Beyond the Resistance

How Novel Neurobiological Understandings of DEPRESSION May Lead to Advanced Treatment Strategies

Slide Notes Companion

Waist Circumference, ABDOMINAL OBESITY, and DEPRESSION Among Overweight and Obese U.S. Adults

The MTHFR POLYMORPHISM is Associated with DEPRESSIVE Episodes in Patients

INFLAMMATION and its Discontents: The Role of Cytokines in the Pathophysiology of MAJOR DEPRESSION

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How Novel Neurobiological Understandings of DEPRESSION May Lead to Advanced Treatment Strategies

Slide Notes Companion

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Beyond the Resistance: How Novel Neurobiological Understandings of Depression May Lead to Advanced Treatment Strategies

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INTRODUCTION

- Waist Circumference, ABDOMINAL OBESITY, and DEPRESSION Among Overweight and Obese U.S. Adults
- The MTHFR POLYMORPHISM Is Associated With DEPRESSIVE Episodes in Patients
- INFLAMMATION and Its Discontents: The Role of Cytokines in the Pathophysiology of MAJOR DEPRESSION
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The Need for Long-term Treatment Options in Depression

• Fourth most disabling condition worldwide; most disabling condition for females (US)
• Increased morbidity of comorbid general medical conditions and increased rate of suicide as percent of total mortality
• Loss of productivity in workplace
• Patients with depression use substantially more healthcare services than do patients without depression
• Depression is life shortening
  • Increased risk of CV events, stroke, etc.


Notes
Chapter 1
Lack of Appropriate Treatment Response: Impact and Neurobiology
STAR-D Remission Rates Are Generally Low Across All 4 Levels

Remission Definition: HAM-D ≤ 7

Level 1
11.9 weeks

Level 2
6-10 weeks

Level 3
≤ 14 weeks

Level 4
≤ 14 weeks

Mono
Augm
Mono
Augm
Mono
Augm
Mono
Augm

Low — Treatment Resistance — High

Mono, single medication regimen; Augm, combination medication treatment.

Notes

STAR-D Reveals Its Secrets—The Dangers of Residual Symptoms & Lack of Remission
Potential Causes of Poor Response to Antidepressant Treatment

- Misdiagnosis
- Inadequate treatment, under-treatment, or starting treatment too late
- Failure to achieve initial remission
- Non-adherence
- Failure to address concurrent disorders
  - Occult substance abuse
  - Occult general medical conditions (GMCs)
  - Concurrent Axis I or II disorders

Patients With MDD Who Did Not Respond to Antidepressants Had Higher Inflammatory Cytokine Levels

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24 healthy controls and 20 patients with depression (HAMD > 20) after 6 weeks of SSRI treatment and 10 euthymic patients (previously resistant to SSRI) currently successfully treated with an SNRI or an addition of lithium to SSRI treatment.

MDD = Major Depressive Disorder; HAMD = Hamilton Depression Rating Scale; SNRI = Selective noradrenergic reuptake inhibitor; TNF = Tumor necrosis factor.
Remission May Protect the Brain From Long-Term Depression-Related Changes

In this prospective, longitudinal study, 28 participants with MDD and 36 controls were followed for 2 years. At the start and end of this period all participants had brain morphometry assessed by MRI. Patients with MDD who went into remission showed significantly less volume reduction in brain areas of direct relevance to the pathophysiology of MDD when compared to patients with MDD who did not achieve remission.

Chapter 2: Inflammation and Depression: Cause, Consequence or Collaborator?

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Stress and Inflammation In MDD

Notes
In a cohort of 644 initially non-depressed females, 48 developed de novo MDD over an approximate 10-year follow-up. Survival analysis showed the probability of remaining free of de novo cases of depression was associated with tertile of hsCRP. The concentration of hsCRP in each tertile was: low, <1.12 mg/l; mid, 1.12-2.87 mg/l; and high, >2.87 mg/l.

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Glia-Neuron Interaction May Influence Neurotrophic Factors
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Relationship Between Depression & Inflammatory Cytokines and Neurotrophic Factors

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Relationship Between Obesity, Metabolic Syndrome and Depression

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MDD, Adiposity and Inflammatory Markers

Interleukin-6 (IL-6) and C-Reactive Protein (CRP) levels were measured in 50 MDD patients compared with 50 healthy matched controls.


Chapter 3

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Body Mass Index Impacts Antidepressant Response

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Chapter 4: Fascinating Folate

1. Genetic Regulation of Folate Metabolism
2. Two Sides of the Coin: L-methylfolate and Homocysteine
3. The Role of L-methylfolate in Tri-Monoamine Synthesis

Notes
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Folate Essentials:

- Folate is a B-vitamin that cannot be synthesized de novo by the body; it must be derived from diet or augmentation
- Dietary folate found in leafy green vegetables, legumes, beans, liver, citrus fruits and yeast
- Folic acid is a synthetic molecule more highly absorbed (85-95%) than is dietary folate (dihydrofolate)
- Multiple biochemical conversions required for dietary folate (or folic acid) to become metabolically active


Folate Essentials

Notes

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Chapter 4
Folate Metabolism

Notes

Chapter 4
How Novel Neurobiological Understandings of DEPRESSION May Lead to Advanced Treatment Strategies

Many Paths Lead to Inflammation and Its Consequences

Factors contributing to chronic, non-resolving inflammation and disease. Numerous environmental and biological factors can conspire to contribute to chronic inflammation, including stress, adiposity and dietary intake.


