ANTIDEPRESSANT DRUGS

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### The Four Humors

<table>
<thead>
<tr>
<th>Blood</th>
<th>Yellow Bile</th>
<th>Phlegm</th>
<th>Black Bile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>Fire</td>
<td>Water</td>
<td>Earth</td>
</tr>
<tr>
<td>Hot and moist</td>
<td>Hot and dry</td>
<td>Cold and moist</td>
<td>Cold and dry</td>
</tr>
<tr>
<td>Sanguine</td>
<td>Choleric</td>
<td>Phlegmatic</td>
<td>Melancholic</td>
</tr>
<tr>
<td>(amorous, happy, generous)</td>
<td>(violent, vengeful)</td>
<td>(dull, pale, cowardly)</td>
<td>(gluttonous, lazy, sentimental)</td>
</tr>
</tbody>
</table>

His life was gentle, and the elements  
So mix'd in him that Nature might stand up  
And say to all the world, "This was a man!“

Shakespeare’s *Julius Caesar*
The four humors

- the high-blooded lover plays the lute for his lady.
- yellow bile drives a man to wife-beating
- phlegm makes a reluctant mistress
- Too much black bile keeps a melancholic man in bed
Melancholia

Albrecht Dürer

1514
Melancholia

Giovanni Benedetto Castiglione

~1648

From the collection of the University of Michigan
But Freud also left an extremely disturbing legacy. As his theories took root and were applied to practice, the biological basis of mental disorder was discounted, and the work of earlier clinicians forgotten and not built upon. … manic depressives were written off as uncooperative behavior problems. Even simple depression was looked on as a neurosis.

The terrible result of all this was that for a good two or three decades following the second world war, money and resources that could have been devoted to finding proper treatments for these disorders - not to mention directed into more practical therapies - were diverted into other projects. (John MacMannamy)
### Lifetime Prevalence Rates of Mental Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety Disorders</td>
<td>15% (Phobias, 13%)</td>
</tr>
<tr>
<td>Alcohol Disorders</td>
<td>13%</td>
</tr>
<tr>
<td>Affective Disorders</td>
<td>8% (MDE, 6%)</td>
</tr>
<tr>
<td>Drug Disorders (non-alcoholic)</td>
<td>6% (Marijuana, 4%)</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>3%</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder</td>
<td>2%</td>
</tr>
<tr>
<td>Post-traumatic Stress Syndrome</td>
<td>1%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1%</td>
</tr>
</tbody>
</table>
Mood Disorders

Mood disorders include major depressive disorder, dysthymic disorder, and bipolar disorder.

Approximately 20.9 million American adults, or about 9.5 percent of the U.S. population age 18 and older in a given year, have a mood disorder.¹

The median age of onset for mood disorders is 30 years.⁵

Depressive disorders often co-occur with anxiety disorders and substance abuse.
Major Depressive Disorder

Major Depressive Disorder is the leading cause of disability in the U.S. for ages 15-44.

Major depressive disorder affects approximately 14.8 million American adults, or about 6.7 percent of the U.S. population age 18 and older in a given year.

While major depressive disorder can develop at any age, the median age at onset is 32.

Major depressive disorder is more prevalent in women than in men.
Dysthymic Disorder

Symptoms of dysthymic disorder (chronic, mild depression) must persist for at least two years in adults (one year in children) to meet criteria for the diagnosis.

Dysthymic disorder affects approximately 1.5 percent of the U.S. population age 18 and older in a given year.¹ This figure translates to about 3.3 million American adults.²

The median age of onset of dysthymic disorder is 31.
Bipolar Disorder

Bipolar Disorder, also known as manic-depressive illness, is a serious medical illness that causes shifts in a person's mood, energy, and ability to function. Different from the normal ups and downs that everyone goes through, the symptoms of bipolar disorder are severe.

