

YU - MEDICINE

PASSION ACADEMIC TEAM

Clinical Psychology

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Sheet# 16
Psychopharmacology

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Psychopharmacology

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Questions from the previous lecture

- What's the difference between Possible and Probable Lewy body dementia ?
- Lewy body dementia are diagnosed during life by exclusion subsequently we can't be sure of diagnosis thus we use Probable and Possible , Probable indicate more likelihood of being ill
- In Schizophrenia , can we describe the flattened effect by masked phase as in the Parkinson disease ?
- Yes we can, part of it is masked phase, but the flat effect is characterized by having no expression, no feelings, no reactions.

Neurotransmitter abnormalities are involved in the etiology of many psychiatric illnesses (e.g., psychotic disorders, mood disorders, anxiety disorders) .

Increase in dopamine

decrease in serotonin

Psychopharmacologic agents may also be useful in the **treatment of symptoms of certain medical conditions** (e.g., gastrointestinal problems, pain, seizures).

ANTIPSYCHOTIC AGENTS

A. Overview

- 1. Antipsychotic agents (formerly called neuroleptics or major tranquilizers) are used in the treatment of schizophrenia as well as in the treatment of psychotic symptoms associated with other psychiatric and physical disorders.**
- 2. Antipsychotics are also used medically to treat nausea, hiccups, intense anxiety and agitation, and Tourette disorder.**
- 3. Although antipsychotics commonly are taken daily by mouth, non adherent patients can be treated with long-acting “depot” forms, such as haloperidol decanoate or fluphenazine decanoate administered intramuscularly every 2–4 weeks.**
- 4. Antipsychotic agents can be classified as traditional (i.e., typical) or atypical depending on their mode of action and side effect profile.**

The Typical (traditional) agents are the first generation
The Atypical agents are the second generation

Antipsychotics

Indications for Antipsychotic medication

- Schizophrenia Spectrum Disorders
- Mania in Bipolar Disorder
- Adjunctive treatment of major depressive disorder
- Psychomotor Agitation
- Personality Disorders
- Behavioral Disturbances in demented patients
- Delirium (we generally treat the underlying cause but we can give haloperidol)
- Adjunctive treatment of OCD (Its main treatment are SSRIs but we can use antipsychotics)
- Tourette syndrome
- Aggressive challenging behavior in adults with intellectual disability

ANTIPSYCHOTIC AGENTS

Both first generation and second generation are meant to reduce dopamine but differs in their effects

B. Traditional antipsychotic agents

1. Traditional antipsychotic agents act primarily by blocking central dopamine-2(D₂) receptors.

2. Although negative symptoms of schizophrenia, such as withdrawal, may improve with continued treatment, traditional antipsychotic agents **are most effective against positive symptoms, such as hallucinations and delusions.**

3. Adverse effects of antipsychotics

a. Low-potency agents (e.g., chlorpromazine, thioridazine) are associated primarily with non-neurologic adverse effects. Because there are better choices (e.g., atypical agents), low-potency agents are now rarely used.

b. High-potency agents (e.g., haloperidol, trifluoperazine, fluphenazine, perphenazine, thiothixene, and molindone) are associated primarily with neurologic adverse effects.

c. Agents related to antipsychotics such as the dopamine receptor antagonist Metoclopramide (Reglan) which is used to reduce nausea and vomiting in medical patients for emergency, can have similar adverse effects, for example, akathisia and extrapyramidal symptoms (EPS).

Low-potency agents give response in high concentrations but High-potency agents give response in low concentrations

ANTIPSYCHOTIC AGENTS

C. Atypical antipsychotic agents

-Usually we start the treatment by the Atypical antipsychotic agents

(e.g., clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, and lurasidone).

1. In contrast to traditional antipsychotic agents, a major mechanism of action of atypical antipsychotics appears to be on **serotonergic systems (5HT_{2A})**. They also affect dopaminergic receptors in addition to D₂ (e.g., D₁, D₃, and D₄).

2. Many of the atypical antipsychotics are also indicated to treat bipolar disorder.

3. Advantages of atypical agents over traditional agents

a. Atypical agents, particularly clozapine, may be more effective when used to treat the negative, chronic, and refractory symptoms of schizophrenia.

b. They are less likely to cause adverse neurological symptoms and dystonias and so are now the first-line agents for treating chronic psychiatric disorders such as schizophrenia.

