Management of Treatment Resistant Depression:
The Art and the Science
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- **Consultant**: Bracket (Clintara); Fortress Biotech; Gerson Lehrman Group, Inc. (GLG) Healthcare & Biomedical Council, America; Janssen Research & Development, LLC; MagStim, Inc.; Prismic Pharmaceuticals, Inc.; Sumitomo Dainippon Pharma; Sunovion Pharmaceuticals Inc.; Taisho Pharmaceutical Inc.; Takeda Pharmaceuticals North America, Inc.; Total Pain Solutions (TPS); Xhale, Inc.
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- **Patents**: 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 Board**: American Foundation for Suicide Prevention (AFSP); Anxiety Disorders Association of America (ADAA); Bracket (Clintara); Brain & Behavior Research Foundation (BBRF) (formerly National Alliance for Research on Schizophrenia and Depression [NARSAD]); Laureate Institute for Brain Research, Inc. RiverMend Health, LLC; Skyland Trail; Xhale, Inc.
- Board of Directors: American Foundation for Suicide Prevention (AFSP); Anxiety Disorders Association of America (ADAA); GratitudeAmerica, Inc.
Learning Objective

Recognize the factors that impact the severity of depression and contribute to treatment resistance.
Learning Objective

Develop a strategy for treatment resistant depression utilizing pharmacologic and nonpharmacologic approaches.
All his life he suffered spells of depression, sinking into the brooding depths of melancholia, an emotional state which, though little understood, resembles the passing sadness of the normal man as a malignancy resembles a canker sore.

Major Depressive Disorder: DSM-5 Diagnostic Criteria

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure:

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)

4. Insomnia or hypersomnia nearly every day.

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

6. Fatigue or loss of energy nearly every day.

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Major Depressive Disorder: DSM-5 Diagnostic Criteria

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A-C represent a major depressive episode.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the person's past history of major depressive episodes, whether the symptoms are disproportionately severe given the nature of the loss, and the individual's cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

# Major Depressive Disorder: DSM-5 Diagnostic Criteria

**Specify:**

If the full criteria are currently met for a major depressive episode, specify its current clinical status and/or features:

- With anxious distress
- With mixed features
- With melancholic features
- With atypical features

1. In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief, the predominant affect is feelings of emptiness and loss, while in MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of MDE. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in MOE. In grief, self-esteem is generally preserved, whereas in MOE feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-à-vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about “joining” the deceased, whereas in MDE such thoughts are focused on ending one’s own life because of feeling worthless, undeserving of life, or unable to cope with the pain of depression.

- With mood-congruent psychotic features
- With mood-incongruent psychotic features
- With catatonic features  **Coding note:** Use additional code 781.99 (R29.818).
- With peripartum onset
- With seasonal pattern (recurrent episode only)

Specify current or most recent episode:

- **Single episode.**
- **Recurrent episode:** Defined as the presence of two or more lifetime major depressive episodes. To be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a major depressive episode.

Specify current severity:

- Mild
- Moderate
- Severe

Specify:

- **Level of concern for suicide** in the current assessment period regardless of current episode or remission status

Major Changes in *DSM-5*

- Bereavement
- Elimination of chronic depression
- Severity/course specifier

The Mood-Disorders Spectrum

- Bipolar I Disorder
- Bipolar II Disorder
- Unipolar Depression
- Cyclothymia
- Dysthymia
- Normals
Unipolar vs. Bipolar Depression: Initial Diagnosis

How Often do Unipolar Patients Become Bipolar?
At Clinic Entry

- Unipolar: 92%
- Bipolar: 8%

At 30-Yr Follow-up

- Unipolar: 57%
- Bipolar: 43%

UP = Unipolar; BP = Bipolar

Risk of Bipolar Disorder in Patients Initially Hospitalized for Unipolar Depression

- 15 year follow-up of 74 patients initially hospitalized for unipolar depression
  - 27% had > 1 episode of hypomania (BPII)
  - 19% had > 1 episode of mania (BPI)
  - 80% with psychotic depression became bipolar compared with 34% with nonpsychotic depression

Underrecognition of Bipolar Disorder in Psychiatric Clinics

Patients with major depressive episodes in France (n = 250)

- Unipolar: 72%
- BP II: 22%
- BP I: 6%

Underrecognition of Bipolar Disorder in Patients Treated for Depression in a Primary Care Clinic

Hirschfeld RMA, et al.


649 outpatients receiving treatment for depression

21% Screened positive* for bipolar disorder

*Using the Mood Disorder Questionnaire (MDQ).
Improving Recognition of Bipolar Disorder in Patients Presenting with Depression

- Ask about history of mania and hypomania
- Ask about family history of bipolar disorder
- Involve family members or significant others in the evaluation process
- Administer a screening instrument for bipolar disorder, the Mood Disorder Questionnaire (MDQ)

Clinical Clues to Bipolarity in “Unipolar” Depressed Patients

- “Loaded” family history
- Early age of onset (< 25 year-old) with high episode rates
- Psychotic features
- Seasonal pattern
- Antidepressant “misadventures”
  - Treatment-emergent hypomania or agitation
  - Erratic or uneven antidepressant responses
  - Multiple antidepressant failures —“treatment-resistant depression”