Bipolar disorder affects approximately 5.7 million American adults, or about 2.6 percent of the U.S. population age 18 and older in a given year.1

The median age of onset for bipolar disorders is 25 years.5
Epidemiology of Major Depression

Lifetime depression incidence: 25%
Depression prevalence: 6%
Age of peak incidence: 55 to 65 years old
Women have higher risk of depression
Men have higher completed suicide rate
Family History: Twin concordance
  Monozygotic twins: 75%
  Dizygotic twins: 38%
Depression is missed in elderly and nursing homes
Overlap among mental disorders
Major Depressive Disorder

• More common than hypertension in primary care practice

• Associated with increased incidence of arthritis, hypertension, diabetes, and back pain.

• Affects at least 15 million Americans annually

• Fifteen percent commit suicide
Major Depressive Episode with Melancholia Diagnostic Criteria

- Loss of pleasure in all or almost all activities
- Lack of reactivity to usually pleasurable stimuli (doesn’t feel much better, even temporarily, when something good happens).
- At least three of a set of additional diagnostic criteria.
Major Depressive Episode with Melancholia
Additional Diagnostic Criteria

• Depression that is regularly worse in the morning hours.

• Early morning awakening (at least two hours before the usual time of awakening).

• Marked psychomotor retardation or agitation.

• Significant anorexia or weight loss.

• Excessive or inappropriate guilt.
Amine Theory of Depression

Melancholia (endogenous depression) results from decreased release of neurotransmitter substances (norepinephrine, serotonin, dopamine) at synapses within the central nervous system.
The Biological Basis of Affective and other Mental Disorders
The Biological Basis of Affective and other Mental Disorders

- Development of isoniazid to treat tuberculosis
- Use of reserpine to treat hypertension
Rauwolfia serpentina
The Biological Basis of Affective and other Mental Disorders

- Development of isoniazid to treat tuberculosis
- Use of reserpine to treat hypertension
- Development of imipramine in the search for better antipsychotic drugs
Chlorpromazine

Imipramine

Structures of CPZ and Imipramine
Amine Theory of Depression

Melancholia (endogenous depression) results from decreased release of neurotransmitter substances (norepinephrine, serotonin, dopamine) at synapses within the central nervous system.
Limbic System

- Cingulate gurus
- Cingulum
- Fornix
- Anterior thalamic nucleus
- Stria terminalis
- Hippocampal formation
- Parahippocampal gyrus
- Subcallosal area with septal nuclei
- Striatum
- Orbitofrontal cortex
- Olfactory bulb
- Uncinate fasciculus
- Amygdaloid body

Antidepressants
Limbic System

- Cingulate gurus
- Cingulum
- Fornix
- Anterior thalamic nucleus
- Stria terminalis
- Hippocampal formation
- Parahippocampal gyrus
- Hypothalamus
- Subcallosal area with septal nuclei
- Striatum
- Orbitofrontal cortex
- Olfactory bulb
- Uncinate fasciculus
- Amygdaloid body
Noradrenergic Neurons in the CNS

- Cingulate cortex
- Neocortex
- Hypothalamus
- Olfactory bulb
- Amygdala and hippocampus
- Locus ceruleus
- Cerebellar cortex
- Visceral cranial nuclei
- A1, A2, A5, A7
- Spinal cord
- Tectum
- Thalamus
Serotonergic Neurons in the CNS

- Striatum
- Neocortex
- Thalamus
- Hypothalamus
- Amygdala
- Olfactory and entorhinal cortices
- Hippocampus
- To hippocampus
- Nucleus linearis
- Dorsal raphe nucleus
- Medial raphe nucleus
- Nucleus raphe pontis
- Nucleus raphe magnus
- Nucleus raphe pallidus
- Cerebellar cortex
- Nucleus raphe obscuris
- To spinal cord
Treatment of Affective Disorders

I. Drugs

- Serotonin Selective Reuptake Inhibitors
- Heterocyclic (Tricyclic) Antidepressants
- Monoamine Oxidase Inhibitors
- Lithium Salts
- α₂-Adrenergic Receptor Blocking Drugs
- Selective Norepinephrine Reuptake Inhibitors
- Serotonin Receptor Antagonists
- β-Adrenergic Receptor Blocking Drugs
- Anticonvulsants
- Psychomotor Stimulants
- Opiate Antagonists
- Hormones
Treatment of Affective Disorders