4. Disadvantages of atypical agents

a. Atypical agents may increase the likelihood of blood dyscrasias such as agranulocytosis (very low granulocyte count leading to severe infections), with clozapine as the most problematic agent.

b. They may also increase the likelihood of seizures, anticholinergic side effects, and pancreatitis.

c. Some atypical agents have more adverse effects than others.

General Adverse effects of antipsychotics

a. Neurologic effects

i. Anticholinergic effects: very common, effects additive if given with other anticholinergic agents; blocks parasympathetic receptors

- Dry mouth
- Blurry vision
- Constipation
- Urinary retention
- Delirium
- Memory impairment
- Especially frequent in the elderly

ii. antagonism of H1 receptors

- Weight gain
- Sedation very common
- Impaired memory

We usually give Anticholinergics medication to avoid extrapyramidal side effects

iii. Extrapyramidal (EP) reactions: due to decreased dopamine in nigrostriatal area; appear in one-half of all patients in first few months

Parkinsonism: the same as Parkinson symptoms but due to medication

- Treat with benztropine, procyclidine, trihexyphenidyl, diphenhydramine

Anticholinergics

Antihistamine

Neurologic Adverse Effects—More Common with Traditional, High-Potency Agents (First generation)

Extrapyramidal Side Effects

- Pseudoparkinsonism (muscle rigidity, shuffling gait, resting tremor, mask-like facial expression) we treat with anticholinergic not dopaminergic because we don't want to increase the Psychotic effect
- Akathisia (subjective feeling of motor restlessness)

First choice for akathisia is beta blockers, second choice is benzodiazepine

- Acute dystonia (prolonged painful muscular spasms; more common in men under age 40)

Treat with anticholinergic (e.g., benztropine) or antihistaminergic (e.g., diphenhydramine) agent

- Tardive dyskinesia (abnormal writhing choreathetoid movements of the tongue, face, and body) dancing like movements which are stressful for the patient (70% of cases are irreversible), called “tardive” because of its late onset (3 to 6 months)

