PSYCHIATRY
BIPOLAR DISORDER AND DEPRESSION

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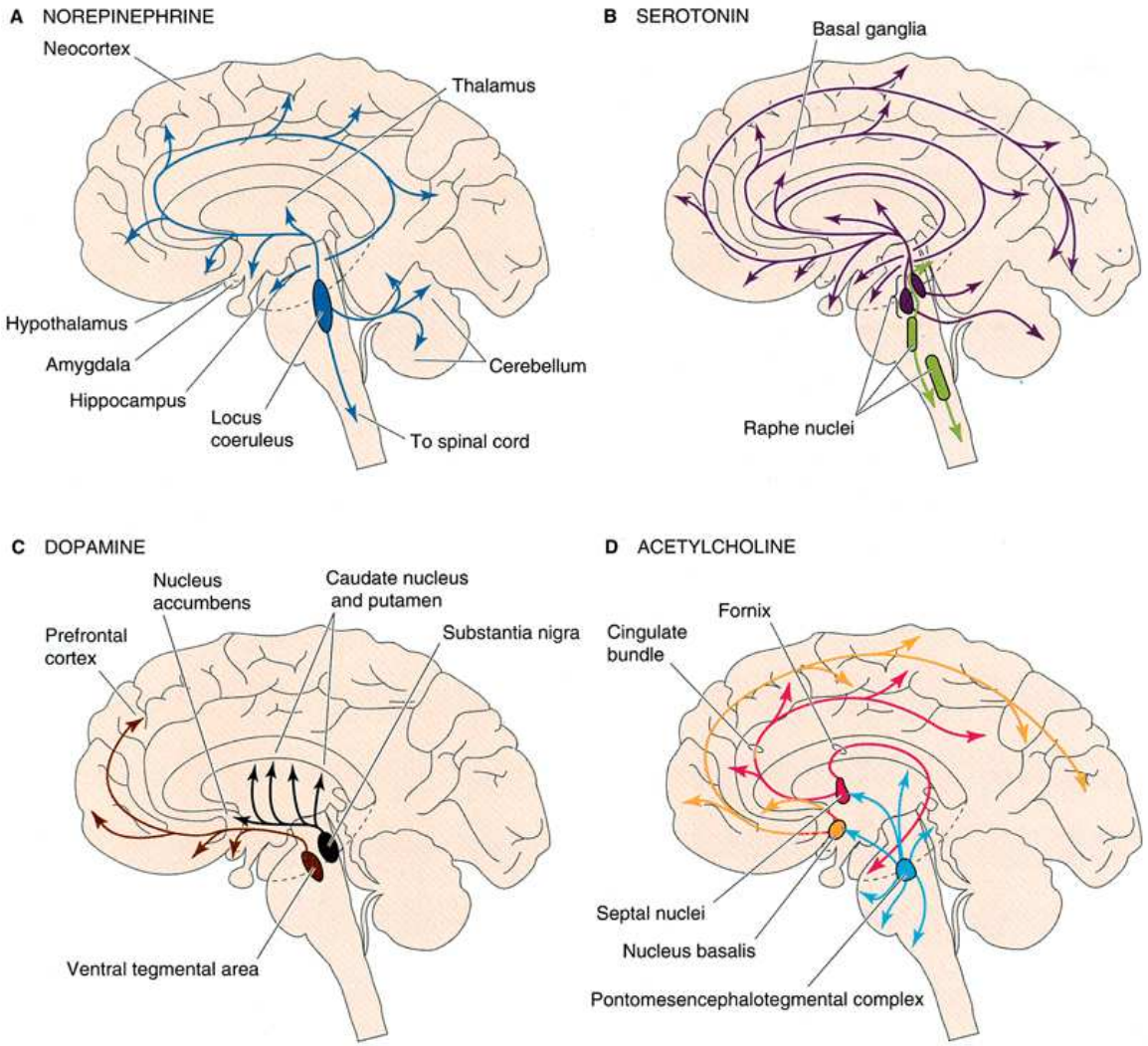
Emotion

- Feelings are cognitive translations of ambiguous peripheral signals.
- Hypothalamus coordinates the peripheral expression of emotional states
- Amygdala coordinates.
- Posterior pituitary and circumventricular organs (area postrema, sub-fornical organ, laminar terminalis, sub-commissural organ, median eminence, neurohypophysis) lack blood-brain barrier.
- Hormonal regulation.