II. Natural products

Tryptophan
St. John’s Wort (*Hypericum perforatum*)

III. Other treatments

ECT
High Intensity Light Therapy
Cognitive Therapy
Interpersonal Psychotherapy
Theories proposed to explain the mechanism(s) of action of antidepressant drugs
Theories as to basis of depression

Antidepressants

Inhibition of neurotransmitter metabolism

Downregulation of postsynaptic receptors

Downregulation of presynaptic receptors

Inhibition of neurotransmitter reuptake

NE → NMN

COMT

DOMA

DOPEG

5-HIAA
Heterocyclic Antidepressants

- Amitriptyline
- Desipramine
- Imipramine
- Maprotaline
- Mianserin
- Nortriptyline
- Protryptyline
Tertiary Amines

- Imipramine
- Amitriptyline
- Doxepin

Secondary Amines

- Desipramine
- Nortriptyline
- Protriptyline
Tricyclic Antidepressants
CNS Effects

• Sedation
Sedative Actions of Tricyclic Antidepressants

Amitriptyline  +++
Doxepin  +++

Imipramine  ++
Nortriptyline  ++
Desipramine  +

Protriptyline  0
Tricyclic Antidepressants
CNS Effects

• Sedation

• Reversal of psychomotor retardation

• Suicide

• Psychomotor stimulant effects: insomnia, excitement, euphoria and hallucinations
Tricyclic Antidepressants
Antimuscarinic Effects

- Dry mouth
- Urinary retention
- Constipation
- Blurred vision

Tolerance develops to the antimuscarinic effects of these drugs
Antimuscarinic Actions of Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Anticholinergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>+++</td>
</tr>
<tr>
<td>Doxepin</td>
<td>+++</td>
</tr>
<tr>
<td>Imipramine</td>
<td>++</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>++</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>++</td>
</tr>
<tr>
<td>Desipramine</td>
<td>+</td>
</tr>
</tbody>
</table>

Most Anticholinergic

Least Anticholinergic
Tricyclic Antidepressants
Cardiovascular Effects

• Orthostatic hypotension
• Tachycardia and other arrhythmias
• EKG abnormalities

Tolerance develops to the orthostatic hypotension
Tricyclic Antidepressants
Other Actions Related to Inhibition of Uptake

- Indirect (amphetamine-like) adrenergic actions (tachycardia, arrhythmias)
- Potentiation of the psychomotor stimulant actions of cocaine and the amphetamine
- Blockade of drugs that act only after transport into neurons (guanethidine)
Tricyclic Antidepressants

Miscellaneous Other Actions

- Hypomania or manic excitation
- Tremor
- Weight gain
- Acute glaucoma
- Impotence
- Jaundice
- Agranulocytosis
- Skin rashes
Tricyclic Antidepressants
Therapeutic Uses

- Melancholia
- Anxiety disorders, agoraphobia with panic attacks
- Obsessive-compulsive neuroses
- Chronic pain, neuralgias, and migraine
- Enuresis in children
Serotonin Selective Reuptake Inhibitors (SSRI’s)

- Citalopram
- Clomipramine
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline
Serotonin-Selective Reuptake Inhibitors

Fluoxetine

Sertraline
Comparison of CNS Effects

- Headache
- Nervousness
- Insomnia
- Anxiety

0 5 10 15 20
Percent Reporting Effect

Fluoxetine
TCA's
Placebo

Antidepressants
Comparison of Anticholinergic Effects

Dry Mouth
Constipation
Blurred Vision

Percent Reporting Effect

Fluoxetine
TCA's
Placebo

0 5 10 15 20 25 30

Antidepressants
Comparison of Gastrointestinal Effects

<table>
<thead>
<tr>
<th></th>
<th>Nausea</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCA's</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
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</tbody>
</table>

Percent Reporting Effect

Antidepressants

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Comparison of Miscellaneous Side Effects

