBRANE



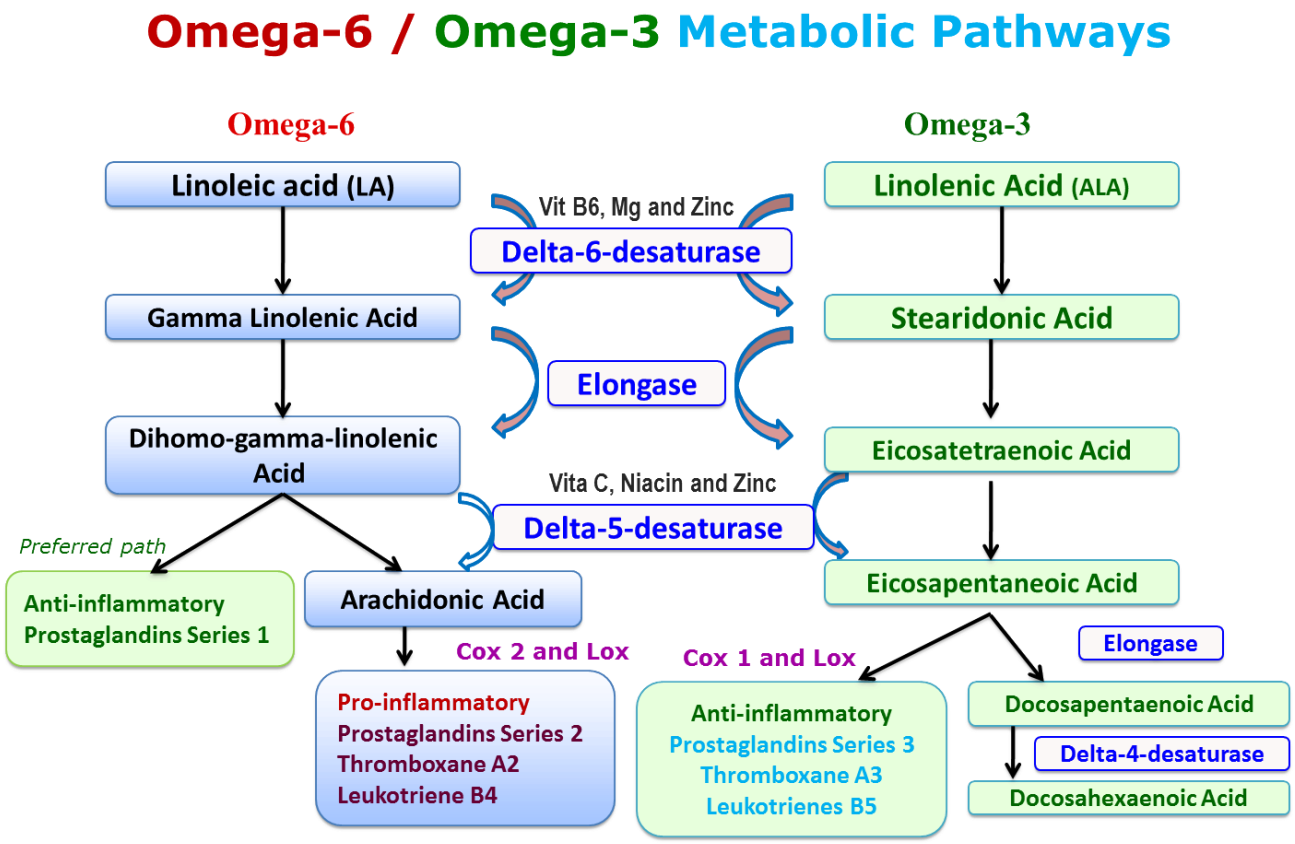
PHOSPHOLIPIDS



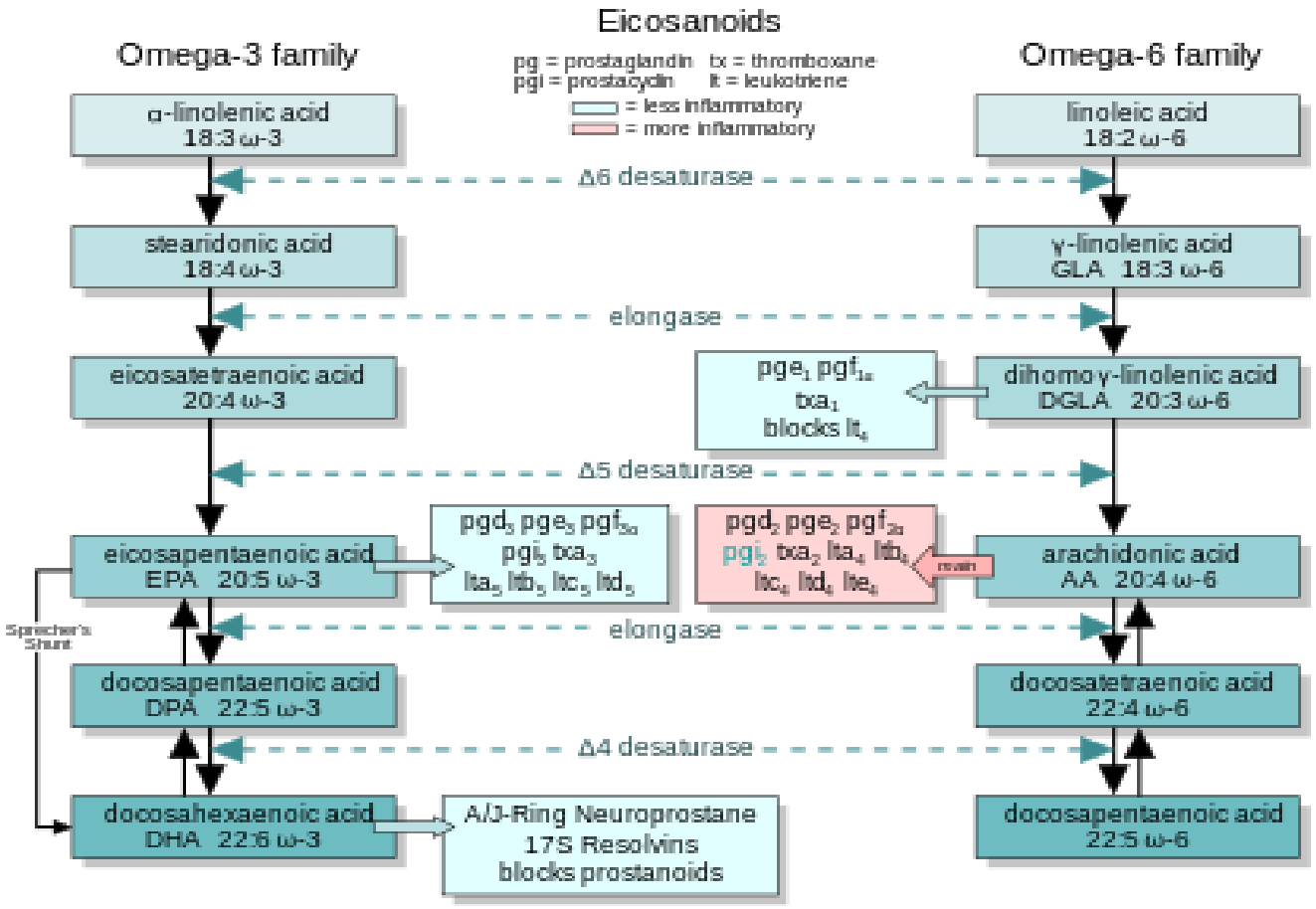
Phosphatidylcholine



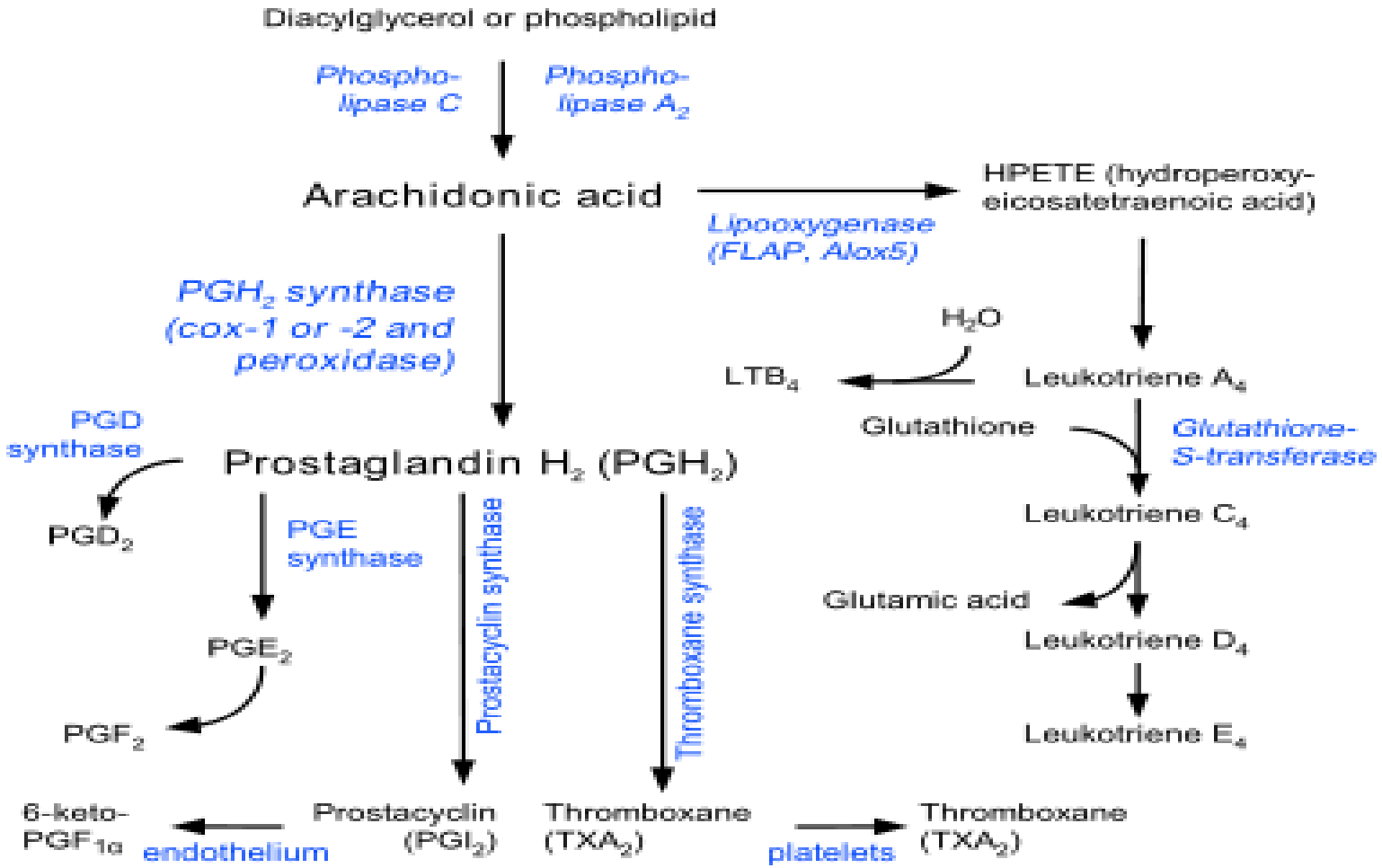
EICOSANOID SYNTHESIS



DHA – CAN BECOME EPA AND REQUIRED FOR BRAIN DEVELOPMENT AND IQ



INFLAMMATORY EICOSANOIDS FROM ARACHIDONIC ACID



Example of Clinical Trials:

In one study EPA dosage of 1500-2000 mg per day resulted in a 50% reduction in depression scores in 8/10 patients (80% success rate) in patients with bipolar depression, when used as single therapy.

Other studies suggest that dosage of up to 8000 mg EPA can be used, and should include some DHA as well (3:1 ratio EPA:DHA approximately).

Not all studies have shown a benefit

Thus, EPA:DHA supplements may be a valuable adjunctive therapy in some cases of unipolar and bipolar depression. I wouldn't recommend it as single therapy unless dealing with pregnant or postpartum women with depression

Pregnant and Postpartum Depression:

Pregnant women often have **depleted omega-3 fat stores** (fetus accumulates the via placental transfer for brain development)

Decreased maternal stores of omega-3 fats associated with increased risk of **bipolar depression during pregnancy**

A number of clinical studies have shown that **EPA:DHA supplementation** effective in **treatment of depression during pregnancy and postpartum depression**, with no adverse effects on fetus

Dosage Range: 3000 – 8000 mg EPA/DHA per day

Quershi, NA, Al-Bedah AM. Mood disorders and complementary and alternative medicine: A literature review. Neuropsychiatric disease and treatment. 2013. 9:639-658

VITAMIN D

Some studies suggest that sub-optimal vitamin D status may increase risk of depression, schizophrenia and possibly other mental health disorders

Depression scores are higher in those with vitamin D blood level below 40 nmol/L compared to those with higher values (at or above 40 nmol/L)

Vitamin D supplementation shown to be helpful as an adjunct in treating depression in several studies, but not all studies have shown a benefit

Mechanism of Action:

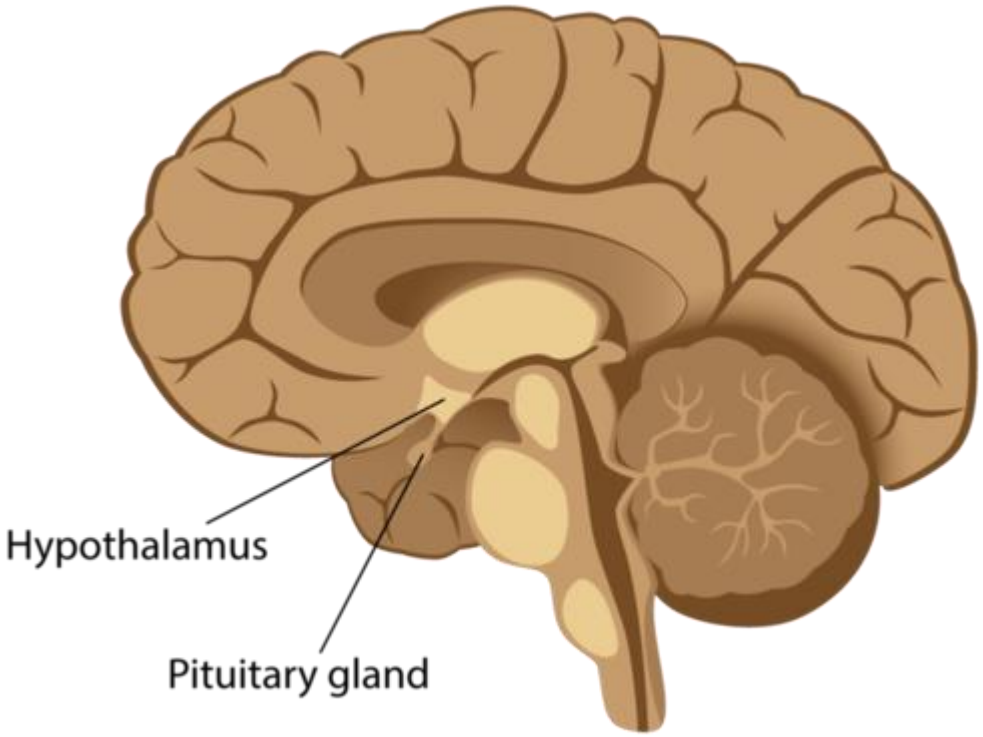
1. Vitamin D receptors present in hypothalamus, which modulates neuroendocrine functioning.
2. Vitamin D also important for brain development

Dosage: 10,000 IU or 20,000 IU, twice per week for one year.

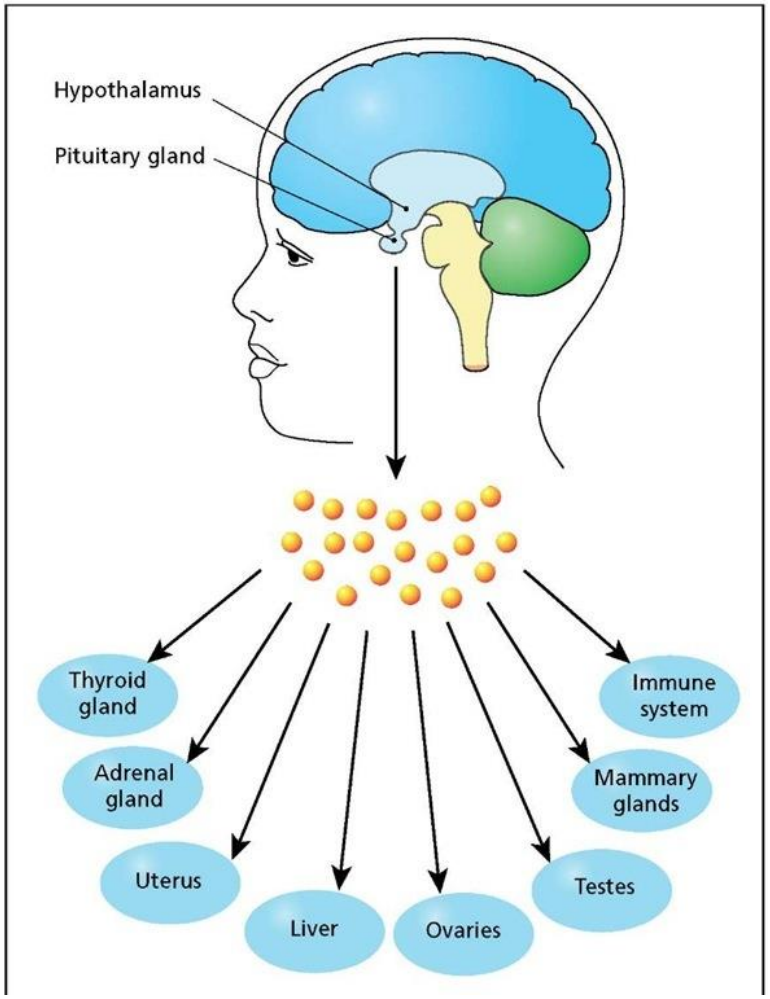
Quershi, NA, Al-Bedah AM. Mood disorders and complementary and alternative medicine: A literature review. Neuropsychiatric disease and treatment. 2013. 9:639-658

Penckofer S et al. Vitamin D and depression: Where is the sunshine? Issuess Ment Health Nurs. 2010. 31(6): 385-393

HYPOTHALAMUS AND PITUITARY GLAND



PITUITARY SECRETES MOLECULES THAT REGULATE MANY ENDOCRINE AND IMMUNE FUNCTIONS



British j psychiatry 2013

- Receptors for vitamin D are present on neurons and glia in many areas of the brain including the cingulate cortex and hippocampus, which have been implicated in the pathophysiology of depression.

- Vitamin D is involved in numerous brain processes including neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity and brain development, **making it biologically plausible that this vitamin might be associated with depression and that its supplementation might play an important part in the treatment of depression.**

- Over **two-thirds** of the populations of the USA and Canada have suboptimal levels of vitamin D.

Anglin RES, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Britisch Journal of Psychiatry. 2013. http://bjp.rcpsych.org/content/202/2/100

Vitamin D Improves Mood and Lowers Blood Pressure in Type 2 Diabetics with Signs of Depression

- Studies have shown that Vitamin D supplementation has the potential to improve mood, blood sugar control and blood pressure regulation. These are important factors in diabetics, as high blood sugar and high blood pressure are frequent findings (1,2).

- Women with Type 2 diabetes tend to have worse outcomes than men. This has been linked to depression to some degree, which affects 25% of women with diabetes. In turn, depression often results in lack of compliance with proper diet, exercise, and medication use, which help control the disease and reduce risk of diabetic complications such as heart disease, kidney failure and stroke (3).

- Approximately 1 in 10 people in the United States has diabetes, and the incidence is projected to increase to 1 in 4 persons by 2050 (3).

- Many Americans do not get enough Vitamin D, and people with diabetes are at especially high risk for Vitamin D insufficiency or deficiency. Reasons include limited intake of foods high in Vitamin D, obesity (increased Vitamin D stored in fat tissue, rather than in circulation), lack of sun exposure, genetic variations and the inflammatory state induced by the disease.

- Vitamin D status is typically low in patients with chronic inflammatory states (e.g. autoimmune disease, diabetes, cancer). Studies have shown that Vitamin D supplementation provided to diabetics can reduce inflammation, improve blood sugar control (by improving insulin receptor activity secondary to a reduced inflammatory state, and by increasing insulin secretion from the pancreas), and increase blood Vitamin D levels into the desirable range (1,3).

- Previous studies have accomplished this by providing diabetics with a daily dosage of 4000 IU of Vitamin D over many months (2).

- A recent pilot study by Sue M. Penckofer, PhD, RN et al, included 46 Type 2 diabetic women (average age 55 years). These women had diabetes for an average of 8 years and also showed low blood levels of Vitamin D (18 ng/ml). They were given a weekly dose (50,000 International Units) of Vitamin D.

- After six months, their Vitamin D blood levels rose to an average level of 38 ng/ml, which is in the desirable range. **There was also objective evidence of improved mood, as indicated by a 20-question depression symptom survey. Scores decreased from 26.8 at the beginning of the study (indicating moderate depression) to 12.2 at six months (indicating no depression.)** (The depression scale ranged from 0 to 60, with higher numbers indicating more symptoms of depression.)

- Blood pressure also improved, with the systolic pressure decreasing from 140.4 mm Hg to 132.5 mm Hg. There was also a small reduction in body weight, which dropped from an average of 226.1 pounds to 223.6 pounds (3).

Summary

- Vitamin D status is emerging as an important variable in diabetes management. Health practitioners treating diabetic patients, and those with metabolic syndrome, should routinely examine blood levels of Vitamin D in these patients.

- If Vitamin D levels are low, it would prudent to provide these patients with sufficient Vitamin D supplementation to achieve blood levels in the desirable range. The desirable range for Vitamin D (25-hydroxycholecalciferol) is reported to be above 35 ng/ml or 90 nmol/L (4).

- **A daily dosage of 4000 IU per day appears to be a safe and reasonable dosage to start with, according to previous studies**. Clinical studies show that Vitamin D supplementation in these cases has the potential to improve diabetic management by increasing insulin sensitivity, insulin secretion, reducing the inflammatory state associated with the diabetes, improving immune function, lowering blood pressure, **and elevating mood,** which may improve patient compliance with lifestyle recommendations and medication use.

