A Tale of Two (Hundred Twenty Seven) Depressions: Melancholic Versus Atypical Subtypes

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Faculty Disclosure

• David J. Scheiderer, MD has served as a member of the Speakers Bureau and/or Advisory Board for the following: Lilly USA, LLC; Merck; Takeda, PamLab, Otsuka; Lundbeck; and Forest.

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As chronic degenerative illnesses (Diseases of Civilization – DOCs) become more common, so too do disorders affecting the brain: depression, anxiety, ADD, autism, Alzheimer’s, PTSD, chronic fatigue, and fibromyalgia.
Depression is the most common psychiatric disorder in the world.

MDD represents a significant healthcare burden:

- #1 contributor to disability worldwide\(^1\)
- 16 million adults affected in the U.S.\(^2\)

Patients have different treatment needs:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Tolerability</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every patient can present with different symptoms, for example(^3):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia or hypersomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss or weight gain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor agitation or psychomotor retardation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant side effects represent different burdens to different individuals(^4)</td>
<td></td>
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</tr>
<tr>
<td>Patients may experience depressive symptoms and functional impairment ranging from mild to very severe(^5)</td>
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</tbody>
</table>

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“Given that our current descriptivist methodology for psychiatric nosology does not in fact establish causes, it is insufficient for determining what depression is. We can talk about what depression does, but not about what it is.”
Nearly half of patients with Depression are not receiving any treatment.

- Receiving no treatment: 48%
- Receiving less than minimally adequate treatment: 32%
- Receiving at least minimally adequate treatment: 20%

STAR*D Study: 2/3 of Patients Remained Symptomatic Following Antidepressant Treatment

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

Percent of Patients

Depressive Symptoms (QIDS-SR score) After up to 12 Weeks of Antidepressant Treatment

Significant Individual Differences in 20 Subjects Treated With An Antidepressant: Or, in Other Words, It’s a Crapshoot.

Complex Neurobiological Underpinnings of Mood Disorders

“Network” Level: Dysregulation of Neural Circuitry
- Functional Changes
- Structural Changes

Psycho-Neuro-Immunological (PNI) Disturbances (cortisol, serotonin, dopamine, norepinephrine, hormones)

Cellular and Subcellular Level Impact on
- Intracellular Signaling
- Gene Transcription
- Neurotrophic Support

Multiple Symptom Domains
- Emotional
- Cognitive
- Behavioral
- Physical

System-Wide Manifestations

*GULCH – Genes, Uterine environment, Life experiences particularly early life adversity, Choices, Habits

Depression is a genetically complex disorder

- There is no single “depression gene”
- Most likely there are mutations in multiple genes, coupled with environmental causes\(^1\)
- Gene alterations interact with each other and with the environment to influence vulnerability or resilience toward a specific disease\(^2\)
- Examples of other genetically complex disorders:\(^2\)
  - Heart disease
  - Type II diabetes
  - Many forms of cancer

Childhood Adversity Represents a Risk for Adulthood Disease

Major depression (panel 1): z=4.94, P<.001. High-sensitivity C-reactive protein (hsCRP) level > 3 mg/L (panel 2): z=3.24, P=.001. Clustering of metabolic risk markers (panel 3): z=4.58, P<.001. ≥1 age-related disease risks (panel 4): z=5.66, P<.001.

32-year prospective study.

Early Life Adversity Interaction with MTHFR Alleles

$P=0.0027$.

BDI, Beck Depression Inventory; MTHFR, methylenetetrahydrofolate reductase.

Subjects With Depression Had an Attenuated Ventral Striatal (Nucleus Accumbens) Response to Positive Stimuli

SD=standard deviation. BOLD=blood-oxygen-level dependent.
Melancholic Versus Atypical Depression

- “Our study supports a different clinical pattern and treatment outcome for melancholic and atypical depression subtypes.”
- “The data provide further evidence that chronic forms of depressive subtypes differ not only in their symptom presentation, but also in their biological correlates.”
“For the diagnosis at least five of nine symptoms including at least one of the two core symptoms must be present. It follows that there are 227 possible combinations of symptoms leading to the diagnosis.”

