Depression
Symptoms of Depression

• Emotional symptoms
• Physical symptoms
• Cognitive symptoms
• Psychomotor symptoms
Depression Pharmacology

Loss of brain tissue due to neuronal cell death in white matter (Cortico-limbic areas)
Monoamines:
- 5-HT (DR)
- NE (LC)
- DA (VTA)

Reduced levels

Depressed mood
Anhedonia
Fatigue
Difficulty concentrating
Changes in weight
Sleep disorders
Depression Pharmacology
Monoamine Hypothesis of Depression

**Pharmacological Evidence:**

- **Reserpine** (antihypertensive)
  - 5-HT, NE, DA
  - Mood depression *(in subset of patients)*

- **Imipramine** (antipsychotic)
  - 5-HT, NE
  - Mood improvement *(in depressed patients)*

- **Iproniazid** (anti-tuberculosis)
  - 5-HT, NE, DA

### Diagram

- **monoamines**
  - Dopamine
  - Norepinephrine
  - MAO
  - Reserpine
  - VMAT
  - Reuptake Transporter
  - “empty”

- **monoamines**
Depression Pathophysiology

- **INCREASED** expression of presynaptic $\alpha_2$ receptors

- **DECREASE** monoamine release

$G\alpha_i$ coupled (inhibitory)
**INCREASED** expression of presynaptic 5-HT receptors

**DECREASE** monoamine release
Depression Pathophysiology

Bone-Derived Neurotrophic Factor: growth factor protein that regulates neuronal differentiation and survival

Auto phosphorylation on five different Tyr residues

- Energy Metabolism
- Cell Proliferation
- Transcription/Translation (new gene expression)
- Cell Survival
- Cell Migration
Depression Pathophysiology

AKT → - GSK3

- Cell Death
  + Gene Expression

New gene expression is essential for synaptic plasticity
Bone-Derived Neurotrophic Factor: growth factor protein that regulates neuronal differentiation and survival

Depression Pathophysiology

- Neuronal differentiation
- Cell Migration

Autophosphorylation on five different Tyr residues

Calcium signaling

+ + + +
Stress-induced depression

- Chronic stress → increase glucocorticoids
  → Disruption of BDNF expression
    (cAMP-CREB signaling)
Depression Pharmacology
HPA axis Hypothesis of Depression

The Hypothalamic-pituitary-adrenal axis may also play a role in depression.

~50% of patients with depression have increased levels of cortisol
Depression Pharmacology
HPA axis Hypothesis of Depression

Hypothalamus

CRH release

Anterior pituitary

ACTH release

Adrenal cortex

Cortisol

Periphery
Depression Pharmacology

Stress → Cortisol elevated → Increase glutamate → Increase Calcium signaling → Calcium-dependent death enzymes → Neuronal cell death
Treatment objectives

• To reduce the symptoms of acute depression
• Help the patient to function at a level comparable to that before the onset of illness
• Prevent relapse/future episodes of depression
Three phases of treatment

• Acute phase:
  – 6-10 weeks
  – Attenuate symptoms or remission

• Continuation phase:
  – 4-9 months after remission is achieved
  – Eliminate residual symptoms
  – Prevent relapse

• Maintenance phase:
  – 12-36 months
  – Prevent relapse
Non-pharmacological therapy

• Psychotherapy:

• Electroconvulsive therapy (ECT):
  – For certain, severe neural disorders
  – If want a quick response, patient has history of poor response to antidepressants but good response to ECT, and patient prefers ECT

• Light therapy:
  – Effective against seasonal affective disorder
Pharmacologic therapy
Drug targets for treatment of depressive disorders

• Inhibit monoamine reuptake transporters
• Block inhibitory presynaptic receptors
• Inhibit monoamine oxidases

• Objective:
  – Increase the concentration of monoamines and their duration in the synaptic cleft
  – Increase monoamine neurotransmission
Antidepressant drugs