- Dizziness
- Drowsiness
- Tremor
- Sweating

0 5 10 15 20 25 30
Percent Reporting Effect

Fluoxetine
TCA's
Placebo
Second-Generation Antidepressant Drugs

- Bupropion
- Trazodone
- Nefazodone
- Venlafaxine
Bupropion

- A metabolite - hydroxybupropion - has a critical role in antidepressant actions
- Free of anticholinergic and cardiovascular actions associated with TCCA’s
- Causes nervousness and insomnia and in higher doses seizures
Trazodone

- Possesses antidepressant, and also some anxiolytic and hypnotic activity
- Used to treat patients with depression and pre-existing cardiovascular disease
- Used as a hypnotic for psychotropic-induced or other insomnias
- Undesirable side effects: drowsiness, orthostatic hypotension, arrhythmias and priapism.
Nefazodone

- Blocks 5-HT$_{2A}$ receptors and inhibits both serotonin and norepinephrine uptake in vitro.

- Causes fewer complaints of nervousness (e.g., agitation, anxiety), insomnia, and tremors.

- Associated with a higher incidence of confusion, dizziness, and vision disturbance than other advanced generation antidepressants.
Venlafaxine

- Inhibits reuptake of both serotonin and norepinephrine
- Lacks muscarinic-cholinergic or alpha-adrenergic effects
- Has a rapid onset of clinical action (about one week or less).
Venlafaxine

● Used to treat melancholia and treatment-refractory depression

● Adverse effects include nausea, somnolence, insomnia, and dizziness, constipation, sweating, nervousness, and abnormal ejaculation, cardiac conduction changes, orthostatic hypotension, and hypertension.
Reboxetine (Edronax)

• Selective inhibitor of norepinephrine reuptake
• Reboxetine was better than fluoxetine in improving social functioning, patient’s positive self perception and motivation toward action.
• Used both to treat depression and prevent relapse
• Fewer side effects than tricyclic antidepressants and different side effects than those of fluoxetine
Mirtazapine

• Blocks $\alpha_2$-adrenergic receptors. Also blocks 5-HT$_2$ and 5-HT$_3$ receptors.

• At least as effective as other antidepressants for relieving symptoms of depression: dysphoric mood, loss of interest in daily activities, weight change, insomnia or hypersomnia, agitation or retardation, impaired concentration, and suicidal ideation
Mirtazapine

- Somnolence is the most common side effect.
- Other side effects are orthostatic hypotension, increased appetite and weight gain, dry mouth, constipation, increase in cholesterol and triglyceride levels, increase in liver enzyme levels, neutropenia, and agranulocytosis.
- The most serious side effect is agranulocytosis.
Lamotrogine

• Used to treat borderline personality disorder.

• One of a number of anticonvulsant drugs (e.g. valproic acid) used to treat depressions that are refractory to other antidepressant treatments.

• Most serious side effect is rash associated with Stephens-Johnson Syndrome.
GOLDEN ST. JOHN'S WORT
Hypericum aureum Borr.
St. Johnswort Family
St. John’s Wort (*Hypericum perforatum*)

Active ingredient might be hypericin, but extracts contain many organic chemicals.

Inhibits reuptake of 5-HT, NE, and DA with similar potencies.

Weak monoamine oxidase inhibitor.

Therapeutic efficacy not proven despite widespread use by physicians in Germany and by laymen in the United States.

Side effects include GI symptoms, allergic reactions, fatigue, anxiety, dizziness, etc.
Monoamine Oxidase

- Mitochondrial enzymes

- Two types:
  - Type A, selectively inhibited by clorgyline
  - Type B, selectively inhibited by l-deprenyl

- Distribution in brain, 20% Type A and 80% Type B

- Inhibitors of these enzymes “elevate mood”
Clorgyline – Type A

-Log [Inhibitor] M

0 20 40 60 80 100

BZA
PEA

Tyr
DA

5-HT
NE

L-Deprenyl – Type B

0 20 40 60 80 100

BZA
PEA

Tyr
DA

5-HT
NE

Clorgyline and Deprenyl
Oxidative Deamination of Norepinephrine

Norepinephrine $\rightarrow$ 3,4-Dihydroxyphenylglycolaldehyde

Norepinephrine $\rightarrow$ DOPEG $\rightarrow$ DOMA

Aldehyde Dehydrogenase

Aldehyde Reductase
Monoamine Oxidase Inhibitors

- Brofaromine
- Clorgyline
- Deprenyl
- Iproniazid
- Moclobemide
- Phenelzine
- Tranylcypromine
Hydrazine and Amphetamine-Like MAO Inhibitors

