Affective or Mood Disorders

Munir Gharaibeh, MD, PhD, MHPE
School of Medicine
The University of Jordan
February, 2019

Note: Rand Khreisat
Affective or Mood Disorders

- **Reactive Depression.** Happens as a reflex to life events (failing a test, someone's death...), not the topic of this lecture.

- **Secondary: Medical** like chorionic illnesses

- **Neurological**

- **Drugs**

- **Major (Endogenous) Depression =**

  **Unipolar:** this needs treatment

Depressed mood, decreased interest in normal activities, anorexia, weight loss, insomnia, fatigue, and decreased concentration. May eventually lead to aggressiveness, and perhaps suicide.
Affective or Mood Disorders

- **Mania:**

  Expansive mood, grandiosity, inflated self-esteem, pressured speech, flight of ideas and poverty of sleep. More common among older people.

- **Manic-Depressive Psychosis = Bipolar**

February 19

Munir Gharibeh MD, PhD, MHPE
Primary Affective Disorders

Bipolar Disorder

Major Depression (Single Episode or Recurrent)

Bipolar, Manic
Bipolar, Depressed
Bipolar, Mixed

Other Specific Affective Disorders (Chronic)

Cyclothymic Disorder
Dysthymic Disorder

Without Melancholia
With Melancholia
With Psychosis
About the previous figure:

- Affective disorders are due to abnormal norepinephrine and serotonin transmission in the brain.
- Norepinephrine has alpha 1, alpha 2 and beta receptors. Alpha 2 is presynaptic. Notice that these are similar to what we have studied in the autonomic nervous system. However, in these disorders what we care about is what goes on in the brain.
- Serotonin has 5HT (1,2,3,4,5) receptors, we are interested in 5HT1a and 5HT1b.
Biogenic Amine Theory

• This theory is one of the two theories that try to explain these disorders, it states that both depression and mania occur due to a deficiency in serotonin levels, the difference is in the norepinephrine level, if the levels of NE decrease this will cause depression, on the other hand an increase in the level of NE will cause mania.

• Depression appears to be associated with changes in central serotonin and/or norepinephrine signaling in the brain.

• Most antidepressant drugs cause changes in amine signaling.
Biogenic Amine Theory

- Reserpine is an antihypertensive agent that causes depression as a side effect, it is a lipophilic compound that can diffuse to presynaptic nerve endings and prevents the storage of serotonin and NE, this causes their deficiency (hence the depression). This phenomena supports the biogenic amine theory.
- Deficiency in central serotonergic activity predisposes to an affective disorder.
- If this is accompanied with decreased adrenergic activity, depression is observed.
- If accompanied with increased adrenergic activity, mania is observed.
Neurotrophic hypothesis of major depression

• This is the 2\textsuperscript{nd} theory.

• Changes in \textbf{trophic factors} (especially brain-derived neurotrophic factor, BDNF) and \textbf{hormones} appear to play a major role in the development of major depression.

• Successful treatment results in changes in these factors.
CERB = cAMP Response Element Binding Protein


Copyright © The McGraw-Hill Companies, Inc. All rights reserved.
Treatment of Affective Disorders

• All modalities of treatment produce immediate effects on some mechanisms of neurotransmission, but the antidepressant or anti manic activity is delayed for a few weeks.

• So, action may be due to desensitization of receptors.

• There are risks due to this delay.

• The difficulty in treating affective disorders is their delayed therapeutic onset of action. (this means the side effects appear before the therapeutic effect)
Clinical Uses of Antidepressants

• Depression

• Anxiety Disorders:
  • Panic Attacks. نوبات الهلع
  • Social Phobia.

• Obsessive-Compulsive Disorders.

• Nocturnal Enuresis. Minimally used nowadays, instead vasopressin is used as tablets.

• Chronic Pain of obscure origin. (phenytoin can be used for obscure chorionic pain)

• Bulimia. An eating disorder

• Premenstrual Dysthymic Disorder.

• Attention Deficit Hyperactivity Disorder (ADHA). فرط النشاط
Tricyclic Antidepressants

• These drugs have 3 rings.

• tertiary Amines:
  Imipramine introduced in 1950s, it is an effective antidepressant.
  Amitriptyline
  Doxepine

• Secondary Amines:
  Desipramine
  Protriptyline
  Nortriptyline
Imipramine

Amitriptyline

Doxepin

Nortriptyline

Desipramine

Clomipramine

Trimipramine


Copyright © The McGraw-Hill Companies, Inc. All rights reserved.
Heterocyclic Antidepressants

- **Maprotiline:**
  - Less anticholinergic effects but enhances seizures.

