Antidepressant
DEPRESSION

- A common, debilitating psychiatric disorder
- Life-time prevalence rate: 4.4-18%
- Causes significant suffering & disability
- Associated with considerable indirect costs to society, especially lost earnings/productivity
- High rates of relapse & recurrence - hence long-term therapy required following resolution of acute episode
- Good tolerability profile essential to ensure long-term compliance
During their lifetime, 1 in 8 persons may require treatment for major depression.

In any year, 1 in 10 depressed persons attempts suicide.

HHS Depression Guideline for Depression in Primary Care. 1993
### RISK FACTORS FOR MAJOR DEPRESSION

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Twice as likely in women</td>
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<tr>
<td>Age</td>
<td>Peak age of onset is 20–40 years</td>
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<tr>
<td>Family history</td>
<td>1.5 to 3.0 times higher risk</td>
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<tr>
<td>Marital status</td>
<td>Higher rates in separated, widowed, and divorced persons</td>
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<tr>
<td></td>
<td>Married males lower than never married</td>
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<td>Married females higher than never married</td>
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Mania

- symptoms of paranoid schizophrenia
- grandiosity
- bellicosity
- paranoid thoughts
- over activity, talkative
- impaired insight, lack of judgement

Depression

- sadness
- loss of interest
- loss of pleasure in activities
- emotional instability
- feelings of guilt, worthlessness, hopelessness
- abnormal sleep, libido, appetite, motor activity,
Amine Theory of Depression

Melancholia (endogenous depression) results from decreased release of neurotransmitter substances (norepinephrine, serotonin, dopamine) at synapses within the central nervous system.
BIOLOGIC BASIS OF DEPRESSION: MONOAMINE HYPOTHESIS

MAO enzyme-destroying neurotransmitter

Monoamine neurotransmitter

Norepinephrine, Dopamine, Serotonin

Reuptake pump

Synapse

Receptor

Postsynaptic receptors abnormally up-regulated

BIOLOGIC BASIS OF DEPRESSION: NEUROTRANSMITTER RECEPTOR HYPOTHESIS

Stahl. Essential Psychopharmacology. 1996
NEUROTRANSMITTERS REGULATE DIFFERENT ASPECTS OF MOOD, COGNITION, AND BEHAVIOR

Commonly accepted clinical correlates of neurotransmitter regulation of mood, cognition, and behavior.
ABNORMALITIES OF NEUROTRANSMITTERS ARE ASSOCIATED WITH DIFFERENT SYMPTOMS

• DOPAMINE
  – Decreased ability to experience pleasure
  – Decreased motivation
  – Apathy
  – Decreased attention
  – Cognitive slowing

• NOREPI NEPHRINE
  – Lethargy
  – Decreased alertness

• SEROTONIN
  – Obsessive compulsive symptoms

ONSET OF ACTION OF ANTIDEPRESSANTS

- Synaptic Effects (hours to days)
- Side Effects (hours to days)
- Therapeutic Effects (1 to 6 weeks)

Time after dosing with antidepressant (in weeks)

PHASES OF TREATMENT FOR DEPRESSION

“Normalcy”

Severity

Symptoms

Disorder

Response

Relapse

Relapse

Recurrence

Acute (6-12 weeks)

Continuation (4-9 months)

Maintenance (1 or more years)

Time

Adapted from AHCPR. Depression in Primary Care. 1993
Antidepressants

- Tricyclics antidepressants (TCA)
- Monoaminooxidases inhibitors (IMAO, RIMA)
- Selective serotonin re-uptake inhibitors (SSRI)
- Antidepressants acting on different receptors (sometimes called SSRI 3rd, 4th or even 5th generation, NaSSA, SNRI, NDRI)
# Mechanisms of Action of Antidepressant Drugs

