Major depression: an overview of phenomenology, epidemiology, and somatic treatments

Pierre Blier, MD, PhD
Endowed Chair, Mood Disorders Research
University of Ottawa Institute of Mental Health Research
Canada Research Chair in Psychopharmacology
Disclosures

Dr Blier has received research support, spoken for, or sits on advisory boards for the following organizations:

- Astra-Zeneca
  - Biovail
- Bristol Myers Squibb
- Canadian Institutes for Health Research (CIHR)
  - Eli Lilly
- Janssen-Ortho
- National Institute of Mental Health (USA)
- Lundbeck/Takeda
- Ontario Brain Institute
- Pfizer
- Meda-Valeant
- Merck
- Servier
- Shire
- Sunovion
DSM-IV criteria for major depression *

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning:

1. Depressed mood most of the day, nearly every day
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
3. Significant weight loss when not dieting, or weight gain
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day
9. Recurrent thoughts of death

At least one of the symptoms must be either:

1. Depressed mood
2. Loss of interest or pleasure

* Unchanged in DSM-5; former criterion E (bereavement) was dropped.
**Depression**
- Persistent depressed mood and inability to anticipate pleasure
- Persistent dysphoria not associated with specific thoughts
- Pervasive unhappiness and misery
- Self-critical or pessimistic thoughts
- Worthlessness
- Thoughts of death related to the deceased

**Grief**
- Feelings of loss and emptiness
- Dysphoria in waves associated with the deceased and decreasing over time
- May be associated with +ve emotions and humor
- Preoccupations with thoughts of the deceased
- Self-esteem preserved
- Thoughts of death self-centered to end the pain
Specifiers for depressive disorders in DSM-5

- With anxious distress
- With mixed features (see mania/hypomania symptoms)
- With atypical features
- With melancholic features
- With psychotic features (mood congruent/incongruent)
- With catatonia
- With post-partum onset
- With seasonal pattern
- +Specification for partial or full remission
- +Specification for severity: mild, moderate, or severe
### DSM-IV criteria for melancholia

**A. Either of the following, occurring during the most severe period of the current episode:**

1. Loss of pleasure in all, or almost all, activities
2. Lack of reactivity to usually pleasurable stimuli

**B. Three (or more) of the following:**

1. A depressed mood that is experienced as distinctly different from the kind of feeling experienced after the death of a loved one
2. Depression regularly worse in the morning
3. Early morning awakening (at least two hours before the usual time of awakening)
4. Marked psychomotor retardation or agitation
5. Significant anorexia or weight loss
6. Excessive or inappropriate guilt

*Unchanged in DSM-5*
Depressive disorders with anxious distress

- Feeling keyed up or tense
- Feeling unusually restless
- Difficulty concentrating because of worry
- Fear that something awful may happen
- Feeling that the individual might loose control of him/herself

- Mild: 2 symptoms
- Moderate: 2 symptoms
- Moderate-severe: 4 or 5 symptoms
- Severe: 4 or 5 symptoms and with motor agitation

(associated with higher suicide risk, longer duration of illness and greater likelihood of treatment non-response)
Depression is Complex, Multidimensional

Emotional Symptoms
- Feelings of guilt
- Suicidal
- Lack of interest
- Sadness

Physical Symptoms
- Lack of energy
- Decreased concentration
- Change in appetite
- Change in sleep
- Change in psychomotor skills

Associated Symptoms
- Brooding
- Obsessive rumination
- Irritability
- Excessive worry over physical health
- Pain
- Tearfulness
- Anxiety or phobias

Major Depressive Disorder May Have Systemic Consequences

1. Hypothalamus stimulates the pituitary glands to release excessive ACTH, continuously during the adrenal gland.

2. The adrenal gland releases excessive amounts of catecholamines and cortisol.

3. Increase in catecholamines can lead to myocardial ischemia, diminished heart rate variability, and can contribute to ventricular arrhythmias.

4. Increase in catecholamines causes platelet activation; increases in cytokines and interleukins may also contribute to atherosclerosis and eventual hypertension.

5. Cortisol antagonizes insulin and contributes to dyslipidemia, type 2 diabetes, and obesity; increases in cortisol also suppress the immune system.