References:

- Sung CC, Liao MT, Lu KC, Wu CC. Role of Vitamin D in insulin resistance: Review article. Journal of Biomedicine and Biotechnology. 2012. (Hindawi Publishing Corporation) http://www.hindawi.com/journals/bmri/2012/634195
- Belanchia, AM, Tosh AK, Hillman LS and Peterson CA. Correcting Vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. Am J Clin Nutr. 2013. **050013**
- Loyola University Health System (2013, June 25). Vitamin D improves mood and blood pressure in women with diabetes. http://www.newswise.com/articles/vitamin-d-improves-mood-and-blood-pressure-in-women-with-diabetes
- Moyad MA. Vitamin D: A rapid review. Dermatology Nursing. 2009;21(1). http://www.medscape.com/viewarticle/589256_7

NEUROTRANSMITTERS AND MENTAL HEALTH

Certain Brain Chemicals (neurotransmitters) are important in mental health and memory

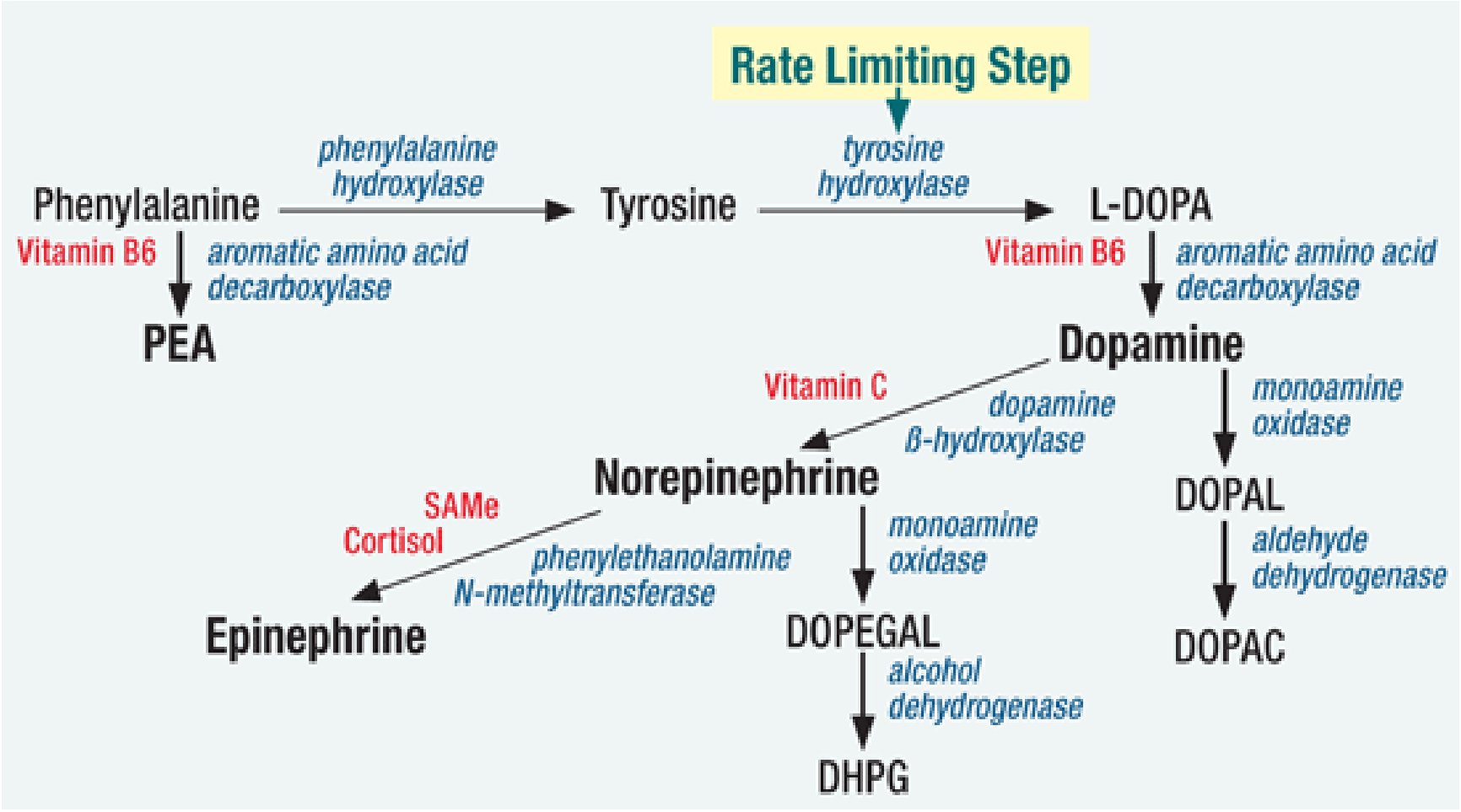
1. Serotonin, Norepinephrine (NE) and Dopamine – required for mood elevation, alertness, reward behaviour, feeling pleasure

2. Acetylcholine – required for memory

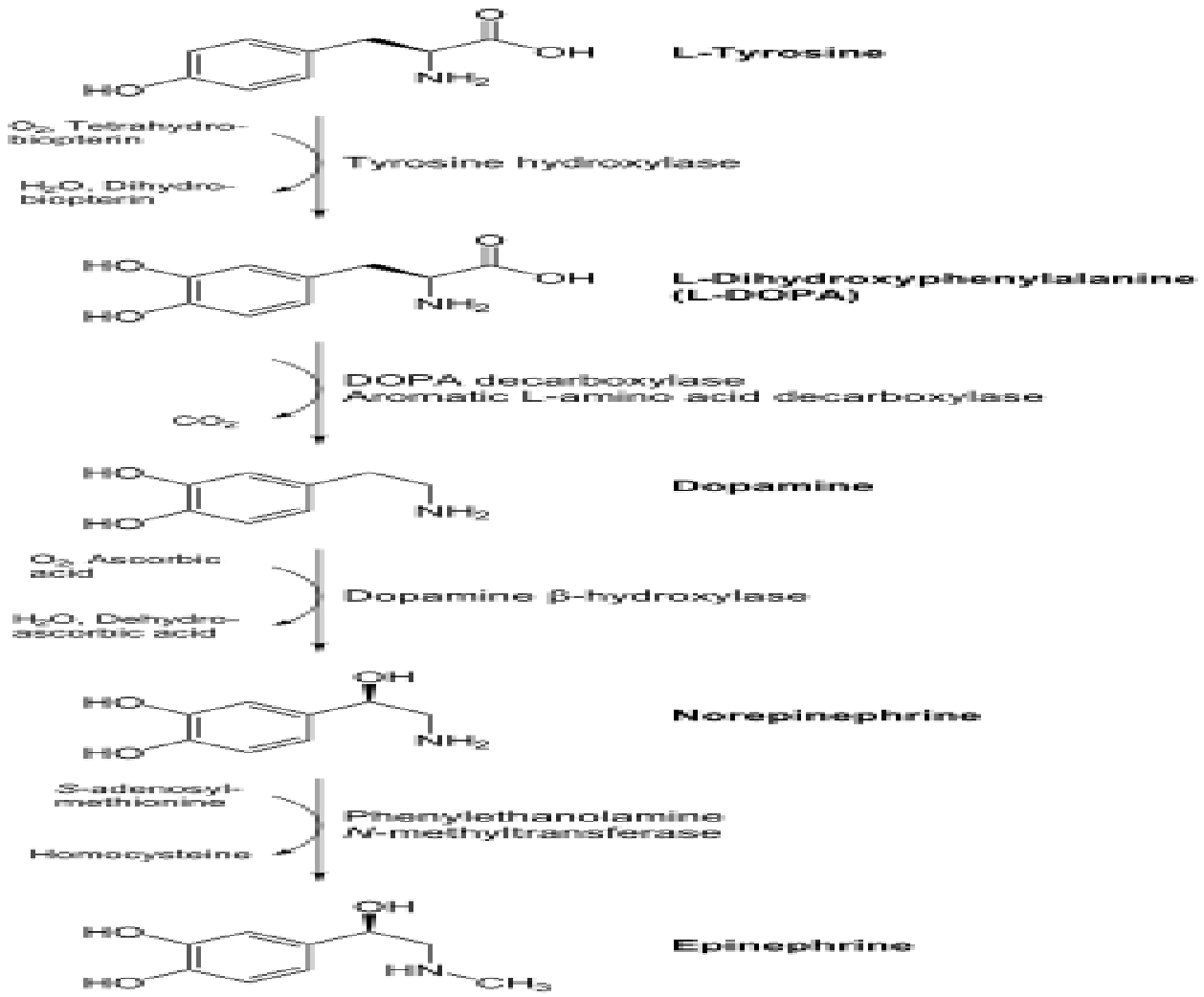
3. Melatonin – required for sleep, immune regulation, other

Many medications used to treat depression work by raising or balancing key neurotransmitters, especially serotonin, dopamine and NE (e.g. SSRI's)

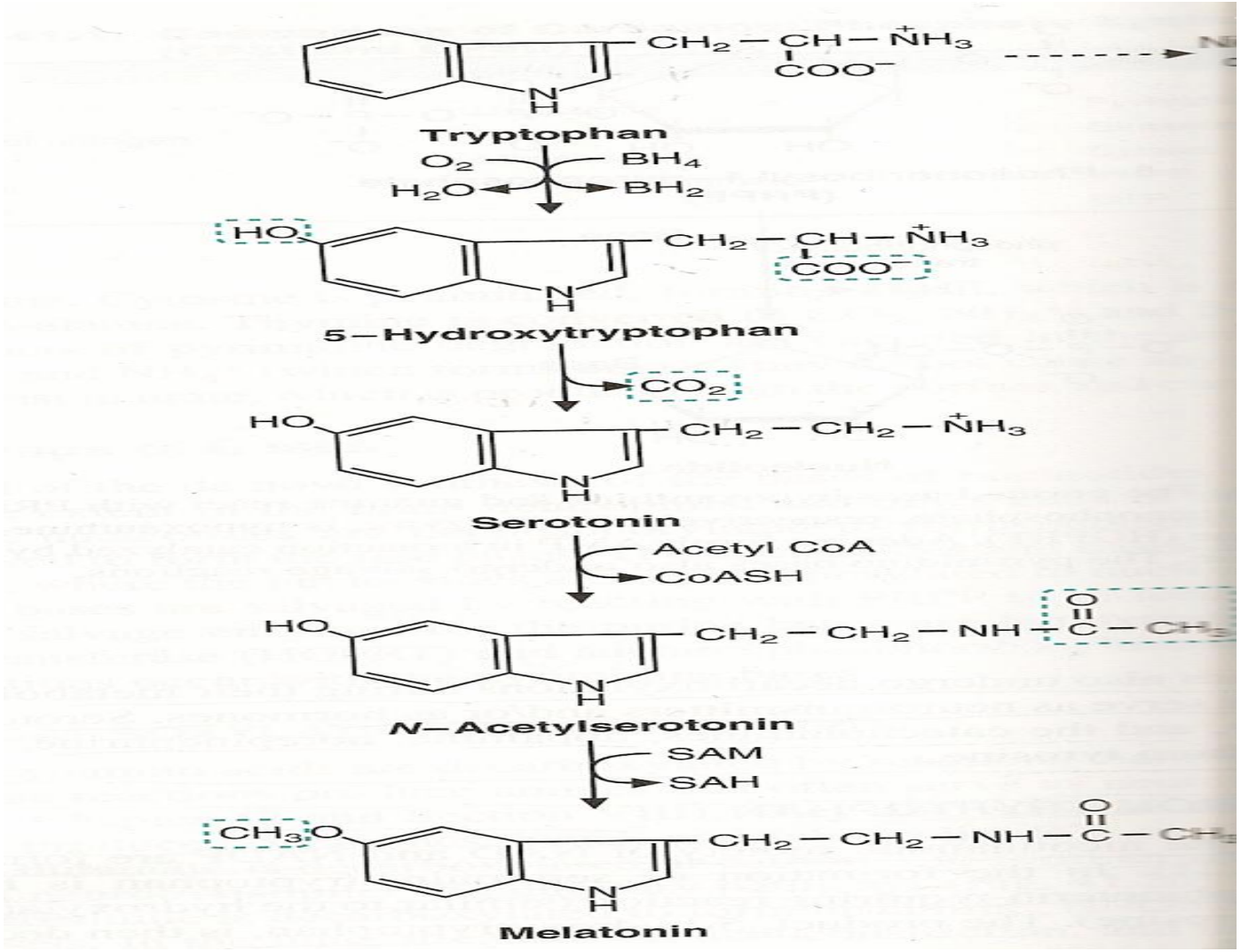
SYNTHESIS OF DOPAMINE, NE AND EPINEPHRINE



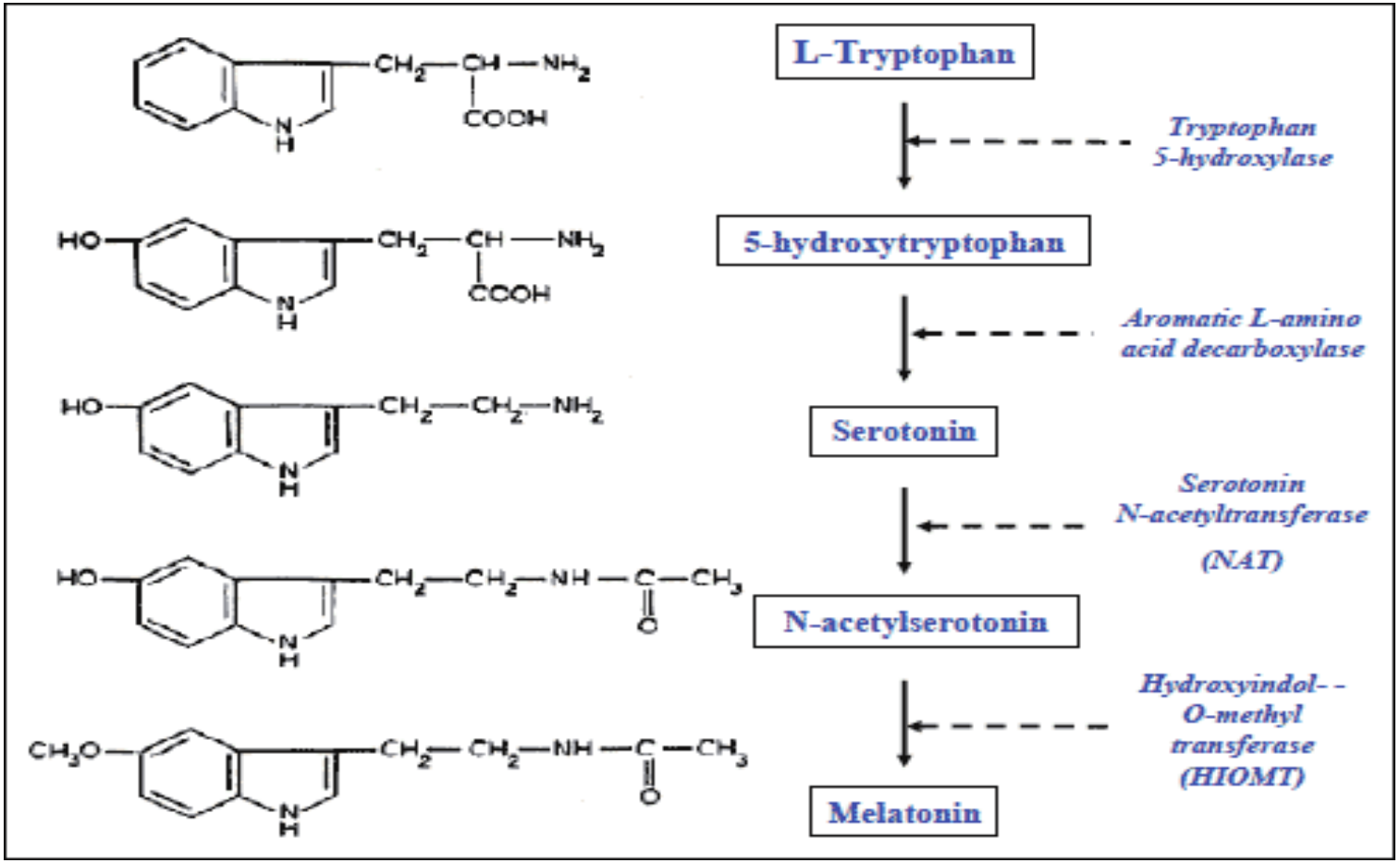
Synthesis of Catecholamines: Dopamine, Norepinephrine and Epinephrine
Recall: phenylalanine is converted into tyrosine



Serotonin-melatonin Synthesis



Serotonin-Melatonin Synthesis

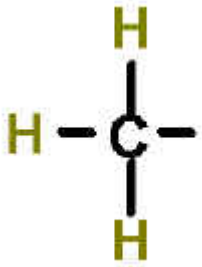


S-adenosylmethionine, Folic Acid, Vitamin B12

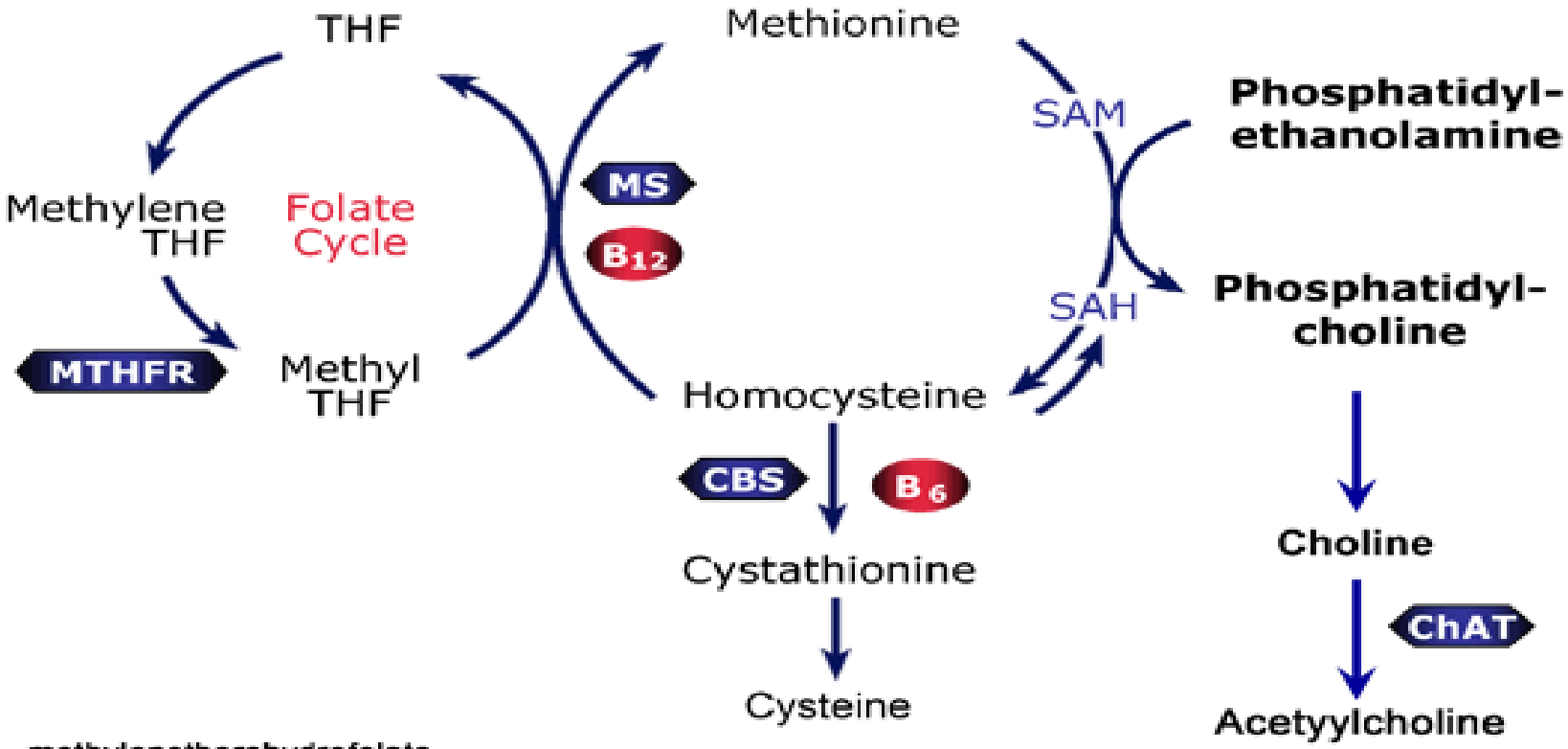
SAMe (S-adenosyl methionine) , folic acid and vitamin B12 required to synthesize Dopamine, Norepinephrine and Epinephrine

Women know that Folic Acid Supplementation During Pregnancy reduces risk of Spina Bifida by 50%. Why? Folic acid allows transfer of methyl group to form DNA.

Methylation reactions also important in synthesis of neurotransmitters, nerve cell membrane phospholipids and other important nervous system structures.



Methyl Group



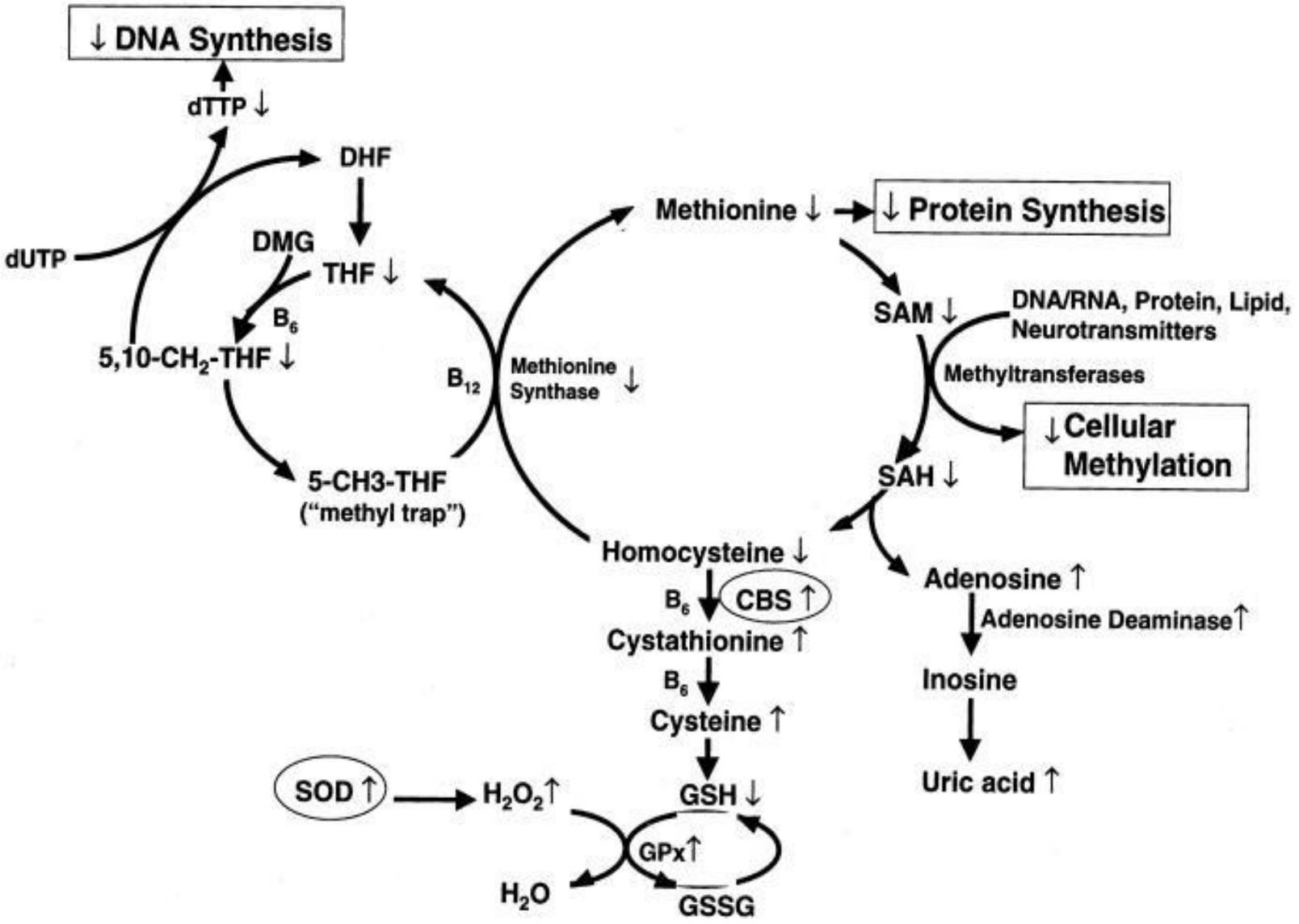
MTHFR - methylenetherahydrofolate reductase

MS - methionine synthase

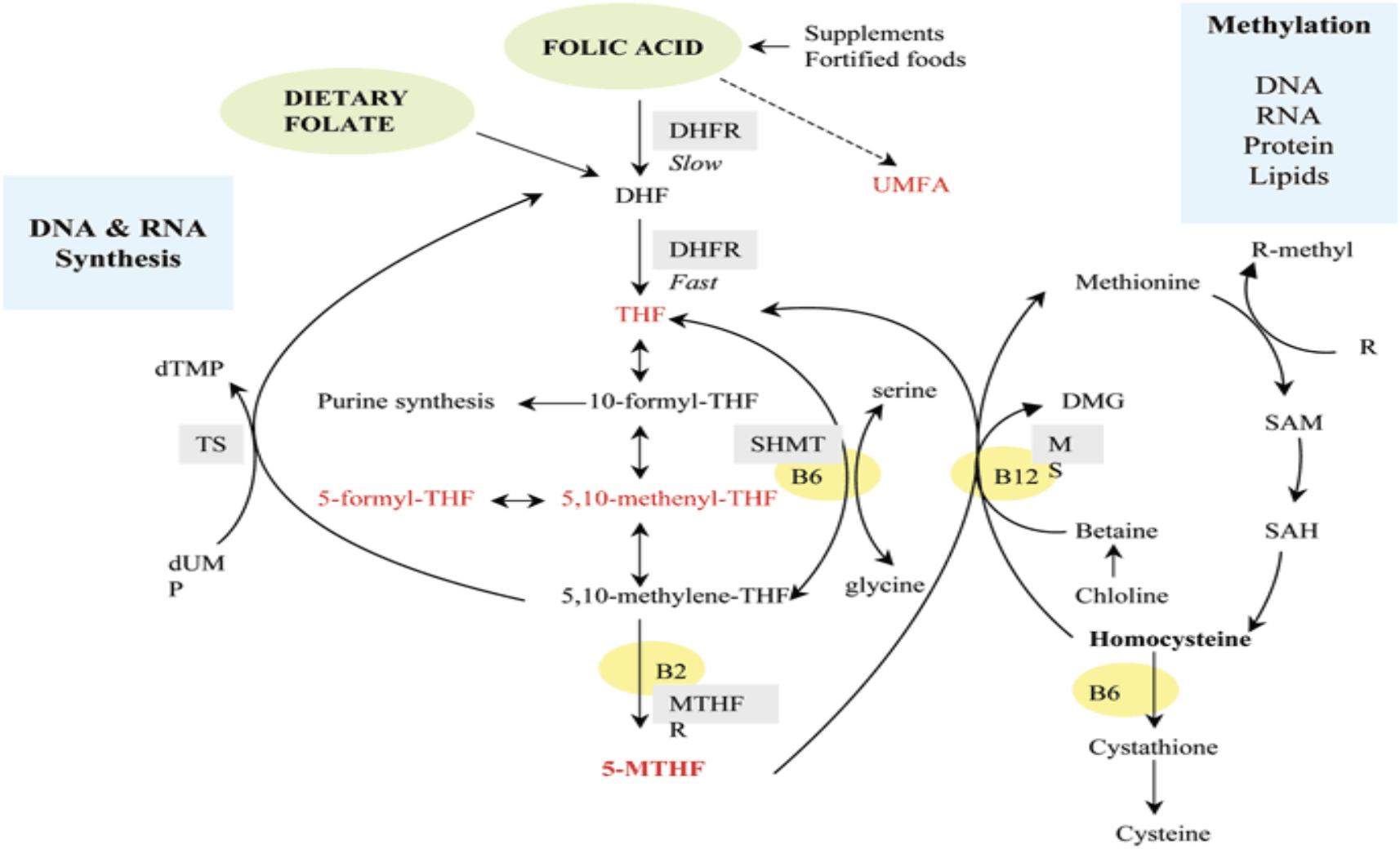
CBS - cystathione beta synthase

ChAT - choline acetyltransferase

Inter-Relationship Between FA, B12 and SAMe



Defects in MTHF Reductase and/or Methionine Synthase



Folic acid and Depression

- Low folic acid levels highly correlated with depression
- 10% of Caucasians have a severe MTHF reductase defect (usually see high blood homocysteine that is unresponsive to folic acid supplementation)
- Another 40% of Caucasians have a heterozygous form of defect (where folic acid supplementation – 1000 mcg per day, can over come defect in many cases) – high homocysteine levels is a clue in presence of normal RBC folate levels
- In MTHR defect cases, supplementation with methylfolate is required to optimize SAMe synthesis and help treat depression.