<table>
<thead>
<tr>
<th>Blockade of Norepinephrine Reuptake</th>
<th>Downregulation of Presynaptic $\alpha_2$ Receptors</th>
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<tbody>
<tr>
<td>Desipramine</td>
<td>Tricyclic Antidepressants</td>
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<tr>
<td>Maprotiline</td>
<td>Monoamine Oxidase Inhibitors</td>
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<tr>
<td>Reboxetine</td>
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<table>
<thead>
<tr>
<th>Blockade of Serotonin (5-HT) Reuptake</th>
<th>Blockade of 5-HT Receptors</th>
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<tbody>
<tr>
<td>Fluoxetine</td>
<td></td>
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<tr>
<td>Citalopram</td>
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<table>
<thead>
<tr>
<th>Blockade of both 5-HT and NE Reuptake</th>
<th>Nefazodone ($5-HT_{1A}$)</th>
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<tbody>
<tr>
<td>Tricyclic Antidepressants</td>
<td>Mirtazapine ($5-HT_2$, $5-HT_3$)</td>
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<tr>
<td>Venlafaxine</td>
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<tr>
<td>Nefazodone</td>
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<tr>
<td>Milnacipran</td>
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<tr>
<th>Blockade of $\beta$-Adrenergic Receptors</th>
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<tr>
<td>Pindolol</td>
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Tricyclics, Tetracyclics (TCA)

• **Secondary Amines:**
  – Desipramine, Nortryptiline, protryptiline

• **Tertiary Amines:**
  – Imipramine, Amitriptiline, Doxepin, Clomipramine

• **Tetracyclic:** Amoxapine
Tricyclics antidepressants (TCA)

Imipramine, desipramine (one of the major metabolites of imipramine) amitriptyline, nortriptyline (one of the major metabolites of amitriptyline), Protryptyline, Maprotaline, Mianserin

Imipramine

Amitriptyline
TCAs

- **Action**: Blockade of
  - reuptake of NE & 5-HT (sometimes DA)
  - Muscarinic, Histamine, Alpha Adrenergic
- **2nd amines safer & better tolerated**
- **Clomipramine most SRI, Doxepine most anticholinergic**
- **Start & Stop slowly**
- **Monitor plasma levels**
TCAs: Indications

- Depression
- Panic DO (low dose IMI)
- GAD (Doxepine)
- OCD (Clomipramine)
- Anorexia, Bulimia
- Enuresis (IMI), ADHD
- Narcolepsy, sleep walking, sleep terrors
TCA: Side Effects

- Important side effects in 15-20%, (increases with age)--most are transient and occur during first few weeks of treatment

- Anticholinergic - dry mouth, urinary retention, constipation, dizziness, blurred vision hallucinations, excitement, confusion

- Alpha 1 blockade:
  - Autonomic: Orthostasis
  - Cardiac: arrhythmias, long QT, depr ST

- Histamine: Sedation, Wt Gain, Sexual SE

- Amoxapine: EPS, akathisia (DA Block)

- Clomipr, Amoxapine lower Sz Treshold

- Overdosage: Serious, often fatal. Delirium, Sz, BP & Temp dysregulation
NEUROTRANSMITTER-SPECIFIC SIDE EFFECTS

• SEROTONERGIC side effects:
  – Sexual dysfunction
  – GI upset
  – Sleep disturbance
  – Suppression of dopamine neurotransmission, which may result in:
    • Decreased ability to experience pleasure
    • Apathy and decreased motivation
    • Decreased attention
    • Cognitive slowing

• NORADRENERGIC side effects:
  – Tremor
  – Tachycardia

• DOPAMINERGIC side effects:
  – Psychomotor activation
  – Aggravation of psychosis

TCAs: Interactions

- P450 2D6
- Cimetidine, Quinidine, SSRI, antipsychotics, antiarrhythmics $\uparrow$ TCA
- Smoking, Li, Cl Hydrate $\downarrow$ TCA levels
- Additive effects CNS depressants:
  - EtOH, benzos, opioids, hypnotics, OTC decongestants
Monoamine Oxidase Inhibitors (MAOIs)

- MAOIs were discovered in the 1950s.
- They are rarely a drug of first choice and are prescribed when other antidepressant therapies do not work.
- MAOIs can have serious interactions with other drugs and with certain foods.
- Although MAOIs are considered by many psychiatrists to be the most effective agents for the treatment of depression, their wide-spread use is limited by tolerability and safety concerns.
Monoamine Oxidase Inhibitors (MAOIs)

- isocarboxazide
- nialamide
- fenelzine
- tranylcypromine
- moclobemide (RIMA)
- selegiline (IMAO$_B$)
MAOIs

Some of the major drugs in this category are:

- Phenelzine (Nardil®)
  
  $$C_8H_{12}N_2$$
  
  $\text{mw: } 136.19$

- Tranylcypromine (Parnate®)
  
  $$C_9H_{11}N$$
  
  $\text{mw: } 133.19$
Monoamine oxidases (MAO) enzymes are important in the normal metabolism of amines including neurotransmitters such as 5-hydroxytryptamine, dopamine and noradrenaline.