- Serotonin reuptake inhibitors (SSRI)
- Serotonin-norepinephrine reuptake inhibitors (SNRI)
- Tricyclic antidepressants (TCA)
- Monoamine oxidase inhibitors (MAOI)
- Others:
  - Aminoketone
  - Triazolopyradines
  - Tetracyclic antidepressants
Depression Pharmacology
Drugs used to treat depression

Pharmaceutical approaches to increase monoamine activity
Inhibit the reuptake of monoamines from the synapse

Reuptake inhibitors (RI):
- DRI: Dopamine RI
- NRI: Norepinephrine RI
- SSRI: Selective serotonin RI

Also...
- SNRI: Serotonin-norepinephrine RI
- NDRI: Norepinephrine-dopamine RI
- SNRDI: Serotonin-norepinephrine-dopamine RI
Serotonin selective reuptake inhibitors (SSRI)

- Generally chosen as first-line antidepressants
- These compounds are structurally unrelated.

Celexa Package Insert, Forest Laboratories, Inc.  
Serotonin selective reuptake inhibitors (SSRI)

- “Selectively” inhibits serotonin reuptake inhibitors
- Generally chosen as first-line antidepressant
  - Improved tolerability
  - Safety (overdose)
Depression
SSRIs

SSRIs approved in US

- Fluoxetine (1987) - Prozac®
- Sertraline (1991) - Zoloft®
- Paroxetine (1992) - Paxil®
- Fluvoxamine (1994) - Luvox®
- Citalopram (1998) - Celexa®
- Escitalopram (2002) - Lexapro®
## Depression Pharmacology
### SSRIs

### Relative affinities of SSRIs

$K_i$ (for reuptake transporters)

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<tr>
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<td>4400</td>
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*LOWEST affinity, selectivity*

*HIGHEST affinity*

*HIGHEST selectivity*
Serotonin-norepinephrine reuptake inhibitors (SNRI)

Venlafaxine  
Desvenlafaxine  
Duloxetine
Serotonin-norepinephrine reuptake inhibitors (SNRI)

- Venlafaxine, Desvenlafaxine, Duloxetine
- Have both serotonin and norepinephrine reuptake inhibitory properties
- Inhibition of 5-HT or NE may vary depending on the dose or may be comparable across all doses
Depression Pharmacology
SNRI

Venlafaxine (1993) - Effexor® - Wyeth (Pfizer)
Duloxetine (2004) - Cymbalta® - Lilly
Desvenlafaxine (2008) - Pristiq® - Wyeth (Pfizer)
Milnacipran (2009) - Savella® - Cypress
Depression Pharmacology
TCA

**Mechanism(s) of action**

1° *Primary mechanism*

**Reuptake inhibitors:**
- SNRI: Serotonin-Norepinephrine reuptake inhibitors

*...but profile varies*

<table>
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<th>SERT &gt; NET</th>
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<tr>
<td>desipramine</td>
<td>amitriptyline</td>
</tr>
<tr>
<td>nortriptyline</td>
<td>clomipramine*</td>
</tr>
<tr>
<td>protriptyline</td>
<td>imipramine</td>
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<tr>
<td></td>
<td>trimipramine</td>
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</table>

↑NE and ↑5-HT eventually cause changes in receptor populations (basis of drug efficacy)

*clomipramine: SERT>>NET*
Tricyclic antidepressants (TCA)

- Blocks serotonin and norepinephrine reuptake
- But also affects other receptor systems

- Amitriptyline
- Clomipramine
- Doxepin
- Imipramine
- Desipramine
- Nortriptyline
Depression Pharmacology
Tricyclics (TCA)

Example: Most tricyclic antidepressants antagonize:

- Sodium channels
- Calcium channels
- Potassium channels
Depression Pharmacology
MAOI

*Pharmaceutical approaches to increase monoamine activity*
Inhibit the enzymatic removal of monoamines

\[ \text{NE, DA, 5-HT} \rightarrow \text{MAO} \rightarrow \text{Inactive metabolites} \]

\[ \text{NE, DA} \rightarrow \text{COMT} \rightarrow \]