Multiple Somatic Symptoms May Be Associated with Depression

*Somatic symptoms included the following:
- Fatigue
- Disturbed sleep
- Menstrual problems
- Dizziness
- GI complaints
- Headache
- Joint or limb pain
- Back pain
- Abdominal pain
- Chest pain
- Sexual dysfunction, lack of interest in sex
- Others

Nature of Presenting Somatic Complaints in Major Depression

Nature of presenting complaints
(N=75)

Psychosocial

Other

17%
7%

Somatic (76%)

Prevalence of varying degrees of somatization (N=1146)

% Depressed Patients

Purely Somatic Symptoms
69%

≥3 Medically Unexplained Symptoms
50%

Denial of Psychological Symptoms
11%

The Montgomery Asberg Depression Rating Scale (MADRS)

- Non hospitalized depression (vs the Hamilton scale)
- Multicultural (limited, however)
- Most sensitive to change
- Ease of use: each item scored from 0-6
- Useful (and time saving) for the clinician and when dealing with insurance companies!
- Remission 10 or 12; Moderate 22; Marked 30’s; Severe 40’s +

<table>
<thead>
<tr>
<th>Signs and symptoms of depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Apparent sadness</td>
</tr>
<tr>
<td>2. Reported sadness</td>
</tr>
<tr>
<td>3. Inner tension</td>
</tr>
<tr>
<td>4. Reduced sleep</td>
</tr>
<tr>
<td>5. Reduced appetite</td>
</tr>
<tr>
<td>6. Concentration difficulties</td>
</tr>
<tr>
<td>7. Lassitude</td>
</tr>
<tr>
<td>8. Inability to feel</td>
</tr>
<tr>
<td>9. Pessimistic thoughts</td>
</tr>
<tr>
<td>10. Suicidal thoughts</td>
</tr>
</tbody>
</table>
Self-rated scales for depression

- Very useful to obtain the patient’s perspective, provided insight is good
- Very informative to gain information about significant residual symptoms following an apparent or numerical remission on a clinician-rating scale
- Very practical if filled in the waiting room
- Examples include: Beck Depressive Inventory (BDI), Quick Inventory of Depressive Symptomatology (QIDS-16; used throughout the STAR*D studies), and the Clinically Useful Depression Outcome Scale (CUDOS by Zimmerman)
INSTRUCTIONS
This questionnaire includes questions about symptoms of depression. For each item please indicate how well it describes you during the PAST WEEK, INCLUDING TODAY. Circle the number in the columns next to the item that best describes you.

RATING GUIDELINES
0 = not at all true (0 days)
1 = rarely true (1-2 days)
2 = sometimes true (3-4 days)
3 = often true (5-6 days)
4 = almost always true (every day)

During the PAST WEEK, INCLUDING TODAY....

1. I felt sad or depressed...
2. I was not as interested in my usual activities...
3. My appetite was poor and I didn't feel like eating...
4. My appetite was much greater than usual...
5. I had difficulty sleeping...
6. I was sleeping too much...
7. I felt very fidgety, making it difficult to sit still...
8. I felt physically slowed down, like my body was stuck in mud...
9. My energy level was low...
10. I felt guilty...
11. I thought I was a failure...
12. I had problems concentrating...
13. I had more difficulties making decisions than usual...
14. I wished I was dead...
15. I thought about killing myself...
16. I thought that the future looked hopeless...
17. Overall, how much have symptoms of depression interfered with or caused difficulties in your life during the past week?
   0) not at all
   1) a little bit
   2) a moderate amount
   3) quite a bit
   4) extremely
18. How would you rate your overall quality of life during the past week?
   0) very good, my life could hardly be better
   1) pretty good, most things are going well
   2) the good and bad parts are about equal
   3) pretty bad, most things are going poorly
   4) very bad, my life could hardly be worse

0-10: no symptoms
11-20: minimal symptoms
21-30: mild symptoms
31-45: marked symptoms
46+: severe symptoms
Epidemiology

- 22 large scale studies reviewed by (Goodwin et al, APA Textbook of Mood Disorders, 2006) provide quite different results for the period 1991-2003
- One month prevalence: from 1-3.9% with most studies in the 3% range
- One year prevalence: from about 2-10% with most studies in the 6-7% range
- Lifetime prevalence: from about 5-24% with most studies in the 16% range (see Kessler, JAMA 289: 3095, 2003)
78,463 ADULTS

5,414 (6.9%) MAJOR DEPRESSIVES

100%

31% NO CONSULTATION

28% NO DRUG TREATMENT

24% NON-ANTIDEPRESSANT DRUG

5% INADEQUATE DOSE OF AN ANTIDEPRESSANT DRUG

12% ADEQUATE DOSE OF AN ANTIDEPRESSANT DRUG

Lépine et al, INT. CLIN. PSYCHOPHARMACOL. 12 : 19, 1997
Epidemiology

- Onset in early adulthood (mean age in the late 20’s)
- Twice more frequent in females, but only from adolescence on
- Marital status: generally never married has higher rates
- Race/ethnicity: variable results, probably more linked to problems facing minorities
- Socioeconomic status: generally higher with low income/unemployment, but possibly higher for lifetime rates in higher income brackets…?
- Urban/rural residence: higher in urban settings
- Increasing rates: possible but methodological factors to consider
Risk factors