Comorbidity

Lifetime comorbidity of mood and anxiety disorders

- 48% of patients with PTSD\(^1\)
- Up to 65% of patients with Panic Disorder\(^2\)
- 67% of patients with Obsessive–Compulsive Disorder\(^4\)
- 67% of patients with Generalised Anxiety Disorder\(^3\)
- 42% of patients with Generalised Anxiety Disorder\(^3\)
- 48% of patients with Social Anxiety Disorder\(^5\)
- Up to 70% of patients with Social Anxiety Disorder\(^5\)

<table>
<thead>
<tr>
<th>Commonly Used Depression Symptom Severity Scales in Treatment Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Beck Depression Inventory (self-report)</td>
</tr>
<tr>
<td>● Hamilton Rating Scale for Depression (clinician-rated)</td>
</tr>
<tr>
<td>● Montgomery Asberg Depression Rating Scale (clinician-rated)</td>
</tr>
<tr>
<td>● Inventory of Depressive Symptoms (full and quick versions self-report and clinician-rated versions)</td>
</tr>
</tbody>
</table>

Montgomery-Asberg Depression Rating Scale (MADRS)

Measures 10 symptoms
1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

Outcome of Depression Treatment: The Five Rs

- Remission
- Recovery
- Relapse
- Recurrence

Symptoms
Syndrome
Treatment Phases

Response

<table>
<thead>
<tr>
<th>Acute</th>
<th>Continuation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12 Weeks</td>
<td>4-9 Months</td>
<td>&gt;1 Year</td>
</tr>
</tbody>
</table>

# Outcomes of Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Commonly Accepted Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Clinical significant reduction in baseline symptom severity</td>
</tr>
<tr>
<td>Remission</td>
<td>Absence of symptoms</td>
</tr>
<tr>
<td>Recovery</td>
<td>Sustained period of remission following an episode of major depression</td>
</tr>
<tr>
<td>Relapse</td>
<td>Return of a major depressive episode during continuation treatment (ie, before recovery)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>New episode of depressive following recovery of previous episode</td>
</tr>
</tbody>
</table>

Depression Guideline Panel; 1993. AHCPR publication 93-0550.
**Remission**

- Minimal or no symptoms
  - No longer meets diagnostic criteria
- Sustained remission: return to “functional normality”
  - Remission for $\geq 8$ wk usually associated with restoration of daily functioning
  - Typically, cannot be distinguished from those without depression

Operational Definition of Remission

Remission = HAM-D_{17} \leq 7

Hamilton Depression Rating Scale (HAM-D_{17})

Potential Consequences of Failing to Achieve Remission

● Increased risk of relapse and treatment resistance
● Continued psychosocial limitations
● Decreased ability to work and decreased workplace productivity
● Increased cost for medical treatment
● Sustained risk of suicide, substance abuse
● Sustained depression can worsen morbidity/mortality of other conditions

Achieving Remission Decreases Risk of Relapse


*After termination of cognitive behavior therapy for depressed patients
Depression Worsens Outcomes of Many General Medical Conditions

- Depression worsens morbidity and mortality after myocardial infarction\(^1,2\)
- Depression increases risk for mortality in patients in nursing homes\(^3\)
- Depression worsens morbidity post-stroke\(^4\)
- Depression can worsen outcomes of cancer, diabetes, AIDS, and other disorders\(^5\)

Risk Factors for Delayed Remission

- Chronicity
  - Longer length of episode
  - Number of previous episodes
- Medical comorbidity
- Older age
- Axis I or II comorbidity
- Severity

Potential Obstacles to Attaining Remission in Clinical Practice

- Patients and clinicians are satisfied with partial improvement in symptoms (ie, response but not remission)
- Treatments may not be well tolerated
- Underdosing
- Failure to recognize residual symptoms

Increasing the Likelihood of Remission

- Measure outcomes!
- Optimize dose/extend trial
- Selection of antidepressant
- Role of adherence
- Pharmacologic adjuncts
- Role of psychotherapy

Age at First Onset of Major Depression

## Gender Differences in Comorbidities with Depression

### More Common in *Men*
- Alcohol abuse/dependence\(^1\)
- Substance abuse/dependence\(^1\)
  - Stimulant
  - Cannabis
  - Cocaine
  - Hallucinogen

### More Common in *Women*
- Panic disorder\(^1\)
- GAD\(^1\)
- Social phobia\(^2\)
- Bulimia\(^1,2\)
- Thyroid disease\(^3\)
- Migraine headaches\(^3,4\)
- Fibromyalgia\(^3\)
- Chronic fatigue syndrome\(^3\)

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\(^1\)Kornstein S et al. *Presented at American Psychiatric Association; May 4-9, 1996; New York, NY.*
Mood and Anxiety Disorders Across the Female Reproductive Cycle

- Depression/anxiety during pregnancy
- Depression/anxiety associated with infertility, miscarriage, or perinatal loss
- Premenstrual depression/anxiety (e.g., PMDD)
- Depression/anxiety during the perinatal period
- Depression/anxiety during the postpartum period
- Menarche
- Pregnancy
- Menopause
PMDD: Background

- 75% of women report minor, isolated, or occasional premenstrual changes
- 20% – 50% report “premenstrual syndrome”
- 3% – 8% of reproductive-age women have PMDD

PMDD = premenstrual dysphoric disorder

### Premenstrual Daily Symptom Chart

**Name:** Jane Doe  
**Month:** March

1. Circle the days of your menstrual period in the row labeled Day of Month.  
2. Record your ratings today. For example, if today is the 13th day of the month, mark your symptoms in the column labeled 13. At the same time each day use a marker or pen to fill in the correct numbered box to show how severe each symptom was over the past 24 hours. Leave the symptom blank if you had no problem with that symptom. See example on the right. If you forget to fill in a day, place an X in the Day of Month bar to signify that you did not fill in the chart for that day.  
3. Continue on new page on the first day of the next month.