Behavior

- Dopamine regulates movement, reward, cognition.
- Norepinephrine regulates mood, arousal, cognition.
- Serotonin regulates mood, anxiety, sleep, pain, and cognition.
- Acetylcholine regulates memory, arousal, cognition.
- Copy number variations in the Ca^{2+} channel gene (CACNA1C, at 12p13) have been identified in bipolar disorder
- Neurotransmitter release is affected.
- SNP mutation in ANK3 (ankyrin at 10q21) involves cytoskeletal change at the nodes of Ranvier).
- MKP 1 gene abnormality common in depression.

Neurotransmitters and pathways



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Neurotransmitters

Neurotransmitter	Areas of Concentration
Acetylcholine (ACh)	Neuromuscular junction, autonomic ganglia, parasympathetic neurons, motor nuclei of cranial nerves, caudate nucleus and putamen, basal nucleus of Meynert, portions of the limbic system
Norepinephrine (NE)	Sympathetic nervous system, locus ceruleus, lateral tegmentum
Dopamine (DA)	Hypothalamus, midbrain nigrostriatal system
Serotonin (5-HT)	Parasympathetic neurons in gut, pineal gland, nucleus raphe magnus of pons
Gamma-aminobutyric acid (GABA)	Cerebellum, hippocampus, cerebral cortex, striatonigral system
Glycine	Spinal cord
Glutamic acid	Spinal cord, brain stem, cerebellum, hippocampus, cerebral cortex

Neurotransmitter hypothesis

- Serotonin hypothesis
- Serotonin stabilizes the catecholamine system and inhibits dopamine release.
- Low serotonin may result in reduced melatonin
- Disrupts the sleep-wake cycle.
- Serotonin is low in both mania and depression.
- There is no evidence to support the serotonin hypothesis in depression.

Neurotransmitter hypothesis

- Catecholamine hypothesis
- Increased dopamine and norepinephrine contribute to psychosis.
- Reduced dopamine and norepinephrine contribute to depression.
- GABA inhibits dopamine and norepinephrine.
- Deficiency in GABA (glutamate may be present in excess) causes mania.
- Acetylcholine hypothesis
- Excess acetylcholine causes depression

Bipolar disorder

- Mood liability is NOT a symptom of bipolar disorder.
- Bipolar disorder requires discrete episodes of euphoria or irritability lasting at least 4 days that are clearly distinct from the patient's normal mood and functioning the rest of the time
- Chronic irritability, emotionally lability, or impulsive behavior is not bipolar disorder

Bipolar disorder

- A true manic episode is a period of abnormally elevated mood, accompanied by abnormal behavior that disrupts life.
- True mania generally is associated with hospitalization or arrest or psychosis.
- It is severe.
- It is unequivocal and unmistakable.
- It is not true mania if only associated with drug use.
- It is not true mania if occurs with hospitalization for depression.

Bipolar disorder

- Mania symptoms may include (3 required for diagnosis):
- Excessive happiness
- Excitement
- Irritability and restlessness
- Increased energy with less need for sleep
- Racing thoughts
- High sex drive
- Tendency to make grand and unattainable plans.

Bipolar disorder

- A person affected by bipolar I disorder has had at least one manic episode in his or her life.
- Suicide is a major risk (10-15%).
- Bipolar II is similar to bipolar I disorder, with moods cycling between high and low over time.
- However, in bipolar II disorder, the "up" moods never reach true mania.
- Associated with Major Depression Disorder

Bipolar disorder

- Depression symptoms may include (five required for diagnosis):
- Sadness
- Anxiety
- Irritability
- Loss of energy with increased need for sleep
- Uncontrollable crying
- Change in appetite causing weight loss or gain
- Difficulty making decisions
- Thoughts of death or suicide.
- Episodes may last for years.