RDoC: Cognitive Systems, Neural Circuits, and Dimensions of Behavior

• “Although many important discoveries have been made in the study of cognition, neuroscience, and mental illness, there is growing frustration with the rate of translation of these efforts into understanding of etiological foundations and new treatments.”

• “Progress toward understanding and treating mental illness has been hindered by the scientific focus on diagnoses that do not reflect the organization of neural circuits and their associated behaviors.”

• As such, “… novel approaches to treatment and prevention may benefit from alternative conceptualizations of mental disorders.”

• The RDoC initiative is part of the NIMH’s strategic plan to classify mental disorders based on dimensions of observable behavior and neurobiological measures.
Biomarker Panels

- There are no clear single biomarkers
- We have, however, mounting evidence of multiple dysregulated contributing and perpetuating factors:
  - Growth factors
  - Pro-inflammatory cytokines
  - Endocrine factors (HPATG)
  - Metabolic factors (insulin resistance)
- Thus, a viable alternative to the single-biomarker approach could be the development and implementation of biomarker panels

HPATG, hypothalamus, pituitary, adrenal, thyroid, gonadal, gut.
The availability of peripheral biomarkers that can both identify patients with specific pathophysiologic processes and serve to objectively monitor therapeutic responses within relevant pathways is truly unique and may represent a major advance in the personalization of the treatment of depression.

Mediators – A Closer Look

- Hormones
- Neurotransmitters
- Metabolic Parameters
- Growth Factors
- Immune Cells
The Study of which is called Psycho-Neuro-Immunology (PNI).
“Psychoneuroimmunology is a convergence of disciplines – namely, the behavioral sciences, the neurosciences, endocrinology, and immunology – intended to achieve a more complete understanding of the way the interactions among these systems serve homeostatic ends and influence health and disease.”

- Robert Ader
Building a Better Biomarker Panel: Allostatic Load

Allostatic load is a commonly utilized metric of health risk based on the hypothesis that recurrent stress engenders progressive dysregulation of multiple physiological systems.

The process of achieving stability through physiologic and behavioral change. This is carried out by alterations in HPA axis hormones, autonomic nervous system, cytokines, and other regulatory systems and is generally adaptive in the short term.

HPA, hypothalamic-pituitary-adrenal.
### Biomarkers Repeatedly Used in Studies of AL

<table>
<thead>
<tr>
<th>Neuro-endocrine</th>
<th>Immune</th>
<th>Metabolic</th>
<th>CV and Respiratory</th>
<th>Anthropometric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>IL-6</td>
<td>HDL</td>
<td>Systolic BP</td>
<td>Waist-Hip Ratio</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>TNF-α</td>
<td>LDL</td>
<td>Diastolic BP</td>
<td>BMI</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Hs-CRP</td>
<td>Triglycerides</td>
<td>Peak Expiratory Flow</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>IGF-1</td>
<td>HgbA1C</td>
<td>Heart Rate</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>Fibrinogen</td>
<td>Glucose Insulin</td>
<td>HRV</td>
<td></td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Vitamin D</td>
<td>Albumin Creatinin</td>
<td>Homocysteine</td>
<td></td>
</tr>
</tbody>
</table>

AL, allostatic load; DHEA-S, dehydroepiandrosterone; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein; IGF-1, insulin-like growth factor-1. Juster RP et al. *Neurosci Biobehav Rev.* 2010;35(1):2-16
Cortisol as Proxy for Allostatic Load

“Chronic stress causes stress hormones to strain many biological systems in a process referred to as allostatic load that is measurable using an index of biomarkers.”