| Symptom                  | Day of Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 |
|--------------------------|--------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Irritability             |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sudden mood changes      |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Tension                  |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sadness                  |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Decreased interest in usual activities | |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Feeling overwhelmed      |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Difficulty concentrating |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Bloating                 |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Breast tenderness        |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Food cravings            |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Lack of energy           |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Change in sleep          |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Relationship problems    |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Other Cumulus            |              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
# Depression

![Premenstrual Daily Symptom Chart](chart.png)

**Premenstrual Daily Symptom Chart**

**Name:** Jane Doe  
**Month:** July

1. Circle the days of your menstrual period in the row labeled Day of Month.
2. Begin your ratings today. For example, if today is the 12th day of the month, mark your symptoms in the column labeled 12. At the same time each day, use a marker or pen to fill in the correct numbered box to show how severe each symptom was during that day. For example, use a 1 for mild, 2 for moderate, and 3 for severe. Use example on the right. If you forget to fill in a day, place a 0 in the Day of Month bar to signify that you did not fill in the chart for that day.
3. Continue on new page on the first day of each month.

<table>
<thead>
<tr>
<th>Day of Month</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td><img src="chart_example.png" alt="Chart Example" /></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Inflability**
- **Sudden mood changes**
- **Tension**
- **Sadness**
- **Decreased interest in usual activities**
- **Feeling overwhelmed**
- **Difficulty concentrating**
- **Bloating**
- **Breast tenderness**
- **Food cravings**
- **Lack of energy**
- **Change in sleep**
- **Relationship problems**
- **Other:**

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Treatment Resistance and Depressive Sub-Types

- Atypical depression
- “Double” depression
- Psychotic depression
- Severe and melancholic depression
- Co-morbidity — psychiatric or medical
- Psychosocial stressors
Current Treatment Options for Depression

Goal = reduce symptoms of depression and return patient to full, active life

<table>
<thead>
<tr>
<th>Nonpharmacologic</th>
<th>Pharmacologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Psychotherapy</td>
<td>● Antidepressant medications</td>
</tr>
<tr>
<td>● Cognitive behavioral therapy</td>
<td></td>
</tr>
<tr>
<td>● Interpersonal therapy</td>
<td></td>
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<tr>
<td>● Psychodynamic therapy</td>
<td></td>
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<tr>
<td>● Electroconvulsive therapy</td>
<td></td>
</tr>
<tr>
<td>● Phototherapy</td>
<td></td>
</tr>
<tr>
<td>● Repetitive Transcranial Magnetic Stimulation (rTMS)</td>
<td></td>
</tr>
<tr>
<td>● Vagal Nerve Stimulation (VNS)</td>
<td></td>
</tr>
<tr>
<td>● Deep Brain Stimulation (DBS)</td>
<td></td>
</tr>
</tbody>
</table>

STEPS: Factors to Consider in Antidepressant Selection

- **Safety**
  - Drug-drug interaction potential

- **Tolerability**
  - Acute and long term

- **Efficacy**
  - Onset of action
  - Treatment and prophylaxis

- **Payment (cost-effectiveness)**

- **Simplicity**
  - Dosing
  - Need for monitoring

Evaluation of Outcomes with Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice

Madhukar H. Trivedi, M.D., A. John Rush, M.D., Stephen R. Wisniewski, Ph.D., Andrew A. Nierenberg, M.D., Diane Warden, Ph.D., M.B.A., Louise Ritz, M.B.A., Grayson Norquist, M.D., Robert H. Howland, M.D., Barry Lebowitz, Ph.D., Patrick J. McGrath, M.D., Kathy Shores-Wilson, Ph.D., Melanie M. Biggs, Ph.D., G. K. Balasubramani, Ph.D., Maurizio Fava, M.D. and STAR*D Study Team

**INITIAL TREATMENT:** citalopram

**Level 1**

**Level 2**

**Level 2A**

(Only for those receiving cognitive therapy in Level 2)

**Level 3**

**Level 4**

**SWITCH TO:** bupropion-SR or cognitive therapy or sertraline or venlafaxine-ER

**OR AUGMENT WITH:** bupropion-SR or buspirone or cognitive therapy

**SWITCH TO:** mirtazapine or nortriptyline

**OR AUGMENT WITH:** lithium or triiodothyronine (only with bupropion-SR, sertraline, venlafaxine-ER)

**SWITCH TO:** tranylcypromine or mirtazapine combined with venlafaxine-ER

STAR*D Study (N = 2,876)

Depressive Symptoms (QID-SR Score) After Up to 12 Weeks Antidepressant Treatment

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

67%
STAR*D Results Demonstrate Diminishing Effectiveness of TRD Treatments

Remission rates are after 12 weeks of treatment and are based on the HRSD17.

Treatment Intolerance Increases with Each Treatment Level

*Participants were considered to have intolerable side effects if they left the treatment level prior to 4 weeks for any reason or left thereafter citing treatment intolerance as the reason.

Relapse Rate Increases with each Treatment Level

Relapse rate calculated from those who made at least 1 post-baseline call to the interactive voice response system. Treatment step pairwise comparisons showed only Step 1 to be significantly different from the rest ($p < .0001$).