**MAO inhibitors** (MAOI)
* Iproniazid discovered in 1950’s (as TB drug)
* But it causes hepatic failure!

**COMT inhibitors**
* Tried in the 1990’s with MIXED RESULTS
* Not used clinically
Monoamine oxidase inhibitors (MAOI)

- Inhibits monoamine oxidase enzymes
- Increase concentrations of NE, DA and 5-HT
- Isoform specific
- Affects other receptor systems

Phenelzine  
Selegiline  
Tranylcypromine
Depression Pharmacology
MAOI

Two isoforms of MAO

Substrate specificity profile

NE, DA, 5-HT → **MAO-A** → Nonspecific and MAO-A specific: Depression, Anxiety

DA → **MAO-B** → MAO-B specific: Parkinson’s disease

Expression profile

**MAO-A:**
- CNS (neurons, glia, synaptic clefts)
- Peripheral (liver, GI tract)

**MAO-B:**
- CNS (neurons, glia, synaptic clefts)
- Peripheral (platelets)
Other antidepressants

• Triazolopyridines:
  – Trazodone, nefazodone
  – 5-HT\textsubscript{2} antagonists and 5-HT reuptake inhibitors

• Aminoketones:
  – Bupropion
  – Norepinephrine and dopamine reuptake inhibitor

• Tetracyclics:
  – Mirtazapine
  – Central presynaptic $\alpha_2$-adrenergic autoreceptor and heteroceptor antagonist
  – Inhibits 5-HT\textsubscript{2,3} receptors and histamine receptors
Depression Pharmacology
Others

**Bupropion** (1985) - Wellbutrin®— **NDRI** (no effects on 5-HT)

**Trazodone** (1981) - Desyrel®
(now, Oleptro®)

**Nefazodone** (1994) - Serzone®

Various (mechanisms unclear)

- SSRI
- $5-HT_{1A}$ antagonism
- $5-HT_{2A}$ antagonism
- $\alpha_1$ antagonism
- $\alpha_2$ antagonism
Receptors affected by antidepressants
# Classical Neurotransmitters: Summary

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Receptor</th>
<th>Exitatory or Inhibitory</th>
<th>Coupling or Ion</th>
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<tbody>
<tr>
<td>ACh</td>
<td>mAChR\textsubscript{1,3,5}</td>
<td>Excitatory</td>
<td>G\alpha_q (PLC)</td>
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<tr>
<td>ACh</td>
<td>mAChR\textsubscript{2,4}</td>
<td>Inhibitory</td>
<td>G\alpha_i (AC, K\textsuperscript{+})</td>
</tr>
<tr>
<td>ACh</td>
<td>nAChR</td>
<td>Excitatory</td>
<td>Na\textsuperscript{+}, Ca\textsuperscript{2+}</td>
</tr>
<tr>
<td>DA</td>
<td>D\textsubscript{1,5}</td>
<td>Excitatory</td>
<td>G\alpha_s (AC)</td>
</tr>
<tr>
<td>DA</td>
<td>D\textsubscript{2,3,4}</td>
<td>Inhibitory</td>
<td>G\alpha_i (AC, K\textsuperscript{+})</td>
</tr>
<tr>
<td>5-HT</td>
<td>5-HT\textsubscript{4,6,7}</td>
<td>Excitatory</td>
<td>G\alpha_s (AC)</td>
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<tr>
<td>5-HT</td>
<td>5-HT\textsubscript{2A, 2c}</td>
<td>Excitatory</td>
<td>G\alpha_q (PLC)</td>
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<tr>
<td>5-HT</td>
<td>5-HT\textsubscript{3}</td>
<td>Excitatory</td>
<td>Na\textsuperscript{+}</td>
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<tr>
<td>5-HT</td>
<td>5-HT\textsubscript{1A, 1D}</td>
<td>Inhibitory</td>
<td>G\alpha_i (AC, K\textsuperscript{+})</td>
</tr>
</tbody>
</table>
### Classical Neurotransmitters: Summary