Inhibition of MAO - increases the levels of amine neurotransmitters in neurons and increases the levels of neurotransmitters which are released.

MAO exists in two forms, A and B which are encoded by separate genes. Both forms of MAO are found mostly in the outer membranes of mitochondria in both neurones and glial cells.

5-HT and NA - metabolized by MAO A

DA is metabolised by both forms of MAO

Non isoform-selective MAO inhibitors have been widely prescribed for depression (e.g. tranylcypromine, isocarboxazide, phenelzine, pargyline).
RIMAs - Reversible Inhibitors of Monoamine Oxidase

**Moclobemide** preferentially inhibits MAO-A; at a 300 mg dose, the inhibition of MAO-A is approximately 80%, while that of MAO-B is approximately 20 to 30%.

The estimated MAO-A inhibition is short-lasting (maximum 24 hours) and reversible, unlike previous MAO inhibitors.

It is a benzamide derivative which inhibits the deamination of serotonin, noradrenaline (and dopamine). This action leads to increased concentrations of these neurotransmitters, which may account for the antidepressant activity of moclobemide.
MAOIs - SE

- Tyramine (↑BP) metabolized GI MAO
- Hypertensive Crisis:
  - headache, N, V, stiff neck, photophobia, diaphoresis, palpitations
- Serotonin Syndrome:
  - autonomic instability, hyperthermia, myoclonus, confusion, delirium, coma
- No longer first line, but very effective
- SE: orthostasis, sedation, sex dysfx, ↑wt
MAO-inhibitors (MAOIs) - interactions

- **Must:** LOW TYRAMINE DIET: no cheese, smoked/aged meats, wine, beans, liver
- **Avoid:**
  - OTC decongestants (OK ASA, tylenol, ibuprofen, benadryl, plain robotussin)
  - Diet pills (ephedrine)
  - DA agonists (Bupropion)
  - SSRIs, Venlafaxine, most TCAs
  - L-Tryptophan
  - Antihypertensives & Diuretics
  - Narcotics
Re-uptake inhibitors

- **SSRI (serotonin)**
  - citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram

- **SNRI (serotonin and noradrenaline)**
  - venlafaxine, milnaciprane

- **NARI (noradrenaline)**
  - reboxetine

- **NaSSA**
  - mirtazapine, trazadone, nefazodone (antagonists of the 5-HT and alpha adrenergic receptors)

- **DNRI**
  - bupropione
SSRIs

- Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citalopram, Escitalopram
  - Clomipramine (TCA) also SRI
  - Sertraline: weak DA uptake inh
  - Paroxetine: weak anticholinergic

- 5-HT potency: parox>fluvox>sertr>fluox

- Similar efficacy to TCA, better safety
Selective Serotonin Reuptake Inhibitors (SSRI)

Best selling class of antidepressants **fluoxetine** (Prozac), **paroxetine** (Paxil), **sertraline** (Zoloft), **citalopram**, **fluvoxamine**, clomipramine

**Mechanism of action:** Inhibit the reuptake of serotonin, with almost no effect on noradrenaline and dopamine.

**Efficacy:** similar to tricyclics, but may be better tolerated for long-term treatment and with fewer side effects

**Therapeutic uses:**
major depression, bulimia, secondary depression, aggression, obsessive-compulsive disorder, panic disorder, premenstrual depression, chronic fatigue syndrome, posttraumatic stress syndrome
SSRIs

- Treatment of acute & maintenance depr. (prevent relapse & recurrence)

- Relapse: 1 yr 2 yr
  - 70% 80% placebo
  - 50% 70% psychotherapy
  - 20% 20% SSRI
SSRIs

- Absolute contraindication in combination with MAOI or L-Tryptophan (5-HT syndr)