Summary of Challenges in TRD

- High suicide risk

- Significant relapse/recurrence rates with all currently available antidepressant treatments

- High healthcare utilization

- Chronic depression is a common manifestation of TRD

Factors to Consider in Patients Failing First Trial of Antidepressant Monotherapy

# System for Staging Antidepressant Resistance

| STAGE 1 | Failure of an adequate trial of one class of major antidepressant |
| STAGE 2 | Failure of adequate trials of two distinctly different classes of antidepressants |
| STAGE 3 | Stage II plus failure of a third class of antidepressant, including a TCA |
| STAGE 4 | Stage III plus failure of an adequate trial of MAOI |
| STAGE 5 | Stage IV plus failure of an adequate course of ECT |

Childhood Maltreatment Predicts Unfavorable Course of Illness and Treatment Outcome in Depression: A Meta-Analysis

Valentina Nanni, M.D.
Rudolf Uher, M.U.Dr., Ph.D.
Andrea Danese, M.D., Ph.D.

Objectives: Evidence suggests that childhood maltreatment may negatively affect not only the lifetime risk of depression but also clinically relevant measures of depression, such as course of illness and treatment outcome. The authors conducted the first meta-analysis to examine the relationship between childhood maltreatment and these clinically relevant measures of depression.

Results: A meta-analysis of 16 epidemiological studies (23,544 participants) suggested that childhood maltreatment was associated with an elevated risk of developing recurrent and persistent depressive episodes (odds ratio=2.27, 95% confidence interval [CI]=1.80–2.87). A meta-analysis of 10 clinical trials (3,098 participants) revealed that childhood maltreatment was associated with lack of response or remission during treatment for depression (odds ratio=1.43, 95% CI=1.11–1.83). Meta-regression analyses suggested that the results were not significantly affected by publication bias, choice of outcome measure, inclusion of prevalence or incidence samples, study quality, age of the sample, or lifetime prevalence of depression.

Conclusions: Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression.

Meta-Analysis of Clinical Trials Investigating the Association Between Childhood Maltreatment & Treatment Outcomes of Depression (Fixed Effects)

<table>
<thead>
<tr>
<th>Authors (Reference)</th>
<th>Odds Ratio (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nemeroff et al. (46)</td>
<td>0.80 (0.41–1.55)</td>
<td>6.32</td>
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<tr>
<td>Barbe et al. (47)</td>
<td>1.76 (0.44–7.03)</td>
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<td>Shirk et al. (52)</td>
<td>3.75 (1.13–12.54)</td>
<td>1.94</td>
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<td>Lewis et al. (53)</td>
<td>0.60 (0.14–2.49)</td>
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<tr>
<td>Sakado et al. (45)</td>
<td>1.75 (0.62–4.97)</td>
<td>2.59</td>
</tr>
<tr>
<td>Nemeroff et al. (46)</td>
<td>1.29 (0.67–2.40)</td>
<td>6.55</td>
</tr>
<tr>
<td>Asarnow et al. (49)</td>
<td>0.56 (0.27–1.14)</td>
<td>5.56</td>
</tr>
<tr>
<td>Johnston et al. (50)</td>
<td>0.98 (0.61–1.56)</td>
<td>12.74</td>
</tr>
<tr>
<td>Klein et al. (51)</td>
<td>1.54 (1.13–2.09)</td>
<td>30.18</td>
</tr>
<tr>
<td>Lewis et al. (53)</td>
<td>1.93 (0.40–9.21)</td>
<td>1.15</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nemeroff et al. (46)</td>
<td>1.41 (0.75–2.64)</td>
<td>7.15</td>
</tr>
<tr>
<td>Enns and Cox (49)</td>
<td>2.18 (1.04–4.52)</td>
<td>5.25</td>
</tr>
<tr>
<td>Asarnow et al. (49)</td>
<td>3.60 (1.70–7.60)</td>
<td>5.04</td>
</tr>
<tr>
<td>Lewis et al. (53)</td>
<td>2.59 (0.80–8.42)</td>
<td>2.03</td>
</tr>
<tr>
<td>Minniti et al. (54)</td>
<td>1.51 (0.90–2.53)</td>
<td>10.63</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.40 (1.19–1.66)</td>
<td>100.00</td>
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</table>

<table>
<thead>
<tr>
<th>Reasonable Strategies for Stage I Resistant Depression (Non-Remission to One Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Switch within same class</td>
</tr>
<tr>
<td>● Switch across classes</td>
</tr>
<tr>
<td>● Augmentation strategies</td>
</tr>
<tr>
<td>● Focused Management of Residual Symptoms</td>
</tr>
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</table>
## Switching vs. Augmentation

<table>
<thead>
<tr>
<th><strong>Switching</strong> (typically used in nonresponders)</th>
<th><strong>Augmentation</strong> (typically used among partial responders at maximal doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>● A simpler strategy than augmentation, conducive to compliance</td>
<td>● Avoids loss of benefit already achieved</td>
</tr>
<tr>
<td>● Lower risk of drug interactions</td>
<td>● More rapid response</td>
</tr>
<tr>
<td>● Fewer side effects</td>
<td>● Allows the maximization of each drug trial before considering other options</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>● Delays onset of action of second agent</td>
<td>● Not conducive to compliance</td>
</tr>
<tr>
<td></td>
<td>● Higher risk of drug interactions</td>
</tr>
</tbody>
</table>

---

Raising Antidepressant Dose

- Popular choice when presented with
  - Antidepressant partial responder
  - Antidepressant nonresponder