Folic Acid Supplementation Studies

- Folate deficiency strongly linked to depression and cognitive decline, as well as lack of motivation and social withdrawal which are folate-responsive symptoms.

- Depression patients with low folate levels show poor response to anti-depressant drugs.

- Studies using folic acid supplementation alone, or in conjunction with psychotropic drugs (for one year) have shown good results with mood, cognitive function, and social recovery.

- The question remains what form of folic acid is best for this purpose (folic acid, folinic acid, or perhaps methyl folate – which is the form that crosses the blood-brain barrier).

- http://www.direct-ms.org/sites/default/files/B12%20folic%20acid%20nervous%20system.pdf)

A. In a randomized, double-blind, placebo-controlled study, 123 patients with schizophrenia and major depression on standard psychotropic medications were augmented with 15 mg per day of methyl-folate supplementation or placebo.

- Results - methyl-folate group showed superior response regarding clinical and social symptoms

B. A study of 127 patients on fluoxetine were provided with 400 mcg. of folic acid or placebo.

- The folic acid group showed a 94% response rate compared to 61% in the fluoxetine plus placebo group.

Vitamin B12 and Mental Health

- Psychiatric Symptoms - Mood, behavioural changes, psychosis, memory impairment, and cognitive decline can result from low folate and/or vitamin B12.

- Up to 1/3 of psychiatric patients, and especially psychogeriatric admissions have low serum or RBC folate, mostly **without** anemia or macrocytosis.

- About 5% have low vitamin B12, but for elderly patients – 10-20% show low vitamin B12 levels.

- Low vitamin B12 linked primarily to cognitive decline.

- http://www.direct-ms.org/sites/default/files/B12%20folic%20acid%20nervous%20system.pdf

Methionine Synthase Defects in B12 Metabolism

- In the presence of normal serum vitamin B12, high homocysteine levels, plus high methylmalonic acid (MMA) levels, suggest a methionine synthase enzyme defect, where by higher amounts of vitamin B12 are required to overcome the enzyme polymorphism.

- Depression in the Elderly - A dosage of Vitamin B12 is typically **100-500 mcg to correct the deficiency, then a maintenance dose of 25-75 mcg per day**.

- Supplementation with folic acid, vitamin B12 and vitamin B6 are often used to lower homocysteine in the prevention of cardiovascular disease and Alzheimer's disease (and osteoporosis).

Folic Acid and B12 Status

- In January 1998, the U.S. Food and Drug Administration (FDA) began requiring manufacturers to add folic acid to enriched breads, cereals, flours, corn meals, pastas, rice, and other grain products
- The fortification program was projected to increase folic acid intakes by approximately 100 mcg/day but the program actually increased mean folic acid intakes in the United States by about 190 mcg/day.

- The Canadian government has also required the addition of folic acid to many grains, including white flour, enriched pasta, and cornmeal, since November 1, 1998

- However, certain groups, including women of childbearing age and non-Hispanic black women, are at risk of insufficient folate intakes.

- **Even when intake of folic acid from dietary supplements is included, 19% of female adolescents aged 14 to 18 years and 17% of women aged 19 to 30 years do not meet the EAR. Similarly, 23% of non-Hispanic black women have inadequate total intakes, compared with 13% of non-Hispanic white women.**

- No appreciable storage of folic acid, so must be supplied daily at optimal intake levels

- http://ods.od.nih.gov/factsheets/Folate-HealthProfessional

B12 Deficiency and Depression in Patients over 60

B12 Deficiency Common In Aging:

- Decreased Stomach Acid
- Decreased Intrinsic Factor
- Increased use of Antacids, H2 blockers and Proton Pump Inhibitors
- Decreased food intake

- B12 storage in liver contains 1-3 year supply

Recent Report New York Times 2011

Subject: Old Age and Vitamin B-12

New York Times Personal Health

- **It Could Be Old Age, or It Could Be Low B12**
- By JANE E. BRODY Published: November 28, 2011

(Excerpt)

- Ilsa Katz was 85 when her daughter, Vivian Atkins, first noticed that her mother was becoming increasingly confused.

- A workup at a memory clinic resulted in a diagnosis of early Alzheimer's disease, and Ms. Katz was prescribed Aricept, which Ms. Atkins said seemed to make matters worse. But the clinic also tested Ms. Katz's blood level of vitamin B12. It was well below normal, and her doctor thought that could be contributing to her symptoms.

- Weekly B12 injections were begun. "Soon afterward, she became less agitated, less confused and her memory was much better," said Ms. Atkins. "I felt I had my mother back, and she feels a lot better, too."
- http://www.nytimes.com/2011/11/29/health/vitamin-b12-deficiency-can-cause-symptoms-that-mimic-aging.html?ref=health

2005 Review J. Psychopharmacology

Abstract

- Both low folate and low vitamin B12 status have been found in studies of depressive patients, and an association between depression and low levels of the two vitamins is found in studies of the general population.

- Low plasma or serum folate has also been found in patients with recurrent mood disorders treated by lithium. A link between depression and low folate has similarly been found in patients with alcoholism.

- Low folate levels are furthermore linked to a poor response to antidepressants, and treatment with folic acid is shown to improve response to antidepressants.

- A recent study also suggests that high vitamin B12 status may be associated with better treatment outcomes. Folate and vitamin B12 are major determinants of one-carbon metabolism, in which S-adenosylmethionine (SAM) is formed. SAM donates methyl groups that are crucial for neurological function.

- Increased plasma homocysteine is a functional marker of both folate and vitamin B12 deficiency. **Increased homocysteine levels are found in depressive patients.** In a large population study from Norway increased plasma homocysteine was associated with increased risk of **depression but not anxiety.**

- **There is now substantial evidence of a common decrease in serum/red blood cell folate, serum vitamin B12 and an increase in plasma homocysteine in depression.**

- Furthermore, the MTHFR C677T polymorphism that impairs the homocysteine metabolism is shown to be overrepresented among depressive patients, which strengthens the association. **On the basis of current data, we suggest that oral doses of both folic acid (800 mcg daily) and vitamin B12 (1 mg daily) should be tried to improve treatment outcome in depression.**

- Coopen A, Bolander-Gouaille C. Treatment of depression: time to consider folic acid an vitamin B12. J Psychopharmacol. 2005. 19(1): 59-65

Personalized Supplementation Plan to Enhance Treatment of Depression

Required Blood Test to Determine What Supplements Will Improve Drug Treatment of Depression in PTSD

1. Serum and RBC Folic Acid (% of RBC folate in methyl-folate form)
2. Serum Vitamin B12
3. Homocysteine
4. Methylmalonic acid (MMA) this may be clue individual has polymorphism in vitamin B12-dependent enzymes (one of which is methionine synthase)- an expensive test, however.

If RBC folic acid, serum B12 and MMA are normal and homocysteine is high then suspect a MTHFR defect. Treatment requires methyl-folate.

If RBC folate and serum B12 is normal, and homocysteine and MMA is high, then suspect a Methionine Synthase defect. Treatment requires therapeutic doses of Vitamin B12

Alcohol and Folic acid depletion

- Alcohol—Inhibits folic acid **absorption** from gut
- Alcohol—Decreases **activation** of folic acid
- Alcohol—Speeds up folic acid **excretion** in urine
- **Alcohol—Promotes hypomethylation of DNA**

And Cancer Risk

- Alcohol—Generates free radicals
- Alcohol—Is a co-carcinogen
- Alcohol—Increases secretion of estrogen (breast cancer risk)

- Alcohol consumption linked to double the risk of breast and colon cancer (3 drinks/wk)

S-Adenosylmethionine

SAMe

- Acts as a methyl donor in cellular methylation reactions, to methylate DNA, RNA to synthesize phospholipids (phosphatidylcholine from phosphatidylethanalomine, and to synthesize and various neurotransmitters such as **epinephrine and melatonin.** And surprisingly required to make dopamine, norepinephrine and serotonin as we will see shortly.

- It may restore the underlying G protein-receptor coupling-uncoupling dysfunction seen in some mental health disorders (see next slide)

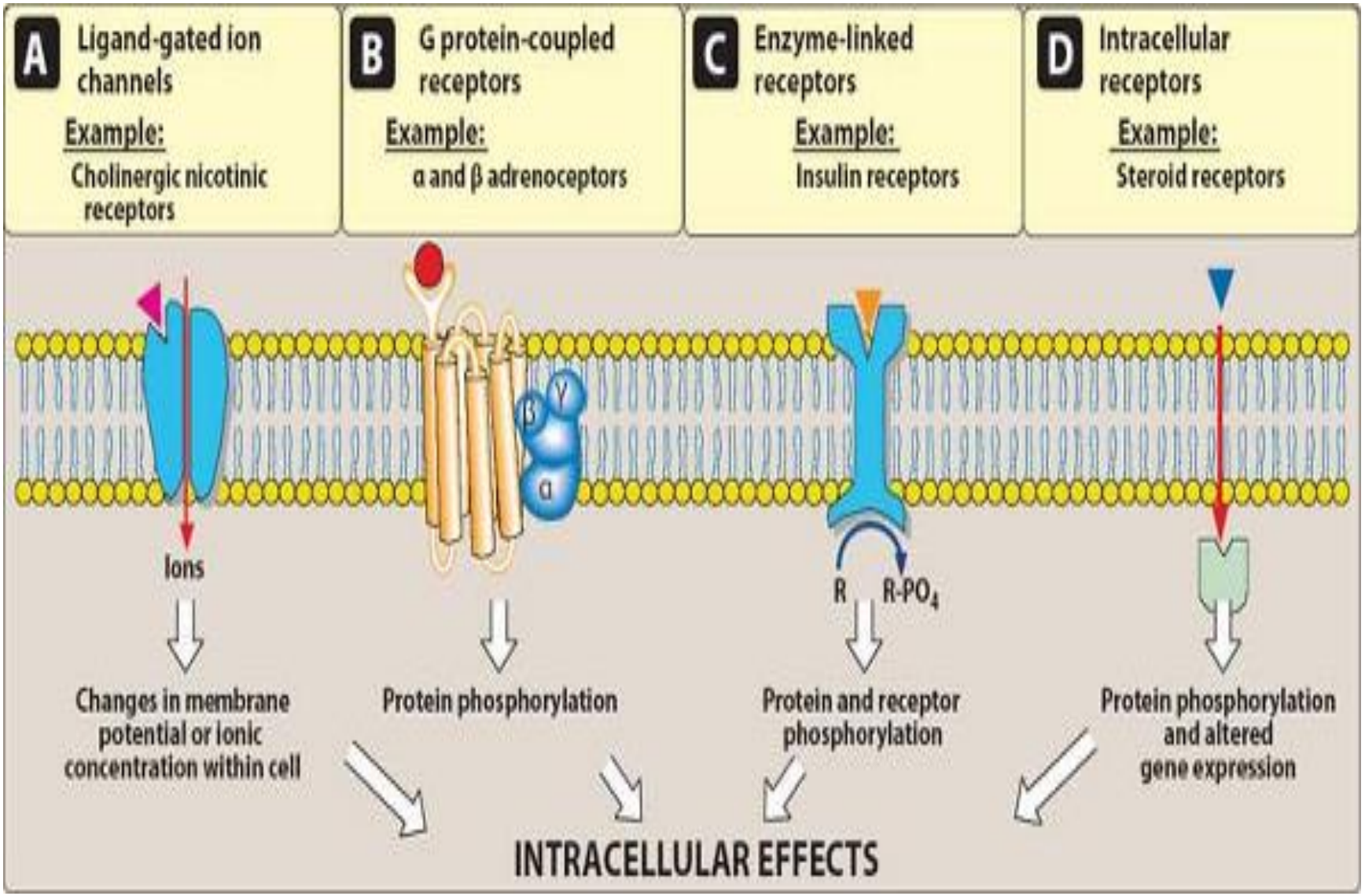
- Shown to reverse regional brain volume loss in depressive rat models via natural **polyamines** such as spermidine and spermine, and their diamine precursor putrescine, has also been postulated. (see upcoming slides)

- S-adenosyl methionine as treatment for depression: A systematic review. http://works.bepress.com/cgi/viewcontent.cgi?article=1009&context=vivianmcalister&sei-redir=1&referer=http%3A%2F%2Fscholar.google.ca%2Fscholar%3Fq%3DSAMe%2Bsupplementation%2Bin%2Bmental%2Bhealth%26hl%3Den%26as_sdt%3D0%26as_vis%3D1%26oi%3Dscholart%26sa%3DX%26ei%3DB9pHVeuFLcjFggTZgIHgCA%26ved%3D0CBsQgQMwAA#search=%22SAMe%20supplementation%20mental%20health%22

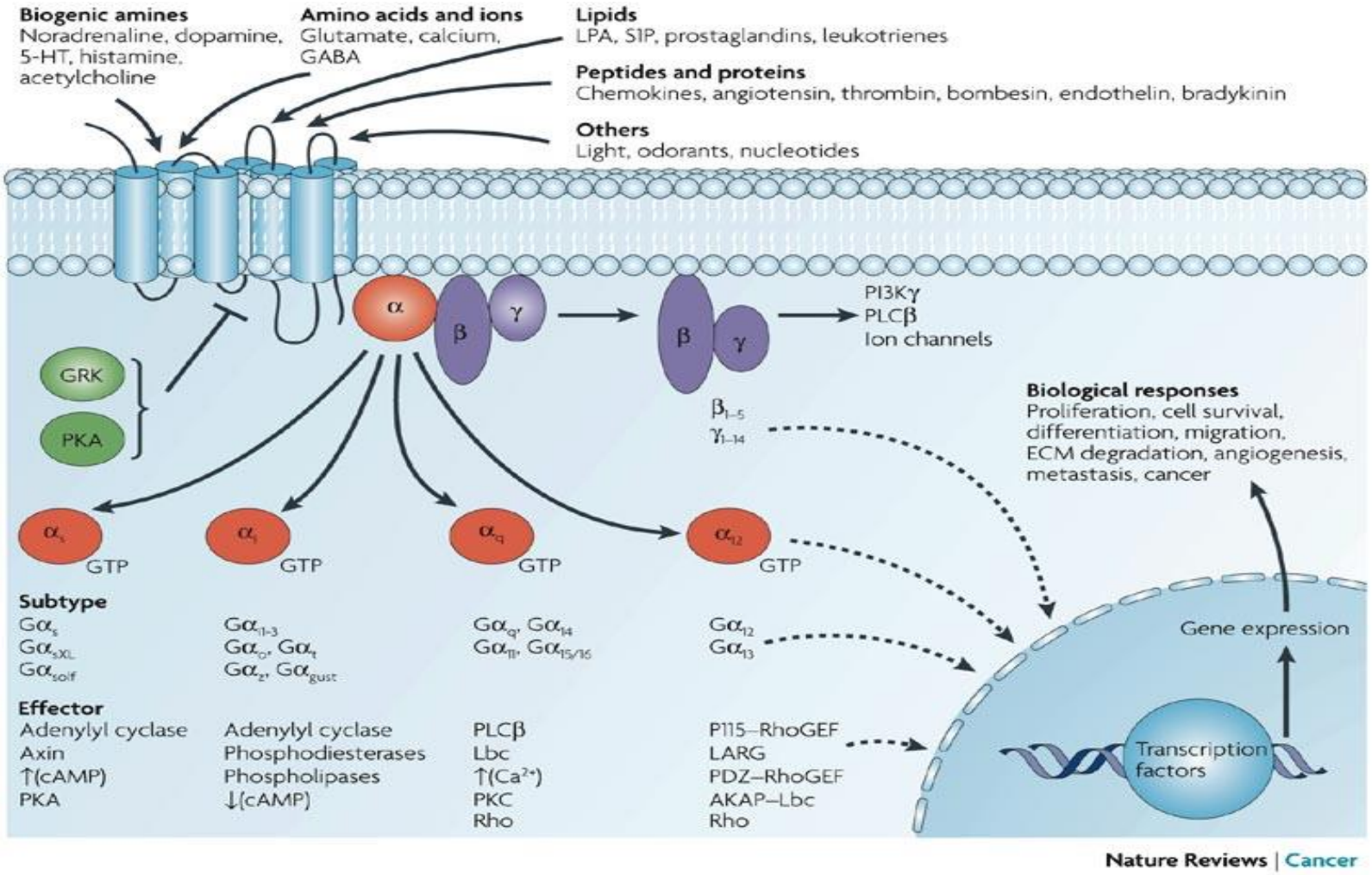
G-coupled Protein Receptors - Integral membrane proteins that possess seven member domains, all of which traverse the cell membrane.

Some Physiological Roles Include:

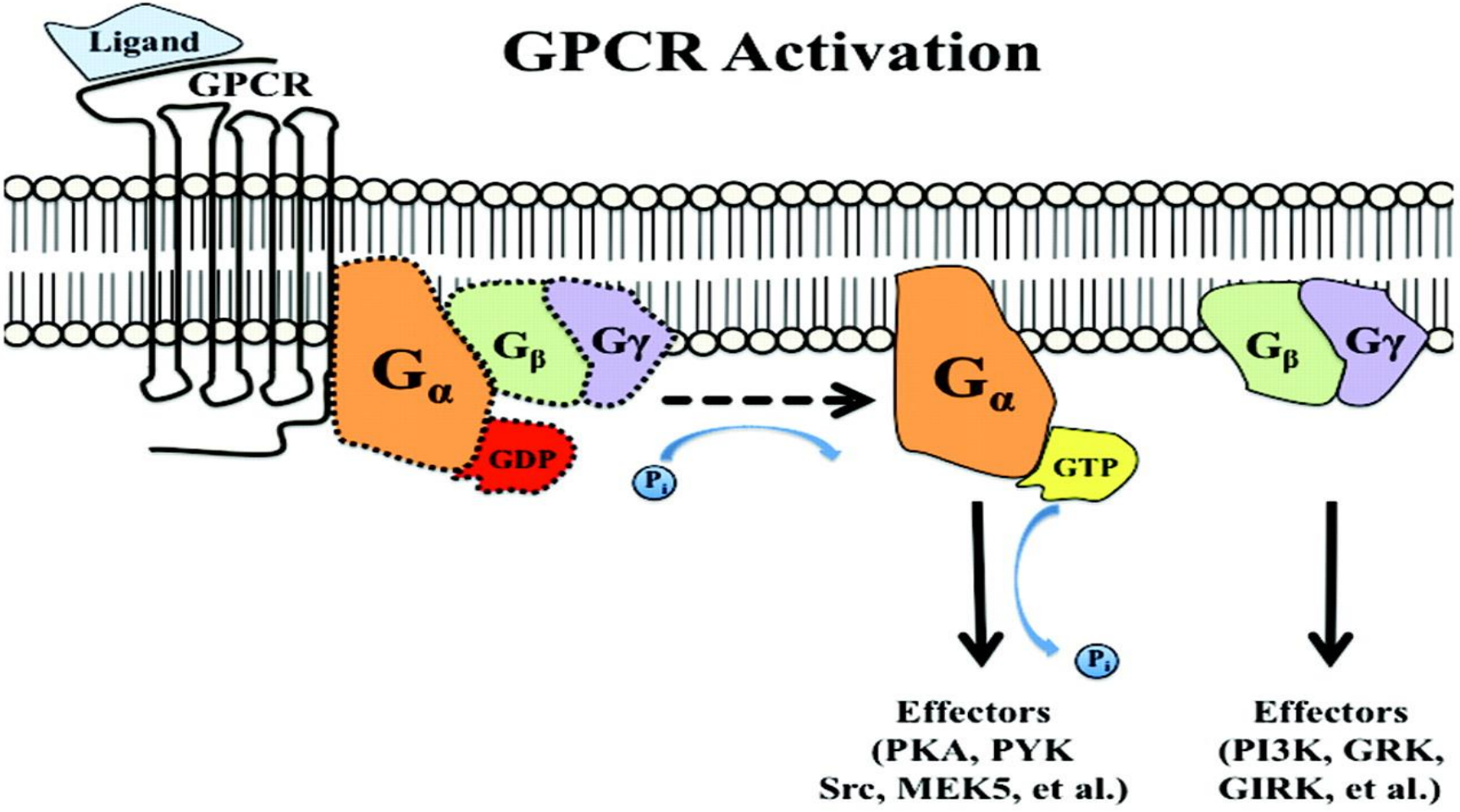
- Visual Sense:
- Taste Cells
- Sense of Smell
- **Behavioral and Mood Regulation – receptors in the mammalian brain bind different neurotransmitters, including serotonin, dopamine, GABA and glutamate.**
- Immune System Regulation
- Autonomic Nervous System Transmission
- Cell Density Sensing
- Homeostasis (water balance e.g.)
- Involved in Growth and Metastasis of some tumors