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Receptor</th>
<th>Exitatory or Inhibitory</th>
<th>Coupling or Ion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>$H_1$</td>
<td>Excitatory</td>
<td>$G\alpha_s$ (AC)</td>
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<tr>
<td>Histamine</td>
<td>$H_3$</td>
<td>Inhibitory</td>
<td>$G\alpha_i$ (AC, K$^+$)</td>
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<tr>
<td>Glu</td>
<td>NMDA</td>
<td>Excitatory</td>
<td>Na$^+$, Ca$^{2+}$</td>
</tr>
<tr>
<td>Glu</td>
<td>AMPA</td>
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<td>Na$^+$</td>
</tr>
<tr>
<td>Glu</td>
<td>mGluR$_i$</td>
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<td>$G\alpha_q$ (PLC)</td>
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<tr>
<td>Glu</td>
<td>mGluR$_{II,III}$</td>
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<td>$G\alpha_i$ (AC, K$^+$)</td>
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<td>Cl$^-$</td>
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<tr>
<td>Gly</td>
<td>GlyR</td>
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<td>Cl$^-$</td>
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</tbody>
</table>
Side effects
Anticholinergic effects
Muscarinic ACh receptor regulation

- Blurred vision
- Dry mouth
- Sinus tachycardia
- Constipation
- Urinary retention
- Memory dysfunction
Histamine (H₁) Blockade

- Sedation and drowsiness
- Weight gain
- Hypotension
Orthostatic reflex effects

$\alpha_1$-Adrenergic Receptor

- Adrenergic receptor regulation
- Vasodilation
- Decreased peripheral resistance
Seizures

• Dose dependent

• Increase susceptibility:
  – In patients with history of head trauma
  – In patients who had CNS tumor
  – In bulimics and anemic patients (prone to electrolyte imbalance)
### Depression Pharmacology

**SSRIs and SNRIs**

#### SSRI and SNRI Adverse Effects

SSRIs and SNRIs **DO NOT** cause the same side effects as TCAs

*example: fluoxetine vs. desipramine*

<table>
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<th>$K_i$ (nM)</th>
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<td>SERT</td>
<td>25</td>
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<td>NET</td>
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<tr>
<td>$H_1$</td>
<td>1000</td>
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<tr>
<td>$\alpha_1$</td>
<td>1300</td>
</tr>
<tr>
<td>$M_1$</td>
<td>500</td>
</tr>
</tbody>
</table>

SSRI and SNRI do **NOT** cause sedation, orthostatic hypotension, tachycardia, and anticholinergic effects.*

*(paroxetine is mildly anticholinergic)*
Depression Pharmacology
SSRIs and SNRIs

*SSRI and SNRI Adverse Effects*

Sexual dysfunction
Serotonin Syndrome

CNS excitation
• agitation
• insomnia
• anxiety

Enteric excitation
• GI upset
• nausea
Depression Pharmacology
TCA

Mechanism(s) of action

Receptor binding:

- Antagonism of various receptors (high affinity examples)
  - $\alpha_1$ (amitriptyline, doxepin, trimipramine)
  - $H_1$ (amitriptyline, doxepin, trimipramine)
  - $M_1$ (amitriptyline, clomipramine)
  - 5-HT$_2$ (amitriptyline, doxepin) - may explain clinical benefit

Explains side effects:
- Orthostatic hypotension
- Tachycardia (supine and postural)
- Sedation
- Weight gain
- Anticholinergic (dry mouth, constipation, etc.)
TCAs block sodium and other membrane ion channels.

The influx of sodium is the major event responsible for the zero phase of depolarisation in cardiac muscle and Purkinje fibres.

As the degree of Na+ channel block increases with use, the QRS width will increase with increasing heart rates.
Other cardiac channel effects include reversible inhibition of the outward potassium channels responsible for repolarisation giving a mechanism for QT prolongation and arrhythmia generation.