- Studies show mixed results from increasing SSRI dose

- Some SSRIs show flat dose-response curves
Switching Agents

- Switching to different antidepressant with distinct pharmacologic profile
  - TCAs to SSRIs
  - SSRIs to SNRIs
- Switching to antidepressant within the same class
  - SSRIs to SSRIs
Pooled Analysis of Venlafaxine vs. SSRIs in Depressed Patients

Augmentation Strategies

- Thyroid
- Lithium
- Ad infinitum
- pindolol
- Atypical Antipsychotic
- Mood Stabilizer
- Buspirone
Strategies for Antidepressant Nonresponse

- Optimization: Full Dose and Duration
- Combination: Addition of Second Antidepressant Agent
- Augmentation: Addition of Second Agent (Not an Antidepressant)
- Electroconvulsive Therapy
T3 vs T4 Augmentation Therapy

Triiodothyronine Augmentation in the Treatment of Refractory Depression: A Meta-Analysis

Ronnie Aronson, MD; Hilary J. Offman, MD; Russell T. Joffe, MD; C. David Naylor, MD, PhD

Lithium Carbonate Addition in Tricyclic Antidepressant-Resistant Unipolar Depression
Correlations with the neurobiologic actions of tricyclic antidepressant drugs and lithium ion on the serotonin system

Claude de Montigny, MD, PhD, FRCP(C);
Gerard Cournoyer, MD;
Raymond Morissette, MD, FRCP (C);
Robert Langlois, MD, CSPQ;
Gilles Caille, PhD

Effect of Adding Lithium to TCA Therapy

<table>
<thead>
<tr>
<th>Pretreatment (No. of Observations)</th>
<th>Mean HAMD Score (% improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-TCA Baseline</td>
</tr>
<tr>
<td>Amitriptyline (16)</td>
<td>24.8</td>
</tr>
<tr>
<td>Imipramine (12)</td>
<td>24.8</td>
</tr>
<tr>
<td>Trimipramine (6)</td>
<td>23.7</td>
</tr>
<tr>
<td>Desipramine (4)</td>
<td>19.0</td>
</tr>
<tr>
<td>Doxepin (4)</td>
<td>25.7**</td>
</tr>
<tr>
<td>TOTAL (42)</td>
<td>24.2***</td>
</tr>
</tbody>
</table>

* $p < .001$ vs scores before Li addition
** $p < .05$ vs scores before Li addition
*** $p < .001$ vs scores before Li addition

Meta-analysis of 10 augmentation studies
Overall pooled rates of response: lithium 53/131 or 40.5% vs 24/138 or 17.4%

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauman 1996</td>
<td>6/10</td>
<td>2/14</td>
<td>4.48 [1.27, 63.89]</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>Browne 1990</td>
<td>3/7</td>
<td>2/10</td>
<td>6.33 [0.35, 25.87]</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>Heninger 1983</td>
<td>5/8</td>
<td>0/7</td>
<td>1.38 [1.00, 556.08]</td>
<td>23.57</td>
<td></td>
</tr>
<tr>
<td>Joffe 1993</td>
<td>9/17</td>
<td>3/16</td>
<td>9.78 [1.01, 23.57]</td>
<td>4.88</td>
<td></td>
</tr>
<tr>
<td>Kantor 1986</td>
<td>1/4</td>
<td>0/3</td>
<td>2.61 [1.09, 9.48]</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>Nierenberg 2003</td>
<td>2/18</td>
<td>3/17</td>
<td>18.44 [0.08, 4.01]</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Schoepf 1989</td>
<td>7/14</td>
<td>0/13</td>
<td>1.74 [1.35, 541.57]</td>
<td>27.00</td>
<td></td>
</tr>
<tr>
<td>Stein 1993</td>
<td>2/16</td>
<td>4/18</td>
<td>22.15 [0.08, 3.19]</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Zusky 1988</td>
<td>3/8</td>
<td>2/8</td>
<td>8.40 [0.21, 15.41]</td>
<td>1.80</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>131</td>
<td>138</td>
<td>3.11 [1.80, 5.37]</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 53 (Treatment), 24 (Control)
Test for heterogeneity: Chi² = 11.90, df = 9 (p = .22), I² = 24.4%
Test for overall effect: Z = 4.06 (p < .0001)

Augmentation with Atypical Antipsychotics
Risperidone Augmentation in Patients Non-Responsive to an SSRI

*No return visit or Ham-D score; patient and referring psychiatrist noted complete remission

**Risperidone Treatment of Citalopram Nonresponders: Trial Design**

**I** Pre-Treatment
- Screening
  - Weeks -2 to 0
    - Screening Visit
    - Taper of prior Medications
    - Baseline Visit

**II** Open-Label Treatment
- SSRI Confirmation
  - Weeks (Period 1) S-1 to S-6[S-4]
  - Citalopram 20 - 60 mg/day
- RIS Augmentation
  - Weeks (Period 2) A-1 to A-4
  - Citalopram 20 - 60 mg/day
  - Young adults: RIS 0.5 - 2.0 mg/day
  - Older adults: RIS 0.25 - 1.0 mg/day

**III** Double-Blind Treatment
- Relapse Prevention
  - Weeks (Period 3) R-1 to R-24
  - Citalopram + placebo OR Citalopram + RIS
- Taper
  - Weeks T-1 to T-2
  - Citalopram + placebo OR Citalopram + RIS reduced By 50% then discontinued