A
Ligand-gated ion channels
Example:
Cholinergic nicotinic receptors
B
G protein-coupled receptors
Example:
α and β adrenoceptors
C
Enzyme-linked receptors
Example:
Insulin receptors
D
Intracellular receptors
Example:
Steroid receptors
Ions
R
R-PO4
Changes in membrane potential or ionic concentration within cell
Protein phosphorylation
Protein and receptor phosphorylation
Protein phosphorylation and altered gene expression
INTRACELLULAR EFFECTS

G-coupled Proteins transmit signals to inner cell signal transduction network

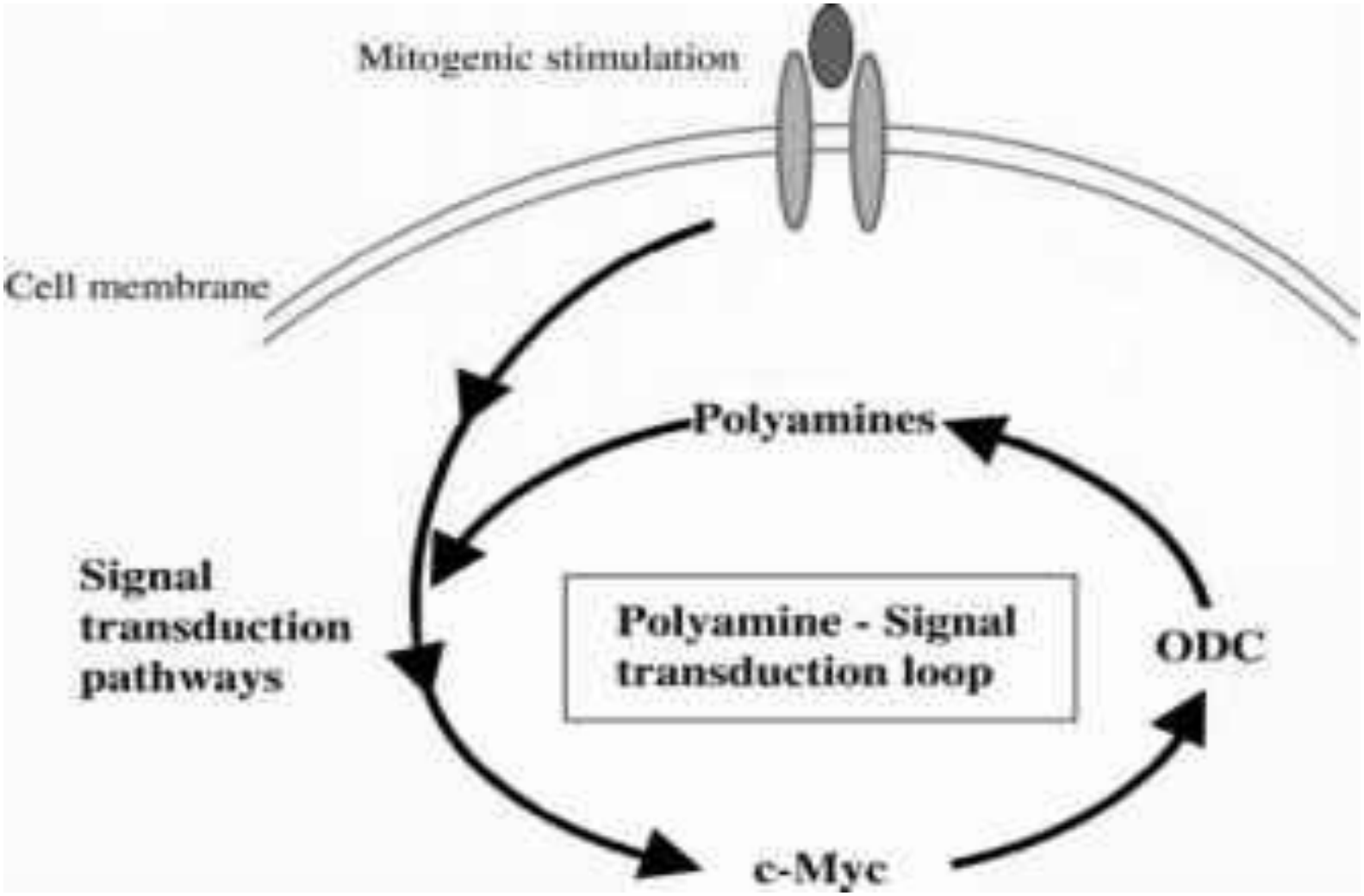


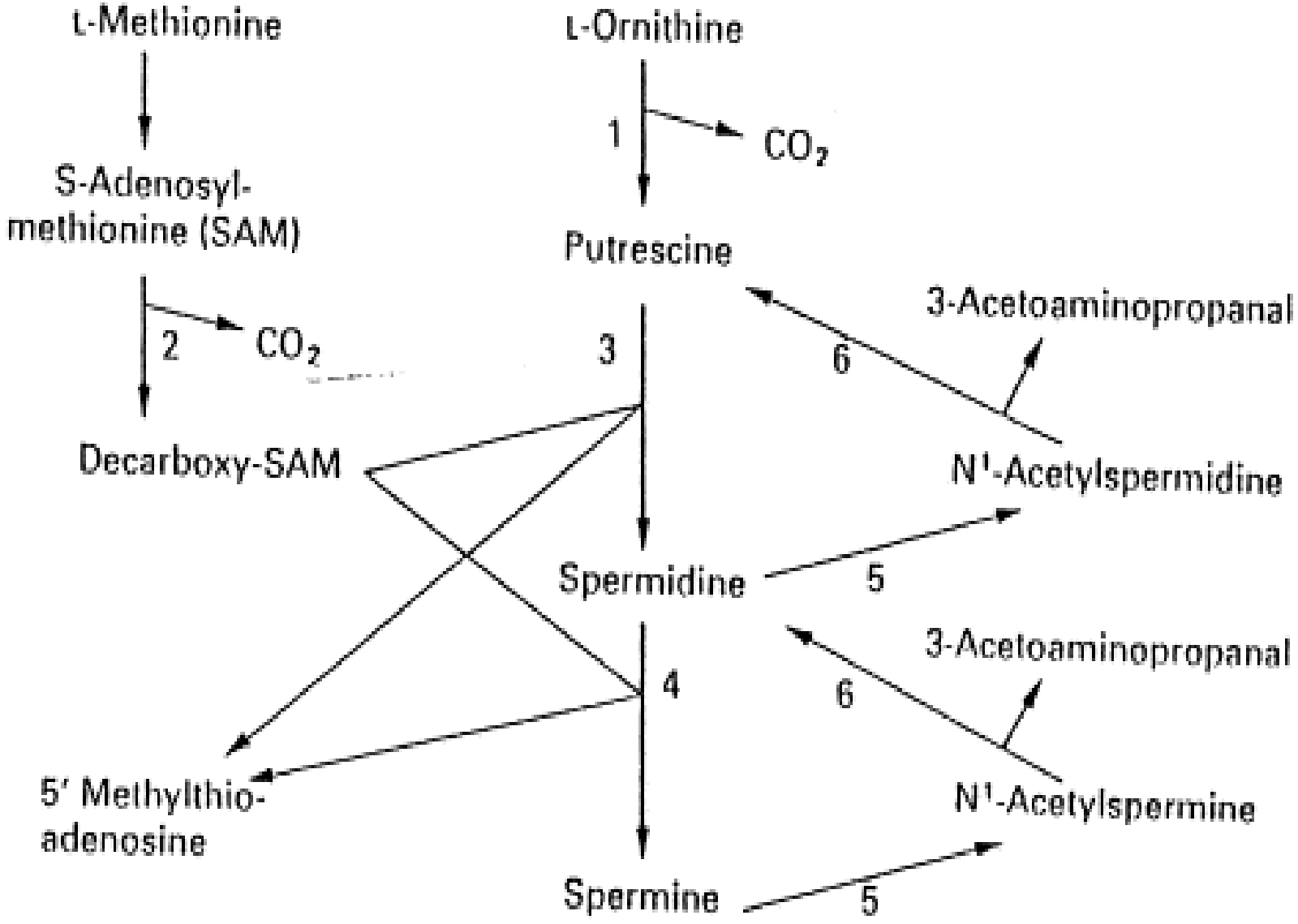
G-coupled proteins work better with
optimal phospholipid synthesis and membrane fluidity.
These are somewhat SAM-E DEPENDENT

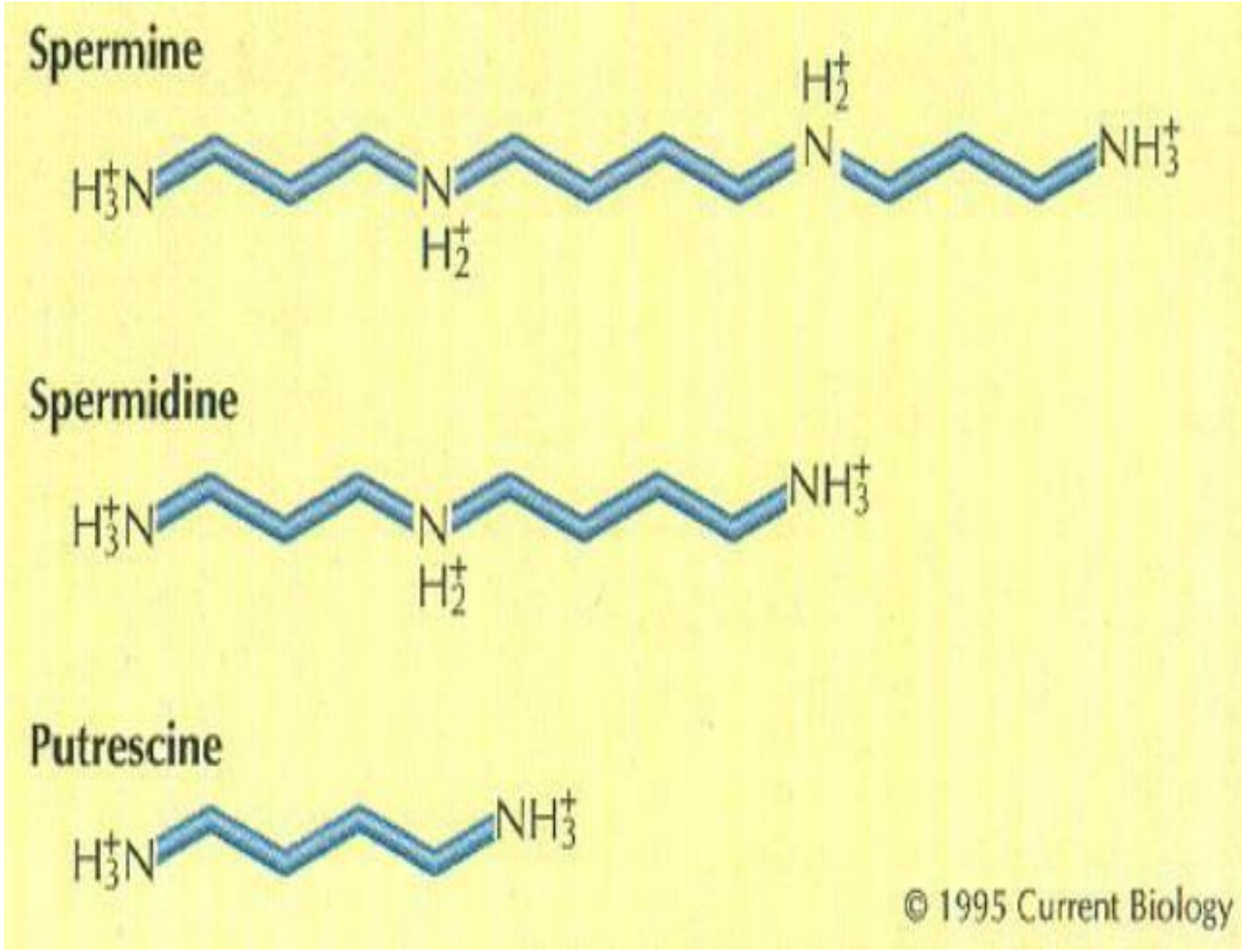


Polylamine Pathway in Mental Health Disorder

- The polyamine pathway has an essential role in many cellular functions and has been implicated in several pathological conditions.
- Accumulating evidence suggests that the polyamine system also plays a role in the etiology and pathology of mental disorders.
- Alterations in the expression and activity of polyamine metabolic enzymes, as well as changes in the levels of the individual polyamines, have been observed in multiple conditions, including schizophrenia, mood disorders, anxiety and suicidal behaviour.
- Additionally, these components have been found to be altered by various psychiatric treatments.
- Further, the polyamines and their precursors have demonstrated both antidepressant and anxiolytic effects.


Mitogenic stimulation
Cell membrane
Polyamines
Signal transduction pathways
Polyamine - Signal transduction loop
ODC
c-Myc


L-Methionine
S-Adenosyl-
methionine (SAM)
2
CO_2
Decarboxy-SAM
L-Ornithine
1
CO_2
Putrescine
3
Spermidine
4
5' Methylthio-
adenosine
Spermine
6
3-Acetoaminopropanal
N^1-Acetylspermidine
5
6
3-Acetoaminopropanal
N^1-Acetylspermine
5


Spermine
H_3^+N
N
H_2^+
H_2^+
N
NH_3^+
Spermidine
H_3^+N
N
H_2^+
NH_3^+
Putrescine
H_3^+N
NH_3^+
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- Despite the success of monoamine-related pharmacologic treatments, they are not effective in many patients, indicating that these systems are not the sole factors involved in these conditions.

- The role in mental illness of an alternative pathway, the polyamine system, has been gaining support.

- Although they are known better for their role in modulating the cell cycle, and consequently their relevance to cancer, research in the last few decades has shown the importance of the polyamines in numerous neurodegenerative conditions, and substantial evidence is emerging that supports their role in the pathophysiology of psychiatric disorders.

- Accordingly, the polyamines represent an important system for understanding the causes of mental illnesses and, in addition, provide a new pharmacologic target for their treatment.

- The polyamines are ubiquitous aliphatic molecules comprising putrescine, spermidine and spermine, which contain 2, 3 and 4 amino groups, respectively.

- The polyamines and their biosynthetic enzymes are found throughout the body, including the CNS, where they display specific regional distributions

- Putrescine, spermidine and spermine possess only a limited capacity to cross the blood–brain barrier, and as such, their localization in the healthy CNS largely represents those which have been endogenously synthesized

- Because of their vital roles, the polyamine metabolic pathways are highly regulated.

- The major rate-limiting enzymes are ornithine decarboxylase (ODC), **S-adenosylmethionine (SAMe) decarboxylase (AMD1),** and spermidine/spermine N^1-acetyltransferase (SAT1), whose activities are controlled at multiple levels by numerous mechanisms, including feedback control by the polyamines themselves.

- The activities of spermidine synthase (SRM) and spermine synthase (SMS) are generally constant.

- The polyamines are involved in many aspects of gene expression. In addition, polyamines influence the properties of proteins and membranes and function as antioxidants and scavengers of reactive oxygen species.

- Owing to their interactions with several transmembrane channels, they also influence the electrical properties of excitable cells.

- Agmatine is believed to act as a neurotransmitter by its actions through several receptors, and this theory is supported by its storage in synaptic vesicles and its capacity to be released on depolarization.

- Spermine has also been shown to be released from synaptic vesicles on depolarization, indicating that the polyamines may function as neuromodulators.

- **Additionally, polyamines influence the properties of several neurotransmitter pathways known to be involved in mental disorders, including the catecholamines, γ-amino-butyric acid, nitric oxide, and glutamate.**

Schizophrenia - certain treatments for schizophrenia have been shown to alter both polyamine levels and the activities of polyamine-related enzymes, supporting the role of the polyamine system in the pathophysiology of this disorder

Mood disorders and suicide

- As with schizophrenia, the ability of antimalarials to produce depressive symptoms has been proposed as an indication that the polyamines have a role in depression.

- Although there have been fewer studies examining the polyamine system in mood disorders in humans, evidence also exists to implicate this system in their pathology. In addition, emerging evidence points to a role of the polyamine system in suicidal behaviour

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2265312/

- The mechanism(s) of the antidepressant activity of S-adenosyl-L-methionine (SAMe) have not yet been elucidated.

- SAMe is essential for the synthesis of polyamines, which have a key role in protein synthesis, cell proliferation, and neuronal plasticity.

- On the other hand, accumulating data indicate that depression is associated with a reduction in regional brain volume and that antidepressants increase neurogenesis in defined brain regions and also influence neuronal plasticity.

- Here we show that in a validated rat model of depression (chronic unpredictable mild stress-induced anhedonia) there is a significant reduction of putrescine, spermidine and spermine in the hippocampus, and of only putrescine in the nucleus accumbens septi.

- SAMe, at a fully antidepressant dose (300 mg/kg i.m., daily for 7 days), completely restores the levels of putrescine in the nucleus accumbens, and restores in part the levels of both spermidine and spermine in the hippocampus.

- These results may suggest (i) a role for brain polyamines in depression and in reward processes, and (ii) that the antidepressant effect of SAMe may be due, at least in part, to a normalization of putrescine levels in the nucleus accumbens septi.

- https://www.ncbi.nlm.nih.gov/pubmed/11742215

Investigating SAM-e for Depression
Psychiatric Times Publication: 2001
Interview with Dr. R.P. Brown

- For more than eight years, Richard P. Brown, M.D., associate professor of clinical psychiatry at Columbia University College of Physicians and Surgeons, has used the natural dietary supplement S-adenosylmethionine (SAM-e) to treat more than an estimated 400 patients suffering from depression, many of whom were treatment-resistant.

- Although SAM-e has only been on the U.S. market since 1999, it has been studied for decades internationally and is approved as a prescription drug in Spain, Italy, Russia and Germany. **More than 1 million Europeans have used it, primarily for depression and arthritis**.

- Distributed throughout the body, SAM-e is most concentrated in the **brain and liver** and is crucial to three central pathways of metabolism that stimulate more than 35 different reactions.

- The three major pathways are transmethylation, transulfuration and transaminopropylation (synthesis of polyamines).

- Animal studies show that the transmethylation pathway boosts levels of the neurotransmitters **serotonin, dopamine and norepinephrine.** This process probably contributes to the antidepressant action" (Andreoli et al., 1978; Curcio et al., 1978; Czyrak et al., 1992; Fava et al., 1990; Losada and Rubio, 1989; Otero-Losada and Rubio, 1989).

- **Donation of carbon groups by SAM-e protects catecholamine neurons and that SAM-e improves nerve cell membrane uptake of phospholipids, enabling the coupling of protein receptors to second messengers within a more fluid lipid bilayer and enhancing transmission of impulses by neurons**.

- SAM-e is vital to the production of our most important antioxidant, glutathione, as well as the secondary antioxidants, cysteine and taurine.

- The American diet yields insufficient quantities of SAM-e either for wellness or treatment of illness. Moreover, the form of SAM-e found in food is not stable. It oxidizes too rapidly to absorb well. Our bodies can only generate a small amount of SAM-e...**Therefore, SAM-e levels are most easily increased through dietary supplementation.“**

- According to Brown, lower than normal levels of SAM-e are found in cerebral spinal fluid in some patients with depression, Alzheimer's disease, dementia, Parkinson's disease treated with levodopa (Atamet, Sinemet), disorders of folate metabolism and other illnesses (Bottiglieri et al., 1990; Bottiglieri et al., 1994).

- He cited a study indicating that folate, B_{12} and B_6 are necessary for efficient use of SAM-e (Crellin et al., 1993) and reported that SAM-e has been effective for treating major depressive disorder in 13 trials comparing it to placebo and 19 trials comparing it to tricyclic antidepressants, with more than 1,400 patients studied.

- Since 1988, double- and single-blind studies using higher doses of SAM-e have shown it to be effective in treating **major depression** (Bressa, 1994; Delle Chiaie and Boissard, 1997; Delle Chiaie et al., 2000), **depression secondary to medical illness (**Criconia et al., 1994), **postpartum depression** (Cerutti et al., 1993), **postmenopausal depression** (Salmaggi et al., 1993) **and treatment-resistant depression** (Rosenbaum et al., 1990), Brown reported.

- Rapid response to SAM-e was shown in a double-blind trial of 30 depressed inpatients who received either 1600 mg/day of oral SAM-e or imipramine (averaging 140 mg/day) for six weeks," Brown added. "**The SAM-e group was significantly better by day 10**. Both groups were comparably improved by week 6" (De Vanna and Rigamonti, 1992).

- Furthermore, Brown reported that in a small, double-blind, four-week inpatient study of oral SAM-e (1600 mg/day) versus 250 mg/day of desipramine (Norpramin), improvement in depression in those who responded to either SAM-e or desipramine correlated with their SAM-e blood levels (Bell et al., 1994).

- These findings highlight the need for larger and longer-term studies to elucidate the role of SAM-e in recovery from depression and the use of SAM-e in combination with prescription antidepressants.

- He added that the longest controlled-trial studies of SAM-e efficacy for depression were 42 days (Delle Chiaie et al., 2000; De Vanna and Rigamonti, 1992; Fava et al., 1992).

- Brown noted that American companies only sell SAM-e in 50 mg, 100 mg and 200 mg tablets. **He recommended a daily dose of 400 mg for mild depression**.

- Keep in mind that absorption is better on an **empty stomach.**

- Starting patients with 200 mg 30 minutes before breakfast and 30 minutes before lunch minimizes the overstimulation and insomnia which some patients report in the first few weeks. This can be switched to 400 mg before breakfast after a few weeks.

- Patients typically notice improvement in energy within two weeks.

- Some investigators reported an overstimulation and/or insomnia rate of about 5%, which is the same as placebo (Berger and Nowak, 1987), according to Brown.

- As with most medications, clinical sense indicates starting with lower doses in geriatric, medically ill and anxious patients. SAM-e, like all antidepressants, should be used with some caution in patients with a history of cardiac arrhythmia.

- In several depression studies, SAM-e induced mania in a significant proportion of patients who had a prior history of bipolar disorder (De Vanna and Rigamonti, 1992; Kagan et al., 1990).

- "As with any antidepressant medication, SAM-e can trigger hypomania or mania in patients with bipolar disorder," Brown warned, adding he would not recommend a patient with bipolar disorder take SAM-e unless that patient is under close medical supervision.

- "If a patient has a personal or family history of bipolar disorder, lower starting doses of 100 mg once or twice a day, careful monitoring and concurrent use of mood stabilizers are indicated," Brown advised, adding "the dose can be raised by 200 mg to 400 mg every three to seven days."

- Treatment for severe depression, Brown said, generally requires higher doses. "Some studies have started unipolar patients on 800 mg or 1600 mg per day," he said. **Side effects occurring at the higher doses include mild jitteriness, loose bowels and headaches.**

- Brown said he has treated more than 30 patients with treatment-resistant depression who responded well to SAM-e augmentation of all categories of antidepressants without adverse reactions, and noted a review of four studies suggesting that **SAM-e boosted and hastened response to tricyclic antidepressants,** mianserin and fenoterol, a ß-agonist (Friedel et al., 1989).

- He also cited a randomized double-blind study (Berlanga et al., 1992) of 40 outpatients with moderate to severe major depression that confirmed his own clinical experience of using **SAM-e to augment imipramine.**

- Brown said he has also found SAM-e effective for **fibromyalgia** (Jacobsen et al., 1991; Tavoni et al, 1987, and Tavoni et al., 1998, as cited in Brown et al., 2000), **depression in Parkinson's disease, the aging brain, liver diseases** (Friedel et al., 1989) and arthritis (Bradley et al., 1994, as cited in Brown et al., 2000; Konig, 1987).

- It also seems to reverse some effects of **alcoholic hepatitis and cirrhosis** (Mato et al., 1999) and is used **to dissolve gallstones**. There is only one small open case series of SAM-e **for attention-deficit/hyperactivity disorder** (Shekim et al., 1990), but Brown mentioned that he has seen some anecdotal cases of his own (Brown et al., 2000).