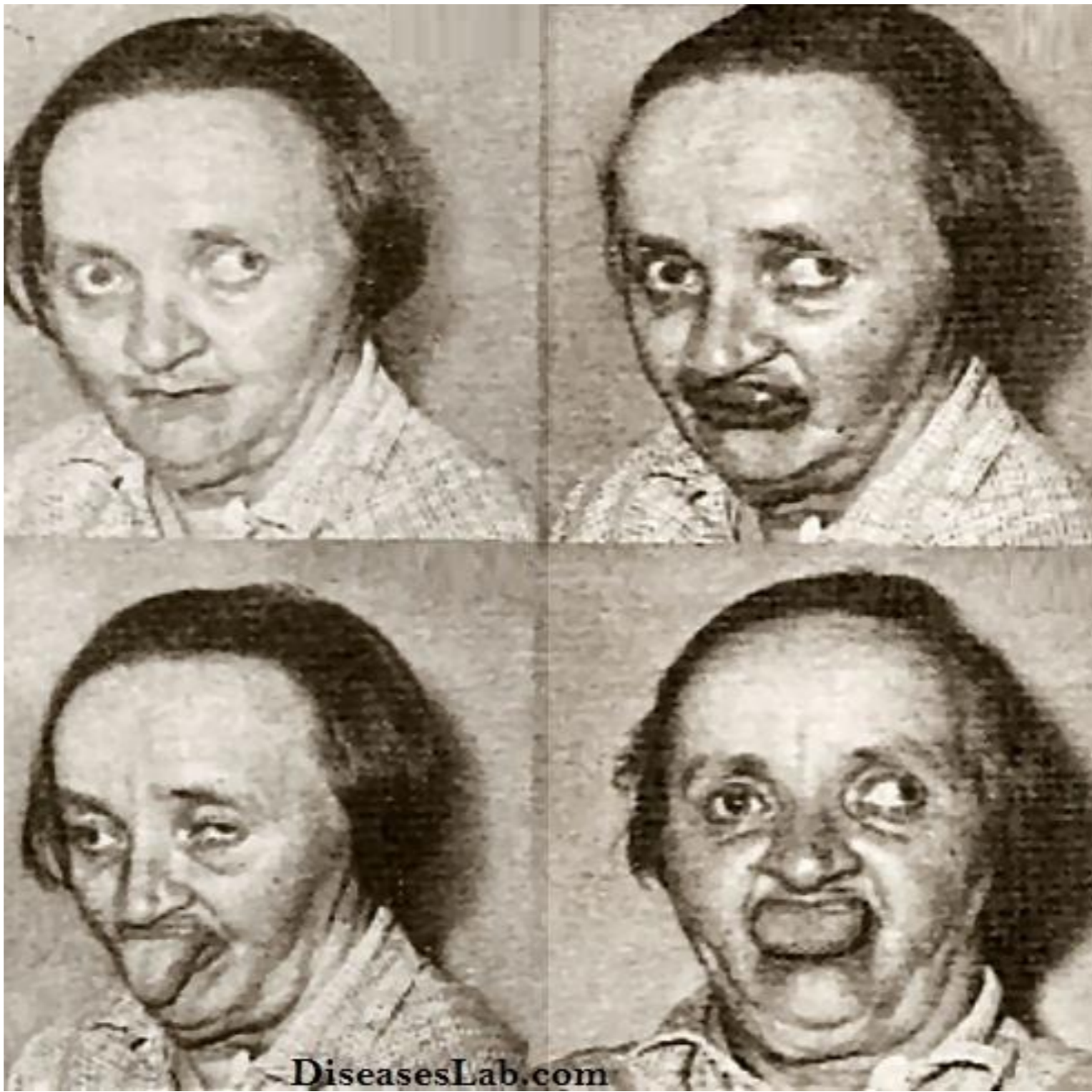
- Neuroleptic malignant syndrome (high fever, sweating, increased pulse and blood pressure, dystonia, apathy; more common in men and early in treatment; mortality rate about 20%); to treat, stop agent, give a skeletal muscle relaxant (e.g., dantrolene), and provide medical support

High CPK → Kidney injury → rhabdomyolysis → Myoglobinuria → Acute Kidney Injury

iv. Tardive dyskinesia (TD)

- Rarely before 3 to 6 months, 1 month if older than 60
- Signs: tongue protrusion, tremors and spasms of the neck, body, and limbs
- Persists after medications are terminated (2/3 of cases are irreversible); incapacitating in 5% of cases
- Cause: super sensitivity of postsynaptic dopamine receptors
- Predisposing factors include older patients, female gender, affective symptoms, long treatment, smoking, diabetes mellitus
(avoid first generation agents in these patients)
- Symptoms do not occur during sleep
- Stress and movements in other body parts aggravates
- No treatment, focus on prevention: pimozide or loxapine has less chance of inducing TD, clozapine not associated with TD at all

Not painful as much as the Dystonia



TD (Tardive dyskinesia)

b. Non-neurologic effects

- i. Cardiovascular effects: orthostatic hypotension(do not use epinephrine, lowers blood pressure further) , prolongation of QT interval
 - ii.Particular taste (also dental cavities)
 - iii.Vomiting common with long-term use, especially among smokers
 - iv.Sexual effects: prolactin elevated
- Men: decreased libido, inhibition of ejaculation, retrograde ejaculation
 - Women: breast enlargement and lactation, changes in libido
- v. Altered bodily response to temperature

Potency of Antipsychotic Medications

Potency	Extrapyramidal Symptoms	Anticholinergic Effects
High (haloperidol)	High	Low
Low (chlorpromazine)	Low	High

Typical versus Atypical Antipsychotics

Typical

Atypical

Dopamine

Dopamine and serotonin

Treats mostly positive symptoms

Treats positive and negative symptoms

More side effects

Fewer side effects

Typical Anti-Psychotics

Haloperidol (Typical) and Fluphenazine (Typical)

- i. Short- and long-acting preparations
- ii. Still used frequently for Delirium, agitated patients, psychotic patients

Thioridazine (Typical) (Low Potency)

