Exploring Nonpharmacological Anti-inflammatory Strategies in Mental Health: Connecting Science to Clinical Practice

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This program is paid for by Otsuka Pharmaceutical Development & Commercialization, Inc. and Lundbeck, LLC.

Speakers are paid consultants and/or employees of Otsuka Pharmaceutical Development & Commercialization, Inc.
Learning Objectives

- Review underlying mechanisms of inflammation and understand how they may affect physical and mental health
- Discuss nonpharmacological interventions that may have anti-inflammatory effects
- Explore practical approaches for implementing nonpharmacological interventions
Inflammation: Effects on Physical and Mental Health
Role of Immunity Has Evolved Alongside Human Development

Hunter-gatherer period

- High mortality
- Acute stress
  - Predators
  - Pathogens
  - Interhuman conflict
- Immunity
  - Wound healing
  - Fighting infection

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Hunter-gatherer period

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Modern life

- Low mortality
- Chronic stress
  - Environmental stress
  - Medical illness
  - Psychosocial stress
- Immunity
  - High inflammation
  - High autoimmunity

Inflammatory Responses: Balance Between Neuroprotection and Neurotoxicity

Unchecked excitotoxicity can lead to cell death and eventual tissue atrophy, potentially making the brain unable to respond and adapt to stimuli\(^1\) and manifesting as a mental illness\(^2\)


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Stress Activates Inflammatory Pathways in Peripheral Blood Mononuclear Cells

Stress activates the sympathetic nervous system, stimulating bone marrow to produce and release monocytes.

Monocytes throughout the body interact with injured tissue, DAMPs, bacteria, and bacterial products, activating additional inflammatory signaling pathways and stimulating the release of other pro-inflammatory cytokines that can enter the brain.

Activated macrophages in the brain can perpetuate these inflammatory responses.

DAMPs, danger-associated molecular patterns.
Stress Can Create a Pro-inflammatory Feedback Loop

The greater a person’s inflammatory response to a psychosocial stressor, the more likely he/she is to develop depression over subsequent months.

Chronic Mild Inflammation May Have Lasting Effects

Chronic mild inflammation may increase the risk of mental and physical disorders

- Posttraumatic stress disorder
- Bipolar disorder
- Major depressive disorder
- Cardiovascular disease
- Cancer
- Diabetes

Inflammatory Cytokines Are Increased in Patients With Major Depressive Disorder

Patients with MDD* demonstrated significantly elevated plasma levels of IL-6 ($P<0.001$) and TNF-α ($P<0.001$) compared with healthy controls.

*Patients were diagnosed with major depressive disorder without psychotic features (DSM-IV-TR) and scored >17 on the 17-item Hamilton Depression Rating Scale. All patients were free of any psychotropic medications for at least 6 weeks prior to enrollment in the study.

DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; IL-6, interleukin 6; MDD, major depressive disorder. TNF-α, tumor necrosis factor alpha.

Depression Severity Influences Cytokine and Neurotrophic Factor Expression

More severe depression is correlated with higher levels of IL-6

More severe depression is correlated with lower levels of BDNF

BDNF, brain-derived neurotrophic factor; HAM-D, Hamilton Rating Scale for Depression; IL-6, interleukin 6;

Increasing concentration of IL-6

Increasing concentration of BDNF

P=0.0062

P=0.0012
Targeting Inflammation: Beyond Pharmacology

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Some Nonpharmacological Interventions Target Discrete Components of Wellness

Exercise Can Reduce Chronic Inflammation Through Multiple Mechanisms

Adipose cells
- ↑ Angiogenesis
- ↑ Blood supply
- ↓ Vasoconstriction
- ↓ Hypoxia

Endothelial cells
- ↓ Adhesion molecules
- ↑ Cell regeneration

Muscle cells
- ↑ Interleukin-6
- ↓ Pro-inflammatory cytokines
- ↑ Anti-inflammatory cytokines

Immune cells
- ↓ Toll-like receptors
- ↓ Inflammatory monocytes
- ↑ Regulatory T cells

Exercise Induces Muscles and Astrocytes to Express Neuroprotective Genes

PGC-1α1, peroxisome proliferator-activated receptor-γ coactivator 1-alpha 1.
Evidence for Increased Remission Rates With Add-on Exercise in Patients With Nonremitted MDD

Adjusted rate of remission, as measured by IDS-C$_{30}$, in patients with inadequate response to SSRI who received add-on exercise in the TREAD study

IDS-C$_{30}$, 30-Item Inventory of Depressive Symptomology (Clinician-Rated); MDD, major depressive disorder; NNT, number needed to treat; SSRI, selective serotonin reuptake inhibitor; TREAD, Treatment with Exercise Augmentation for Depression study.

*NNT of 7.8 for high-exercise vs low-exercise group based on remission rate at week 12.

Audience Polling Question

All mechanisms that contribute to possible anti-inflammatory effects of exercise training depend on weight loss

A. TRUE
B. FALSE
Mindfulness Training May Positively Affect Inflammatory Responses

Mindfulness training reduced cortisol production in response to a psychological stressor*.


*Participants included 49 volunteers without previous experience with meditation or other mind-body techniques. †Program consisted of 8 weekly 2.5-hour sessions + 1 full-day session + daily home-based practice, 45 minutes to 1 hour. ‡HEP program matched MBSR in structure, instructor expertise, and content. Test is the Trier Social Stress Test.

