Depression and Inflammation: The Interplay With Autoimmune Disease

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Disclosures

- Research/Grants: Agency for Healthcare Research and Quality (AHRQ); National Institutes of Health (NIH)
- Consultant: Eli Lilly and Company; Shire Pharmaceuticals Inc.; SK Pharma; Roche; Takeda Pharmaceuticals North America, Inc.; Xhale, Inc.
- Stockholder: CeNeRx BioPharma; NovaDel Pharma, Inc.; PharmaNeuroBoost, Reva Pharmaceuticals LLC; Xhale, Inc.
- Other Financial Interest: CeNeRx BioPharma; PharmaNeuroBoost
- Patent: Method and devices for transdermal delivery of lithium (US 6,375,990B1)
- Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2)
- Scientific Advisory Boards: American Foundation for Suicide Prevention (AFSP); Anxiety Disorders Association of America (ADAA); CeNeRx BioPharma; National Alliance for Research on Schizophrenia and Depression (NARSAD); PharmaNeuroBoost; Xhale, Inc.; Skyland Trail; AstraZeneca Pharmaceuticals (2009)
- Board of Directors: American Foundation for Suicide Prevention (AFSP); Gratitude America, Mt. Cook Pharma, Inc. (2010) NovaDel Pharma, Inc. (2011); Skyland Trail
Learning Objective

Recognize the interplay of inflammation and depression and use this knowledge to accurately and consistently assess patients with inflammatory disease for depression.

Proinflammatory Cytokines Play a Central Role in Classic Autoimmune Conditions

- Rheumatoid arthritis
- Inflammatory bowel disease
- Multiple sclerosis
- Psoriasis
- Ankylosing spondylitis

But also:
- Coronary artery disease
- Diabetes and the metabolic syndrome
- Cancer
- Alzheimer’s disease

Major Clinical Disorders Associated with Inflammation

- Cardiovascular disease
  - Inflammatory markers (CRP/IL-6) are potent predictors of disease outcome; involvement of inflammation in plaque formation and cardiac irritability
- Diabetes/metabolic syndrome/obesity
  - High correlation between insulin resistance and IL-6 and other inflammatory markers
- Cancer
  - Activation of inflammatory signaling pathways (e.g., NF-kB) implicated as a fundamental mechanism of carcinogenesis and chemotherapy resistance
**Is Major Depressive Disorder a Pro-Inflammatory State?**


**Major Depressive Disorder and Systemic Illnesses**

- Patients with MDD have a doubling of mortality and coronary artery disease at any age, independent of smoking, hypertension, and other risk factors for poor health.

- 20% to 25% premenopausal patients with MDD have premature osteopenia and osteoporosis.

- MDD is associated with an ~ 2-fold increase in the risk for Type II diabetes.

Basis for the Hypothesis that Inflammation and an Activated Innate Immune Response May Play a Role in Depression

- Patients with depression (both medically ill and medically healthy) have been found to exhibit all the cardinal features of inflammation:
  - Increased plasma and CSF concentrations of innate immune cytokines (IL-6 most reliable)
  - Increased acute phase reactants (CRP most reliable)
  - Increased chemokines
  - Increased cellular adhesion molecules

- In the majority of studies, inflammatory markers decrease with successful antidepressant therapy ("state marker")
- Depressed patients with increased inflammatory markers are more likely to be treatment resistant
  - In our study:
    - 2/3 with "high" inflammation according to CDC/AHA guidelines with CRP > 3mg/L
      - 5 million depressed individuals in US
    - 1/3 with CRP > 5mg/L
      - 3 million depressed individuals in US

Depression is Associated with Elevated Body Temperature in Medically Healthy Patients

IL-6 Concentrations In Patients With Depression And Cancer

![IL-6 Concentrations Graph](image)

<table>
<thead>
<tr>
<th>Study Group*</th>
<th>Healthy Controls (n = 10)</th>
<th>Depressed Controls (n = 12)</th>
<th>Cancer Patients (n = 13)</th>
<th>Depressed Cancer Patients* (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmas IL-6 Concentration (pg/ml)</td>
<td>0</td>
<td>100</td>
<td>200</td>
<td>300</td>
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</tbody>
</table>

