Non pharmacological Modulation of Neurotransmitters

- Brief Review of Neurochemistry
- Biochemical Basis of Psychiatric Disease
- Non pharmacological Interventions

J.Lombard@Genomind.com
Neurobehavioral Disorders: How common are they?

- Mental disorders are the leading cause of disability in the U.S. and Canada for ages 15 - 44
- About 1 in 4 adults, an estimated 26.2 percent of Americans ages 18 and older, suffer from a diagnosable mental disorder in a given year (57.7 million people)
- 1 in 17, about 6 percent, suffer from a serious mental illness

www.nimh.nih.gov
More than 2/3 of patients had unresolved symptoms

STAR*D Study (N=2876)

- Remission: ~33%
- Mild symptoms: ~28%
- Moderate symptoms: ~23%
- Severe symptoms: ~12%
- Very severe symptoms: ~4%

Depressive symptoms (QIDS-SR score) after up to 12 wks antidepressant treatment

Where are we now?

Drug-Free America:

Age 0-4 Amoxicillin
4-12 Ritalin
12-18 Appetite Suppressants
18-24 No-Doz
24-38 Prozac
38-65 Viagra
65 and everything else
Superior doctors prevent the disease.
Mediocre doctors treat the disease before evident.
Inferior doctors treat the full-blown disease.

Huang Dee Nai-Chan. 2600 BC; 1st Chinese Medical Text.
Ancient Precedent

“It’s far more important to know what person the disease has than what disease the person has.”

Hippocrates (ca. 400 BCE)
A Modern Caveat:

Psychiatric disorders are not homogeneous or unitary by cause or pathophysiology.

They are likely the consequence of the interaction of numerous factors, both inherited and environmental, which differ from person to person.
The available data today suggest that clinically relevant differences in the underlying pathophysiology of patients with depression exists. The identification of distinct endophenotypes for major depression will not only improve our understanding of the disease, but will also contribute to more specific treatment strategies.

Antonijevic, IA *Psychoneuroendocrinology* (2006), 31 1-15
Neurobiology Overview

- Lipids and signal transduction
- Neurotransmitters:
  - Dopamine- ADHD, addiction
  - Serotonin- Mood, appetite
  - Glutamate- Stress, depression
Principles of Signal Transduction in Neuropsychiatry

- How is biological information translated?
- What is the role of fatty acids in signal transduction and neuropsychiatry?
- What is the role of insulin and insulin resistance in brain disorders, such as Alzheimer’s disease?
The Yin-Yang of Fatty Acids in the CNS

- Omega 3 fatty acids - calcium influx in neurons: hyperpolarization
- Arachidonic acid – Augments glutamate neurotransmission
- Elevated omega 6/3 ratio associated with severity of depression
- Omega 3 fatty acids reportedly have anti depressant effects
Dopamine pathophysiology and pattern recognition

How dopamine dysfunction influences appetite, attention, addiction and depression
Dopamine neurotransmission relative to ADHD

- Enhances signal
- Improves attention
  - Focus
  - On-task behavior
  - On-task cognition

Domains of impairment

- Academic/Occupational
- Health/Injury
- Self-Esteem
- Substance Abuse
- Social Functioning
- Sexual Behavior
- Criminality

Dr. Jay Lombard
Brain Behavior Center
Dopamine and Addictive Behavior

- Binging
- Alcohol
- Tobacco
- Substance abuse
- Risk taking
Dopamine and Obesity

Dopamine Receptor Concentration

Dopamine D2 receptor imaging

Wang et al, Lancet 2001
Effect of High Fat Diet on Expression of Genes Controlling Dopamine

- High fat diets increase TH and result in brief, pulsatile increases in dopamine, providing a mechanism of the reinforcing/addictive like potential of dietary components

- Nutrition, April 26, 2010
Some Neurotransmitter Precursors

Figure 6.13
The synthesis of serotonin from tryptophan.