HEP, health enhancement program; MBSR, mindfulness-based stress reduction.
Sleep Is Connected to Inflammation and Metabolic Disorders

- Insufficient sleep
  - Periodic limb movement disorder
  - Narcolepsy

- Sleep apnea

- Sleep deficiency

- Obesity
  - Inflammation
  - Oxidative stress
  - Impaired glucose tolerance
  - Insulin resistance

- Type 2 diabetes

Disturbances in Sleep Are Associated With Increases in IL-6

In a meta-analysis of 72 studies (N >50,000), increasing disturbances in sleep were associated with increases in the circulating inflammatory markers CRP and IL-6.

CRP, C-reactive protein; IL-6, interleukin 6.
In an observational study of United States military personnel (N=66), participants who experienced restorative sleep demonstrated significant reductions in plasma CRP levels.

- Participants who experienced restorative sleep also demonstrated significant
  - Reductions in fatigue and depressive symptoms
  - Increases in emotional well-being, social functioning, and physical functioning

CRP, C-reactive protein.
Childhood Social Isolation May Lead to High Inflammation in Adulthood

Negative consequences of early social isolation* may manifest in adulthood†

*Social isolation classified as social rejection or withdrawal and assessed via survey at age 7 and 11 years. †Data from National Child Development Study that aimed to recruit all infants born in Great Britain during 1 week of 1958 (N=17,414). Participants were surveyed at the following ages: 7, 11, 16, 23, 33, 42, 44, 46, and 50 years.

CRP, C-reactive protein; BMI, body mass index.

Low Social Network Ties Are Linked With Higher Inflammation

In a national survey of 1,075 American adults with a history of cancer,* those with lower social ties demonstrated higher levels of the inflammatory marker CRP.


CRP, C-reactive protein.

Select Foods Are Associated With Diet-Related Chronic Illness

Select foods may have differential effects on diet-related chronic illness (eg, cardiovascular disease, cancer, obesity, mental illness)*

- Milk: Protective association
- Wine: Neutral association
- Sweetened beverages: Protective association
- Fruits and vegetables: Neutral association
- Whole grains: Protective association
- Dairy products: Neutral association
- Red/Processed meat: Deleterious association
- Fish: Protective association

Certain Diets May Emphasize Foods With Anti-inflammatory Effects

For example, Mediterranean-based diets promote fresh foods, discourage sweets and processed foods, and may positively affect physical and mental health*

**Fruits and Vegetables**
- Green leafy vegetables, ≥6 servings per week
- Other vegetables, ≥1 serving per day
- Berries, ≥2 servings per week
- Beans, >3 meals per week

**Oils and Cheese**
- Olive oil as the primary oil used
- Fast fried foods, <1 time per week
- Butter or margarine, <1 tablespoon per day
- Cheese, <1 serving per week

**Protein**
- Fish (not fried), ≥1 meal per week
- Poultry (not fried), ≥2 meals per week
- Red meats, <4 meals per week
- Nuts, ≥5 servings per week

**Carbohydrates**
- Whole grains, ≥3 servings per day
- Pastries/sweets, <5 servings per week
- Wine, 1 glass per day


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Implementing Nonpharmacological Interventions May Improve Overall Wellness

Adults (N=36) who implemented nonpharmacological strategies targeting 5 domains for 30 days demonstrated significant improvement in anxiety, depression, and overall well-being.

GAD-7

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<th>Score</th>
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PHQ-9

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WHO-5

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<td>15.6</td>
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*P<0.01 vs baseline score.

GAD-7, Generalized Anxiety Disorder 7-item; PHQ-9, Patient Health Questionnaire-9; WHO-5, World Health Organization Wellbeing Index.
Practical Approaches to Implementing Nonpharmacological Techniques
Simple Suggestions for Implementing Interventions Toward Achieving Wellness*

- Text or call a family member or friend daily for 30 days
- Log what you eat daily for 30 days
- Exercise 30 minutes 6 of 7 days for 30 days at moderate intensity
- Practice mindfulness >8 minutes each day for 30 days
- Implement prosleep hygiene practices each day for 30 days

*Information based on Dr. Jain’s own experience in psychiatric settings.
## Initiate and Maintain Anti-inflammatory Wellness Habits*

<table>
<thead>
<tr>
<th>Initiate</th>
<th>Maintain</th>
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<tr>
<td>Provide encouragement</td>
<td>Continue to provide encouragement</td>
</tr>
<tr>
<td>Provide resources</td>
<td>Check in at regular intervals on progress</td>
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<tr>
<td>Recommend daily practice</td>
<td>Be a gentle coach</td>
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- Remind patient of the studies demonstrating benefits of practices
- Recommend increasing practice with early signs of stress

*Information based on Dr. Jain's own experience in psychiatric settings.
**Audience Polling Question**

How likely are you to implement these strategies into your clinical practice?

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<th>Description</th>
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<tr>
<td>B.</td>
<td>Probably will</td>
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<tr>
<td>C.</td>
<td>Not sure</td>
</tr>
<tr>
<td>D.</td>
<td>Probably won’t</td>
</tr>
<tr>
<td>E.</td>
<td>Definitely won’t</td>
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Summary

Inflammation may have lasting effects on physical and mental health.

Exercise, mindfulness, sleep, nutrition, and social connectedness have been demonstrated to influence inflammatory responses.

Nonpharmacological interventions, including those aimed at encouraging exercise and mindfulness and optimizing sleep, nutrition, and socialization, may positively affect both physical and mental health.
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