* Depressed CA Patients with highest IL-6 plasma concentrations


Basis for the Hypothesis that Inflammation May Play a Role in Depression

- Positive correlation between depressive symptom severity and innate immune cytokines
- Elevated innate immune cytokines predict poor response to antidepressant therapies and are elevated in patients with treatment resistance. Cytokine gene polymorphisms (IL-1, TNF) predict antidepressant treatment response
- Administration of innate immune cytokines, especially IL-1, TNF-alpha, and IL-6, as well as IFN-alpha, produce behavioral changes in laboratory animals and humans that resemble major depression
- Inhibition of cytokine signaling has been found to alleviate depressive and anxiety behaviors in patients with inflammatory disorders and in laboratory animals

Basis for the Hypothesis that Proinflammatory Cytokines Play a Role in Depression and Depressive Symptoms

- Cytokines released peripherally have access to the brain
  - Passage through leaky regions in the BBB
  - Active transport
  - Transmission through afferent nerve fibers (vagus)
- There is a cytokine network in the CNS
  - Glia (microglia) and neurons express/produce cytokines and express cytokine receptors
- Cytokines have effects on neurotransmitter turnover, neuroendocrine function, and behavior (sickness behavior)
Childhood Abuse = Unhealed Wounds


Chronic Pelvic Pain, Fatigue, and Physical Symptoms

General Health Checklist

Patients with Major Depression Exhibit an Exaggerated Inflammatory Response to Stress

A Possible Link Between Stress, Depression, and Illness

Childhood Maltreatment Predicts Adult Inflammation in a Life-Course Study

- The life-course association between childhood maltreatment and adult inflammation was examined in a birth cohort followed to age 32 years as part of the Dunedin Multidisciplinary Health and Development Study.
- Maltreated children showed a significant and graded increase in the risk for clinically relevant C-reactive protein levels, 20 years later.
- The association between maltreatment and adult inflammation also generalizes to fibrinogen and white blood cell count.
- Childhood maltreatment is a previously undescribed, independent, and preventable risk factor for inflammation in adulthood.


The Association of Childhood Maltreatment with Biomarkers of Inflammation

Questions

- Do proinflammatory cytokines, and therefore, the immune system contribute to the pathophysiology of major depression in the medically ill?
- What mechanisms are involved?
- What are the treatment implications?
Interferon-Alpha as a Model System to Study Cytokine-Induced Depression

- Antiviral/antiproliferative cytokine used to treat viral infections and cancer
- Potent inducer of innate immune response including innate immune cytokines (especially IL-6)
- Potent inducer of behavioral toxicity including symptoms of major depression in humans and non-human primates

IFN-Alpha-Induced Behavioral Symptoms in Patients with Malignant Melanoma

Placebo-treated patients (%) experiencing moderate-to-severe intensity in the listed symptom during IFN-alpha therapy

High-Dose Interferon in Malignant Melanoma
Paroxetine Pretreatment

Incidence of Major Depression During the First 12 weeks of IFN-alpha


Paroxetine Pre-treatment Reduces the Incidence of Major Depression During the First 12 weeks of High Dose IFN-alpha for Malignant Melanoma


IFN-alpha-induced Depression is Associated with Tryptophan (TRP) Depletion


IFN-alpha-induced Depression is Associated with Exaggerated HPA Activation

IFN-alpha-induced Depressive-like Behavior ("Huddling") is Associated with Exaggerated HPA Activation in Monkeys

Huddling: a fetal-like self-enclosed position with head at or below shoulders.


IFN-alpha Effects on Basal Ganglia Function Correlate with Fatigue


CSF Homovanillic Acid (HVA), the Major Metabolite of Dopamine, Correlates with Fatigue and CSF IL-6 in IFN-alpha-treated Patients

IFN-alpha ↑ IL-6 ↓ dopamine ↓ HVA ↓ fatigue
Prevalence of Moderate/Severe Depressive Symptoms During Treatment with Pegylated IFN-alpha

Rates of Depression Are Uniformly Elevated in Inflammatory Conditions

- Depressive syndromes are a risk factor for the development of CAD, metabolic syndrome, cancer
- Depression increases morbidity in all inflammatory conditions and has been repeatedly shown to increase risk of mortality in context of CAD and cancer (and its treatment)

