Antidepressant Drugs

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Depression

Introduction

- Antidepressant and antimanic drugs are used to treat the affective disorders. These include
    - major depression
    - Mania
    - Manic depression.
- These disorders may be bipolar (cycling back and forth between mania and depression) or unipolar (mania or depression only).

Symptoms of Depression and Mania

Table 10.1 ► **Symptoms of Depression and Mania**

Affective Disorders	Symptoms
Depression	Intense sadness and despair; fatigue, musculoskeletal complaints, sleep disorders, feeling of worthlessness, and loss of joy in living
Mania	Abnormally elevated mood, feelings of grandiosity, decreased sleep, increased talkativeness, and increased activity or agitation

Mechanism of action

- Antidepressant drugs block the reuptake of the biogenic monoamines norepinephrine and serotonin.
- Their selectivity for different uptake mechanisms varies.

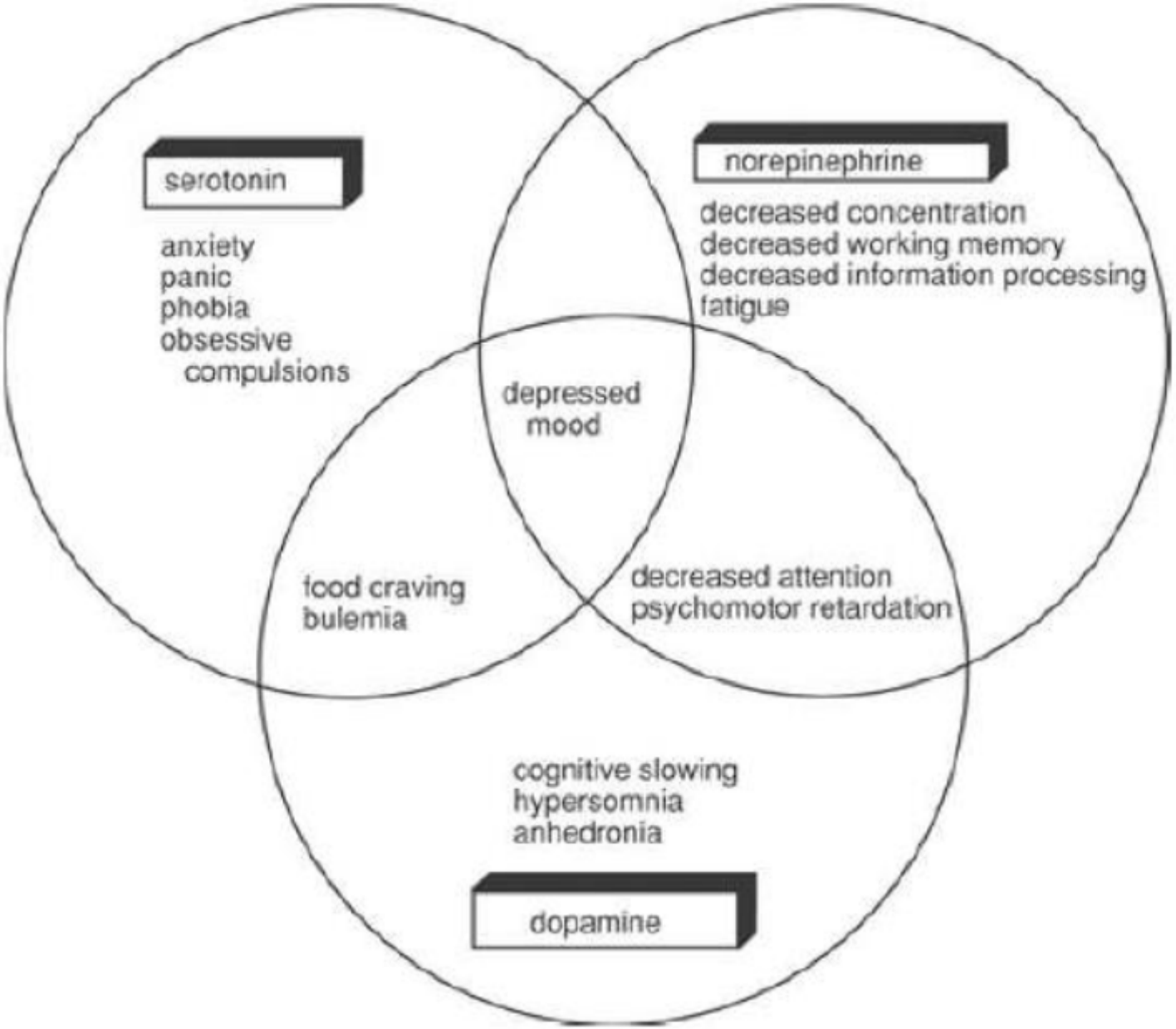

Fig. 21.1. Neurotransmitter deficiency syndromes and their interactions.