Bipolar disorder

- Bipolar disorder is overdiagnosed.
- Schizoaffective disorder requires manic episode that lasts weeks (with or without depression) WITH delusions, hallucinations, or disorganized speech or behavior AND withdrawal
- Mood lability is associated with borderline personality disorder, PTSD, major depression disorders, general anxiety disorders, among others.

Bipolar disorder

- Hypomania presents with same features as mania, but the patient is not socially impaired.
- Symptoms need to last at least 4 days.
- Cyclothymia (cyclothymic disorder) is a relatively mild mood disorder.
- A two year period of hypomania with periods of depressive symptoms but not a major depression (else, is bipolar II).
- In most forms of bipolar disorder, moods alternate between elevated and depressed over time.
- Mixed bipolar disorder is a poorly validated concept.

Bipolar disorder

- About 10% to 20% of people with bipolar disorder have rapid cycling, and experience four or more episodes of mania or depression in one year.
- Bipolar disorders average one episode every 2 years.
- The episodes lasts usually 1-4 months but can last for years.
- Patients who have one manic episode have an 85% probability of having a second.
- Untreated patients will have about 10 episodes over a lifetime.

Bipolar disorder

- Self-injury(cutting, self-mutilation, or self-harm) is an injurious attempt to cope with overpowering negative emotions, such as extreme anger, anxiety, and frustration.
- It is usually repetitive, not a one-time act.
- It is usually associated with borderline personality disorder, not bipolar disorder.

Disruptive mood regulation disorder

- Childhood or adolescence
- Angry, irritable mood
- Aggressive outbursts against property, self, others
- Present at home, school, or with peers
- Generally, males
- 85%, oppositional defiant disorder
- 58%, anxiety
- Possibly SSRI or behavioral therapy

Premenstrual dysphoric disorder

- Mood lability, dysphoria, irritability, or anxiety
- Occurs repeatedly during the premenstrual phase
- Remits after menstruation
- May have behavioral symptoms such as change in appetite or food cravings, hypersomnia or insomnia, feeling “out of control”, loss of interest, difficulty concentrating
- 50%, anxiety
- 25%, mood disorders
- 28%, somatiform disorders

Lithium

- Mood stabilizer.
- May be best for euphoric mania
- Patients with rapid cycling and mixed states generally do less well on lithium.
- Seems to be more effective in treating manic episodes than depressive episodes in bipolar disorder.
- May be more effective in preventing manic relapses than in preventing depressive episodes.
- May decrease suicide and suicide attempts not only in bipolar I, but also in bipolar II and unipolar depression

Lithium

- Blocks Na^+ exchange but does not affect Na^+-K^+-ATPase or affect Na^+-Ca^{2+} exchange.
- Blocks inositol biphosphate (IP_2) conversion to IP and inositol (depleting PIP_2), affecting phospholipase C (PLC) second messenger system for α and muscarinic receptors as well as neuropeptides.
- Diminishes dopamine and norepinephrine turnover without upregulating receptor.
- Minimally increases serotonin.

Lithium

- Long term use decreases the number of β receptors and down-regulates α_2 receptors as well as glucocorticoid receptors and glutamate metabotropic receptors (thought to be cause of improvement in autism patients).
- Lithium has a narrow therapeutic index.
- Most common side effects are gastrointestinal upset, tremor, and muscle weakness.
- May see hypothyroidism, diabetes insipidus.
- Not well tolerated in one-third of patients.
- May see sick sinus syndrome.
- Secreted in breast milk.

Therapy for mania

- Lithium is drug of choice
- If inadequate control in acute phase, add atypical anti-psychotic
- Stop antipsychotic as patient improves.
- Lamotrigine as alternate mood stabilizer in bipolar disorder I
- Carbamazepine is ineffective
- Gabapentin is ineffective
- It is debatable whether antidepressant can be used safely with mood stabilizer in bipolar disorder I

Therapy for depression in bipolar disorder

- Antidepressant monotherapy in bipolar disorder II
- All antidepressants may induce mania ("manic switch").
- Tricyclic antidepressants have highest probability of inducing mania.
- 1st line antidepressants: SSRIs (except fluoxetine) and bupropion.
- 2nd line antidepressants: MAOIs and venlafaxine.