Figure 9-8. The major amino acid neurotransmitters.
Regulation of dopamine synthesis

- Tyrosine hydroxylase (TH) converts tyrosine to L Dopa and is the rate limiting step in dopamine synthesis.
- TH requires folate and iron as cofactors.
- Tyrosine hydroxylase activity inhibited by iron deficient anemia and folate depletion.
Genetic Variants of Folate Metabolism

Folic Acid

Dihydrofolate

Tetrahydrofolate

10-formyl-THF

5,10-methylenyl-THF

5,10-methylene-THF

L-methylfolate

L-methylfolate

Homocysteine

Methionine

SAH

SAMe

DNA

Methylated DNA, RNA, protein, lipids

Tryptophan → Serotonin

Tyrosine → Dopamine → Norepinephrine

BH4

BH2

MTHFR

SHMT

DHFR

MTHFD1

RFC1

Cell Membrane or BBB

Genetic Variants of Folate Metabolism
MTHFR Polymorphism and Depression:

MTHFR C→T genotypes have a 1.36X greater chance of developing depression (and reported to be as high as 4X the general population)³,⁴

1. Popakostas , J. Clinical Psychiatry; 2004, 1090-1095
2. Bottiglieri T, Prog in Neuro-Psychopharm & Bio Psych, 2005
4. Procopciuc L.M., Presented at Biological Psychiatry, Poster P86
5. Arinami T, AM J. Medical Genetics 1997
L-methylfolate as Augmentation for Major Depressive Disorder

- Medical food for suboptimal foliate levels in depression patients (adjunct to antidepressant)
- L-methylfolate is a required cofactor in the synthesis of all 3 monoamines
- L-methylfolate deficiency may be common as a result of genetic polymorphism
- Short-term open label and placebo-controlled trials support use as an add-on therapy
Catecholamine Reuptake Inhibition is a Likely Mechanism of Action (MOA) of ADHD Drugs
Zinc: Dopamine and ADHD

- Dopamine transporter is regulated by zinc, which interacts with the transporter protein.
- Studies suggest the involvement of zinc deficiency in patients with ADHD.
- Human dopamine transporter contains a zinc binding site that modulates transporter function, suggesting that response to stimulants is reduced in zinc-deficient ADHD patients. Zinc supplementation in zinc-deficient ADHD patients improves the binding status of insufficiently occupied zinc binding sites on the dopamine transporter.

1. CNS Drugs: September 2010 - Volume 24. Role of Zinc in the Pathogenesis of Attention-Deficit Hyperactivity Disorder:
Zinc: A Non Pharmacological Dopamine Agonist

- Blocks dopamine reuptake
- Inhibiting dopamine reuptake is a mechanism similar to certain anti depressants such as Buproprione
- Promotes conversion of T4 to T3
- Zinc supplementation may be of benefit as a stand-alone intervention or as an adjunct to conventional antidepressant drug therapy for depression.

Epub 2011 Jul 27.
Catechol-O-methyltransferase (COMT) is the enzyme responsible for degrading dopamine, norepinephrine and estrogen.

<table>
<thead>
<tr>
<th>COMT Polymorphisms</th>
<th>Effect</th>
<th>Possible Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val/Val</td>
<td>🚹COMT</td>
<td>Rapid degradation DA,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>catacholamines, estrogen and metabolites</td>
</tr>
<tr>
<td>Val/Met</td>
<td>Wild type</td>
<td></td>
</tr>
<tr>
<td>Met/Met</td>
<td>🚮COMT</td>
<td>Slow degradation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>catacholamines, estrogen and metabolites</td>
</tr>
</tbody>
</table>
S adenosylmethionine

- Meta analysis of studies have demonstrated approx 6 point reduction on HAM-D depression scores
- Mechanism of action unclear but plays critical role in methylation and synthesis of catecholamines
- Depression associated with reduced brain bionergetic status; SAMe may exert antidepressant effects by increased creatine and ATP

- SAMe methylates guanidinoacetic acid (GAA) to produce creatine
- Faster rate of onset than standard antidepressants
- COMT augmentation
- Use with caution if bipolar suspected
- Cost and off the shelf stability are issues
Subclinical Hypothyroidism & Depression

- Subclinical hypothyroidism is more common than overt hypothyroid in elderly, especially women
- Subclinical hypothyroidism (TSH <1 with normal T, (other values: T3 and rT3 values))
- Increasing evidence to suggest a predisposing factor for depression,
The Serotonin System

Adapted from Kaplan et al. Synopsis Psychiatry. 1994.