TCAs demonstrate a *dose dependent* direct *depressant* effect on *myocardial contractility* that is independent of impaired conduction altering mitochondrial function and uncoupling oxidative phosphorylation.
Other adverse effects

**Delirium Toxicity** – caused by $M_1$ and $H_1$ blockade
Confusion, disorientation caused by high drug levels
Dose dependent (at blood levels $> 300$ ng/ml)
Occurs at lower levels in patients with dementia

**Seizure risk** – dose-dependent
  e.g. Clomipramine
Depression Pharmacology
TCA

Other adverse effects

**Amoxapine** – metabolized to **7-hydroxy metabolite**
with **neuroleptic** (D₂ antipsychotic) activity
Thus – can cause neuroleptic malignant syndrome (rare)
and tardive dyskinesia - rare but worth remembering

**Imipramine** and **desipramine** – have been reported to
cause acute hepatitis (potentially fatal)

**QT prolongation** – TCAs have been reported to increase QT
intervals, potentially cause fatal AV block
(but no Boxed warnings or recalls)
### Antidepressants: targets and side effect profile

<table>
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<th>Generic name</th>
<th>Trade name</th>
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<th>Orthostatic</th>
<th>conduction</th>
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<td>Serotonin</td>
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<td>Sedation</td>
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<td>secondary amines</td>
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<td>Monoamine oxidase inhibitors</td>
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<td>tranylcypromine</td>
<td>Parnate</td>
<td>(++)</td>
<td>(+)</td>
<td>(+)</td>
<td>(++)</td>
</tr>
</tbody>
</table>
Pharmacokinetics of antidepressants
SSRI

SSRI have half life of approximately 1-2 days, up to 7 days for Citalopram. Reaches steady state in 3-6 days, up to 30-60 days with Fluoxetine. Subject to first pass metabolism.

<table>
<thead>
<tr>
<th>SSRI</th>
<th>CYP enzyme metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>2C19 mediates initial step, then 2D6</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>2D6 partially responsible</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>not known</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>2D6 principal P450</td>
</tr>
<tr>
<td>Sertraline</td>
<td>3A3/4 responsible for demethylation</td>
</tr>
</tbody>
</table>
Depression Pharmacology
SSRIs

**SSRI Pharmacokinetics**

**Routes:**
All ORAL

**Absorption:**
Generally well absorbed (small intestine)
Affected by food?
    ONLY sertraline (slower absorption, more complete)

**Distribution:**
Lipophilic – HIGH $V_d$ (10-40 L/kg)
Highly protein bound (75-99%)
High bioavailability 80-95%,
except for Paroxetine and Sertraline
Depression Pharmacology

SSRI Pharmacokinetics

**Half-lives:**
Varies, most about 20-30 hours

**Metabolism:**
Two SSRIs form active metabolites (via CYP2C9, CYP2C19)

- **fluoxetine** $\xrightarrow{P450}$ **norfluoxetine** (equally active)

- **sertraline** $\xrightarrow{}$ **N-desmethylsertraline** (active)

Similar metabolites from other SSRIs are mostly inactive:

- **citalopram** $\xrightarrow{}$ **N-desmethylcitalopram**
  
  (DCT, 10% active)
### Depression Pharmacology
#### SSRIs

**SSRI Drug interactions**

Interactions occur with other classes of antidepressants
- MAOI – serotonin syndrome
- TCA – potentiation of side effects

<table>
<thead>
<tr>
<th>CYP1A2 Inhibitors</th>
<th>CYP2C19 Inhibitors</th>
<th>CYP2D6 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>Fluvoxamine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paroxetine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1A2 Substrates</th>
<th>2C19 Substrates</th>
<th>2D6 Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Some TCAs</td>
<td>Some TCAs</td>
<td>Some TCAs</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Proton pump inhibitors</td>
<td>Some antipsychotics</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Diazepam</td>
<td>β blockers</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Phenobarbital</td>
<td>Antiarrhythmics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opioids</td>
</tr>
</tbody>
</table>
SNRI

• Venlafaxine is well absorbed after oral admin.
• Subject to first-pass metabolism producing desvenlafaxine (active metabolite)
• Has half life of 4 hours
• Metabolized by CYP2D6
• Desvenlafaxine has half life of 8 hours
• Desvenlafaxine is metabolized by CYP3A4