Translational Targets
Inflammation and Treatment Resistance

<table>
<thead>
<tr>
<th>Clinical Predictor of Antidepressant Non-Response</th>
<th>Relation to Inflammation</th>
</tr>
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<tbody>
<tr>
<td>Obesity</td>
<td>Dose response relationship between BMI and inflammatory markers</td>
</tr>
<tr>
<td>Early Life Stress</td>
<td>Increased inflammation and inflammatory response to stress in individuals exposed to early life stress</td>
</tr>
<tr>
<td>Medical Illness</td>
<td>Increased inflammatory markers in cancer and cardiovascular disease</td>
</tr>
<tr>
<td>Personality Disorders/Anxiety</td>
<td>Increased inflammatory markers in patients with Anxiety Disorders, Borderline Personality Disorder and Neuroticism</td>
</tr>
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Inflammation and Depression: The Perfect Storm Cytokines and Treatment Resistance

- Cytokines reduce monoamine synthesis (IDO) and increase reuptake (p38 MAPK)
  - Conventional antidepressants act through increasing the availability of monoamines (block reuptake)
- Cytokines inhibit neurogenesis
  - Conventional antidepressants are less effective in the absence of neurogenesis
- Cytokines impact glutamate metabolism
  - Conventional antidepressants target monoamines and do not act on glutamate metabolism
  - Ketamine, a glutamate antagonist, is effective in treatment-resistant depression

IDO = indoleamine 2,3 dioxygenase; MAPK = mitogen activated protein kinase


Etanercept and Clinical Outcomes, Fatigue, and Depression in Psoriasis

Double-blind Placebo-Controlled Randomized Phase III Trial

Improvement in symptoms of depression were not correlated with objective measures of skin clearance or joint pain

Testing the Cytokine Hypothesis of Depression

Does blockade of inflammatory cytokines reverse depression in patients with treatment-resistant depression (TRD)?


Goal: To Test the Cytokine Hypothesis of Depression in Patients with TRD

TNF-alpha Antagonist

Scientific Reasons
- TNF-alpha reliably elevated in MDD
- TNF-alpha and its soluble receptor correlates with IFN-alpha-induced depression
- TNF-alpha antagonist improved depressed mood in patients with inflammatory disorders
- TNF receptor KO mice exhibit antidepressant-like response and decreased anxiety following immune stimulation


Goal: To Test the Cytokine Hypothesis of Depression in Patients with TRD (cont'd.)

TNF-alpha Antagonist

- Infliximab* – monoclonal antibody directed at TNF-alpha
- Used to treat autoimmune and inflammatory disorders

Pharmacologic reasons
- Biologics (monoclonal antibodies) have no off-target effects or drug-drug interactions (directly test the cytokine hypothesis of depression)
- Limited brain penetrance (central vs. peripheral effects)
- No compliance issues with infusions

*Off label use

Double-Blind, Parallel-Group, Randomized Design

TRD Pts (N = 60)

Baseline

Wk 1

Wk 2

Wk 3

Wk 4

Wk 5

Wk 6

Wk 7

Wk 8

Wk 9

Wk 10

Wk 11

Wk 12

.inflint (mg/kg)

PLACEBO

INFUSION

INFUSION

INFUSION

Clinician-Administered Psychiatric Assessments (HAM-D, CGI)

Adverse Events Evaluation

Blood Draw for Inflammatory Markers and Safety Labs


Inclusion/Exclusion Criteria

- Males/Females ages 25-60
- Medically Healthy (Normal PE and labs)
- MDD or Bipolar depressed by SCID
- QIDS-16 score ≥ 14
- On stable antidepressant regimen or off meds for at least 4 weeks
- No psychotic symptoms or hx of psychosis
- No substance abuse x 6 months
- Not suicidal
- Non-pregnant on birth control


Demographic Characteristics of Study Sample

<table>
<thead>
<tr>
<th></th>
<th>Infliximab* (n = 30)</th>
<th>Placebo (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.) – mean (SD)</td>
<td>42.5 (8.2)</td>
<td>44.3 (9.4)</td>
</tr>
<tr>
<td>Sex (female) – no. (%)</td>
<td>20 (66%)</td>
<td>20 (66%)</td>
</tr>
<tr>
<td>Ethnic Origin – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>23 (77%)</td>
<td>23 (77%)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (20%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Education (Highest Degree) – no. (%)</td>
<td></td>
<td></td>
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<tr>
<td>Graduate Degree</td>
<td>8 (27%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>College Graduate</td>
<td>13 (43%)</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>Partial College</td>
<td>8 (27%)</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>High School Graduate</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Unemployed – no. (%)</td>
<td>12 (40%)</td>
<td>12 (40%)</td>
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*Off label use