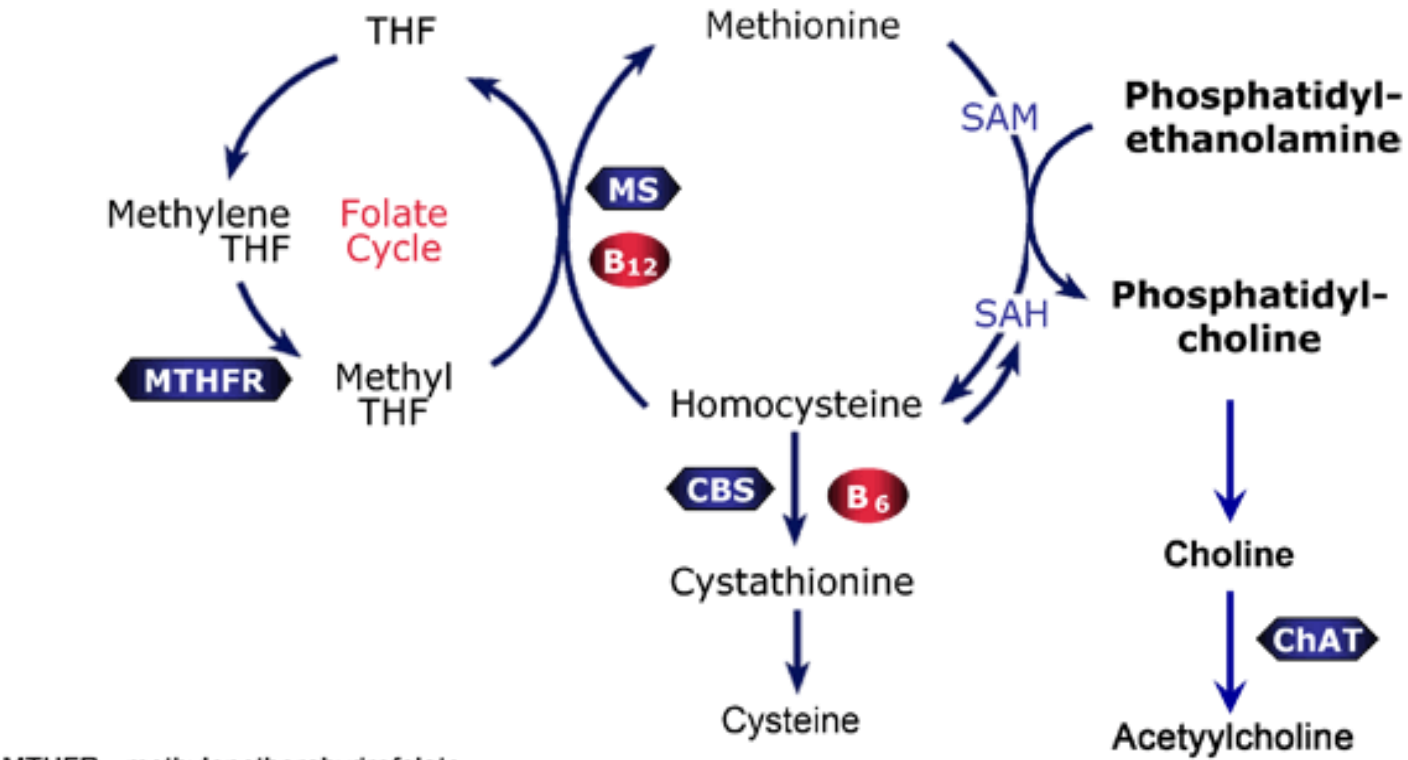
- "Preliminary studies support the use of SAM-e for **depression complicating alcohol and opiate withdrawal"** (Agricola et al., 1994), he said. "In several cases, we have used SAM-e to successfully treat **post-methamphetamine depression and drug craving."**

- "SAM-e starts to work in approximately half the time needed for tricyclics. Studies show very few side effects, and SAM-e **does not cause the sexual dysfunction or weight gain** associated with other medications," he said.

- Brown said that considering SAM-e's efficacy in treating depression, its mild side-effect profile, and its ability to boost antioxidants and protect DNA through methylation, this nutrient has advantages over prescription antidepressants - **as a long-term chronic treatment after an acute episode.**

- http://www.psychiatrictimes.com/depression/investigating-sam-e-depression

Phospholipids- PE, PC and Dopamine
NE, EP and Acetylcholine SAMe dependent



MTHFR - methylenetherahydrofolate reductase

MS - methionine synthase

CBS - cystathione beta synthase

ChAT - choline acetyltransferase

Clinical Effects in Depression

- In one centre (MC3), 1600 mg SAMe/day po (oral dose) was given to **143 patients** for six weeks.
- In another centre (MC4), 400 mg SAMe/day im (intramuscular) was given to **147 patients** for four weeks.
- In both centres, the efficacy and safety of SAMe were compared with those of 150 mg imipramine/day po given to 138 patients for 6 weeks at MC3 and 148 patients for 4 weeks at MC4.
- The results of SAMe and imipramine treatment did not differ for any efficacy measure.
- However, fewer adverse reactions were observed in patients treated with SAMe.
- **The authors concluded that the antidepressive efficacy of 1600 mg SAMe/day po or 400 mg SAMe/day im is comparable with that of 150 mg imipramine/day po, but SAMe is better tolerated.**

S-adenosyl methionine as treatment for depression: A systematic review. http://works.bepress.com/cgi/viewcontent.cgi?article=1009&context=vivianmcalister&sei-redir=1&referer=http%3A%2F%2Fscholar.google.ca%2Fscholar%3Fq%3DSAMe%2Bsupplementation%2Bin%2Bmental%2Bhealth%26hl%3Den%26as_sdt%3D0%26as_vis%3D1%26oi%3Dscholart%26sa%3DX%26ei%3DB9pHVeuFLcjFggTZgIHgCA%26ved%3D0CBsQgQMwAA#search=%22SAMe%20supplementation%20mental%20health%22

Clinical Effects in Depression

- Critical review by Brown et al reported results of 48 studies using SAMe supplementation showing it to be safe and effective for **treatment of depression**

- More recently a review of an additional 14 studies showed improvement in mild-to-moderate depression, where 57% of studies showed positive results.

- **SAMe** is recommended for cases of treatment-resistant depression, as it can be used **in conjunction with anti-depressant drugs (as can folic acid, vitamin B12, vitamin D, omega-3 fats**)

- SAMe combined with SSRI's shown to produce improved outcome than SSRI alone is some studies

- SAMe appears to be particularly helpful in depression associated with co-morbidity health issues MSK, liver diseases, Parkinson's disease, HIV.

- **Postpartum Depression** – 70% reduction in symptoms of **depression and anxiety**, compared to 50% reduction in placebo group, with dosage 1600 mg per day in 30 patient clinical trial.

- Like omega-3 fats, SAMe is safe to use during pregnancy and breast feeding.

- Quershi, NA, Al-Bedah AM. Mood disorders and complementary and alternative medicine: A literature review. Neuropsychiatric disease and treatment. 2013. 9:639-658

SAMe Final Comments:

1.Should provide concurrent Folic acid, B12 and B6 supplementation to guard against elevation in homocysteine (and related CVD and Alzheimer's disease)

2. Clinical Applications:

- Depression (including postpartum depression)
- Anxiety
- Dementia
- Parkinson's depression (?)
- Depression in drug withdrawal

3. Dosage: Depression and Anxiety: 400 mg, 1-3 times per day, depending on severity.

4. SAMe should not be taken by individuals with bipolar (manic) depression, which may trigger a manic phase in these individuals.

5-Hydroxytryptophan

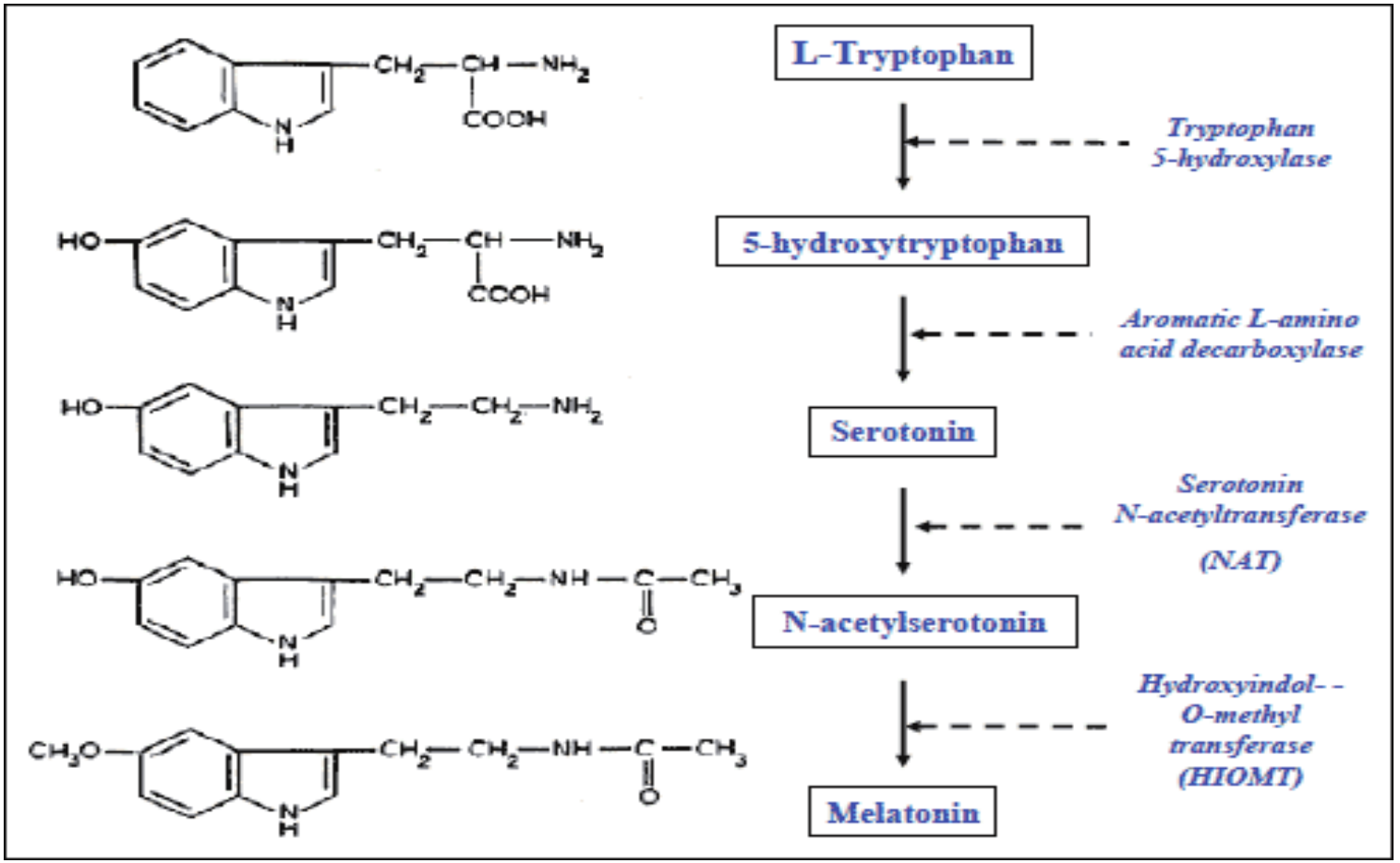
5-Hydroxytryptophan (5-HTP) - a naturally occurring agent extracted from the seed of an African plant, known as the "Griffonia Simplicifolia

Unlike tryptophan, 5HTP easily crosses the blood-brain barrier. Only 3% of oral dose of tryptophan is converted to serotonin in the brain, whereas over 70% of oral dose of 5-HTP is converted to serotonin, which elevates mood and improves sleep quality

Clinical Applications:

1. Depression
2. Insomnia
3. Other conditions where a rise in serotonin levels may be desirable (obesity – curbing appetite)

Serotonin Synthesis from 5-HTP



- Some small studies have used 5-HTP alone to treat depression (limited evidence)

- More convincing data shows that it is a **good adjunct** to the use of antidepressant medications. (adjunctive treatment)

- No reported cases of 5-HTP causing Serotonin Syndrome when combined with antidepressant drugs

Dosage:

1. Depression: 100 mg, three times daily
2. Insomnia: a single dose of 25-100 mg, one hour before bedtime

Side Effects:

1. Gastrointestinal upset (i.e. nausea, diarrhea, vomiting)
2. Less often - headache, insomnia, muscle pain, or anxiety.

Drug-Nutrient Interactions and Contraindications

1. 5-HTP requires physician monitoring for Serotonin Syndrome if taken with other antidepressants, weight control drugs, other serotonin-modifying substances.

2. Individuals with liver disease or scleroderma should also avoid 5-HTP

Quershi, NA, Al-Bedah AM. Mood disorders and complementary and alternative medicine: A literature review. Neuropsychiatric disease and treatment. 2013. 9:639-658

CDP-Choline

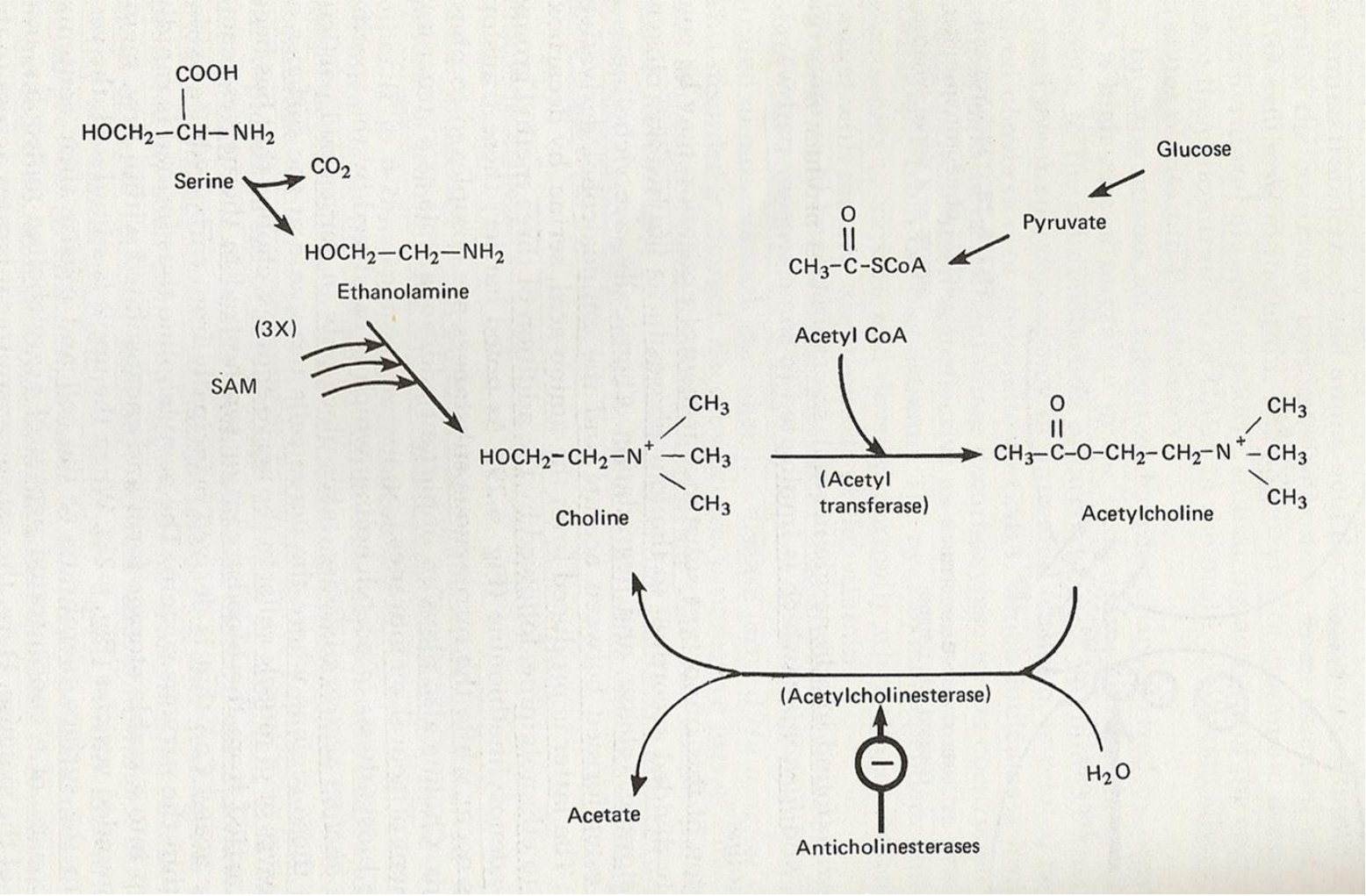
Cytidine 5- diphosphocholine (CDP-choline)

- Naturally occurring CDP-choline has been shown to increase brain levels of choline, phosphatidylcholine, acetylcholine and possibly other neurotransmitters (dopamine, serotonin, norepinephrine)

Choline is required by brain cells for the following purposes:

- Neurotransmitter synthesis (acetylcholine)
- Cell membrane phospholipid synthesis (e.g. phoshatidylcholine, phophatidylethanalomine)
- Cell membrane signaling

Acetylcholine Synthesis



- With aging, the choline transporter is less efficient depriving brain cells of optimal choline status.

- Food and Lecithin alone cannot maintain optimal brain choline levels.

- CDP-choline becomes the most efficient source of brain choline in aging, and has been used successfully (mostly in Europe and Japan) to treat:
  - Senile Dementia (age-related memory loss)
  - Dementia related to Cerebral Vascular Disease – most effective supplement
  - Stroke recovery –most effective supplement
  - Early-stage Alzheimer's disease
  - Concussion treatment – most effective supplement

Animal studies show that it also increases dopamine synthesis, and has been used as an adjunct in Parkinson's disease treatment with some success

Choline and Mental Health

Choline in Bipolar Depression:

Free choline has been used successfully to control manic phase in bipolar depression when used as adjunct to lithium (several small trials)

Dosage: 2000-7200 mg/day (Fish odour breath with Lecithin Supplementation)

Each tablespoon (7.5 grams) of lecithin granules contains about 217 mg of free choline, 1700 mg of phosphatidylcholine, 1000 mg of phosphatidylinositol, and about 2,200 mg of essential fatty acids as linoleic acid and the omega-3 fat alpha - linolenic acid.

CDP-choline Safety:

- No serious side effects (even at 1,000 mg/day)
- Well tolerated
- Toxicity studies (negative)

Quershi, NA, Al-Bedah AM. Mood disorders and complementary and alternative medicine: A literature review. Neuropsychiatric disease and treatment. 2013. 9:639-658

Fioravanti M, Yanagi M. Cytidinephosphocholine (CDP) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly . The Cochrane Library 2004, Issue 2 (Wiley) www.thecochranelibrary.com

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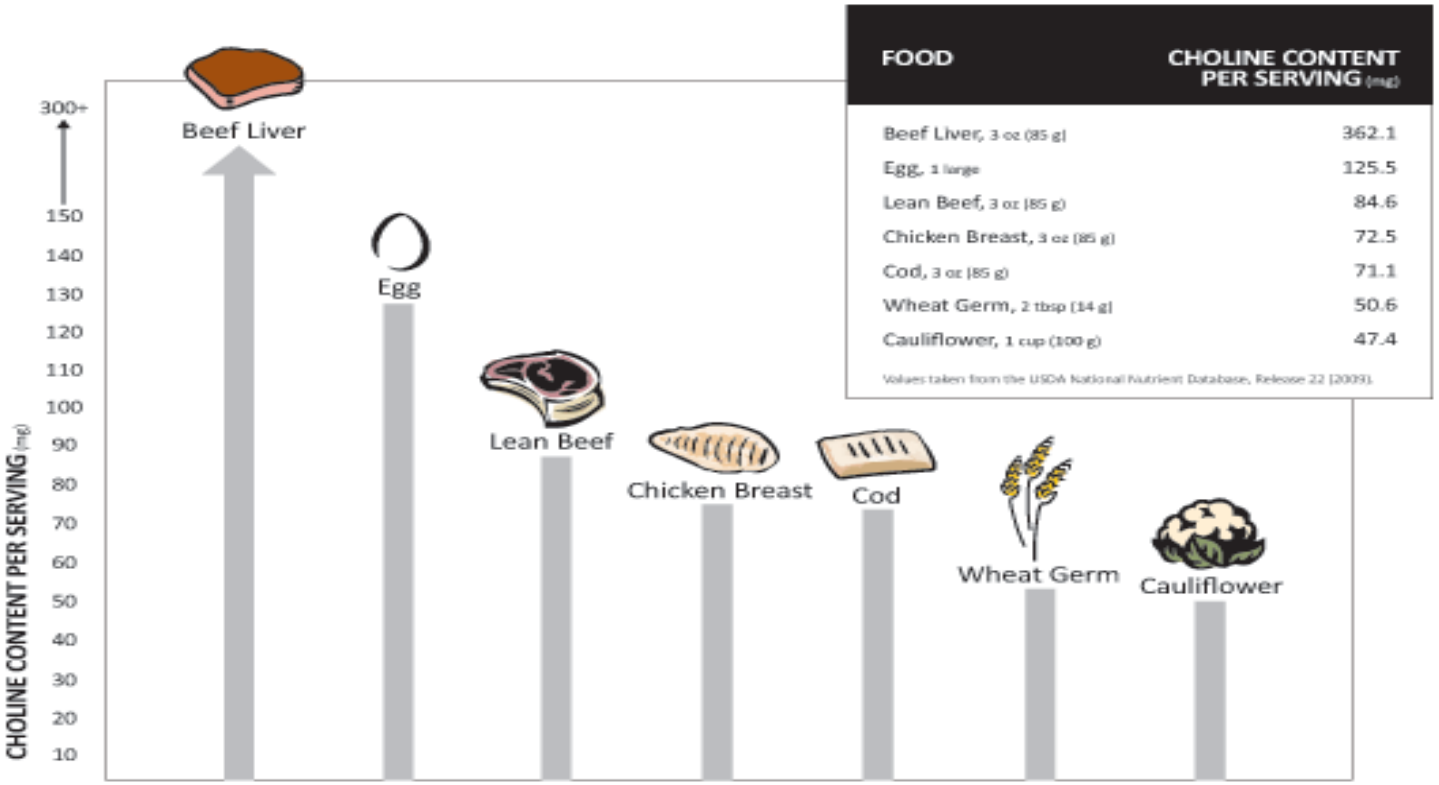
Some Food Sources of Choline:

15 gm (1 tablespoon) soy lecithin = 450 mg
1 cup many Nuts = 75 mg
2 cups firm tofu = 142 mg



FOOD	CHOLINE CONTENT PER SERVING (mg)
Beef Liver, 3 oz (85 g)	362.1
Egg, 1 large	125.5
Lean Beef, 3 oz (85 g)	84.6
Chicken Breast, 3 oz (85 g)	72.5
Cod, 3 oz (85 g)	71.1
Wheat Germ, 2 tbsp (14 g)	50.6
Cauliflower, 1 cup (100 g)	47.4

Values taken from the USDA National Nutrient Database, Release 22 (2009).

St John's wort

St. John's wort

Mechanism of Action - inhibits reuptake of serotonin, norepinephrine, and dopamine

Shown to be effective for Mild to Moderate Depression

Some of these studies showed similar efficacy for St. John's wort to use of various antidepressant drugs (imipramine, fluoxetine, paroxetine, citalopram), in head-to-head trials

Dosage: Mild to Moderate Depression- 300 mgs, 3X/day (usually 0.3% hypericin content)

Severe Depression: The use of 600 mgs, three times per day with meals for severe depression did prove to be effective in a single trial, but the use of St. John's wort in these cases is not widely accepted at this time

Reduction of Relapse Rate:

Patients with a high degree of depression chronicity, showed significant **reduction in relapse rate** after recovery from acute depression when using St. John's wort prophylactically.