Major depression

- Prevalence
- Major depression 4.8-8.6%
- Dysthymia, 2.1-3.7%
- Depression, not otherwise specified, 4.4-5.4%.

Major depression

- There is no advantage to using a questionnaire tailored to any specific group.
- All questionnaires perform equally well.
- None differentiates varying degrees of depression.
- The two question PRIME-MD is a good screening tool (positive likelihood ratio, LR+, 2.6, LR- 0.15).
- One positive answer is considered a positive result for depression:
- Little interest or pleasure in doing things? Feeling down, depressed, hopeless?

Major depressive disorder

- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Five or more of the following symptoms must 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, as indicated by either subjective report (e.g., feels sad or empty) or observation;
- (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.

Major depressive disorder

- (3) A change of more than 5% of body weight in a month when not dieting or weight gain, or decrease or increase in appetite nearly every day;
- (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;

Major depressive disorder

- (8) diminished ability to think or concentrate, or indecisiveness, nearly every day;
- (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a specific plan for committing suicide, or a suicide attempt.
- AND and at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
- AND the symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

Major depressive disorder

- 60% have suicidal ideation
- 15-20% die of suicide
- Generally as are recovering from depression low
- 80% comorbid with insomnia
- 90% comorbid with anxiety
- Twice as common in those of European as opposed to African or Asian ancestry
- 10% have chronic course
- Relapse common

Major depressive disorder

- Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis
- Reduced volume of hippocampus
- Reduced activity in prefrontal cortex (PFC)
- Antidepressants increase neurotrophins
- Restoring neuronal growth and activity
- Act as neuromodulators

Dysthymia

- Depressed mood for most the time almost every day for at least two years,
- AND, while depressed, at least two of the following symptoms:
- Overeating or lack of appetite.
- Sleeping to much or having difficulty sleeping.
- Fatigue, lack of energy.
- Poor self-esteem.
- Difficulty with concentration or decision making.
- Feeling hopeless.

Dysthymia

- During the 2 year period of depression, the person has never been without other symptoms for more that 2 months at a time.
- During the two-year time period (one-year for children and adolescents) there has not been a major depressive episode.
- No manic, mixed, or hypomanic episode.
- Symptoms are a cause of great distress or difficulty in functioning at home, work, or other important areas.
- Symptoms are not caused by direct physiological effect of substances.

Other major depressive disorders

- Melancholia is a major depressive disorder characterized by anhedonia, excessive guilt, with mood worse in the morning.
- Atypical depression is characterized by oversleeping, overeating, leaden paralysis, and mood reactivity. Does not respond well to tricyclic antidepressants.

Other major depressive disorders

- Psychotic depression is characterized by nihilism, delusions, and hallucinations.
- May be confused with bipolar disorder.
- Seasonal depression has its highest incidence in the late Fall until Spring.
- Responds to light therapy as well as antidepressants.
- Postpartum depression begins within one month after birth of infant.

Unipolar depression

- Prefrontal cortex, hippocampus, amygdala, and Brodmann 25 involved circuit
- Cognitive therapy may be attempted
- Tricyclic antidepressants
- Electroconvulsive therapy
- There is no evidence of efficacy of SSRI or SNRis
- Associated with increased suicidal thoughts in young
- Severe withdrawal symptoms
- Those treated with antidepressants convert to bipolar disorder at rate three times higher than those not receiving those medications (7.7% per year)

SSRI

- Fluoxetine and desipramine upregulate glucocorticoid receptors, enhancing brain derived neurotorophic factor signaling and neurogenesis in hippocampus.
- Reverse HPA abnormality
- SSRIs block serotonin re-uptake.
- This is first noted at the somato-dendritic portion of the serotonin dependent neuron.
- Serotonin is released down the axon (the cause of delay in response seen clinically)
- There is increased release of serotonin at the synapse.

SSRI

- First downregulate pre-synaptic $5HT_{1A}$ receptors, then downregulate post-synaptic 5HT receptors.
- Low affinity for histaminergic, α1- adrenergic, and muscarinic receptors.
- Adverse effects may be due to unwanted increases in serotonin at receptors not involved in therapeutic actions.
- Cognitive and affective “flattening” may be due to diminished dopamine release.
- Fluoxitene and mirtazapine associated with doubled risk of Clostridium dificile infection.