- Fluoxetine longest t1/2: 9-11 days, the others 20-24 hrs

- SSRI good GI absorb, Liver metabolized
SSRIs Side Effects

• Usually safe & well tolerated
  – CNS
    • Nervousness, jitteriness
    • Insomnia / sedation, fatigue
    • Headaches, Tremors
  – GI
    • Naus / Vom 11-16%, Diarr, Constip, anorexia, dry mouth
    • Caution in Hepatic Disease
  – Sexual 5-HT2 (25-50%)
    • delayed orgasm, ↓libido, ↓erection/lubrication
  – Induction of Mania
  – Pregnancy: Fluoxetine OK, others no data
SSRIs Interactions

• Absolute contraind. MAOI, L-Tryptophan
  – Wait 2 wks (more with fluoxetine) if switching

• p450 system:
  • Fluvoxamine: 1A2 (↑TCA, clozapine, theoph, tylenol, propranolol levels) & 3A4 (arrhythmias with ↑astemizole (hismanal) & terfenadine (seldane), cisapride (propulsid)
  • Fluoxetine 2D6, 3A4, 2C19
  • Paroxetine 2D6
SSRIs Dosage

- Fluoxetine 10-80 mg/d
- Paroxetine 10-50 mg/d
- Sertraline 25-200 mg/d
- Fluvoxamine 50-300 mg/d
- Citalopram 20-50 mg/d

- Initial response 2-4 wks, if not better after 3-4 wks ↑dose
Major Advantages over the TC and MAOI

- less severe side effects and less likely to lead to discontinuation of therapy
- titration of dosing not necessary
- increased compliance, especially during long-term exposure
- well tolerated
- extremely safe in terms of overdosing
- effective for tricyclic nonresponders to when tricyclics are contraindicated
Venlafaxine (SNRI)

- XR & Regular (t1/2=5 hrs) available
- Potent 5-HT, NE uptake inh.
- Prot. Binding (27%), low p450 problems
- SE SRI-like: N/V, dizziness, sedation
- Dosage:
  - 37.5 bid, optimal dose 175-225
  - XR 37.5 qd 5-7 d., 75 qd, 150 qd after wk 3
  - Monitor Blood Pressure
Bupropion (DNRI)

- DA Agonist
- Structure similar to amphetamine
  - decrease sleep & appetite, Tx ADHD
- Liver metab, kidney excreted
- t1/2: 8-12 hrs (bid, tid)
- Indications: Depression & ADHD
- Risk of Seizures @ 450-600 mg/d
  - Single dose <150, >4hrs apart
  - Max dose 400 mg/d
Bupropion: SE

- N, V, ↓sleep, restlessness, irritability, agitation,
  - No sexual SE
- Do not use with MAOI
- Delirium, psychosis, dyskinesias combined with DA agonists (amantadine, L-dopa, bromocriptine)
- Risk of Seizures
  - Contraind. Hx HI, brain tumor, ↓Sz threshold
Trazodone

A weak 5-HT reuptake inhibitor and blocks alpha 2, 5-HT2A receptors; causes sedation but this can be advantageous

• Blocks 5-HT 2 & 1 receptors
• Weak inhibitor 5-HT reuptake
• Helpful for sleep
• GI absorbed, t1/2 3-9 hrs
• Dose: 150 mg/day divided doses, max 400
• SE:
  • Sedation, occasional orthostasis
  • Rare: Priapism (1 in 6,000) (alpha-1 block)
Nefazadone

- Similar to Trazodone
  - less sedating, no priapism
- 5-HT2 antagonist: little sexual SE
- Mild inhibition 5-HT, NE reuptake
- t1/2 18-24 hrs:
- Metabolite of p450 3A4:
  - interaction: alprazolam, ketokonazole, terfenadine, astemizole, cisapride
Mirtazapine

- Presynaptic alpha2 blockade
  - (blocks feedback that \(\downarrow\) release of NE, 5-HT)
- Postsynap 5-HT2 block: \(\downarrow\) sexual SE
- Postsynap 5-HT3 block: \(\downarrow\) N,V,HA
- 5-HT to 5-HT1 antidepressant effect
- SE: Sedation, Constipation, Wt gain
Mianserin

blocks alpha 2 adrenergic, 5-HT2A and Histamine H1 receptors;
causes sedation but this can be advantageous
blood monitoring for mianserin required as can cause agranulocytosis.
Buspirone