SSRI treatment
Citalopram

RIS
Augmentation
Treatment

Relapse
Prevention

Screening
≥1 AD treatment

Study Conduct

<table>
<thead>
<tr>
<th>SSRI Phase</th>
<th>Adjunct Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entered</td>
<td>Completed</td>
</tr>
<tr>
<td>502</td>
<td>445</td>
</tr>
<tr>
<td>91%</td>
<td>90.2%</td>
</tr>
</tbody>
</table>

Remission at Period Endpoints


MADRS Total Scores

P < 0.001 vs baseline at each time point

Kaplan-Meier Estimates of the Time to Relapse in Nonresponders (<50% Reduction in HAM-D Scores)

Kaplan-Meier Estimates of the Time to Relapse in Patients Who were Fully Nonresponsive (<25% Reduction in HAM-D Scores)

Olanzapine and Fluoxetine in Treatment-Resistant Major Depression

- Patients: MDD without psychotic features (n = 28)
- Treatment resistance
  - One SNRI and one SSRI for four weeks at adequate dose
  - Fluoxetine run-in (six weeks) at 40 – 60 mg/d (< 30% improvement on the HAM-D-21)

- Eight-week, double-blind treatment
  - Fluoxetine (20 – 60 mg/d) + placebo (n = 10)
  - Olanzapine (5 – 20 mg/d) + placebo (n = 8)
  - Olanzapine + fluoxetine (n = 10)
  - Eight-week olanzapine + fluoxetine open-label

MADRS Score: Mean Change From Baseline (LOCF)

N = 28

N = 28

Ziprasidone Augmentation in Treatment-Resistant Depression: Improvement in HAM-D-17 Scores

Ziprasidone titrated up to 160 mg/day

Adjunctive Ziprasidone in TRD: A Randomized, Double-Blind, 8-Week, Pilot Study


MADRS Score Change

- Sertraline
  - BL = 30.7
  - LS Mean Change MADRS (LOCF) = -4.1
  - N = 20

- Sertraline + Ziprasidone 80 mg/d
  - BL = 30.2
  - LS Mean Change MADRS (LOCF) = -6.8*
  - N = 21

- Sertraline + Ziprasidone 160 mg/d
  - BL = 28.9
  - LS Mean Change MADRS (LOCF) = -7.9*
  - N = 19

*p = NS
Sertraline dose = 100-200 mg/d (flexible)
Aripiprazole Augmentation of Antidepressants for the Treatment of Partially Responding and Non-Responding Patients with Major Depressive Disorder

Jeffrey S. Simon, MD
Charles B. Nemeroff, MD, PhD

Total Scores on the 17-item HAM-D for Major Depressive Disorder Patients Receiving Augmentation Therapy with Aripiprazole

Adjunctive Aripiprazole in Treatment-Resistant Depression

Study Design¹,²

Phase A: (Screening phase)

Screening (7–28 days)

Phase B: (Prospective Tx phase)

Assigned ADT + single-blind PBO* (8 weeks)

Phase C: Nonresponders (Randomized, double-blind Tx phase)

ARI + ADT (6 weeks)*

PBO + ADT (6 weeks)*

Phase B+: Responders (Not randomized)

PBO + ADT (6 weeks)

Week 0 8 14

*There was no significant treatment-by-ADT interaction observed in either study (P=.472).
ADT = antidepressant therapy.

Mean Change in MADRS Total Score (LOCF)

*From end of prospective treatment phase; †P<.01; ‡P<.001.
MADRS total score reduction in ARI vs PBO groups at study end for study 1 and study 2 was –8.5, –8.8 vs –5.7, –5.8, respectively.

**MADRS Remission Rates**

*Remission = MADRS total score ≤10 and 50% reduction in MADRS total score from end of prospective phase to study end; †P < .05; ‡P < .01; §P < .001.*

### Atypical Antipsychotic Augmentation Randomized Clinical Trials (RCTs)

<table>
<thead>
<tr>
<th>Study</th>
<th>Antipsychotic</th>
<th>Adjunctive Medication</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shelton et al 2001</td>
<td>Olanzapine</td>
<td>Fluoxetine</td>
<td>8</td>
</tr>
<tr>
<td>Shelton et al 2005</td>
<td>Olanzapine</td>
<td>Fluoxetine</td>
<td>12</td>
</tr>
<tr>
<td>Corya et al 2006</td>
<td>Olanzapine</td>
<td>Fluoxetine</td>
<td>12</td>
</tr>
<tr>
<td>Keitner et al 2006</td>
<td>Risperidone</td>
<td>Various</td>
<td>4</td>
</tr>
<tr>
<td>Khullar et al 2006</td>
<td>Quetiapine</td>
<td>SSRI or SNRI</td>
<td>8</td>
</tr>
<tr>
<td>Mattingly et al 2006</td>
<td>Quetiapine</td>
<td>SSRI or SNRI</td>
<td>8</td>
</tr>
<tr>
<td>McIntyre et al 2006</td>
<td>Quetiapine</td>
<td>SSRI or SNRI</td>
<td>8</td>
</tr>
<tr>
<td>Thase et al 2006</td>
<td>Olanzapine</td>
<td>Fluoxetine</td>
<td>8</td>
</tr>
<tr>
<td>Thase et al 2006</td>
<td>Olanzapine</td>
<td>Fluoxetine</td>
<td>8</td>
</tr>
<tr>
<td>Gharabawi et al 2006</td>
<td>Risperidone</td>
<td>Various</td>
<td>6</td>
</tr>
</tbody>
</table>

Atypical Antipsychotic Augmentation in TRD: Meta-analysis of 10 RCTs* (n = 1,500)

![Bar chart showing remission and intolerance (d/c) for Atypicals and Placebo.]