- Demographics: most striking is the female gender with regards to hormonal changes
- Familial transmission: +ve history linked to higher rates, severity, earlier onset, and more sensitive to life stressor
- Early adverse life events: physical, sexual abuses and neglect
- Comorbidities: any mental disorder increases the risk of depression (persistence, severity and recurrence), esp. anxiety disorders as preceeding depression
- Negative life events: kindling & genetic vulnerability?
Progression of Depression: Adverse Effects of each Successive Episode

Female subjects only N=2395

Global burden of diseases—World Health Organization

<table>
<thead>
<tr>
<th>Disease or injury</th>
<th>DALYs (millions)</th>
<th>Per cent of total DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>World</strong></td>
<td></td>
<td></td>
</tr>
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<td>1 Lower respiratory infections</td>
<td>94.5</td>
<td>6.2</td>
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<td>72.8</td>
<td>4.8</td>
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<tr>
<td>3 Unipolar depressive disorders</td>
<td>65.5</td>
<td>4.3</td>
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<tr>
<td>4 Ischaemic heart disease</td>
<td>62.6</td>
<td>4.1</td>
</tr>
<tr>
<td>5 HIV/AIDS</td>
<td>58.5</td>
<td>3.8</td>
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<tr>
<td>6 Cerebrovascular disease</td>
<td>46.6</td>
<td>3.1</td>
</tr>
<tr>
<td>7 Prematurity and low birth weight</td>
<td>44.3</td>
<td>2.9</td>
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<tr>
<td>8 Birth asphyxia and birth trauma</td>
<td>41.7</td>
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<tr>
<td>9 Road traffic accidents</td>
<td>41.2</td>
<td>2.7</td>
</tr>
<tr>
<td>10 Neonatal infections and other (^b)</td>
<td>40.4</td>
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<thead>
<tr>
<th>Disease or injury</th>
<th>DALYs (millions)</th>
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<tr>
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<td>76.9</td>
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<td>3 HIV/AIDS</td>
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<td>5.2</td>
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<td>4 Malaria</td>
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<td>4.0</td>
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<td>5 Prematurity and low birth weight</td>
<td>32.1</td>
<td>3.9</td>
</tr>
<tr>
<td>6 Neonatal infections and other (^b)</td>
<td>31.4</td>
<td>3.8</td>
</tr>
<tr>
<td>7 Birth asphyxia and birth trauma</td>
<td>29.8</td>
<td>3.6</td>
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<tr>
<td>8 Unipolar depressive disorders</td>
<td>26.5</td>
<td>3.2</td>
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<tr>
<td>9 Ischaemic heart disease</td>
<td>26.0</td>
<td>3.1</td>
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<tbody>
<tr>
<td><strong>Middle-income countries</strong></td>
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<td>5.1</td>
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<tr>
<td>2 Ischaemic heart disease</td>
<td>28.9</td>
<td>5.0</td>
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<td>3 Cerebrovascular disease</td>
<td>27.5</td>
<td>4.8</td>
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<td>4 Road traffic accidents</td>
<td>21.4</td>
<td>3.7</td>
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<td>5 Lower respiratory infections</td>
<td>16.3</td>
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<td>6 COPD</td>
<td>16.1</td>
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<td>7 HIV/AIDS</td>
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<td>2.6</td>
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<td>8 Alcohol use disorders</td>
<td>14.9</td>
<td>2.6</td>
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<tr>
<td>9 Refractive errors</td>
<td>13.7</td>
<td>2.4</td>
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<tr>
<td>10 Diarrhoeal diseases</td>
<td>13.1</td>
<td>2.3</td>
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<tbody>
<tr>
<td><strong>High-income countries</strong></td>
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<td>2 Ischaemic heart disease</td>
<td>7.7</td>
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<td>3 Cerebrovascular disease</td>
<td>4.8</td>
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<tr>
<td>4 Alzheimer and other dementias</td>
<td>4.4</td>
<td>3.6</td>
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<tr>
<td>5 Alcohol use disorders</td>
<td>4.2</td>
<td>3.4</td>
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<tr>
<td>6 Hearing loss, adult onset</td>
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<tr>
<td>7 COPD</td>
<td>3.7</td>
<td>3.0</td>
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<td>8 Diabetes mellitus</td>
<td>3.6</td>
<td>3.0</td>
</tr>
<tr>
<td>9 Trachea, bronchus, lung cancers</td>
<td>3.6</td>
<td>3.0</td>
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<tr>
<td>10 Road traffic accidents</td>
<td>3.1</td>
<td>2.6</td>
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</table>
Global burden of diseases—World Health Organization