- **Amoxapine:**
  - Less cardiovascular effects but has more dopamine antagonistic activity.
Amoxapine

Maprotiline

Mirtazapine

Bupropion


Copyright © The McGraw-Hill Companies, Inc. All rights reserved.
Inhibition of nerve terminal NE neuronal uptake system

↓

Increase in synaptic concentrations of NE

↓

Desensitization of nerve terminal $\alpha_2$-adrenoceptors

↓

Increase in neuronal NE release

↓

Further increase in synaptic concentrations of NE

↓

Desensitization of postsynaptic $\beta$-adrenoceptors with no change in postsynaptic $\alpha_1$-adrenoceptor sensitivity

**FIGURE 33.2**
Cascade of adaptive changes occurring at norepinephrine (NE) synapses following chronic TCA drug treatment.
TCA mechanism of action

• Similar effect to cocaine in the autonomic NS.
• We care about the CNS effect, where they inhibit the reuptake of NE, this will cause the accumulation of the NE in the synapse and will cause desensitization of alpha 2 receptors which are presynaptic, remember that alpha 2 receptors inhibit the release of NE, so decreasing the number alpha 2 receptors will enhance the release NE, this will now affect beta receptors.
• notice the 1\(^{st}\) effected receptor is the alpha 2 then the beta. Alpha 1 receptors are not affected by TCA.
Side Effects and Toxic Reactions of TCA

• Very toxic TI=3, so drug monitoring. (TI the therapeutic index and is equal to ED50/LD50. If the TI is low then the drug is toxic, an acceptable drug should have a TI equal to 100, this means if we triple the dose there is a 50% chance the patient \ animal will die)

• Antimuscarinic Reactions:
  Tachycardia, Blurring of vision, confusion, constipation, dry mouth, urinary retention, etc.

• Cardiovascular:
  Orthostatic and postural hypotension, arrhythmias, conduction defects.

• Sedation.

Side effects appear early in the treatment before therapeutic effects are established and are very common
Again, notice side effects appear before the therapeutic effect. Also, note that CVS and CNS toxicity occur at higher doses.
Side Effects and Toxic Reactions of TCA

• Toxic delirium, seizures, withdrawal syndrome.
• Weight gain, sexual disturbances.
• Involuntary movements, Lactation; Gynecomastia, neuroleptic malignant syndrome.
Selective Serotonin Reuptake Inhibitors “SSRI”

• Newer drugs, selective to serotonin and do not affect NE.

• Very safe drugs.

• No sedative or anticholinergic or cardiovascular effects.

• Can cause stimulation rather than sedation, N,V, D, and sexual dysfunction.
Fluoxetine

Paroxetine

Citalopram, escitalopram

Sertraline


Copyright © The McGraw-Hill Companies, Inc. All rights reserved.
Selective Serotonin Reuptake Inhibitors “SSRI”

Mechanism of Action:

• Selective inhibition of 5HT (serotonin) reuptake.

• Desensitization of:
  • $5HT_{1A}$ receptors leading to increased firing rate.
  • $5HT_{1B}$ receptors leading to increased 5HT release.

Consequently, 5HT neurotransmission is enhanced.
Selective Serotonin Reuptake Inhibitors "SSRI"

**Fluoxetine:** "Prozac", 1987.
- Greatly revolutionized the treatment of depression.
- Highly bound to plasma proteins.
- Inhibits P450 enzymes.
- Very safe

**Fluvoxamine.**
Selective Serotonin Reuptake Inhibitors “SSRI”

Paroxetine:
• Increases weight, more sedating

Citalopram:
• Least effect on P450 enzymes.

Sertraline.
Monoamine Oxidase Inhibitors

• Very effective.
• Considered as old fashioned drugs.
• Considered very toxic (headache, drowsiness, weight gain, postural hypotension, sexual disturbances).
• Mostly cause CNS stimulation.
• Hypertension due to dietary interactions.
• May still be used.
• These are more dangerous than the TCA.
• One of the major problems is food drug interaction, when the food contains tyramine patient may develop hypertension.
Monoamine Oxidase Inhibitors