St John's wort Side effects

Adverse Side Effects and Precautions:

1. Speeds up detoxification of drugs (phase 1 detox) – many drug-nutrient interactions (warfarin, digitalis etc)
2. Photosensitivity dermatitis (rash)
3. Excess Sedation
4. Can not combine St John's wort with anti-depressant or any mood altering drugs (mental health treatment drugs of any kind) – serotonin syndrome or other disturbances may result.

Quershi, NA, Al-Bedah AM. Mood disorders and complementary and alternative medicine: A literature review. Neuropsychiatric disease and treatment. 2013. 9:639-658

PTSD

- Post-traumatic stress disorder (PTSD) is a severe type of anxiety disorder that will affect between 8 to 9% of Canadians and Americans at some point in their lives.

- **PTSD causes a change in the body's natural response to stress and affects the stress hormones and chemicals that carry information throughout the nervous system**.

- A wide array of medications are commonly prescribed for the treatment of PTSD and it is usual for patients to be on a treatment regime involving numerous pharmaceuticals.

- Recent studies conducted by the American Medical Association and the National Academies have found that the **vast majority of currently prescribed medications provide little to no benefit for patients**.

DEPRESSION AND PTSD

How common is depression following trauma?

- In any given year, almost 1 in 10 adult Americans has some type of depression (1). Depression often occurs after trauma. For example, a survey of survivors from the Oklahoma City bombing showed that 23% had depression after the bombing, compared to 13% who had depression before the bombing (2).

- PTSD and depression are often seen together. Depression is nearly 3 to 5 times more likely in those with PTSD than those without PTSD (3).

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MARIJUANA IN PTSD RX

- Anecdotal reports of medical marijuana providing relief for patients with PTSD have led researchers to investigate the endocannabinoid system as a therapeutic target for the treatment of this disorder.

- **The endocannabinoid system** appears to be a promising target due to evidence of its role in the regulation **of sleep, pain, anxiety, and stress**.

- A review of the medical literature surrounding PTSD and medical marijuana reveals only 2 previous studies:

:In 2009, Canadian researchers found that administration of nabilone (synthetic THC) was able to **either abolish or greatly reduce the nightmares** experienced by patients with PTSD that persisted despite the use of conventional treatments.

Combating Effects of stress in PTSD

High Cortisol Levels – available via salivary test if required, can produce following effects:

- High Blood Glucose (due to rapid glycogenolysis)
- Weight Gain (due to deposition of fat into visceral fat and blocking thyroid function)
- Weakened Immunity and Chronic Fatigue State
- Gastro-intestinal Disturbances, including ulcers
- Cardiovascular Problems due to vasoconstriction of coronary vessels (along with adrenaline and nor-adrenaline)
- Libido and Sexual Performance Problems
- Memory Loss
- Sleep Disturbances

Supplements to Lower Cortisol

In addition to exercise, meditation, yoga, deep breathing, visualization, there are specific adaptogen herbs shown to decrease the release of cortisol from the adrenal glands when individuals are under stress.

In addition, some of these herbs have other effects on improving energy, well being, memory, sleep regulation and work capacity.

The key adaptogen herbs (with no drug-nutrient interactions) include:

- Ashwaghanda
- Schisandra
- Rodiola

BLOOD TESTS SUMMARY (DEPRESSION/ANXIETY/PTSD)

1. CBC
2. RBC Folate
3. Serum Vitamin B12
4. Homocysteine
5. MMA
6. Serum vitamin D (25-hydroxyl-cholecalciferol)

Optional: Urinary Organic Acids Test – checking for urine levels of end products of neurotransmitter synthesis (http://www.integrativepsychiatry.net/organic_acids_test.html)

Research Review: https://www.integrativepsychiatry.net/_uploaded_files/validity_of_neurotransmitter_testing.pdf

BURNOUT AND RODIOLA

- Official definition of burnout, “the subjective perception of chronic demand-related stress with subsequent emotional exhaustion and decreased performance in work-related or self-set tasks”.

- The symptoms include not only changes in mood and emotional wellbeing, such as fatigue, cynicism, impaired sexual life, lack of concentration, or general negative attitude toward work, but also physical symptoms such as headache, spasticity and rigidity, or irritable stomach.

- Studies show that burn out increases risk for subsequent development of serious mental or physical disorders, including **depression, anxiety, and cardiovascular conditions** – which are the most prevalent conditions associated with a history of burnout.

- In recent years, researchers have performed a number of clinical trials with patients diagnosed with burnout, by giving them an herbal supplement known as Rodiola.

- Rodiola is an herb that is classified as an adaptogen, as studies show that it mitigates the effects of stress on the body and the brain via multi-dimensional mechanisms, such as reducing the secretion of stress hormones and preserving balance of key brain neurotransmitters, when organisms are under stress.

- An important study was published in the journal Neuropsychiatric Diseases and Treatment on March 22, 2017. Researchers treated 118 male and female outpatients, age 30-60 years of age, who were suffering from burnout symptoms. The subjects had similar daily stress burdens (i.e. home caring of handicapped or demented family member).

- The patients ingested 400 mg of a standardized grade of Rodiola rosea extract, over a 12-week period. The study results were impressive.

RESULTS

- As reported by the researchers, subjective stress symptoms underwent significant improvement, which suggests an increase in coping ability and a decrease in subjectively perceived demand after the intervention.
  A significant percentage of patients reported improvement in the following specific parameters:
- lack of joy
- loss of zest for life
- improved alertness
- personal accomplishment
- improved interest in sex (combating stress-induced impairment of sex life)
- Some of the patients experienced improvement in these symptoms as early as the first week of Rodiola supplementation. And the majority of patients saw clear benefit in burnout symptoms over the course of the 12-week treatment period.

- The researchers note that other trials evaluating the effects of Rodiola extract in improving the physical and mental performance under stressful conditions confirm and support these findings.

- Rodiola should be standardized to 3.5% Rosavins content to ensure that you are getting sufficient medicinal ingredients from the 400mg total daily dosage that is recommended.

Reference:

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- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5370380/

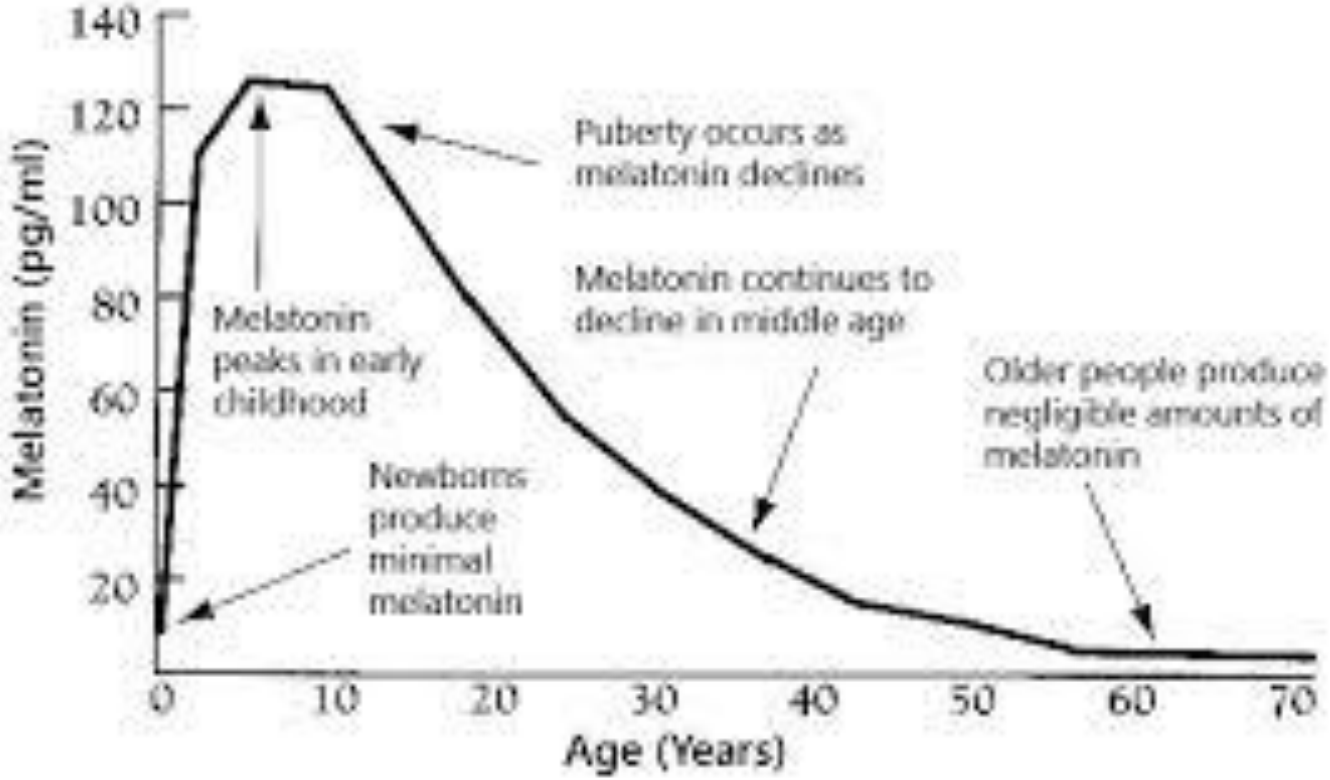
Sleep Disturbances

Supplements Known to Improve Sleep:

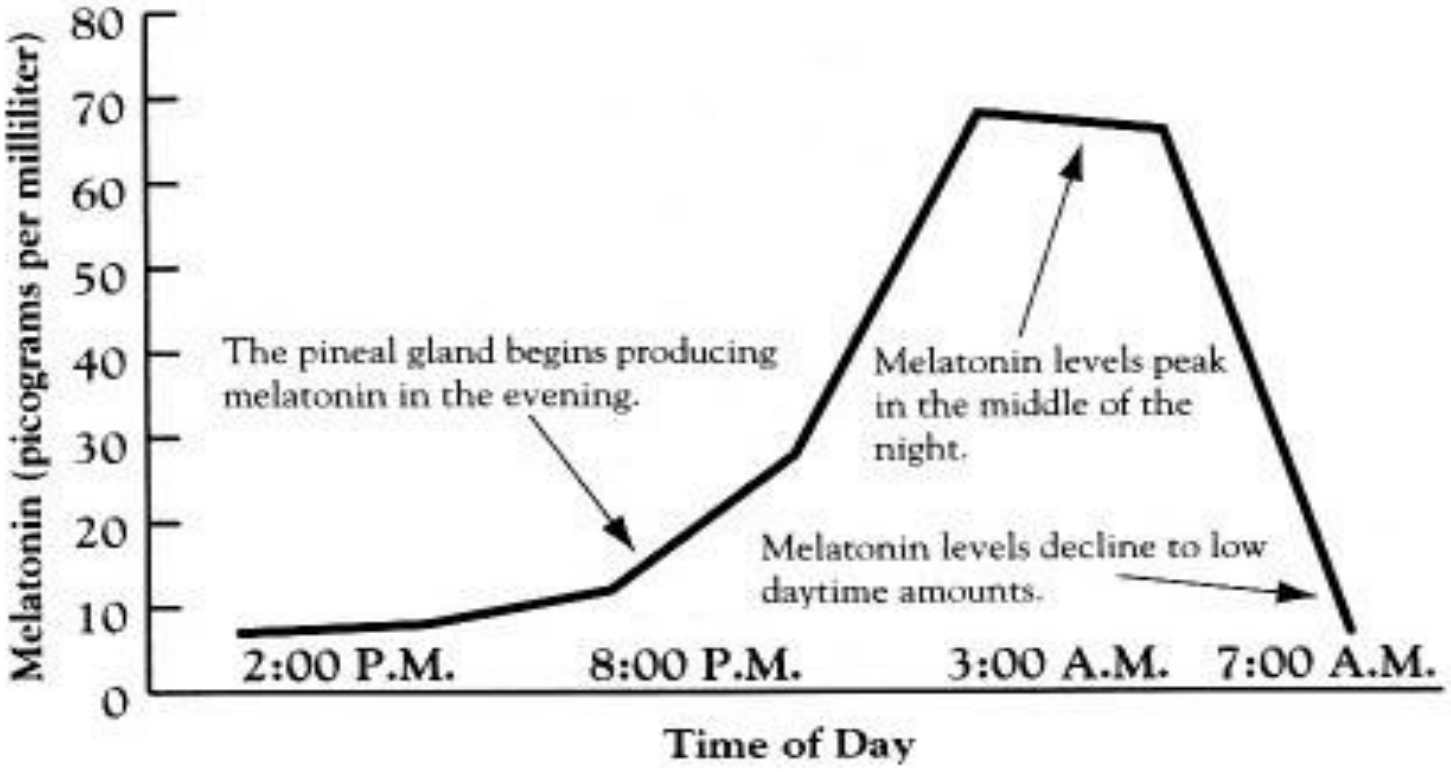
1. Melatonin
2. 5-HTP (5-hydroxytryptophan)
3. GABA (gamma- amino butyric acid) – also anxiety
4. Valerian – also anxiety

Sleep Disorders

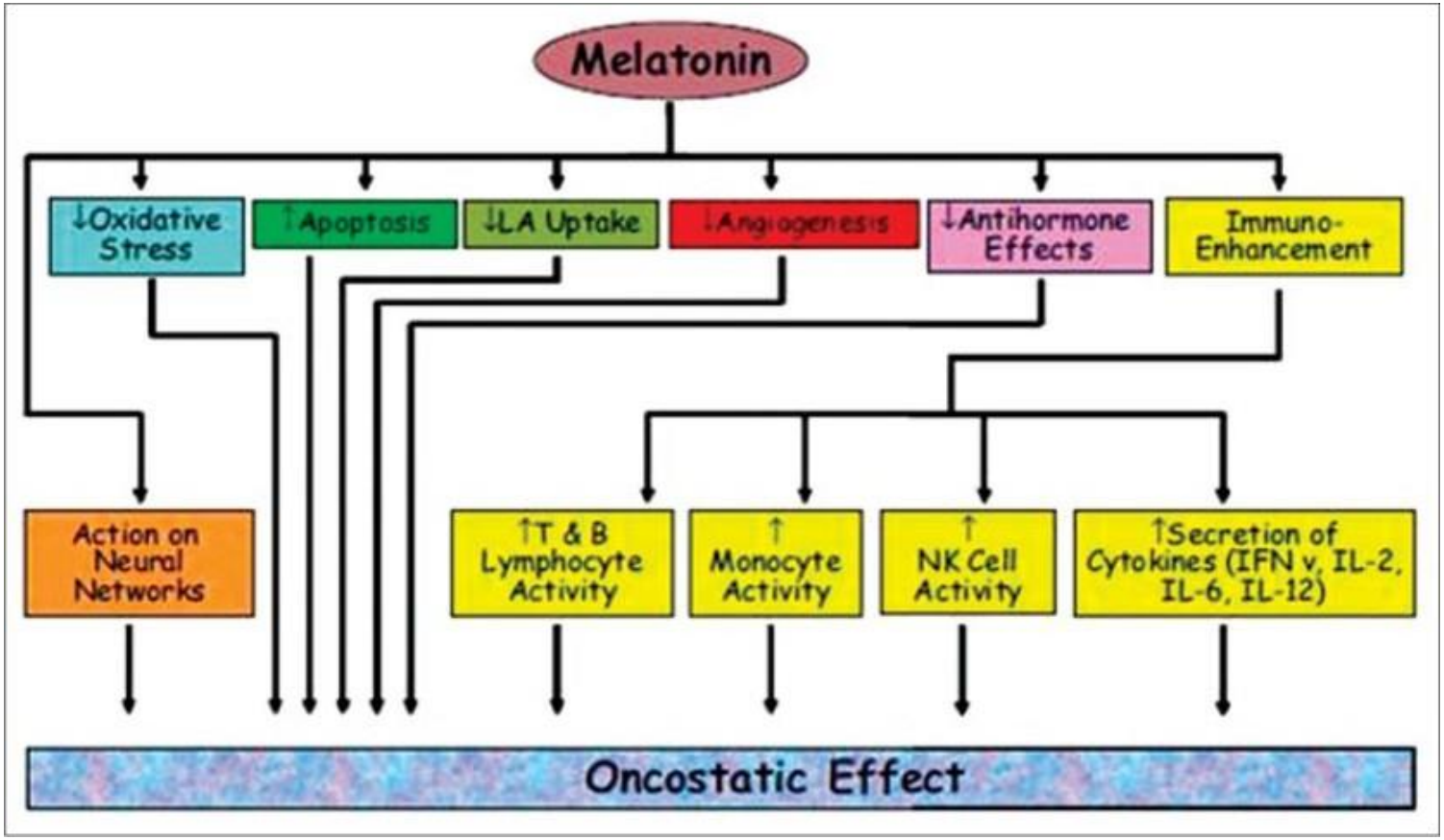
Decline in Melatonin Levels With Age



Melatonin Release – Circadian Rhythm

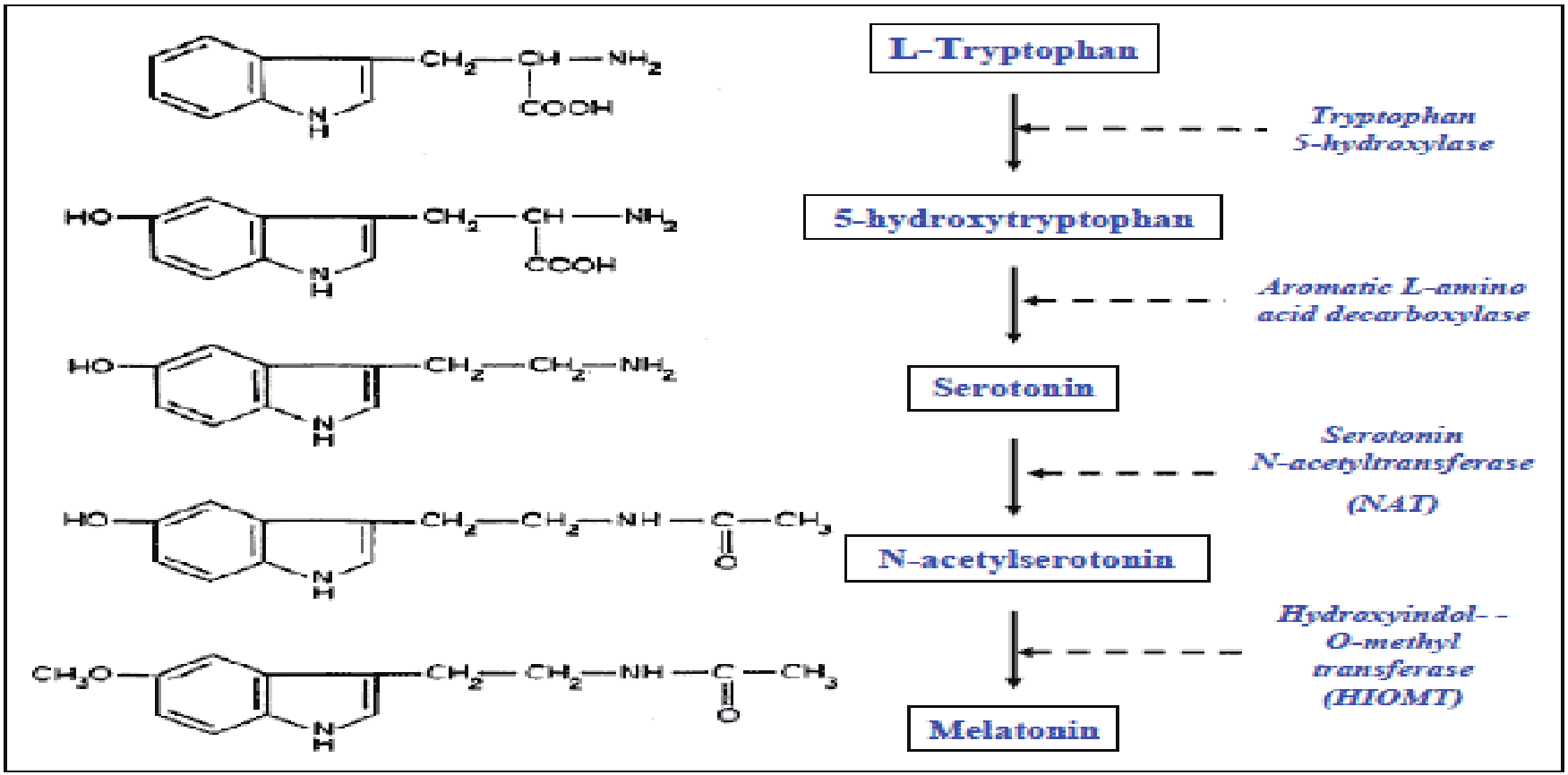


Melatonin Also Improves Immune Modulation



5 HTP

Body converts 5-HTP into Serotonin (Melatonin), which helps to induce sleep and improve feeling of well being and reduce over eating

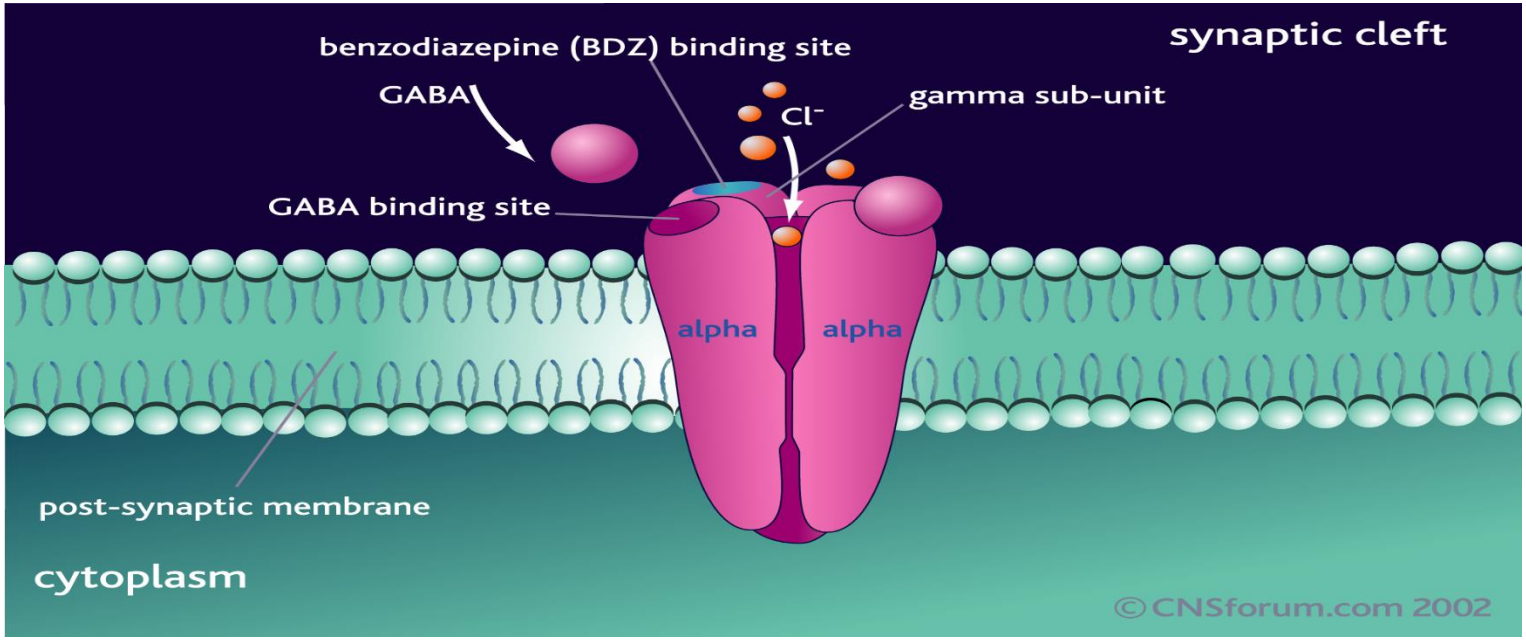


5 –HTP Supplementation Shown to:

- Improve Sleep
- Improve Feeling of Wellbeing
- Reduce Appetite and Over eating

GABA

- GABA activates GABA receptors in brain, which decreases anxiety and tension, allowing sleep to occur more easily. No addiction potential



Valerian Root

- 200 plant species belonging to the genus Valeriana, but the most common one, and the one used for medicinal purposes is **Valeriana officinalis.** [1,9 10]

- This plant grows wild all over Europe, but most of the Valerian used in consumer health products is cultivated. [10]

- The **rootstock** contains its active constituents, which are concentrated into health products used primarily for the treatment of insomnia and anxiety. [1,9,10]

- Scientific studies evaluating the effects of Valerian on humans began in the 1970's, which subsequently lead to its approval as a sleep aid by the Germany's Commission E Monograph in 1985. [9]

Principle Active Constituents

- Valepotriates (iridoid molecules) and **valerenic acid.** These compounds are exclusive to Valerian.[1] It now appears that valerenic acid is a possible active constituent, but not the valepotriates. [9]
- Volatile Oils [12]

Clinical Application and Mechanism of Action

Insomnia

- Valerian acts as a sedative in that its active constituents, which are not fully understood or known, are capable of binding to the same brain receptors as Valium and other benzodiazepine drugs.