<table>
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<tr>
<th>Clinical Characteristics of Study Sample</th>
<th>Infliximab</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>Age of Onset of MDD (yrs.) – mean (SD)</td>
<td>19.1 (8.3)</td>
<td>18.9 (10.7)</td>
</tr>
<tr>
<td>Lifetime Episodes of MDD – no. (SD)</td>
<td>8.7 (24.8)</td>
<td>7.8 (24.8)</td>
</tr>
<tr>
<td>Duration of Current Episode (mos.) – mean (SD)</td>
<td>184.4 (148.8)</td>
<td>238.7 (165.25)</td>
</tr>
<tr>
<td>Antidepressant Trials in Current Episode – no. (SD)</td>
<td>4.6 (3.2)</td>
<td>3.7 (2.1)</td>
</tr>
<tr>
<td>MGH-S score – mean (SD)</td>
<td>7.73 (6.6)</td>
<td>6.1 (3.5)</td>
</tr>
<tr>
<td>Family History of MDD – no. (%)</td>
<td>27 (90%)</td>
<td>23 (77%)</td>
</tr>
<tr>
<td>Mood-Related Psychotropic Medication – no. (%)</td>
<td>16 (53%)</td>
<td>21 (70%)</td>
</tr>
<tr>
<td>Co-Morbid Medical Illness – no. (%)</td>
<td>13 (43%)</td>
<td>19 (63%)</td>
</tr>
<tr>
<td>Bipolar Disorder – no. (%)</td>
<td>3 (10%)</td>
<td>6 (20%)</td>
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<table>
<thead>
<tr>
<th>Clinical Characteristics of Study Sample (cont’d.)</th>
<th>Infliximab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m2) – mean (SD)</td>
<td>31.2 (6.9)</td>
<td>32.7 (8.6)</td>
</tr>
<tr>
<td>Baseline hs-CRP (mg/L) – mean (SD)</td>
<td>6.21 (9.1)</td>
<td>5.7 (6.1)</td>
</tr>
<tr>
<td>Baseline HAM-D 17 – mean (SD)</td>
<td>24.1 (4.0)</td>
<td>23.6 (3.8)</td>
</tr>
<tr>
<td>Baseline CGI-severity – mean (SD)</td>
<td>4.8 (0.59)</td>
<td>4.8 (0.81)</td>
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<thead>
<tr>
<th>Change in HAM-D-17 in Infliximab* vs. Placebo-Treated TRD Patients</th>
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Significant interaction among treatment, time and log hs-CRP (t = 2.65, df = 302, p = .01)

Change in HAM-D-17 Score from Baseline to Week 12 (Infliximab*- Placebo) in TRD Patients Subgrouped By Baseline Plasma hs-CRP

Standardized Effect Size = 0.41 favoring infliximab at CRP > 5mg/L


Change in HAM-D-17 Scores from Baseline to Week 12 in Infliximab*- or Placebo-Treated TRD Patients with a Baseline CRP > 5 mg/L versus ≤ 5mg/L

*A off label use


Percent Treatment Responders in Infliximab*- vs. Placebo-Treated TRD Patients with a Baseline hs-CRP ≤ 5mg/L or >5mg/L

Treatment Response (≥ 50% reduction in HAM-D-17 at any point during treatment)


*Off label use
Symptoms Responsive to Infliximab* and Placebo in TRD Subjects with Baseline hs-CRP>5


*Off label use

Summary

- Depression is associated with evidence of increased inflammation, which in turn may contribute to the impact of depression on comorbid medical disorders
- Stress is capable of activating the inflammatory response (likely through SNS pathways)
- Activation of the inflammatory response can induce behavioral symptoms that overlap with MDD
Summary (cont’d.)

- Cytokine (IFN-alpha)-induced depression appears to be mediated by alterations in serotonin metabolism, activation of CRH pathways, and alterations in basal ganglia circuitry.
- Aggressive preventative treatment strategies can be used to limit depression in high-risk medically ill.
- Treatments targeting the immune system may be relevant for the treatment of depression in both medically ill and medically healthy patients.

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