A partial agonist at the 5-HT1A receptor
few side effects but the most common are dizziness, headache, drowsiness and nausea (<10%).
Usually prescribed for short-term relief of excessive anxiety in generalised anxiety disorder
New perspectives of pathophysiology of depressive disorder

- Modern drugs are no more efficacious and act no more rapidly, than the agents discovered four decades ago.
- The fact that monoaminergic modulators are effective in the treatment of depressive disorder need not implicate monoamines in the aetiology of the illness at all.
- Treatments from different antidepressant classes appear to have the common property of increasing the expression of neuroprotective proteins, important in the function and growth of neurons.
• Antidepressant-induced increases in presynaptic monoamine release arise via a variety of mechanisms (monoamine oxidase inhibition, reuptake blockade, presynaptic or somatodendritic autoreceptor downregulation), and result in activation of a range of post-synaptic receptors that are coupled to ‘second messenger’ signal transduction mechanisms. Activation of these enzyme systems ultimately results in the phosphorylation of transcription factors that control gene expression

• transcription factor ‘cAMP response-element binding protein’ (CREB).
• It was proposed that CREB activates genes controlling the expression of the neurotrophic protein designated ‘brain-derived neurotrophic factor’ (BDNF) and its receptor, tropomyosin receptor-related kinase B (TrkB).

• In accord with this hypothesis, they have shown parallel increases in BDNF and TrkB mRNA in the hippocampus of rats exposed chronically to a wide range of antidepressants.
• rats exposed to restraint stress show a reduction in BDNF expression in the hippocampus, and this effect is opposed by antidepressants (Smith et al, 1995)

• direct infusion of BDNF itself into rat brain has putative antidepressant effects in preclinical animal models of depression (Siuciak et al, 1997).
Table 3  Direct and indirect evidence implicating impairments of structural plasticity and cellular resilience in MDDs

- Stress produces atrophy, endangerment and, if prolonged, death of hippocampal neurons
- Stress inhibits hippocampal neurogenesis
- MDD patients have regionally selective volumetric reductions demonstrable on MRI, CT
- MDD patients have reductions in glial number and reductions in the sizes and number of neurons in discrete brain areas

- Antidepressants increase the expression of BDNF and neurotrophin-3 in discrete brain regions
- Antidepressants increase hippocampal neurogenesis
- Antidepressants may prevent stress-induced atrophy of hippocampal neurons
- Lithium and valproate increase the expression of the cytoprotective protein Bcl-2
- Lithium, VPA inhibit GSK-3β (? Substrate-specific inhibition) and increase β-catenin levels
- Lithium exerts neuroprotective effects against diverse insults
- Valproate activates the ERK–MAP-kinase pathway, and promotes neurite outgrowth
- Lithium increases the levels of NAA in human brain
- Lithium increases gray matter volumes in human brain
Bipolar disorder
Treatment

- Lithium + Valproic acid, Carbamazepine
- Lamotrigine
- Gabapentin, Topiramate
- Antidepressants, Antipsychotics
- ECT
Lithium Carbonate
-rapidly absorbed orally, widely distributed, excreted by the kidneys
-narrow margin of safety

Mechanism
1. Effects on electrolytes & ion transport
   - lithium inhibits Na\(^+\) exchange across membranes
2. Effects on neurotransmitters
   - increased actions of serotonin
   - decreased NE and dopamine turnover
3. Effects on second messengers
   - inhibits several important enzymes in normal recycling of membrane phosphoinositides (PIP\(_2\), IP\(_3\), & DAG)
Use
-used in treatment of bipolar disorder by decreasing manic behaviour and frequency & magnitude of mood swings -takes 2-3 weeks for onset of effect
-effective in 60-80% of patients
-maintenance therapy is required to prevent relapse into mania or depression

Toxicity
-unlike antipsychotic or antidepressant drugs lithium produces only mild sedation & no autonomic blocking effects
-adverse effects are diarrhea, tremor, edema, diabetes insipidus thyroid enlargement