Phenelzine

Isocarboxazid

Tranylcypromine
MAO-A Inhibitors

Clorgyline (Irreversible)

Moclobemide (Reversible)
MAO Inhibitors
CNS Effects

- Reversal of psychomotor retardation of depressed patients
- Increase psychomotor activity of normal individuals
- Psychomotor stimulant actions: agitation, hallucinations, hyperreflexia, hyperpyrexia, convulsions
MAO Inhibitors
Cardiovascular Effects

- Orthostatic hypotension
- Symptomatic relief of angina pectoris
- Indirect adrenergic actions: hypertension, arrhythmias
MAO Inhibitors
Foods to be Avoided!

- Cheeses
- Beer
- Wine
- Yeast
- Coffee
- Chicken livers
- Pickled Herring
- Canned Figs
- Broad Beans

Foods that contain tyramine
Antidepressants
MAO Inhibitors
Therapeutic Uses

- Depression with Comorbid Anxiety
- Atypical Depression
- Refractory Depression
- Bulimia
  - Anxiety-phobic disorders
  - Obsessive-compulsive neuroses
  - Hypertension
Lithium Salts

- Used prophylactically to treat manic depressive (bipolar) illness. Effective in 60 to 70 percent of cases.

- Mechanism of action unknown.

- Generally safe. Toxic effects fall into two groups, those related to dose and those not related to dose.

- Toxicity usually secondary to impaired renal function.
Pharmacological Actions of Lithium on the Kidney

- Nephrogenic diabetes insipidus

  Mild intermittent thirst or severe persistent thirst with polyuria

- Electrolyte and water balance – edema and weight gain

  Occurs early in course of treatment. All patients on lithium should have periodic renal function tests.

  Frequent side effect. Water retention alone does not account for all of the weight gain.
Pharmacological Actions of Lithium on the Kidney

- Renal tubular lesions mainly in the distal convoluted tubule and collecting ducts.

- Reduced concentrating ability with increased risk of water and electrolyte loss and lithium intoxications.

Occurs early in course of treatment. All patients on lithium should have periodic renal function tests.

Occurs early in course of treatment and in association with nephropathy or renal tubular lesions.
Pharmacological Actions of Lithium on the Kidney

- Chronic nephropathy
  - Focal nephron atrophy and/or fibrosis
  
  Occurs with prolonged treatment, especially in those with lithium induced nephrogenic diabetes insipidus or episodes of lithium intoxication.

  Lesions progress slowly and can impair the clearance of lithium.
Pharmacological Actions of Lithium on the Thyroid Gland

- **Hypothyroidism, often with goiter**
  Can occur at low doses, usually of late onset and reversible or treatable with thyroxine while lithium is continued.

- **Thyrotoxicosis**
  Less common than hypothyroidism. Late onset and reversible. Can occur in absence of goiter.
Pharmacological Actions of Lithium
Neurological and Psychiatric

- **Tremor**
  
  Common. Can be controlled by propranolol. Occurs at usual therapeutic doses.

- **Choreoathetosis, motor hyperactivity, ataxia, dysarthria, aphasia, marked mental confusion, bizarre motor movements.**
  
  Occur at “usual” therapeutic dose levels.
Pharmacological Actions of Lithium
Gastrointestinal

- Nausea
- Vomiting
- Diarrhea
- Abdominal pain

Adaptation might occur; might be due to associated gastrointestinal disorders; fasting
Pharmacological Actions of Lithium
Cutaneous

- **Acneiform eruptions** Occurs early in treatment. Might or might not recur with resumption of treatment

- **Folliculitis** Asymptomatic. Might recur with resumption of treatment.
Pharmacological Actions of Lithium
Miscellaneous

- T-wave abnormalities
- Arrhythmias
- Erectile impotence

Frequent if looked for carefully. Occasional reports
Uncommon