Subtypes of Major Depression

- Subtypes of major depressive disorder were found to be stable across a 2-year follow-up and to have distinct determinants, supporting the notion that the identified subtypes are clinically significant\(^1\)

- Significant heterogeneity in depressive symptomatology exists in United States samples. Profiling symptom patterns is potentially useful as a first step in developing tailored intervention and treatment programs\(^2\)

- In the National Comorbidity Survey, 36% of individuals with MDD had atypical features and 53% had melancholic features\(^3\)

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“Biological Correlates” in Melancholic vs Atypical Depression

- hs-CRP
- IL-6
- TNF-α
- Metabolic Syndrome Components
- BMI
- Saliva Cortisol Awakening Curves (AUCg & AUCi)
- Diurnal Cortisol Slope

AUCg, area under the curve with respect to the ground; AUCi, area under the curve with respect to the increase.
## Melancholic vs Atypical Depression

<table>
<thead>
<tr>
<th>SSx</th>
<th>Melancholic</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of arousal</td>
<td>Hyperaroused</td>
<td>Hypo-aroused, apathetic</td>
</tr>
<tr>
<td>Anxiety level</td>
<td>anxious</td>
<td>Generally not anxious</td>
</tr>
<tr>
<td>Reactivity to environment</td>
<td>Relatively unreactive</td>
<td>Reactive to environment</td>
</tr>
<tr>
<td>Emotional memory</td>
<td>Broods over painful past</td>
<td>Emotionally detached</td>
</tr>
<tr>
<td>Cognition</td>
<td>↓ concentration, perseveration</td>
<td>Poor focus</td>
</tr>
<tr>
<td>Behavior</td>
<td>Regression</td>
<td>Unmotivated, inactive</td>
</tr>
<tr>
<td>Strong link to bipolar</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sleep</td>
<td>Decreased, poor quality</td>
<td>Increased, poor quality</td>
</tr>
<tr>
<td>Appetite</td>
<td>Decreased with wt. loss</td>
<td>Increased with wt. gain</td>
</tr>
<tr>
<td>Energy</td>
<td>Variable</td>
<td>“Leaden paralysis”</td>
</tr>
<tr>
<td>Diurnal variation</td>
<td>Worse in morning</td>
<td>Worse in evening</td>
</tr>
</tbody>
</table>

## Melancholic vs Atypical Depression (cont’d)

<table>
<thead>
<tr>
<th>SSx</th>
<th>Melancholic</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA axis</td>
<td>Centrally-activated</td>
<td>Centrally-mediated hypo-activity</td>
</tr>
<tr>
<td>Cortisol/ CRF output</td>
<td>High/high</td>
<td>Low/low</td>
</tr>
<tr>
<td>DST</td>
<td>Low suppression</td>
<td>High suppression</td>
</tr>
<tr>
<td>Response to prednisone</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Sympathetic activity</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>BMI</td>
<td>Normal</td>
<td>High</td>
</tr>
<tr>
<td>Lean body mass</td>
<td>Decreased (sarcopenia)</td>
<td>Normal</td>
</tr>
<tr>
<td>Immune function</td>
<td>Immunosuppressed, increased infections</td>
<td>Immuno-enhanced, increased inflammation</td>
</tr>
<tr>
<td>Heart disease</td>
<td>Premature CHD</td>
<td>Premature CHD</td>
</tr>
<tr>
<td>Bone Density</td>
<td>Premature osteoporosis</td>
<td>Normal bone</td>
</tr>
</tbody>
</table>

Either Road Leads to Metabolic Syndrome

Are People with Atypical Depression Sicker?

“The presence of atypical features during an MDE was associated with greater rates of lifetime psychiatric comorbidity, including….”

- Alcohol abuse
- Drug dependence
- Dysthymia
- Social anxiety disorder
- Specific phobia
- Any personality disorder except antisocial
- Female gender
- Younger age at onset
- More MDEs
- Greater episode severity and disability
- Higher rates of family history of depression, bipolar I disorder, and suicide attempts
- Larger mental health treatment-seeking rates

Atypical Depression Associated With Obesity, Diabetes, and Metabolic Syndrome

“To conclude, results emphasize the need to subtype depression and to pay particular attention to the atypical subtype.”