**Phenelzine:**
- Hepatotoxic.

**Isocarboxamide.**

**Tranycypromine:**
- Increases weight.

**Selegiline:**
- No liver toxicity or dietary-induced hypertension.
Miscellaneous Agents

**Venlafaxine:** “Effexor”.
- Decreases the reuptake of both 5HT & NE.
- Elevates BP.

**Bupropion:**
- Weak reuptake inhibitor.
- Causes CNS stimulation, ? Convulsions.
- No impotence.
Mirtazapine

• Noradrenergic and specific serotonergic antidepressant (NaSSA).
• Doesn’t have effects as monoamine reuptake inhibitor.
• A significant feature is its effect as histamine 1 antagonist. This effect is linked to sedation and weight gain.
• Commonly used in the elderly. In this group of patients insomnia and low weight might benefit from sedation and weight gain.
• Mirtazapine has no significant drug-drug interactions, this makes it attractive for use in combination with other antidepressants as augmenting option.
When prescribing antidepressants consider the side effects, and choose a drug that suits the pt most.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Sedation</th>
<th>Anticholinergic</th>
<th>Orthostasis</th>
<th>Weight Gain</th>
<th>Sexual Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>+/-</td>
<td>0</td>
<td>0</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>TCAs</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>+++</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>+*</td>
</tr>
<tr>
<td>Bupropion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>+/-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>MAOIs</td>
<td>0</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor. 0, no effect; +, +++, +++ indicate increasing effect.

*Priapism.
*Venlafaxine can cause a dose-dependent increase in blood pressure.
Electroconvulsive Therapy

- Causes decreased β- receptor activity and number.
- Highly indicated in severe bipolar depression associated with suicidal thoughts or attempts.
- Seems inhumane !!!.
- Other options include quetiapine, and olanzapine/fluoxetine combination (OFC)
Lithium Carbonate

- Drug of choice for acute mania and bipolar depression.
- No actions in normal people.
- Blocks manic behavior in combination with phenothiazines and anxiolytics.
- Inhibits release and increases reuptake of NE, does not interfere with 5HT.
- High Na lowers Li and vice versa. ?Diuretics
- Competes with Na causing altered neuronal function.
- Competes with Mg on G-proteins.
- Li is very toxic, pts using diuretics Na is loss so more activity of Li this will lead to toxicity
Lithium Carbonate
Toxicity Reactions
• TI = 2-3, so drug monitoring
• Has delayed action (2-3 weeks), so do not increase the dose.

• **Mild toxicity:**
  - N, V, abdominal pain, diarrhea, polyurea, thirst and edema.
  - Fatigue, muscular weakness, slurred speech, ataxia, sedation and tremor.
Lithium Carbonate
Toxicity Reactions

• **Severe toxicity:**
  Impaired consciousness, confusion, rigidity, increased reflexes, tremor, seizures, coma and death.

• **Chronic toxicity:**
  Hypothyroidism (5%).
  DI.
  Leukocytosis.
  Renal toxicity.
Other Drugs

• Lamotrigine, Carbamazepine and Valproic acid: Anticonvulsants, but also used for maintenance and prophylaxis of bipolar affective disorders.

• Clonazepam and Lorazepam, alone or with neuroleptics: Antipsychotics, but also used for acute mania.
<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Tertiary amine tricyclic antidepressants (TCAs), duloxetine, theophylline,</td>
<td>Fluvoxamine, fluoxetine, moclobemide, ramelteon</td>
<td>Tobacco, omeprazole</td>
</tr>
<tr>
<td></td>
<td>phenacetin, TCAs (demethylation), clozapine, diazepam, caffeine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2C19</td>
<td>TCAs, citalopram (partly), warfarin, tolbutamide, phenytoin, diazepam</td>
<td>Fluoxetine, fluvoxamine, sertraline, imipramine, ketoconazole,</td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>omeprazole</td>
<td></td>
</tr>
<tr>
<td>2D6</td>
<td>TCAs, benztropine, perphenazine, clozapine, haloperidol, codeine/oxydopine,</td>
<td>Fluoxetine, paroxetine, duloxetine, hydroxybupropion, methadone,</td>
<td>Phenobarbital, rifampin</td>
</tr>
<tr>
<td></td>
<td>risperidone, class Ic antiarrhythmics, β blockers, trazodone, paroxetine,</td>
<td>cimetidine, haloperidol, quinidine, ritonavir</td>
<td></td>
</tr>
<tr>
<td></td>
<td>maprotiline, amoxapine, duloxetine, mirtazapine (partly), venlafaxine,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>bupropion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3A4</td>
<td>Citalopram, escitalopram, TCAs, glucocorticoids, androgens/estrogens,</td>
<td>Fluvoxamine, nefazodone, sertraline, fluoxetine, cimetidine,</td>
<td>Barbiturates, glucocorticoids,</td>
</tr>
<tr>
<td></td>
<td>carbamazepine, erythromycin, Ca²⁺ channel blockers, protease inhibitors,</td>
<td>fluconazole, erythromycin, protease inhibitors, ketoconazole,</td>
<td>rifampin, modafinil,</td>
</tr>
<tr>
<td></td>
<td>sildenafil, alprazolam, triazolam, vincristine/vinblastine, tamoxifen,</td>
<td>verapamil</td>
<td>carbamazepine</td>
</tr>
</tbody>
</table>