Figure 23: Leading causes of disease burden for women aged 15–44 years, high-income countries, and low- and middle-income countries, 2004

<table>
<thead>
<tr>
<th>Disease</th>
<th>Low- and middle-income countries</th>
<th>High-income countries</th>
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<tbody>
<tr>
<td>Unipolar depressive disorders</td>
<td></td>
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<tr>
<td>HIV/AIDS</td>
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<td>Abortion</td>
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<td>Schizophrenia</td>
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<tr>
<td>Maternal sepsis</td>
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<td>Bipolar disorder</td>
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<td>Road traffic accidents</td>
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<td>Self-inflicted injuries</td>
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<td>Panic disorder</td>
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<td>Migraine</td>
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<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Alcohol use disorders</td>
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</table>

DALYs: disability adjusted life years; WHO 2008 report
### Figure 27: Ten leading causes of burden of disease, world, 2004 and 2030

<table>
<thead>
<tr>
<th>2004 Disease or injury</th>
<th>2004 As % of total DALYs</th>
<th>2004 Rank</th>
<th>2030 Disease or injury</th>
<th>2030 As % of total DALYs</th>
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<tr>
<td>Unipolar depressive disorders</td>
<td>4.3</td>
<td>3</td>
<td>Road traffic accidents</td>
<td>4.9</td>
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<tr>
<td>Ischaemic heart disease</td>
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<td>4</td>
<td>Cerebrovascular disease</td>
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<tr>
<td>HIV/AIDS</td>
<td>3.8</td>
<td>5</td>
<td>COPD</td>
<td>3.8</td>
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<tr>
<td>Cerebrovascular disease</td>
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<td>6</td>
<td>Lower respiratory infections</td>
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<tr>
<td>Prematurity and low birth weight</td>
<td>2.9</td>
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<td>Hearing loss, adult onset</td>
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<td>Birth asphyxia and birth trauma</td>
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<td>Refractive errors</td>
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<td>9</td>
<td>HIV/AIDS</td>
<td>2.5</td>
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<tr>
<td>Neonatal infections and other*</td>
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<td>Diabetes mellitus</td>
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<td>COPD</td>
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<td>Hearing loss, adult onset</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1.3</td>
<td>19</td>
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</table>

*Neonatal infections and other* refers to premature birth and congenital anomalies.
Neurobiology of Depression

**Neurobiological underpinnings**

- MDD may be progressive, mediated by structural and functional changes

- Decreased serotonin, norepinephrine, and dopamine function may be associated with MDD, but not causative *per se*

- Brain derived neurotrophic factor (BDNF) may play an important role in neurological changes

- MDD, pain, and stress are all associated with similar suppression of neurotrophic factors and compromised neuroplasticity

*MDD* = major depressive disorder

*BDNF* = brain-derived neurotrophic factor
Functional Overlap Between Aminergic Systems: Features of Depression

- NE
- 5-HT

- Mood, emotion, cognitive function
- Anxiety
- Irritability
- Energy
- Sex Appetite
- Aggression
- Impulsivity
- Motivation
- Drive
- Interest

Courtesy of S.M. Stahl
Functional Connectivity Between 5-HT, DA and NE Neurons
Some anomalies of the 5-HT system

- Decreased 5-HT transporter binding density in depression
- Increased 5-HT$_2$ binding density in the cerebral cortex
- Decreased 5-HT levels in the cerebral cortex/brainstem
- Increased 5-HT$_{1A}$ density in the raphe nucleus
- But acute tryptophan depletion does not produce depression
Some anomalies of the NE system

- Increase in density of alpha 2 adrenergic presynaptic receptors in the locus coeruleus

- Increased density of beta adrenergic receptors in the cerebral cortex

- Variables results in the levels of the main metabolite of NE (MHPG) in the CSF; increased in the periphery

- Norepinephrine (and dopamine) depletion does not produce depression, although depression can occur in up to 50% of patients with Parkinson’s disease
Areas of the Brain Implicated in MDD

Depressed Patients Experience Increased Blood Flow In The Amygdala And Ventrolateral PFC

Increased Blood Flow (Areas in Red) in Patients with Depression

Patients with depression (n=13) had increased blood flow in the amygdala and left medial and lateral orbital cortex, extending to ventrolateral PFC, relative to healthy controls (n=33)


Images reprinted with permission from Elsevier.
Antidepressant Treatment May Normalize Amygdala Activity

fMRI Study of MDD Patients (n=11) and Healthy Controls (n=11)