10% bioavailable

80% bioavailable
SNRI Pharmacokinetics

Less protein binding than TCAs or SSRIs
ONLY 10-30% bound (except duloxetine, 90% to albumin)

Lower $V_d$ than TCAs or SSRIs (3-10 L/kg)
Depression Pharmacology

SNRIs

SNRI Metabolism

SNRI Drug Interactions

Interactions occur with other classes of antidepressants
MAOI – serotonin syndrome
TCA – potentiation of side effects

Duloxetine + alcohol abuse → hepatitis (contraindicated)
Depression Pharmacology
TCAs

- Well absorbed after oral administration
- Reach plasma concentrations within 2-6 hours
- Extensively bound to plasma proteins (63-97%)
- Active metabolites
- Metabolized by CYP2D6, CYP2C19, CYP1A2, CYP3A4
Depression Pharmacology
MAOIs

- Pharmacokinetic parameters not well defined
- Half lives, distribution, metabolism, excretion not well known
- Half lives of little interest because these are irreversible MAO inhibitors
- Selegiline is metabolized to methamphetamine and levo-amphetamine
- May account for some of the clinical effects
Pharmacokinetics of other antidepressants
Tetracyclic antidepressant

- Mirtazapine is rapidly absorbed after oral administration
- Subject to first-pass metabolism
- Bioavailability about 50%
- Half life of 20-40 hours
- Reach steady state levels after 4-9 days
- Metabolized by four or more CYP enzymes
- Metabolites have no activity
Triazolopyradines: nefazodone

- Rapidly absorbed after oral administration
- Subject to first-pass metabolism
- Metabolized to produce active metabolite (m-CPP)
- Metabolized by CYP2D6
- Half life is 2-4 hours
- Metabolites have longer half lives
Triazolopyradines: trazodone

- Rapidly absorbed after oral administration
- Subject to first-pass metabolism
- More than 90% is bound to plasma protein
- Metabolized by CYP2D6
- Has active metabolite (m-CPP)
- Has a half life of 4-14 hours
Depression Pharmacology
Trazodone and Nefazodone

Metabolism

Trazodone
Nefazodone

CYP3A4

m-Chlorophenylpiperazine (M-CPP)

Serotonin AGONIST at many different receptors

Illicit drug
(psychoactive - anxiogenic)
Bupropion

- Rapidly absorbed after oral administration
- Subject to first pass metabolism
- Metabolized by CYP2D6 and CYP2B6
- Half life of 14 hours

\[
\text{Bupropion} \rightarrow \text{Hydroxybupropion (ACTIVE)}
\]

Bupropion is a \underline{CYP2D6 Inhibitor}

\underline{2D6 Substrates}
- Some TCAs
- Some antipsychotics
- \(\beta\) blockers
- Antiarrhythmics
- Opioids
## Summary: Pharmacokinetics of antidepressants