## HPA Axis Activity and DOCs

<table>
<thead>
<tr>
<th>Increased HPA Axis Activity</th>
<th>Decreased HPA Axis Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe chronic disease</td>
<td>Atypical depression</td>
</tr>
<tr>
<td>Melancholic depression</td>
<td>Seasonal depression</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>Chronic fatigue syndrome</td>
</tr>
<tr>
<td>OCD</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>PTSD</td>
</tr>
<tr>
<td>Chronic excessive exercise</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Adrenal suppression</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Asthma</td>
</tr>
<tr>
<td>Central obesity</td>
<td>Postpartum</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>RA</td>
</tr>
</tbody>
</table>


“Individuals with atypical depression may be partially driving the overall depression-inflammation relationship and may be a subgroup at elevated risk for coronary artery disease.”
The 4 Faces of Depression

- **“Weeping and A-wailing”**
  - High Cortisol, High Excitatory (Ex) NTs
  - “Doom, Despair, and Agony on Me”

- **“Wired and Tired”**
  - High Cortisol, Low Ex NTs
  - Allergic and Infected

- **“Wired and Tired”**
  - Low Cortisol, High Ex NTs
  - Inflamed and in Pain

- **“Just Plain Tired”**
  - Low Cortisol, Low Ex NTs
  - Situation Critical
Depression With Excess Negative Emotions and Cognitions: Melancholia

Symptoms
• Terminal insomnia
• Decreased appetite
• Ahedonia
• Dread about the future
• Sense of doom
• Worthlessness, helplessness
• Worse in the morning

“Internal Comorbidities”
• OCD
• Panic disorder
• Severe chronic disease
• Hyperthyroidism
• Excessive exercise
Depression With Deficient Positive: Atypical

Symptoms
• Excessive sleepiness
• Increased appetite with carb cravings
• Fatigue
• Anhedonia
• “Leaden paralysis”
• Rejection sensitivity
• Symptoms worsen as day progresses

“Internal Comorbidities”
• PTSD
• Fibromyalgia
• Chronic fatigue
• Heart disease
• Metabolic syndrome
• Obesity
• Hypothyroidism
Pharmacogenetic Testing: How Far Are We From Clinical Application?

• Pharmacogenetics studies how genetic variation influences the response of patients to drugs. This discipline has a greater impact in those medical specialties that treat complex diseases in which the therapeutic response is insufficient and/or have high costs such as psychiatry.

• As such, there is again great potential for pharmacogenetics to facilitate improved and more effective pharmacotherapy. However, clinical implementation of these discoveries can only be realized with adequate assistance from the appropriate regulatory, professional, healthcare, and third-party payer organizations. Although not as quick as technology advancements, it seems that these agencies are at least making incremental strides to ultimately facilitate clinical pharmacogenetics into more routine patient care.

<table>
<thead>
<tr>
<th>Test</th>
<th>Genes</th>
<th>Tendencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative Stress</td>
<td>SOD1, SOD2, SOD3, GPx1, CAT</td>
<td>Heart disease, Aging, Diabetes, Alzheimer’s</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>VDR, CYP27B1, GC</td>
<td>Bone loss, MS, Heart disease, Inflammation</td>
</tr>
<tr>
<td>Neurotransmitter Synthesis/ Folate Methylation</td>
<td>COMT, MTHFR</td>
<td>Fibromyalgia, Fatigue, ADD, Autism, Depression, Anxiety</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>HLA-DQ2.5, HLA-DQ8</td>
<td>Gluten sensitivity, brain fog, GI distress</td>
</tr>
<tr>
<td>Metal Detoxification</td>
<td>GSTM1</td>
<td>Chronic fatigue syndrome, Detox issues, Fibromyalgia,</td>
</tr>
<tr>
<td>Multiple Drug Resistance</td>
<td>MDR1</td>
<td>Altered response to drugs, Detox issues</td>
</tr>
</tbody>
</table>
MTHFR Polymorphism & Depression

- MDD is most likely a neurobiological, heterogeneous disorder.¹
- Genome-wide association studies have so far failed to identify specific genes involved in etiology of MDD.²
- MDD is most likely a product of complex interactions between multiple genes, epigenetic changes, and environmental adversity.¹,²
- MTHFR is associated with reduced antidepressant efficacy.³
- MTHFR polymorphism is associated with increasing the risk and severity of depression.⁴,⁵
- ELA interaction with MTHFR predicts increased risk of depression.⁶

BH4 - Tetrahydrobiopterin

Inflammation and Oxidative Stress

Summary

Phenotype: 4 Faces of Depression

“Internal Comorbidities”

Personalized Treatment

Biological Correlates: PNI Perturbations