*P < 0.05 compared to Control

*P < 0.05 compared to PreTreatment

Limbic-cortical Metabolic Changes May Be Associated With Depression Remission

All Patients at 1 Week

Responders

Non-responders

6 Weeks

Cg - cingulate
Cg25 - subgenual cingulate
pCg - posterior cingulate
pCg31 - posterior cingulate
Cd - caudate
p - pons
hc - hippocampus
ph - parahippocampus
F9 - prefrontal cortex
F46 - prefrontal cortex
Ins - anterior insular cortex

Images reprinted with permission from Elsevier.

green = limbic-paralimbic decreases in glucose metabolism
red = cortical increases in glucose metabolism
## Cerebral atrophy and depression

<table>
<thead>
<tr>
<th>Brain Structure</th>
<th>No. Studies</th>
<th>Cohen’s $d$ (95% CI)</th>
<th>P Value</th>
<th>% Difference</th>
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<tbody>
<tr>
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<td>-0.77 (-1.32 to -0.22)</td>
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<td>-11.91</td>
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<td>&lt;.001</td>
<td>-3.35</td>
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<td>caudate</td>
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<td>-6.74</td>
</tr>
<tr>
<td>hippocampus</td>
<td>31</td>
<td>-0.41 (-0.54 to -0.28)</td>
<td>&lt;.001</td>
<td>-5.07</td>
</tr>
</tbody>
</table>

Adapted from Koolschijn et al. 2009. Hum Brain Mapp. 30: 3719-35
MDD May Impact The Structure of The Subgenual Prefrontal Cortex

Patients with MDD had a 48% lesser Volume in the Subgenual PFC$^2$

Hippocampal Volumes Are Decreased In Depressed Patients with Multiple Episodes (ME) but Not In The First Episode (FE)

MacQueen et al, PNAS, 2003
Decreased Glial Density in Familial BD and MDD in Subgenual Prefrontal Cortex

Antidepressants and Neurotrophic Factors May Help Restore Communication in Depression


Reprinted with permission from Elsevier.
Brain-Derived Neurotrophic Factor (BDNF), Stress, and Neurogenesis in the Adult Brain

- Neurogenesis (the birth of new neurons) may continue postnatally and into adulthood*
  - BDNF is associated with production of new neurons
  - BDNF and other neurotrophic factors may be critical for growth and function of the nervous system, as well as for learning and memory
- The hippocampus appears to have important functions related to both mood and memory
  - Data indicate that neurogenesis occurs in the hippocampus
  - Data from depressed patients have shown reduced hippocampal volume
- BDNF influences regulation of mood in adults and perception of pain in animal models
- BDNF and other neurotrophic factors may be down-regulated in depression, anxiety, and pain
- Both 5-HT and NE are believed to play roles in the modulation of BDNF
- Treatment of MDD may restore BDNF function


Antidepressants Modulate Complex, Interconnected Signaling Cascades

Reprinted with permission from Science and Elsevier.
BDNF is Increased in Human Hippocampus After Antidepressant Treatment

Summary: Neurobiological Underpinnings

- Structural changes in the hippocampus and cerebral cortex often accompany MDD\(^1\)

- MDD may be associated with diminished neurotrophic support, resulting in impaired neuroplasticity, neurogenesis, and cellular resilience\(^2\)

- Cerebral areas affected by MDD have significant noradrenergic, dopaminergic, and serotonergic innervation\(^2\)

---

Outcomes During Acute-Phase Therapy

Symptom Severity
- Nil
- Mild
- Moderate
- Severe
- Marked

Syndromal threshold

Treatment Week
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8

Response w/o remission
- Partial response
- Remission
- Nonresponse

Assessment and decisions
Clinical question:
If the patient has no improvement, how long should the clinician wait before changing treatment strategy?

Relevant measure:
False negatives rate = percentage of patients without improvement at week x, who nevertheless became responders at week 4 and week 6
Definitions

- **Principle of the analysis:** Individual improvement in the early course of treatment is used as a test to predict later individual outcome.
- **Predictor** = Early improvement (at least 20% score reduction by week 2)
- **Response** criterion:
  At least 50% reduction of HAMD total scores at week 4 and week 6 ("stable response")
- **Remission** criterion:
  Reduction of HAMD total scores to 7 or less at week 4 and week 6 ("stable remission")
False negatives

Rate of patients with wrong prediction

Week 1: Mirtazapine
Week 2: Mirtazapine
Week 3: Paroxetine
Week 4: Paroxetine

% of patients
Probability to obtain a sustained remission based on a 20% change after two weeks of treatment