Serotonin and Brain Function

- Neuroendocrine homeostasis
- Sleep regulation
- Appetite
- Mood
- Social engagement
Serotonin Imbalance: Core Symptoms

- Disruption in homeostasis
- Reduced appetite
- Anxiety
- Hypervigilance
- Depression
- Sleep Disorders
### Physiology of Serotonin 5HT2C Receptor
- Mediates satiety signaling in the hypothalamus

### C allele: Clinical Significance
- Increased risk for weight gain and metabolic syndrome with Atypical Antipsychotics

### Relevant Therapies
- Use caution when prescribing Atypical Antipsychotics
- Consider therapies that reduce weight gain
Hypothalamic 5Ht2C Receptor

VM nucleus regulates satiety
Inositol in Depression, PCOS and Metabolic Syndrome

- Inositol is a sugar found in melons
- May enhance insulin signal transduction and serotonin receptor activity
- Doses of myo inositol and/or chiro inositol between 1gm- 4 gms/day have seen benefit in a variety of conditions including PMDD, PCOS and metabolic syndrome
Neurobiology of GABA and Glutamate
Glutamate and Brain Function

- Excitability
- Role in Cellular Memory
- Pain Perception
- Potentiation
- Amplification
Glutamate Imbalance: Phenomenology

- Irritable
- Cyclical/paroxysmal disorders
- Migraines
- Chronic pain
- Mood swings
- Anxiety
- Insomnia
Glutamate in Disease States

**NEUROLOGIC**
- Seizures
- Migraine
- Neuropathic pain

**PSYCHIATRIC**
- Bipolar disease
- Schizophrenia
- PTSD
- Treatment refractory depression
- Autism
Glutamate
Channels cycle between open and closed conformations. When open, a channel provides a continuous pathway through the bilayer, allowing flux of many ions. Calcium channels are examples of a channel.

**Mechanism of Ion Channels**

- **Closed**
- **Open**
- **Conformation change**

**Channels**
- continuous pathway through the bilayer
- Calcium channels
Non Pharmacological Glutamate Antagonists

- Omega 3 Fatty acids
- Magnesium
- N acetylcysteine
- Vitamin D
Omega-3 Fatty Acids

- Positive evidence of efficacy in unipolar and bipolar depression
- Meta-analysis (15 trials)
  - Eicosapentaenoic acid (EPA) is the effective component [vs. docosahexaenoic acid (DHA)]
  - >60% EPA (of total EPA + DHA) is needed
Because, as long as the membrane remains polarised, the pore of the channel is blocked by physiological, extracellular concentration of Mg$^{2+}$. 
Magnesium: An Endogenous Glutamate Antagonist

- Magnesium blocks NMDA voltage gated receptors
- Inhibits intracellular calcium and sodium influx
- Magnesium used clinically for pre eclampsia, migraine, neuroprotection, anxiety
N-Acetylcysteine: Novel Glutamate Antagonist

- NAC is the n-acetyl derivative of L-cysteine and plays a major role in hepatic glutathione production.
- **Down regulates glutamate activity by its involvement with the cysteine-glutamate transporter:** Intracellular cysteine entry in exchange for export of glutamate.
- Significant effects reported in psychiatric disorders including: Augmentation of serotonin reuptake inhibitors for the treatment of OCD.

*Psychopharmacology* 2006. Jan 254-6); Reduction of self injurious behavior (*J Clinical Psychiatry* Nov 05, 1494-97) and Autism (publication pending).
Neurobiology of Dementia
Brain aging starts at 40

“We found genes involved in learning and memory were among those most significantly reduced in the aging human brain.”

Other glitches appear in a set of genes that regulate energy protection and transport of proteins in cells.