- Remission:
  - Atypicals: 47.4
  - Placebo: 22.3

- Intolerance (d/c):
  - Atypicals: 37
  - Placebo: 12

p < 0.05 for remission and intolerance (d/c)

Baseline mean MADRS scores were 27.3 for ADT + placebo (n = 178) and 26.9 for ADT + brexpipraole (n = 175).

P values based on mixed model repeated-measures analysis:
- *p < .05
- **p < .01
- ***p < .001

ADT = antidepressant treatment; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; SE = standard error
Baseline mean MADRS scores were 26.5 for ADT + placebo (n = 203) and 26.9 for ADT + brexpiprazole 1 mg (n = 211), and 26.5 for ADT + brexpiprazole 3 mg (n = 213).

- *P* < .05
- **P** < .01

ADT = antidepressant treatment; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; SE = standard error

Lurasidone Monotherapy in the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study

Antony Loebel, M.D.
Josephine Cucchiaro, Ph.D.
Robert Silva, Ph.D.
Hans Kroger, M.P.H., M.S.
Jay Hsu, Ph.D.
Kaushik Sarma, M.D.
Gary Sachs, M.D.

Mean MADRS scores at baseline were 30.3 (SD = 4.9), 30.6 (SD = 4.9), 30.5 (SD = 5.0) for lurasidone 20-60 mg, lurasidone 80-120 mg, and placebo, respectively.; Mean CGI scores at baseline were 4.52 (SD = .62), 4.55 (SD = .64), and 4.48 (SD = .61) for lurasidone 20-60 mg, lurasidone 80-120 mg, and placebo, respectively. *p < .05, **p < .01, ***p < .001 Loebel A, et al. Am J Psychiatry 2014;171:160-168.
An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar I Depression

Suresh Durgam, M.D., Willie Earley, M.D., Alan Lipschitz, M.D., Hua Guo, Ph.D., István Laszlovszky, Pharm.D., György Németh, M.D., Eduard Vieta, M.D., Ph.D., Joseph R. Calabrese, M.D., Lakshmi N. Yatham, M.B.B.S., F.R.C.P.C.
MAO Inhibitors: Other Association Practice Guidelines

- MAOI treatment recommended for patients with atypical major depression
  - British Association for Psychopharmacology\(^1\)
  - Texas Medication Algorithm Project (TMAP)\(^2\)
  - Agency for Health Care Policy and Research (AHCPR)\(^3\)

---

Optimizing Current Treatments

- Monoamine oxidase inhibitors effective for depression\(^1\)
  - Diet restrictions, drug-drug interactions limit utility
- Transdermal selegiline
  - Efficacious for depression\(^2,3\)
  - No diet restrictions at 6mg/day
  - Limitations:
    - Diet restrictions required at higher doses
    - Drug-drug interactions still a concern

Combination Therapy

- Combining two antidepressants with well-established efficacy
- Two well-established agents from different classes
- Evoke dual-action approach
- TCAs + SSRIs
Desipramine Alone and an Combination with Fluoxetine

SSRI + MIRTAZAPINE: A Double-Blind, Placebo-Controlled Study of Antidepressant Augmentation with Mirtazapine

- RCT followed preliminary positive results
- N = 26 outpatients with partial or nonresponse on SSRI (83%), bupropion or venlafaxine at “maximum recommended or tolerated doses”
- Mean pre-combination treatment 19.4 wks
- Mirtazapine 15 mg/d x 1 wk, then 30 mg/d

Carpenter LL, Biol Psychiatry. 2002;51(2):183-188.
A Double-blind, Placebo-Controlled Study of Antidepressant Augmentation with Mirtazapine

- Response rates: Mirtazapine 63.6% vs Placebo 20%
- Remission rates: Mirtazapine 45.5% vs Placebo 13.3%
- Discontinuation for adverse events similar to placebo
- Most frequent side effect = weight gain
- Concerns:
  - No data on effect of mirtazapine alone
  - Switch from ineffective SSRI in another study showed 37.8% remission with mirtazapine

Nefazodone/CBASP Chronic Depression Study

CBASP = Cognitive Behavioral Analysis System of Psychotherapy; NFZ = nefazodone.
Observed cases, least-squares (LS) means.; *P < .05, NFZ vs. CBASP; †P < .01, NFZ + CBASP vs. CBASP; ‡P < .01, NFZ + CBASP vs. NFZ.
No statistical difference between NFZ vs NFZ + CBASP through Week 4.
Ketamine*

- Anesthetic agent
- Used intravenously primarily
- Used for chronic pain
- N-methyl-D-aspartate antagonist
- Can cause psychotic-like symptoms
- Acute antidepressant efficacy not sustained

*Not approved by the US FDA for MDD
Ketamine*: Change in the 21-item Hamilton Depression Rating Scale (HDRS)

The 21-item Hamilton Depression Rating Scale (HDMS) over 1 week (n = 18)

*Not approved by the US FDA for MDD
Change in Depression Scale Scores During 2 Weeks in Patients with Bipolar Disorder Given Placebo and Ketamine (n = 18)

Change in Depression Severity Over Time in Patients with TRD Given a Single Infusion of Ketamine* or Midazolam

- Modified intention-to-treat group. MADRS scores range from 0-60 with higher scores indicating greater severity of symptoms.
- Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group ($p \leq 0.002$).