*41 double-blind studies with a variety of antidepressants

Other Studies Supporting the Concept of a Lack of Early Onset Predicting a Negative Outcome

- 3369 patients with bipolar illness (double-blind)
  - Negative predictive value: 12%-remission, 14%-response

- Wade et al, 2011: in 851 MDD patients (escitalopram)
  - Negative predictive value: 22%-remission

- Kim JM et al, 2011: in 568 MDD patients (open label)
  - Negative predictive value: 19%-remission, 33%-response
Only one patient in three fully recovers after a first medication trial

Antidepressant Effects After 6-8 Weeks

- Full Remission: HRSD $\leq 7$
- Partial Response: $8 \leq$ HRSD $\leq 15$
- No response: HRSD $\geq 16$

See Trivedi et al, Am J Psychiat Jan 2006; STAR*D, phase I: 28 % remission
Achieving Remission is Critical

Remission (or lack of it) can impact

- Physical Functioning\(^1,2\)
- Social Functioning\(^1,2\)
- Children’s Mental Well-being\(^3\)
- Occupational Functioning\(^1,2\)
- Marital Functioning\(^4\)
- Likelihood of Future Episodes\(^1,2\)
- Risk of Suicide\(^5\)

Relation Between Maternal Remission Status and Change in Child's Specific Diagnoses (Baseline to 3 Months)

*Confirmed in a sample of 145 children (82 mothers) from New York City and Ottawa; Weissman et al, Psychological Medicine, in press 2014).
Rates of Recovery Diminish with Duration of Major Depressive Episode

Recovery=8 weeks of Psychiatric Status Rating (PSR) 1 or 2. Recovery=sustained remission.

N=431
MDD Patients with Residual Symptoms May Experience Worse Outcomes

Weeks to First Relapse With Any Depressive Episode (Major, Minor, Dysthymic)

Survival Distribution Function = cumulative proportion of cases surviving to given time interval

Efficacy/Tolerability/Compliance

Psychotherapy

- Many studies support cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) as first-line treatment for depression.
- Availability and cost may be limiting factors.
- A combination of pharmacotherapy and psychotherapy may result in higher remission rates.
- The increased suicide risk at the beginning of the treatment is the same as with antidepressants (Simon, Am J Psychiat 164:1029, 2007).
Regulatory vs Practice Guidelines

- They follow different principles and perspectives
- They do not compete with each other, but complement each other
- Regulatory guidelines provide only limited information about the clinical value of a single drug compared to other treatment options
- Regulatory guidelines are not set in stone and they are regularly updated to take into account current scientific and clinical knowledge
## CANMAT Guidelines for MDD

<table>
<thead>
<tr>
<th>Antidepressant[brand name(s)]</th>
<th>Mechanism</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line recommendations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agomelatine* [Valdoxan]</td>
<td>MT₁ and MT₂ agonist; 5-HT₂ antagonist</td>
<td>25–50 mg</td>
</tr>
<tr>
<td>Bupropion [Wellbutrin]</td>
<td>NDRI</td>
<td>150–300 mg</td>
</tr>
<tr>
<td>Citalopram [Celexa, Cipramil]</td>
<td>SSRI</td>
<td>20–60 mg</td>
</tr>
<tr>
<td>Desvenlafaxine [Pristiq]</td>
<td>SNRI</td>
<td>50–100 mg</td>
</tr>
<tr>
<td>Duloxetine [Cymbalta]</td>
<td>SNRI</td>
<td>60–120 mg</td>
</tr>
<tr>
<td>Escitalopram [Cipralex, Lexapro]</td>
<td>ASRI</td>
<td>10–20 mg</td>
</tr>
<tr>
<td>Fluoxetine [Prozac]</td>
<td>SSRI</td>
<td>20–80 mg</td>
</tr>
<tr>
<td>Fluvoxamine [Luvox]</td>
<td>SSRI</td>
<td>100–300 mg</td>
</tr>
<tr>
<td>Mianserin* [Tolvon]</td>
<td>α₂-adrenergic agonist; 5-HT₂ antagonist</td>
<td>60–120 mg</td>
</tr>
<tr>
<td>Milnacipran* [Ixel]</td>
<td>SNRI</td>
<td>100–200 mg</td>
</tr>
<tr>
<td>Mirtazapine [Remeron]</td>
<td>α₂-adrenergic agonist; 5-HT₂ antagonist</td>
<td>30–60 mg</td>
</tr>
<tr>
<td>Moclobemide [Manerix]</td>
<td>Reversible inhibitor of MAO-A</td>
<td>300–600 mg</td>
</tr>
<tr>
<td>Paroxetine [Paxil]</td>
<td>SSRI</td>
<td>20–60 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25–50 mg for CR version</td>
</tr>
<tr>
<td><strong>Second-line recommendations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline, clomipramine and others</td>
<td>TCA</td>
<td>Various</td>
</tr>
<tr>
<td>Quetiapine [Seroquel]</td>
<td>Atypical antipsychotic</td>
<td>150–300 mg</td>
</tr>
<tr>
<td>Selegiline transdermal* [Emsam]</td>
<td>Irreversible MAO-B inhibitor</td>
<td>6–12 mg daily transdermal</td>
</tr>
<tr>
<td>Trazodone [Desyrel]</td>
<td>Serotonin reuptake inhibitor; 5-HT₂ antagonist</td>
<td>150–300 mg</td>
</tr>
<tr>
<td><strong>Third-line recommendations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenelzine [Nardil]</td>
<td>Irreversible MAO inhibitors</td>
<td>45–90 mg</td>
</tr>
<tr>
<td>Tranylcypromine [Parnate]</td>
<td></td>
<td>30–60 mg</td>
</tr>
</tbody>
</table>