Many Paths Lead to Inflammation and Its Consequences

Notes

Chapter 4
**Interface of Inflammation and Neurotransmitter Synthesis in MDD**

![Diagram A](image1)

De Novo Synthesis of BH₄

- GTP
- BH₄
- Serotonin
- Melatonin
- Dopamine

The synthetic de novo BH₄ is a critical cofactor for the covalent enzymes involved in the synthesis of the neurotransmitters, including:
- the synthesis of serotonin synthase
- the synthesis of dopamine synthase
- the synthesis of L-tyrosine hydroxylase
- the synthesis of L-tryptophan hydroxylase
- the synthesis of L-tryptophan deaminase

**Interface of Inflammation and Neurotransmitter Synthesis in MDD**

![Diagram B](image2)

Increased Need for L-methylfolate

- GTP
- XPH₄
- Inflammatory cytokines
- Serotonin
- Dopamine

The increased need for L-methylfolate is a critical cofactor for the synthesis of the neurotransmitters, including:
- the synthesis of serotonin synthase
- the synthesis of dopamine synthase
- the synthesis of L-tyrosine hydroxylase
- the synthesis of L-tryptophan hydroxylase
- the synthesis of L-tryptophan deaminase

BH₄ is degraded in MDD, which can be re-converted to BH₄ through pathways supported by folate acid, L-methylfolate, and SAHA. BH₄ is also metabolized via the one-carbon metabolism leading to the irreversible degradation of BH₄ in MDD.

How Novel Neurobiological Understandings of DEPRESSION May Lead to Advanced Treatment Strategies

![Diagram: Interface of Inflammation and Neurotransmitter Synthesis in MDD]

Interface of Inflammation and Neurotransmitter Synthesis in MDD

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Notes

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Chapter 4
Up to 70% of MDD Patients Have a Genetic Mutation Reducing Ability to Convert Folic Acid to L-methylfolate

- Patients with the C677T MTHFR polymorphism have low CNS L-methylfolate.
- Low CNS L-methylfolate is associated with low production of serotonin, norepinephrine and dopamine.


Notes
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Risk Factors for Low CNS L-methylfolate

- Drugs: Anticonvulsants such as lamotrigine, carbamazepine, phenobarbital and valproate, methotrexate, sulphasalazine, oral contraceptives, metformin, niacin and fenofibrate, fluoxetine, warfarin
- Disease: Diabetes, atrophic gastritis, Crohn's, colitis, bypass surgery, renal failure and hypothyroidism
- Lifestyle: Excess alcohol, smoking and poor nutrition
- Aging: CNS L-methylfolate levels markedly decrease in individuals over 70 years of age

Notes

Chapter 4
Chapter 5
Folate: Clinical Studies and Their Usefulness in Clinical Practice

Notes
How Novel Neurobiological Understandings of DEPRESSION May Lead to Advanced Treatment Strategies

Study Inclusion Criteria

Study Subjects
- Adults meeting DSM-IV criteria for MDD, current
- QIDS-SR ≥ 12 at screen and baseline visit
- Has not failed more than 2 antidepressant trials of adequate dose and adequate duration in current MDE (adequate duration = at least 8 weeks)
- Treated with SSRI during current episode for ≥ 8 weeks with stable SSRI dose in therapeutic range X 4 weeks
- 75 depressed patients with inadequate response to SSRIs were enrolled in a 60-day trial which was divided into two, 30-day periods (Phases 1 and 2)

Notes


Efficacy Results of Study II
HDRS-17 Response Rates—30 Days

Notes

Chapter 5

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Safety Results and Overall Discontinuation

No Difference in Discontinuation Due to Adverse Events

<table>
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<th>% of Patient Discontinuation</th>
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<th>Antidepressant + Placebo n = 2/54</th>
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<td>10%</td>
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<td>3.7%</td>
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L-methylfolate patient was removed from the trial due to mood elevation.

Patient’s medical history included bipolar disorder which was not detected at baseline.

Safety Results and Overall Discontinuation

Notes

Chapter 5
HDRS-28 Treatment Effect by MTHFR C677T Genotype

Notes
Efficacy Results and Obesity HDRS-17 Mean Change—30 Days

Notes
Summary:

- L-methylfolate 15mg/day as adjunctive treatment to antidepressant therapy resulted in superior treatment outcome in 30 days (efficacy) compared to continued antidepressant therapy plus placebo in:
  - both co-primary outcome measures achieving statistical significance in:
    - response rates (50% ↓ HDRS-17, p=0.04)
    - degree of improvement (Reduction in HDRS-17, p=0.05)
  - as well as in most secondary measures, including change in scores
    - QIDS-SR (p=0.04)
    - Clinical Global Impression Severity scale (CGI-S, p=0.01)
    - Obese patients (BMI > 30; HDRS-17, p = 0.02; CGI-S, p = 0.001)
    - Genetic variations of folate metabolism
  - Clinical management of MDD may be optimized with adjuvant L-methylfolate 15mg/day

Summary

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