*Not approved by the US FDA for MDD
Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression


*Not approved by the US FDA for MDD
Conclusions

- The antidepressant efficacy of ketamine, and perhaps E-cycloserine and rapastinel, holds promise for the future glutamate-modulating strategies; however, the ineffectiveness of other NMDA antagonists suggests that any forthcoming advances will depend on improving our understanding of ketamine’s therapeutic benefit, couple with its potential for abuse and neurotoxicity, suggest that its use in the clinical setting warrants cautions.

*Not approved by the US FDA for MDD
Use of ECT in Patients with MDD

- Patients with MDD most likely to benefit from ECT
  - Patients with delusions
  - Elderly patients
  - Patients presenting with high suicide risk
  - Patients with history of poor response to pharmacotherapy
  - Patients with history of responsiveness to ECT
  - Patients who choose it
  - Patients with bipolar disorder

- ECT is a treatment typically used for MDD after multiple treatments have been poorly tolerated or do not yield a therapeutic response

Efficacy of ECT in MDD and TRD

- The acute effect of ECT in MDD is well established
  - Continuation therapy is required to prevent relapses\(^1\)
  - In 1 recent study, within 24 weeks of achieving remission (HAMD reduced by 60% and ≤10), 64% of patients had relapsed\(^2\)

- TRD is predictive of post-ECT relapse
  - Patients with TRD are at high risk for relapse within 1 year following ECT response\(^3\)
    - Only 32% of patients with TRD maintained their response during the year after ECT treatment\(^4\)

Transcranial Magnetic Stimulation (TMS or rTMS)

- rTMS approved by the FDA for patients who have failed 1 antidepressant trial
- A series of focal electrical pulses are delivered to the cortex via an electromagnetic coil placed on the scalp
- Non-surgical and potentially amenable to administration in the office setting
rTMS in Major Depression

MADRS Total Score
Baseline to Endpoint Change, LOCF Analysis

HAM-D-24 Total Score
Baseline to Endpoint Change, LOCF Analysis

Vagus Nerve Stimulation (VNS)

- FDA-approved (1997) for treatment of medication-refractory epilepsy
- FDA-approved (2005) for treatment of depression that has not responded to four or more medications
- Achieved by implanting a pulse generator attached to (usually) the left vagus nerve
Deep Brain Stimulation (DBS)

- FDA-approved for the treatment of essential tremor, Parkinson’s Disease and dystonia
- Involves (often bilateral) implantation of an electrode into a specific neural structure
  - Different structures chosen for different disorders
  - Side effects often related to site of stimulation
- Stimulation is controlled by a pulse generator implanted in the chest wall
DBS

- Open study of DBS for depression\(^1\)
  - Target: Brodmann Area 25 white matter (based on imaging and other data)
  - 6 patients with extensively treatment-refractory depression
  - 4 of 6 patients responded by 6 months
    - 2 were remitters
  - All 4 remained responders at 12 months\(^2\)
    - 3 were remitters
  - DBS well tolerated with no stimulation-related adverse events
- Confirmatory trial underway at Emory

---

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 peripheral blood and csf innate immune cytokines (IL-6 and TNF-alpha 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”).
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 (esp. 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.
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)?

TRD Pts (N = 60)

Stratification
Male vs. Female
CRP > 2 vs. CRP ≤ 2

Randomization

Baseline  Wk 1  Wk 2  Wk 3  Wk 4  Wk 6  Wk 8  Wk 10  Wk 12

INFUSION

INFLIX* (5mg/kg) N = 30

PLACEBO N = 30

Clinician-Administered Psychiatric Assessments (HAM-D, CGI)
Adverse Events Evaluation
Blood Draw for Inflammatory Markers and Safety Labs

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

*Off label use

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

Review

Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine

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Mesenchymal stem cells (MSCs) are partially defined by their ability to differentiate into tissues including bone, cartilage and adipose in vitro, but it is their trophic, paracrine and immunomodulatory functions that may have the greatest therapeutic impact in vivo. Unlike pharmaceutical treatments that deliver a single agent at a specific dose, MSCs are site regulated and secrete bioactive factors and signals at variable concentrations in response to local microenvironmental cues. Significant progress has been made in understanding the biochemical and metabolic mechanisms and feedback associated with MSC response. The anti-inflammatory and immunomodulatory capacity of MSC may be paramount in the restoration of localized or systemic conditions for normal healing and tissue regeneration. Allogeneic MSC treatments, categorized as a drug by regulatory agencies, have been widely pursued, but new studies demonstrate the efficacy of autologous MSC therapies, even for individuals affected by a disease state. Safety and regulatory concerns surrounding allogeneic cell preparations make autologous and minimally manipulated cell therapies an attractive option for many regenerative, anti-inflammatory and autoimmune applications.

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We propose the first study of mesenchymal stem cell therapy for the treatment of refractory depression.
### Antidepressant Augmentation Strategies

- Vagus nerve stimulation
- Electroconvulsive therapy
- Lithium
- Thyroid hormone (T3)
- Atypical antipsychotics
- Stimulants
- Buspirone
- Modafinil
- Carbamazepine
- Divalproex sodium
- Lamotrigine
- Dopamine agonists (eg, pramipexole)
- Estrogen replacement
- Buprenorpine
- SAMe
- Inositol
- Phototherapy
- Psychotherapy (time-limited)
- Cognitive-behavioral therapy
- Cognitive-behavioral analysis system
- Interpersonal therapy