* Not commercially available in Canada

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SSRIs

- Never use paroxetine and fluoxetine with tamoxifene; higher doses of citalopram, escitalopram, and sertraline can also inhibit P450 2D6 (tamoxifene)

- Switching abruptly from higher doses of paroxetine to another SSRI can lead to cholinergic discontinuation symptoms

- In pregnancy, exposure to SSRIs is only starting to be compared to depressed women without drug exposure (i.e. complications of due to untreated depression)
CYP2D6 and Tamoxifen Metabolism

Tamoxifen $\rightarrow$ CYP3A4 $\rightarrow$ N-desmethyl-tamoxifen

CYP2D6 $\rightarrow$ 4-hydroxy-tamoxifen

CYP2C9 $\rightarrow$ N-desmethyl-tamoxifen

CYP2C19 $\rightarrow$ 4-hydroxy-N-desmethyl-tamoxifen (Endoxifen)

4-hydroxy-tamoxifen $\rightarrow$ ACTIVE

4-hydroxy-N-desmethyl-tamoxifen (Endoxifen) $\rightarrow$ ACTIVE

N-desmethyl-tamoxifen $\rightarrow$ INACTIVE
SNRIs

- **Venlafaxine**: dose-dependent effect with 225 mg/day+ with greater AD effect (NE effect), monitor blood pressure at 225+, beware of the generics*

- **Desvenlafaxine**: plasma levels at 50 mg/day are the same as venlafaxine 75/day; 100 mg tablets same cost as the 50’s; inappropriate titration in studies examining 100-400 mg/day

- **Duloxetine**: a moderate inhibitor of 2D6, 60 mg is therapeutic but 120 mg/day may be superior**

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*Chenu et al, J Clin Psychiatry 70: 958-966, 2009  
Serotonin and Norepinephrine: Modulation of Mood and Pain Perception
Other agents

- Mirtazapine: sedative in the first 7-10 days, do not start with half-dose (H1 vs $\alpha_2$), weight gain if it occurs is early, more in younger females, no cytochrome inhibition, metabolized by 3 enzymes thus no concern of pk interactions

- Bupropion: moderate inhibitor of 2D6, range 150-300 mg/day (US:450 mg), may be used in depressed patients with anxiety despite generally being an activating agent,* beware of generics*

**Woodcock et al NEJM 367: 2463-2465, 2012
Ghanbari et al, Psychopharmacology 217: 61-73, 2011 (MOA bupropion)
Other agents

- Moclobemide: bad reputation for lack of efficacy but more effective at 750-900 mg/day, may be used with other augmentation strategies, no SSRI/SNRI

- Nefazodone: still available in the US, produced by TEVA

- Vilazodone: available in US only, SSRI + 5-HT\textsubscript{1A} agonist, needs titration 10, 20, 40 mg mainly because of GI side effects

- Vortioxetine (Trintellix): low occupancy SSRI+active on 5 serotonin receptors, less sexual dysfunction at 5 & 10 not 20 mg/day, long-half-life (~65 hours), cross titrate when switching from SSRI/SNRI
Tricyclics

- Subject to plasma variations depending on 2D6 genotype (slow ~ 10% & rapid metabolizers ~2%, possibly over-represented in specialized settings)

- Low doses effective in chronic pain not likely via reuptake inhibition; trimipramine is sedative yet not a reuptake inhibitor, do not stop abruptly (anticholinergic problems, serotonin with clomipramine)

- Can be effective in treatment-resistant depression to other strategies
Irreversible MAOIs