Some of these alterations show up in people as young as their 40s.”
Acetylcholine and Brain Function

- Acetylcholine synthesis occurs in the hippocampus
- Acetylcholine function is critical for cognitive processing, memory, arousal, and attention
- Diminished Acetylcholine correlates with severity of cognitive dysfunction
- Acetylcholine dysfunction associated with insulin resistance
Behavioral Symptoms as AD Progresses

The Emergence of Type 3 Diabetes: 
*The Dementia of the 21st Century*

“...The co-existence of brain insulin... deficiency and resistance suggests that Alzheimer’s disease may represent a brain-specific form of diabetes, i.e., Type 3 diabetes.”

(de la Monte et al. J AlzDis 2006; 10:89-109)

Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer’s disease – is this type 3 diabetes?

Eric Steen, Benjamin M. Terry, Enrique J. Rivera, Jennifer L. Cannon, Thomas R. Neely, Rose Tavares, X. Julia Xu, Jack R. Wands and Suzanne M. de la Monte* 
From the Departments of Pathology and Medicine, Rhode Island Hospital and Brown Medical School, Providence, RI, USA
The Mediterranean Diet and Cognition

Higher adherence to the MeDi is associated with a trend for reduced risk of developing MCI and with reduced risk of MCI conversion to AD.

Figure 2.
Survival curves based on Cox analysis comparing cumulative MCI incidence in subjects cognitively normal at 1st evaluation by each Mediterranean diet (MeDi) tertile (p for trend 0.05). The figure is derived from a model that is adjusted for cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, body mass index and time between 1st dietary and 1st cognitive assessment. Duration of follow-up is truncated at 10 years. Log-rank test for pairwise comparisons: middle vs. low MeDi tertile $x^2 = 0.91$, $p = 0.33$, low vs. high MeDi tertile $x^2 = 3.72$, $p = 0.05$, middle vs. high $x^2 = 1.22$, $p = 0.26$.

Figure 3.
Survival curves based on Cox analysis comparing cumulative AD incidence in subjects with MCI at 1st evaluation by Mediterranean diet (MeDi) tertile (p for trend 0.02). The figure is derived from a model that is adjusted for cohort, age, gender, ethnicity, education, APOE genotype, caloric intake, body mass index and time between 1st dietary and 1st cognitive assessment. Duration of follow-up is truncated at 10 years. Log-rank test for pairwise comparisons was as follows: middle vs. low MeDi tertile $x^2 = 4.2$, $p = 0.03$, low vs. high MeDi tertile $x^2 = 1.3$, $p = 0.23$, middle vs. high $x^2 = 0.12$, $p = 0.72$. 
Non Pharmacological Neurotransmitter Modulators

- Low dopamine- associated with ADD: MTHF genotype folic acid, zinc
- Check thyroid, B12, folate and iron levels in people with depression and fatigue
- Excess dopamine- associated with excessive stress and COMT genotype: S adenosylmethionine
- Serotonin imbalance- associated with 5HT2C genotype: Myoinositol
- Glutamate imbalance- associated with mood swings, Calcium channel genotype variants: Omega 3 fish oil, magnesium, vitamin D
- Cognitive decline- associated with insulin resistance: Med diet
Food As Medicine

A Feast of Science & Wisdom

June 6 - 9, 2013

JW Marriott

Indianapolis, IN

www.cmbm.org/fam
Food As Medicine: Integrative RDNs

“An inspiring program for RDNs lead by RDN’s”

• **Kathie Madonna Swift MS RDN:** Curriculum Designer, Food As Medicine

• **Brenda Davis, MS RD:** Vegetarian, Vegan and Raw Food Diet Nutrition Expert

• **Coco Newton MPH RDN CCN:** Nutrition-Focused Physical, University of Kansas Fellowship Program in Nutrition
Food As Medicine

• Continuing Education: 24.5 CPEUs

• DIFM DPG Member Discount

• Contact Amy for discount code: info@integrativeRD.org

• www.cmbm.org/fam for more info