- Central nervous system sedation is regulated by receptors in the brain known as GABA-A receptors (gamma amino butyric acid). Experimental test tube studies indicate that active constituents in Valerian may weakly bind to GABA-A receptors in the brain, producing a sedation effect.

- Human trials suggest that Valerian tends not to impair mental function or produce a morning hangover, and dependency has not been reported with its use. Studies have demonstrated improved sleep quality and insomnia relief.[1,2,3,9,11,12]

- Overall, studies suggest that Valerian improves sleep quality (more restful sleep), and the transition into sleep. However, it may not increase total sleep time. These findings arise from several double-blind trials, that provide evidence for Valerian as an effective treatment for individuals with mild to moderately severe insomnia.[2,3,4,13,14,15,16]

- A 28-day study, involving 121 subjects, showed that Valerian supplementation provided significant improvement in insomnia cases, compared to the placebo.

- A 14-day trial, involving 78 elderly patients, also showed that Valerian supplementation provided significant improvement in insomnia cases, compared to placebo.

- As shown in other studies, it often takes a number of days before the effects of Valerian appear. As such, patients tend to report more consistent improvement in relief of insomnia after several days of Valerian supplementation (its effects are not immediate as would be the case for many drugs prescribed for this condition). [14]

- There is also convincing evidence from animal studies that Valerian produces a calming effect, as well as enhanced sleepiness, and reduced activity patterns. These studies provide important objective proof of Valerian's natural sedative capabilities. [18,19,20,21]
- In head-to-head trials testing Valerian against the drug oxazepam (10 mg at bedtime) and bromazepam, Valerian supplementation demonstrated that it could provide equal relief for insomnia, as did these common sleep-aid medications. [15,16]

Anxiety

- Several preliminary studies indicate that Valerian may be an effective treatment in cases of uncomplicated anxiety (not linked to major depression) and it has been used for this problem historically and clinically, although more research is needed to better understand its application in this regard. [1,2,3,17]

Dosage and Standardized Grade

- Insomnia: As a mild sedative, Valerian may be taken 30-45 minutes before retiring at the following dosage and standardized grade: Valerian extract, 200 –400 mg (standardized to 0.8% valerenic acids content) [8,11]

- Anxiety and Stress Reduction: 200 mg, twice per day (standardized to 0.8% valerenic acids content). [11]

Adverse Side Effects, Toxicity and Contraindications

- Animal studies show that it takes enormously large doses of Valerian to produce any serious side effects, and in one suicide attempt, a human subject experienced no life threatening effects (stomach cramps, fatigue, chest tightness, tremors and light-headedness), after taking 20 gms of valerin (20-40 times the recommended dose). [22,23]

- There have been approximately 50 reported cases of overdose when subjects took a product called Sleep-Qik, containing Valerian as well as conventional medications, but no liver damage was noted. [24,25]

- Generally speaking, Valerian is considered to be safe and usually causes only mild gastrointestinal upset on rare occasions. It is on the GRAS list (generally recognized as safe) of the FDA.

- Some mild impairment to attention ability may occur for a couple of hours after intake, and thus, driving immediately after Valerian supplementation is not advised. However, Valerian is not reported to cause morning drowsiness when taken the night before. [9,10,11] If morning sleepiness does occur, simply reduce the dosage.[1]

Drug-Nutrient Interactions

Valerian may potentiate the actions of the following medications and thus, it is considered to be prudent to not take Valerian concurrently with these drugs:

- Barbituates or Sedatives [26]
- Antidepressants [27,28,29]
- Anti-anxiety medications [30,31,32]
- Hypnotic drugs [33,34,35]

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Natural Sleep Aid

Example

1. Melatonin
2. 5-HTP
3. GABA
4. Bacopa monnieri

Dosage: 1-4 capsules one hour before bedtime based on age and severity of sleep disorder.

TRANSTHEORETICAL MODEL OF CHANGE -PROCHASKA AND DICLEMENTE – CORE PROCESSES OF CHANGE USED IN SUBSTANCE ABUSE THERAPY

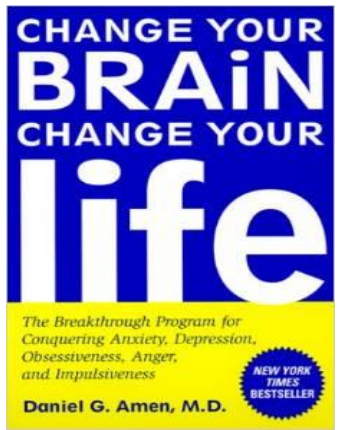
1. **Consciousness Raising** – increasing patient's awareness of their own behavior and its consequences.
2. **Self-liberation** – freeing the client from victimhood; that they have choices and not a passive victim of mental health and/or substance abuse.
3. **Social liberation** – introducing social environment that offers opportunities to get needs met through non-destructive means (i.e. social housing or drug-free hobby groups)
4. **Counterconditioning** – unlearning destructive behaviors that have become automatic responses to triggering events.
5. **Stimulus Control-** avoidance of emotional states or situations that tend to trigger undesirable behaviors.
6. ***Self-re-evaluation*** – reassessing one's strengths and weaknesses in the light of new insights. In mental health – realizing many capabilities of mind persist, and for substance abuse compare present behaviour to more desirable behavior
7. **Environmental re-evaluation** – realizing that some rejection from others is not based on inherent dislike for them but rather their own symptomatic behavior
8. **Contingency Management** – Changing consequences of behavior, making certain behaviors less rewarding and self-reinforcing
9. **Dramatic Relief** – opportunity to verbalize frustrations before problem solving begins – very helpful
10. **Helping Relationship** – establishing the therapeutic bond btw patient and practitioner, which often prompts patient to behave better to maintain positive relationship and meet practitioner's expectation of them. (Dual Diagnosis – Watkins TR- Sage publications)

Dr. Daniel Amen M.D.

Dr. Amen uses supplements (diet and exercise) a first method of treatment for many mental health disorders (depression, anxiety, OCD, etc.), as he noted that medications cause brain damaging effects, while correcting the chief mental health problem.

These brain damaging effects were evident on SPECT SCANS of the brain, which he uses to help pinpoint the diagnosis and view brain physiology

Single-Photon Emission Computed Tomography

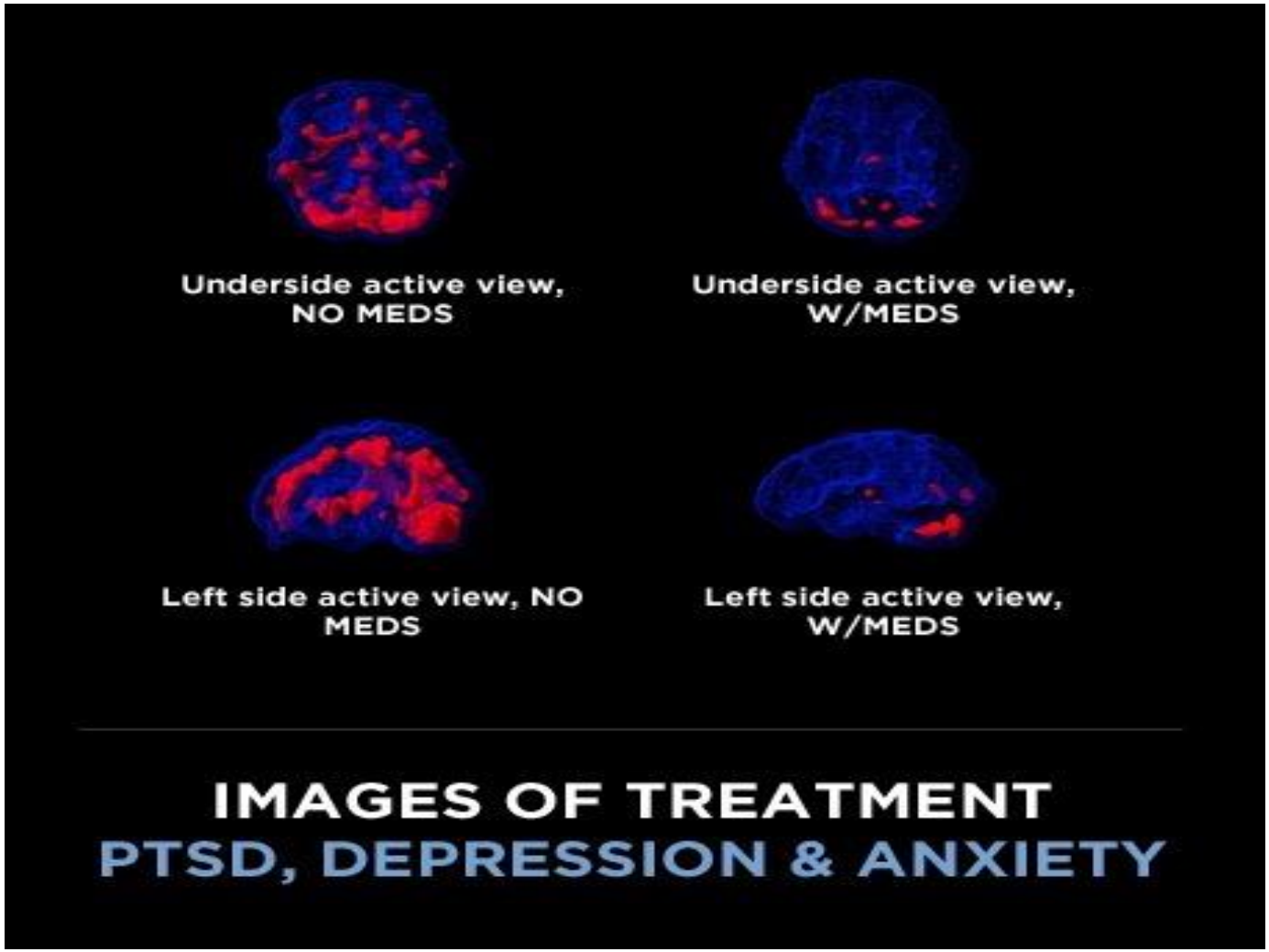


- Dr Amen has developed nutrition, exercise, supplementation and psychological strategies shown to improve many mental health problems.

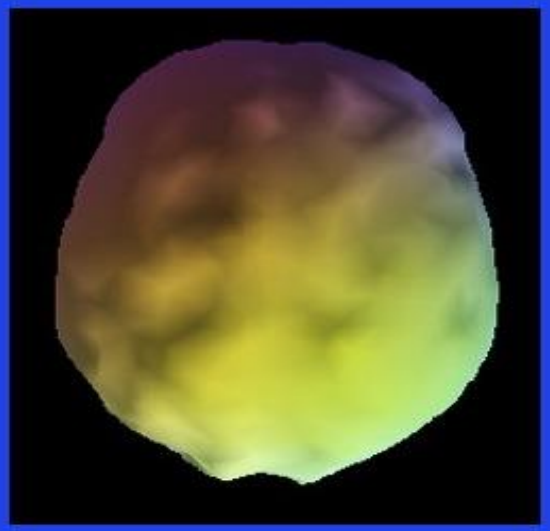
- He is also able to show the success of his method on pre and post SPECT Scans, as well as patient assessment tools (e.g. Hamilton Depression Index)

- His book is well worth reading: Change Your Brain Change Your Life

Single Photon Emission Computed Tomography (SPECT Scan)

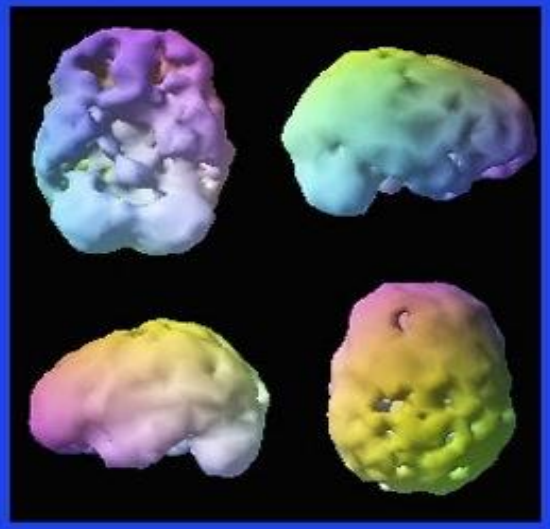


What Alcohol Does to the Brain



Surface SPECT of a healthy brain

SPECT Surface Scan Courtesy **Amen Clinics, Inc.**
www.amenclinics.com

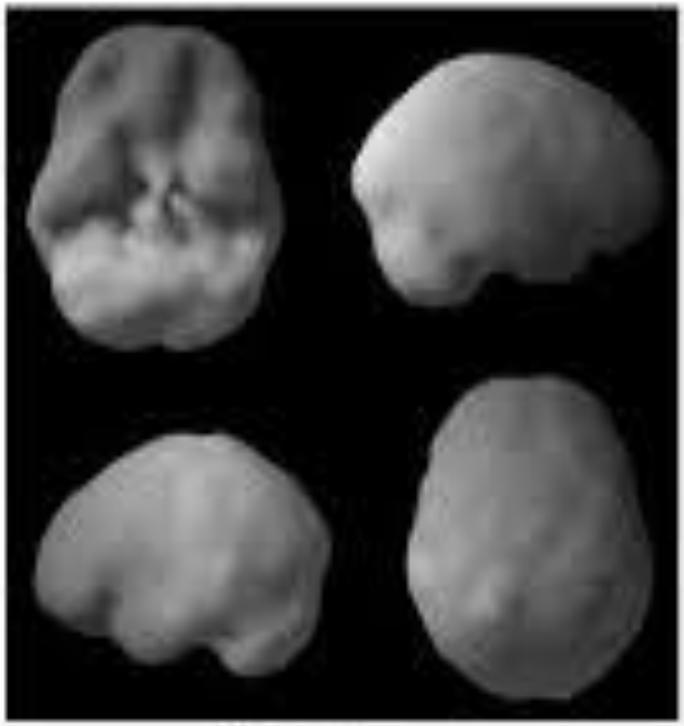


Surface SPECT of 56 year old brain with daily use - 3-4 drinks/day - but NOT an alcoholic

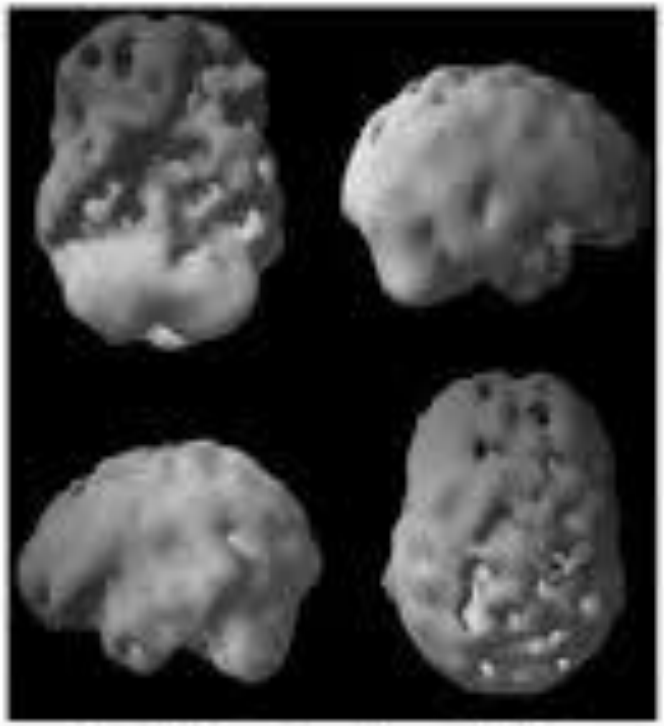
SPECT Surface Scan Courtesy **Amen Clinics, Inc.**
www.amenclinics.com


Three 60 Year Old Brains
Which brain do you want?
Alzheimer's
Overweight/
Sleep Apnea
Healthy

Your Brain on Cocaine



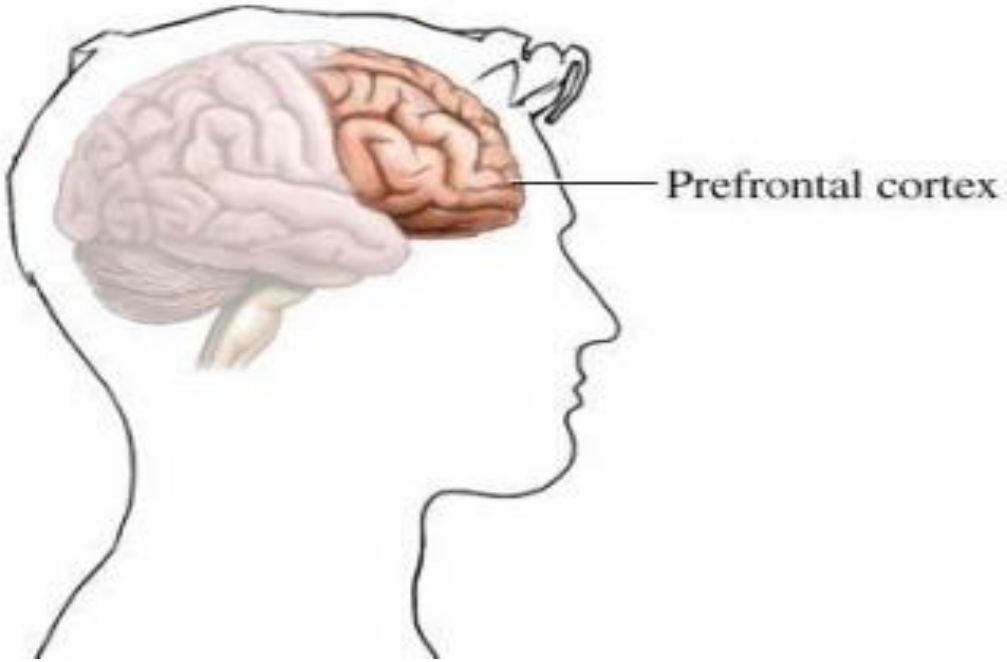
Healthy



20 Year Cocaine Addict

Prefrontal Cortex

- **PFC** - Executive Function: Decision-making, attention, judgement, planning, impulse control, empathy
- Low activity linked to short attention span, **impulsivity**, lack of goal setting, procrastination.

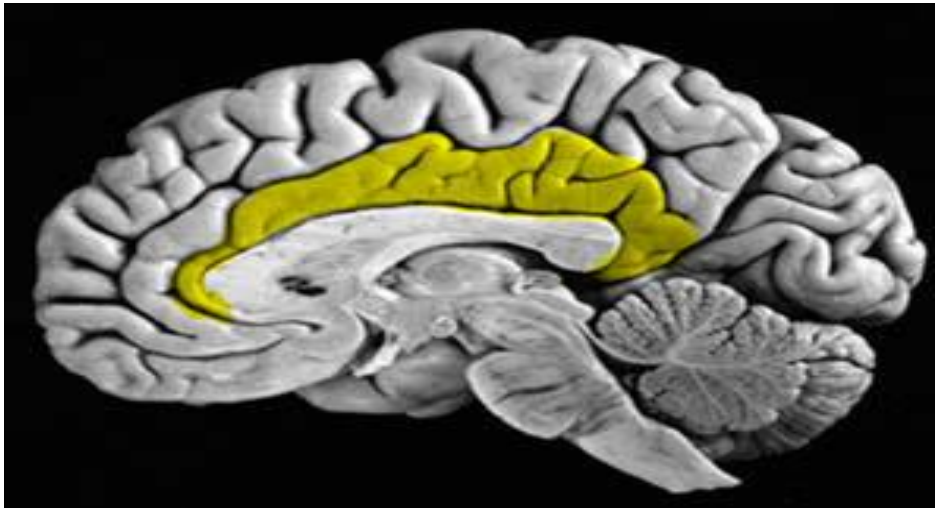


Anterior Cingulate Gyrus

ACG – brain gear-shifting centre

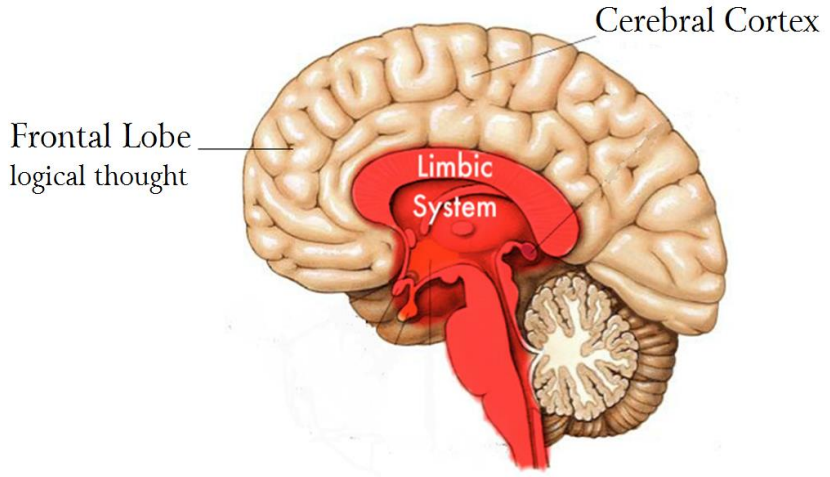
- Allows us to shift thinking and be adaptable to change when needed

- Hyperactivity in this area linked to getting stuck on negative thoughts or actions, argumentative, hold grudges. Often struggle with **OCD or compulsive behaviour**



Deep Limbic System

- **DLL** – sets emotional tone
- When less active people are more positive and hopeful
- Over activity seen in negativity, decreased drive, decreased self-esteem, feelings of guilt and helplessness. Strongly associated with **mood disorders**

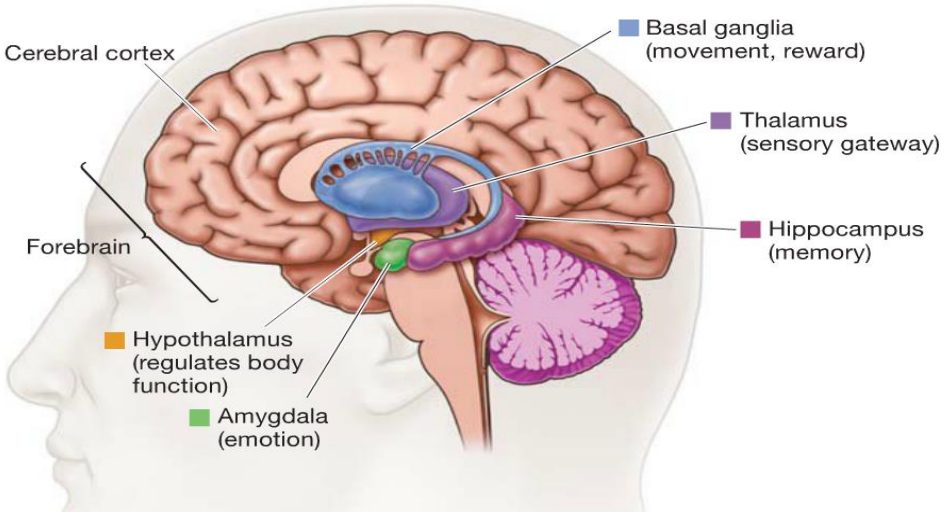


Basal Ganglia

BL – sets anxiety level (integrating thoughts, feelings and movements) and involved in feeling of pleasure and ecstasy. Cocaine works in this part of brain

Hyperactivity- linked to **anxiety disorders**, stomach aches, headaches, muscle tension

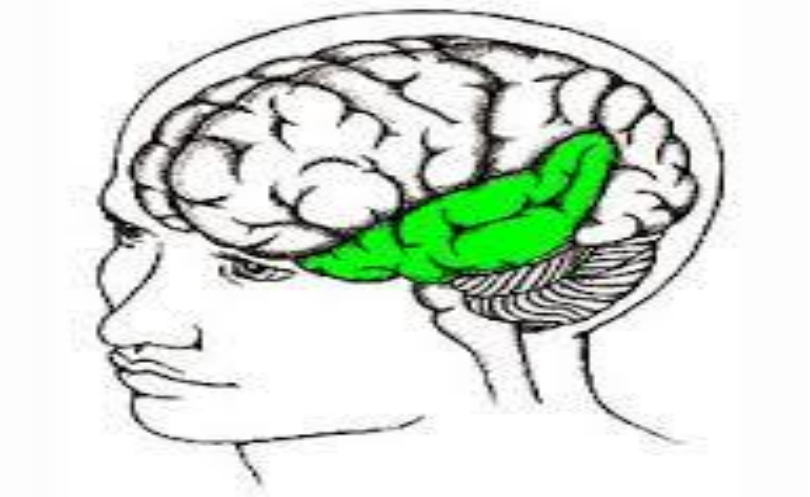
Low activity – linked to lack of motivation



Temporal Lobes

- **TL** – language, short-term memory, mood stability, **temper issues**. Remembers names of thing as well.