Tricyclic antidepressants

- First pass metabolism.
- High lipid solubility and protein binding
- Have large volume of distribution.
- Block $5HT_{2A}$ and $5HT_{2C}$ post-synaptic receptors as well.
- Tertiary amines boost 5-HT over NE
- More potent anticholinergics and histamine blockers than are secondary amines.

Tricyclic antidepressants

- Secondary amines boost NE over 5-HT
- Less sedating (block histamine receptors)
- Less orthostatic change (block α_1 adrenergic receptors)
- Less anticholinergic activity (block muscarinic receptors).
- Both secondary and tertiary amines block dopamine reuptake to some extent.

Other pharmacologic agents

- Serotonin-norepinephrine re-uptake inhibitors (SNRI's) block both pre-synaptic re-uptake pumps.
- Norepinephrine-dopamine re-uptake inhibitors (NDRI's) block both re-uptake pumps.

MAO inhibitors

- Block the serotonin and norepinephrine re-uptake pump in pre-synaptic membranes.
- This leads to increased availability of the amine and down-regulation of receptors at the synapse.
- $5HT_{2A}$ and $5HT_{2B}$ receptors are also blocked in post-synaptic membranes.
- High tyramine foods may lead to serotonin syndrome

Interactions

- All antidepressants added to MAO inhibitors may lead to serotonin syndrome (hyperkinesia, muscle rigidity, myoclonus).
- Not unique to fluoxetine
- Also may be seen when antidepressant added to the antibiotic linezolid (has MAOI structure)
- Buspirone probably has no MAO interaction.
- May cause orthostatic hypertension, seizures.
- Inhibits dopamine reuptake.
- Serone blocks $5HT2_C$ in post synaptic receptors
- No β effect.
- Elderly.

Interactions

- Sexual dysfunction in 59% of those on SSRIs
- SSRIs not for use in pregnancy
- Associated neurodevelopment disorders in newborn
- 4-6 times greater risk for persistent pulmonary hypertension in newborn

Serotonin Syndrome

- If patient remains agitated after use of benzodiazepines and stabilization of vital signs, consider administration of serotonin antagonists.
- 5HT-2A receptor antagonists (cyproheptadine, chlorpromazine)
- Direct-acting sympathomimetics in low doses to treat hypotension arising from monoamine oxidase inhibitor (MAOI) interactions (phenylephrine)
- Short acting cardiovascular agents (nitroprusside or esmolol) if hypertension and tachycardia present.
- Veccuronium for paralysis in patients with severe illness and hyperthermia.
- Avoid anitpyretics, propranolol, bromocriptine, succinylcholine (due to risk of severe hyperkalemia) , and prolonged use of physical restraint

Major Depression therapy

- Psychotherapy may be of benefit if mild functional impairment with an acute onset related to adverse events and is the first depressive episode.
- Cognitive therapy attempts to address the abnormal thought process.
- Behavioral therapy focuses on behaviors that allow stress reduction.
- SSRI recommended as drug of choice for depression, bulimia, obsessive compulsive disorder, impulse control problems, panic disorder, generalized anxiety disorder, post traumatic stress disorder, social anxiety, premature ejaculation.

Major Depression therapy

- SSRIs as effective as MAOIs to treat atypical depression.
- For patients not responding well to therapy,
- Switch to another antidepressant
- Add cognitive behavioral therapy
- OR augment with buspirone, bupropion, lithium, or liothyronine AND continue cognitive behavioral therapy
- Treat Major Depressive Disorder to full remission as the presence of residual symptoms increase the risk of relapse

Major depression therapy

- Tricyclic antidepressants now used more for severe depressions.
- Do not combine with SSRIs as it may lead to serotonin syndrome.
- May also be used to treat neuropathic pain.
- Patients with insomnia and depression respond well to trazodone.

Major depression therapy

- Buspirone used in generalized anxiety disorder or medication induced sexual dysfunction.
- ECT may be indicated for depression or mania unresponsive to medication.
- Retrograde amnesia may be induced.