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug</th>
<th>t1/2 (hr)</th>
<th>Time to Peak (plasma)</th>
<th>%pl. prot binding</th>
<th>%bioavail</th>
<th>cl. imp. metab.</th>
<th>hep enz</th>
<th>r.o.ad.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5HT reuptake inh</strong></td>
<td>citalopram</td>
<td>33h</td>
<td>2-4h</td>
<td>80</td>
<td>&gt;80</td>
<td></td>
<td>CYP3A4, CYP2C19</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>escitalopram</td>
<td>27-32h</td>
<td>5h</td>
<td>56</td>
<td>80</td>
<td>CYP3A4, CYP2C20</td>
<td>oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>fluoxetine</td>
<td>4-6days</td>
<td>4-8h</td>
<td>94</td>
<td>95</td>
<td>norfluoxetine</td>
<td>oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>fluvoxamine</td>
<td>15-26h</td>
<td>2-8h</td>
<td>77</td>
<td>53</td>
<td></td>
<td>oral</td>
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<tr>
<td></td>
<td>paroxetine</td>
<td>24-31h</td>
<td>5-7h</td>
<td>95</td>
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<td>CYP2D6</td>
<td>oral</td>
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<tr>
<td></td>
<td>sertraline</td>
<td>27h</td>
<td>6-8h</td>
<td>99</td>
<td>36</td>
<td></td>
<td>CYP2B6, CYP2D6, CYP2C9, CYP2C19, CYP3A4</td>
<td>oral</td>
</tr>
<tr>
<td><strong>5HT/NE reuptake inh</strong></td>
<td>venlafaxine</td>
<td>5h</td>
<td>2h</td>
<td>27-30</td>
<td>45</td>
<td>O-desmethylenlafaxine</td>
<td>CYP2D6</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>desvenlafaxine</td>
<td>11h</td>
<td>7.5h</td>
<td>30</td>
<td>80</td>
<td></td>
<td>CYP3A4</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>duloxetine</td>
<td>12h</td>
<td>6h</td>
<td>90</td>
<td>50</td>
<td></td>
<td>CYP2D6, CYP1A2</td>
<td>oral</td>
</tr>
<tr>
<td><strong>Aminoketone</strong></td>
<td>bupropion</td>
<td>10-21h</td>
<td>3h</td>
<td>82-88</td>
<td></td>
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<td>CYP2B6, CYP2D6</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>hydroxybupropion</td>
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<td>threhydrobupropion</td>
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</tr>
<tr>
<td></td>
<td>erythrobupropion</td>
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<tr>
<td><strong>Triazolopyradines</strong></td>
<td>nefazodone</td>
<td>2-4h</td>
<td>1h</td>
<td>99</td>
<td>20</td>
<td>meta-chlorophenylpiperazine</td>
<td>oral</td>
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<tr>
<td></td>
<td>trazodone</td>
<td>6-11h</td>
<td>1-2h</td>
<td>92</td>
<td></td>
<td>meta-chlorophenylpiperazine</td>
<td>CYP3A4</td>
<td>oral</td>
</tr>
<tr>
<td><strong>Tetracyclics</strong></td>
<td>mirtazapine</td>
<td>20-40h</td>
<td>2h</td>
<td>85</td>
<td>50</td>
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<td>CYP2D6, CYP3A4</td>
<td>oral</td>
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<tr>
<td><strong>Tricyclics</strong></td>
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<tr>
<td>tertiary amines</td>
<td>amitriptyline</td>
<td>9-46h</td>
<td>1-5h</td>
<td>90-97</td>
<td>30-60</td>
<td>nortriptyline</td>
<td>CYP2C19, CYP1A2, CYP2D6</td>
<td>oral</td>
</tr>
<tr>
<td></td>
<td>clomipramine</td>
<td>20-24h</td>
<td>2-6h</td>
<td>97</td>
<td>36-62</td>
<td>desmethyldclomipramine</td>
<td>CYP1A2</td>
<td>oral, IM, IV</td>
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<tr>
<td></td>
<td>doxepin</td>
<td>8-36h</td>
<td>1-4h</td>
<td>68-82</td>
<td>13-45</td>
<td>desmethyldoxepin</td>
<td>oral, IM, IV</td>
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<tr>
<td></td>
<td>imipramine</td>
<td>6-34h</td>
<td>1.5-3h</td>
<td>63-96</td>
<td>22-77</td>
<td>desipramine</td>
<td>oral</td>
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<tr>
<td>secondary amines</td>
<td>desipramine</td>
<td>11-46h</td>
<td>3-6h</td>
<td>73-92</td>
<td>33-51</td>
<td>2-hydroxydesipramine</td>
<td>oral</td>
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<tr>
<td></td>
<td>nortriptyline</td>
<td>16-88h</td>
<td>3-12h</td>
<td>87-95</td>
<td>46-70</td>
<td>10-hydroxynortriptyline</td>
<td>CYP2D6</td>
<td>oral</td>
</tr>
</tbody>
</table>
Discussion