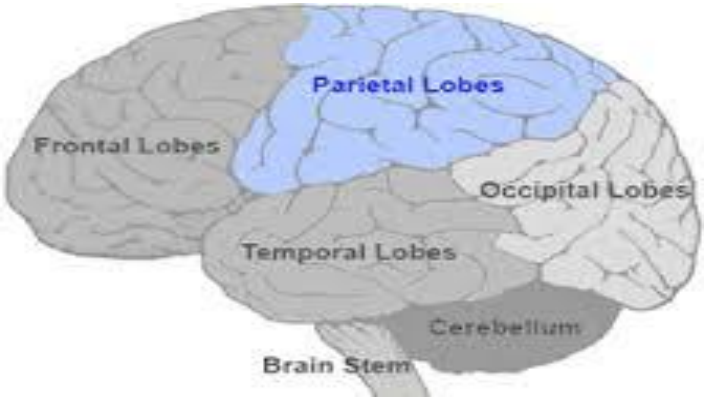
- Altered activity in TL – linked to Memory loss, **mood instability, temper problems**



Parietal Lobes

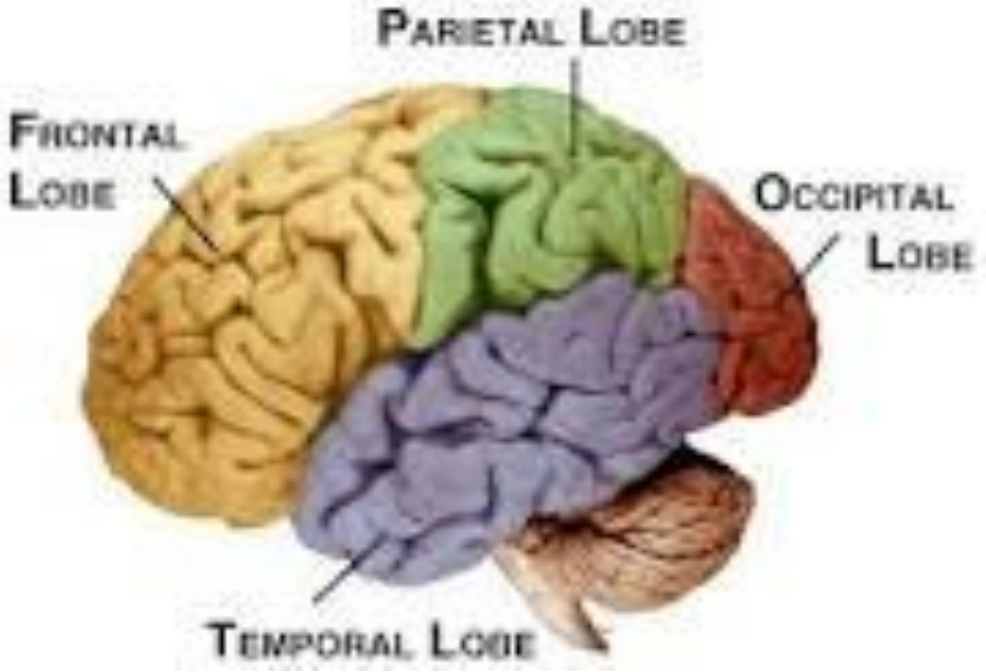
- **PL** – helps us know where things are in space (sensory processing and direction sense) – navigating to the kitchen at night in the dark to eat the rest of the cake. An area of brain damaged earlier in Alzheimer's, so people get lost easily

- Altered activity linked to **eating disorders** and body-distortion syndromes (anorexics who think they are fat)



Occipital Lobe

OL – involved in vision and visual processing



Cerebellum

CB – physical coordination, thought coordination, processing speed

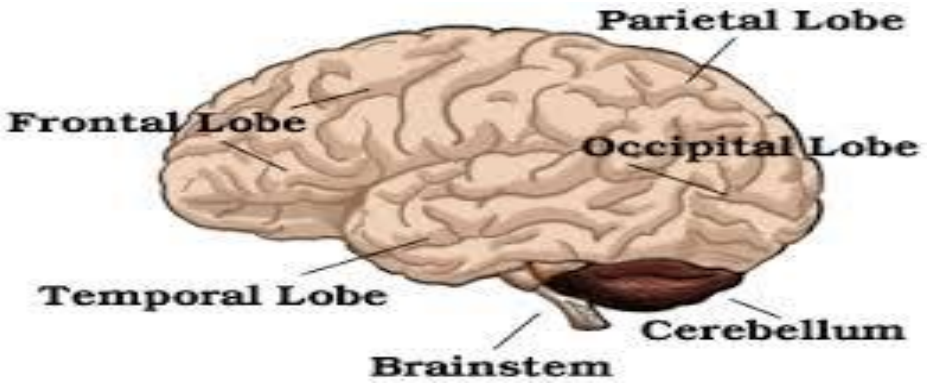
Alterations in CB linked to **judgement and impulse control, trouble learning** –as many neurons connect from Prefrontal Cortex to CB. People also struggle with movement and coordination. **Alcohol is highly toxic to CB**, thus can't walk a straight line on side of the road.

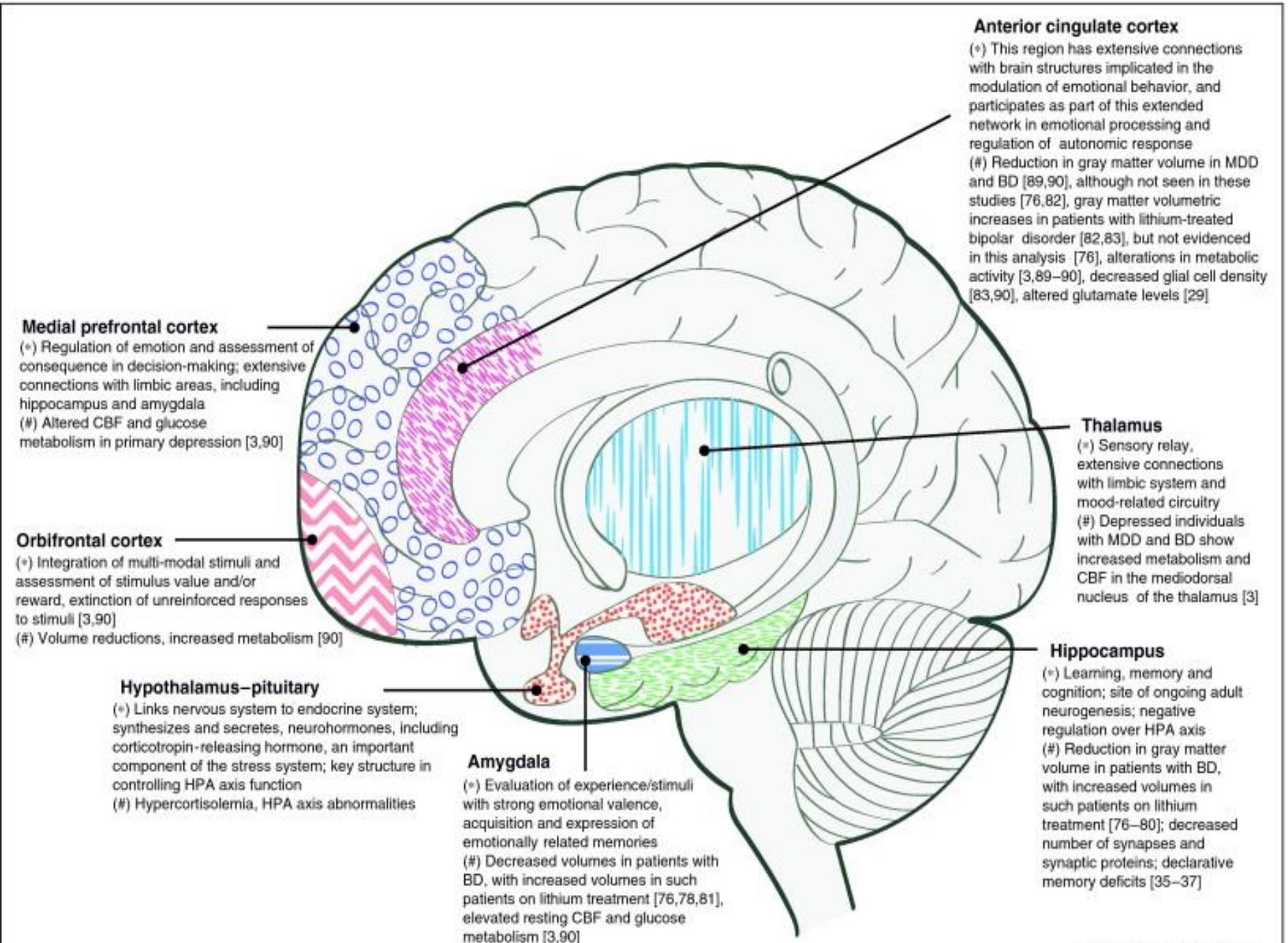
On next slide:

MDD=Major Depression

Disorder

BD= Bipolar Depression




Anterior cingulate cortex
(•) This region has extensive connections with brain structures implicated in the modulation of emotional behavior, and participates as part of this extended network in emotional processing and regulation of autonomic response
(#) Reduction in gray matter volume in MDD and BD [89,90], although not seen in these studies [76,82], gray matter volumetric increases in patients with lithium-treated bipolar disorder [82,83], but not evidenced in this analysis [76], alterations in metabolic activity [3,89–90], decreased glial cell density [83,90], altered glutamate levels [29]
Medial prefrontal cortex
(•) Regulation of emotion and assessment of consequence in decision-making; extensive connections with limbic areas, including hippocampus and amygdala
(#) Altered CBF and glucose metabolism in primary depression [3,90]
Thalamus
(•) Sensory relay, extensive connections with limbic system and mood-related circuitry
(#) Depressed individuals with MDD and BD show increased metabolism and CBF in the mediodorsal nucleus of the thalamus [3]
Orbifrontal cortex
(•) Integration of multi-modal stimuli and assessment of stimulus value and/or reward, extinction of unreinforced responses to stimuli [3,90]
(#) Volume reductions, increased metabolism [90]
Hippocampus
(•) Learning, memory and cognition; site of ongoing adult neurogenesis; negative regulation over HPA axis
(#) Reduction in gray matter volume in patients with BD, with increased volumes in such patients on lithium treatment [76–80]; decreased number of synapses and synaptic proteins; declarative memory deficits [35–37]
Hypothalamus–pituitary
(•) Links nervous system to endocrine system; synthesizes and secretes, neurohormones, including corticotropin-releasing hormone, an important component of the stress system; key structure in controlling HPA axis function
(#) Hypercortisolemia, HPA axis abnormalities
Amygdala
(•) Evaluation of experience/stimuli with strong emotional valence, acquisition and expression of emotionally related memories
(#) Decreased volumes in patients with BD, with increased volumes in such patients on lithium treatment [76,78,81], elevated resting CBF and glucose metabolism [3,90]
TRENDS in Neurosciences

Mental Health in Helping Patients succeed with Wellness Goals: The Psychology of Wellness

Here's What Doesn't Work:

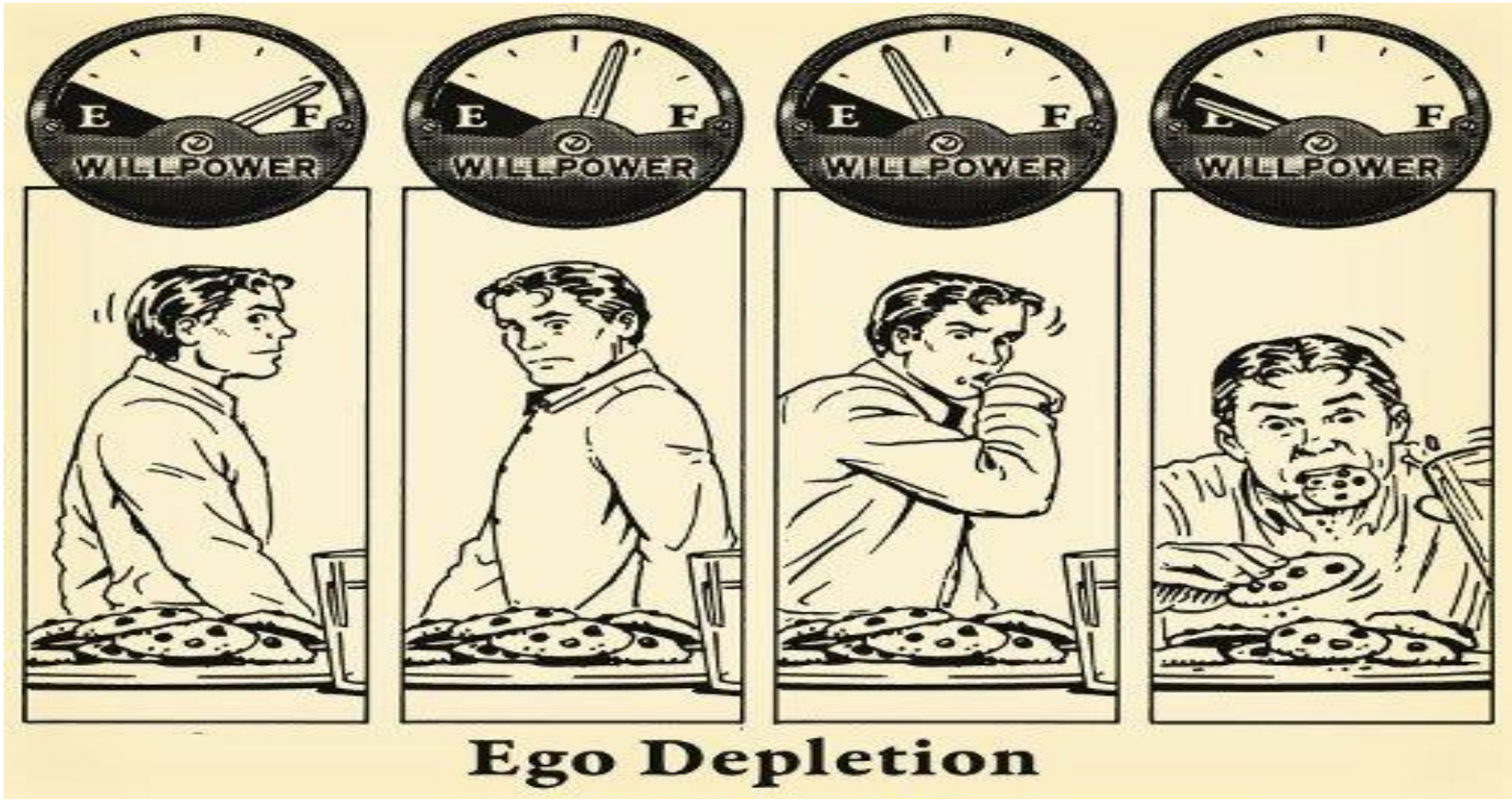
1. Just focusing on what you're giving up by using will power. (I won't eat cake anymore)

2. Going around feeling hungry

3. Not getting enough sleep

All of these lead to Ego Depletion – (Draining Will Power Fuel Tank)

Will power and Ego Depletion: Fatigue, Stress, Frustration, Anxiety, Extreme Hunger, Disappointment



When does ego depletion occur

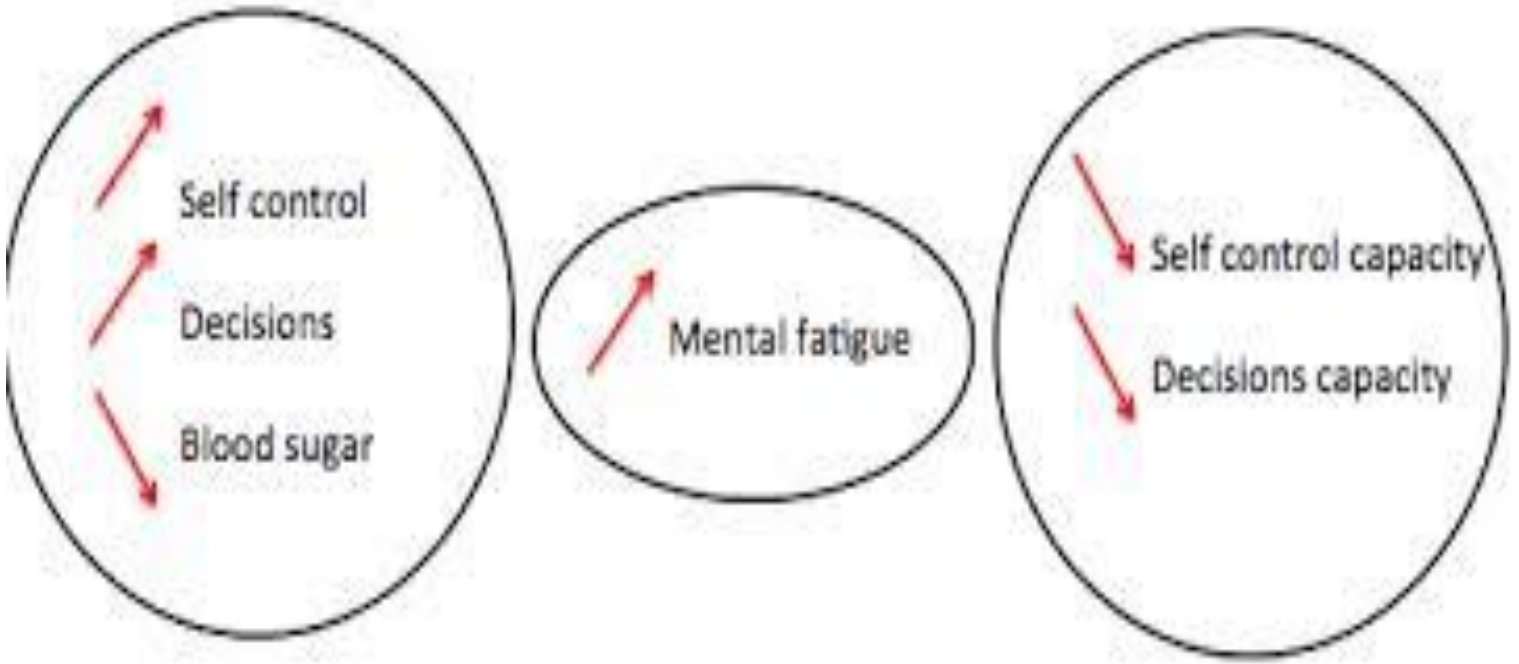
- After a long day
- Physically tired
- After experiencing self control
- After making difficult choice

Drop in blood sugar – leads to sabotage

Studies show a bit of sugar improves decision making when mental fatigue sets in

Super Low carb diets are doomed to failure

Too worn out to go to the gym – have a small snack – brain is rejuvenated = better decision making



Sign of Ego Depletion and Mental Fatigue

Effective Strategies for Change

1. Focus on what you can have and do, not what you're giving up. Find realistic substitutions that reduce feelings of deprivation.
2. Don't allow yourself to get hungry (ravenous) – lose your will power reserve
3. Find a distraction to keep your mind focused on something other than what you are giving up. The distraction should be positive (dance, musical instrument, research, hobby, working out, learning a new sport, going for a walk etc.)
4. Have daily checklist – to hold yourself accountable and keep goals top of mind until they become a habit. Once it's a habit it requires no will power energy or very little
5. Get the rest (sleep) required to keep your will power fuel tank recharged
6. Don't plan to reward yourself with some huge indulgence because you've been so good
7. The best strategy for many things is **Abstinence** (French fries, alcohol, cheese etc.). It takes less mental energy than trying to use moderation. Or use small indulgence that has been previously planned (low fat timbit, mini-crispies). Know your cheat outlets to reduce temptation of other offerings.

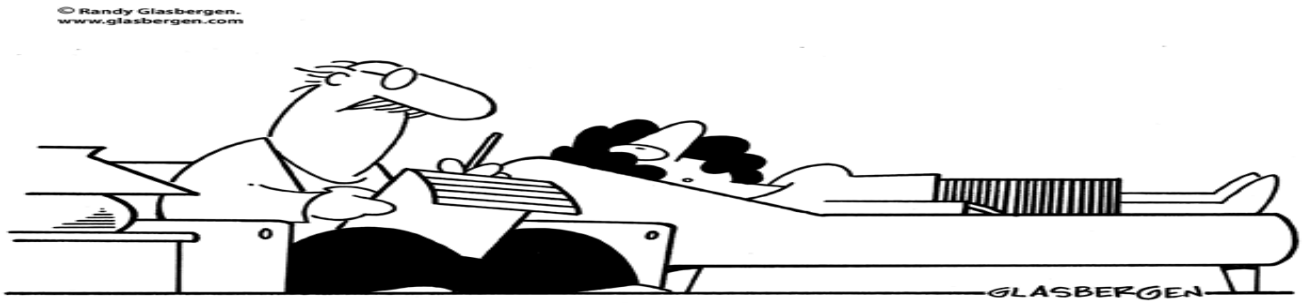
Mastering Positive Habits And Moving Life Forward

- Sleep
- Move
- Eat and Drink Right
- Unclutter – clear the slate, which provides a fresh start mentally
- Renewal - Books-Lectures, Seminars, CD's, DVD's Webprograms
- Find Substitute Activity (or food) for the Damaging Activity – Make it Pleasurable and Convenient
- Turn on the Lights
- Remove the Anchors and the Temptations – out of sight out of stomach
- Start The New Habit Now (discard the tomorrow logic) – start small but start
- A small change in daily routine can be a Lightening Bolt Moment (Protein Shake, First Dance Lesson) for dramatic positive change
- The Less We Indulge the Less We Crave it (Absence only makes the heart grow fonder for a while then it DOESN'T)

Self-check

"Be careful that your favourite medicine doesn't turn to poison, and temporary comfort become a source of guilt, regret, and feelings of lack of control- which can lead to more indulgence in bad habits. It's a secret of Adulthood: Make sure the things we do to make ourselves feel better (in the moment) don't make us feel worse (in the long-term)." (G. Rubin – Better Than Before)

- Food – I eat because I'm unhappy, and I'm unhappy because I eat
- Alcohol, Drugs – self medication to feel better or numb in the moment feelings of sadness, anxiety, frustration etc.
- Watching TV because we feel listless, then we feel listless because we sat around watching TV
- Overspending



"When I spend money, I'm happy. When I run out of money, I'm sad. I'm buypolar!"