- Phenelzine, tranylcypromine: can be effective in treatment-resistant depression; tranylcypromine under-dosed in STAR*D
- Low tyramine diet has initially been overestimated; see Stahl’s book for concrete examples
- Tranylcypromine more stimulant than phenelzine
- They can be used with augmentation strategies, BUT MUST NEVER USE ANYTHING THAT INHIBITS SEROTONIN REUPTAKE
ECT

- Always an option in case of emergencies
- Memory problems
- Generally requires about 9 sessions on a thrice weekly basis
- High response rates (70%+), but high relapse rates
- In some difficult cases maintenance treatment can be an option
- Certainly do not deserve their bad press!
Treatment durations (minimal) for Depression

6 months

2 years

3 episodes

2 steps if:
1) serious suicide attempt
2) marked familial history
3) age \( \geq 65 \) years
4) Treatment resistance

5 years

4 episodes or more

Lifetime

1 episode

2 episodes

1 episode

(Prolonged first episode?)

Consistent with CANMAT guidelines
Strategies for reaching and sustaining remission

Initial Treatment

Optimization (monitor every 2 weeks)

Assess response at 6 wks

- maintain
- switch
- combine
- augment
- refer
Problems with drug substitution when facing treatment failure

1) Possible loss of a partial response
2) Discontinuation phenomena
3) Negative psychological aspect of the washout period
4) Long duration of a second trial: 6 to 8 weeks
Time courses of interventions

**Substitution**

First trial \[\rightarrow\] Second trial

0 6 8 14

**Combination (sequential)**

First trial \[\rightarrow\]

0 6 8 11 14

*Lithium, Mirtazapine, Bupropion, Desipramine (Atomoxetine), Buspirone, Atypical antipsychotics, T3, Pramipexole*
| Recommendations for non-response and incomplete response to an initial antidepressant. |
|---|---|---|
| **First-line** | **Switch to an agent with evidence for superiority** | **- Duloxetine [Level 2]**  
**- Escitalopram [Level 1]**  
**- Milnacipran [Level 2]**  
**- Mirtazapine [Level 2]**  
**- Sertraline [Level 1]**  
**- Venlafaxine [Level 1]** |
| **Add-on another agent** | **- Aripiprazole [Level 1]**  
**- Lithium [Level 1]**  
**- Olanzapine [Level 1]**  
**- Risperidone [Level 2]** |
| **Second-line** | **Add-on another agent** | **- Bupropion [Level 2]**  
**- Mirtazapine/mianserin [Level 2]**  
**- Quetiapine [Level 2]**  
**- Triiodothyronine [Level 2]**  
**- Other antidepressant [Level 3]** |
| **Switch to an agent with evidence for superiority, but with side effect limitations** | **- Amitriptyline [Level 2]**  
**- Clomipramine [Level 2]**  
**- MAO Inhibitors [Level 2]** |
| **Third-line** | **Add-on another agent** | **- Buspirone [Level 2]**  
**- Modafinil [Level 2]**  
**- Stimulants [Level 3]**  
**- Ziprasidone [Level 3]** |

# Augmentation Strategies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Reported effectiveness when combined with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>600 to 900 mg HS</td>
<td>All antidepressant drugs</td>
</tr>
<tr>
<td>Buspirone</td>
<td>10 to 15 mg TID</td>
<td>SSRI</td>
</tr>
<tr>
<td>T3</td>
<td>25-50 μg/day</td>
<td>Tricyclics/SSRIs? ?</td>
</tr>
<tr>
<td>Desipramine</td>
<td>50 to 125 mg/day</td>
<td>SSRI</td>
</tr>
<tr>
<td>Bupropion</td>
<td>150 to 300 mg/day</td>
<td>SSRI/SNRI/mirtazapine</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15 to 45 mg/day</td>
<td>SSRI/SNRI/bupropion</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5-15 mg/day</td>
<td>SSRI/SNRI</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.5-2 mg/day</td>
<td>SSRI/SNRI</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2-10 mg/day</td>
<td>SSRI/SNRI (approved in Canada)</td>
</tr>
<tr>
<td>Quetiapine XR</td>
<td>150-300 mg/day</td>
<td>SSRI</td>
</tr>
</tbody>
</table>
STAR*D Remissions at Treatment Exit

Venlafaxine = Augmentation (SNRI)

Mean dose: 190 mg/day

Functional connectivity:
Fixed dose versus variable doses of aripiprazole in patients with TRD

The serotonin (5-HT) system and the 5-HT syndrome
Comparison of lithium and ECT addition in tricyclic-resistant patients

Dinan and Barry (1989)
Acta Psychiat Scand