First-generation Antidepressant Drugs
Tricyclic Antidepressants

- **Amitriptyline, Nortriptyline, Imipramine, and Desipramine**.
- Mechanism of action.
    - These agents block the reuptake of the biogenic monoamines norepinephrine and seratonin.
    - They also interact with many other receptor types, including muscarinic (M1), histamine (H1), and adrenergic (α1)

First-generation Antidepressant Drugs Tricyclic Antidepressants

- Desipramine is the most potent inhibitor of norepinephrine reuptake. It is 1000 times less potent on serotonin reuptake.
- Amitriptyline blocks both norepinephrine and serotonin reuptake equally.
- Tricyclics also block muscarinic, serotonergic, histaminic, and α-adrenergic receptors.
- These actions are thought to be related to their side effects.
- Uses. Depression

First-generation Antidepressant Drugs Tricyclic Antidepressants

- **Effects**
- — Acute effects include drowsiness and decreased blood pressure, but with sustained use will cause an elevation of mood
- — Suppression of rapid eye movement (REM) sleep
- — Sleep promotion
- **Side effects**
- — *Anticholinergic:* dry mouth, blurred vision, urinary retention, and constipation
- — *Antiadrenergic:* orthostatic hypotension and delayed cardiac conduction
- — Weight gain
- — Mania, confusion, and delirium

First-generation Antidepressant Drugs Tricyclic Antidepressants

- **Drug interactions.**
- — When tricyclic antidepressants are taken with other drugs, their effects or side effects can be potentiated.
- — When they are taken with alcohol, this leads to additive sedation.
- — When taken with other anticholinergic drugs, additive anticholinergic effects occur.
- — When they are taken with monoamine oxidase inhibitors (MAOIs), severe central nervous system (CNS) toxicity can occur, but this is rare.
- Monoamine Oxidase Inhibitors (MAOIs)
- Tranylcypromine, Phenelzine, and Isocarboxazid
- Mechanism of action. MAOIs inhibit both monoamine oxidase A and B (MAO-A and MAO-B).

First-generation Antidepressant Drugs Tricyclic Antidepressants

- **Pharmacokinetics**
- — Phenelzine and isocarboxazid are “suicide” inhibitors of the enzyme. This means that once an MAO molecule binds to one of these drugs, its activity cannot be restored.
- Restoration of MAO activity depends on synthesis of new enzyme molecules. The exception to this is tranylcypromine, which is reversible.
- — MAOIs interfere with hepatic metabolism of many drugs and are not selective for MAO-A or MAO-B.
- — The effects of MAOIs take 2 to 3 weeks to become apparent.
- **Uses.** MAOIs are used to treat depression when tricyclic antidepressants are ineffective.

First-generation Antidepressant Drugs Tricyclic Antidepressants

- **Effects**
- — Cardiovascular system: postural (orthostatic) hypotension
- — Suppression of REM sleep
- **Side effects**
- — Hepatotoxicity and CNS stimulation
- *Note:* Acute poisoning causes agitation, hallucinations, hyperreflexia, and convulsions.
- Treatment is by maintaining vital functions in the hospital setting for approximately 1 week.
- **Drug interactions**
- — MAOIs interact with sympathomimetic drugs, leading to hypertensive crisis.
- — MAOIs taken with meperidine (an opioid analgesic) can lead to fever, delirium, and hypertension.

Second-generation Antidepressant Drugs Bupropion, Mirtazapine, Duloxetine, Amoxapine, Maprotiline, and Trazadone

- Second-generation antidepressant drugs were developed in an attempt to eliminate some of the troublesome side effects seen with tricyclic antidepressants, such as cardiac manifestations, orthostatic hypotension, drowsiness, and weight gain.
- Bupropion, Mirtazapine, Duloxetine, Amoxapine, Maprotiline, and Trazadone
- **Mechanism of action.** These agents are pharmacologically very similar to tricyclics. They may act as serotonin and norepinephrine reuptake inhibitors.
- **Uses**. Depression

Second-generation Antidepressant Drugs

- **Effects**
- — *Anticholinergic:* dry mouth, blurred vision, urinary retention, and constipation
- — *Antiadrenergic:* postural (orthostatic) hypotension and delayed cardiac conduction
- — *Antihistaminergic:* sedation
- — Weight gain
- **Side effects**. This generation of antidepressants generally has fewer side effects than tricyclic antidepressants. Exceptions include
- — *Bupropion:* seizures and cardiac arrhythmias
- — *Amoxapine:* extrapyramidal side effects
- — *Maprotiline:* rashes and seizures

Third-generation Antidepressant Drugs Fluoxetine, Paroxetine, Sertraline, Fluvoxamine, Citalopram, and Venlafaxine

- Third-generation antidepressants may be safer than tricyclics in overdose situations.
- Selective serotonin reuptake inhibitors (SSRIs) are not as effective in treating severe depression as first or second-generation agents.
- Fluoxetine, Paroxetine, Sertraline, Fluvoxamine, Citalopram, and Venlafaxine
- **Mechanisms of action**
- — Fluoxetine, paroxetine, sertraline, and fluvoxamine and citalopram are SSRIs.
- — Venlafaxine affects serotonin and norepinephrine reuptake and weakly inhibits dopamine reuptake.

Third-generation Antidepressant Drugs

- **Pharmacokinetics**
- — Completely absorbed from the gastrointestinal (GI) tract and extensively metabolized in the liver
- — Eliminated in the urine and feces
- — The therapeutic effect takes 10 to 14 days to develop.
- — Long half-life (days)
- **Uses**
- — Depression
- — Obsessive-compulsive disorder (fuvoxamine and fluoxetine)

Third-generation Antidepressant Drugs

- Side effects. Fewer anticholinergic and sedative effects are seen than with tricyclics (they do not interfere with cardiac conduction or cause orthostatic hypotension). Side effects do include the following:
- — Headache, tremor, insomnia, diarrhea, and nausea. Diarrhea and nausea diminish or resolve over time.
- — They also stimulate the CNS, with agitation the most frequent adverse effect.
- — Psychotic reactions may be exacerbated in depressed schizophrenics.
- — Liver enzymes are inhibited by fluoxetine and paroxetine but not affected by sertraline.
- — Sexual dysfunction and anorgasmia occur in both men and women.
- — Generally less weight gain than seen with other classes
- — Altered sleep
- — Akathisia (a movement disorder charaterized by motor restlessness)

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