- i. Retinitis pigmentosa
- ii. Retrograde ejaculation

Atypical Anti-Psychotics

Clozapine (Atypical)

Has the highest efficacy but can't be used as first choice

- i. Weak reaction on D2 receptors , works mainly on D4 and 5HT-2A receptors
- ii. High affinity for serotonin receptors
- iii. Affects negative and positive symptoms
- iv. Serious side effects: agranulocytosis (<1%) and myocarditis and seizures (4% of doses >600 mg)
- v. Less incidence of EP, TD, prolactin, or sexual effects
- vi. High risk for weight gain and DM, hyper salivation and sedation

Risperidone (Atypical)

- i. Affects positive and negative symptoms, thought disorders
- ii. Side effects: dizziness, fatigue, dry mouth, tachycardia, hypotension
- iii. Raises prolactin levels, EP effects, highest risk of movement disorders

Olanzapine (Atypical)

Second most common anti-psychotic to cause weight gain

- i. Affects positive and negative symptoms, thought disorders
- ii. Highest incidence of diabetes, ↑weight,

Quetiapine (Atypical)

- i. D2 and 5-HT2 antagonist
- ii. Also affects H1 and alpha-1 receptors
- iii. For schizophrenia and bipolar
- iv. Side effects: somnolence, dizziness, dry mouth, weight gain
- v. Low risk of movement side effects

Aripiprazole (Atypical)

- i. Partial agonist on D2 and 5-HT1 receptors. Antagonist at 5-HT2 receptor.
- ii. Side effects: akathisia, headache, tiredness, nausea
- iii. Also used for bipolar and adjunct therapy for depression
- iv. Partial dopamine agonist at low doses ; Less EPS

Ziprasidone (Atypical)

- i. High affinity for DA, 5-HT, alpha-adrenergic, and histamine receptors
- ii. Some inhibition of 5-HT reuptake
- iii. For acute agitation of psychoses, acute mania
- iv. Intramuscular injection
- v. Prolongs QT interval

- Both above drugs are weight neutral, but are very expensive

Antidepressants

Indications :

- depression and major depressive disorder
- obsessive-compulsive disorders (OCD)
- childhood enuresis, or bedwetting
- generalized anxiety disorder
- bipolar disorder
- posttraumatic stress disorder (PTSD)
- social anxiety disorder
- Panic Disorder

Off-label uses of antidepressants include:

- insomnia
- pain
- migraine
- Premature ejaculation

ANTIDEPRESSANT AGENTS

A. Overview

1. Heterocyclic antidepressants (HCAs) also called tetracyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants are used to treat depression. These agents also have other clinical uses.
2. All antidepressants are believed to increase the availability of serotonin and/or norepinephrine in the synapse via inhibition of reuptake mechanisms (HCAs, SSRIs, SNRIs) or blockade of MAO (MAOIs), which ultimately leads to downregulation of postsynaptic receptors and improvement in mood.
3. All antidepressants take about 3–6 weeks to work and all have equal efficacy.
4. While heterocyclics were once the mainstay of management, because of their more positive side effect profile, SSRIs (e.g., fluoxetine [Prozac]) are now used as first-line agents.

ANTIDEPRESSANT AGENTS

5. Antidepressant agents do not elevate mood in non depressed people and have no abuse potential. They can, however, precipitate manic episodes in potentially bipolar patients.

Mainly used for ADHD but we can use them for Depression

6. Stimulants, such as methylphenidate or dextroamphetamine, also may be useful in treating depression. They work quickly, and thus may help to improve mood in terminally ill or elderly patients. They are also useful in patients with depression refractory to other treatment and in those at risk for the development of adverse effects of other agents for depression. Disadvantages include their addictive potential.
- Remember SSRIs have no addictive potential

7. Thyroid hormones can be used also in the management of mood disorders.

a. Levothyroxine is a synthetic form of thyroxine(T₄)which has mood stabilizing effects in patients with bipolar disorder.

b. Liothyronine is asynthetic form of T₄'s metabolically active form triiodothyronine (T₃) which can augment the effects of antidepressants.

C. SSRIs and SNRIs

1. SSRIs selectively block the reuptake of serotonin only; SNRIs block the reuptake of both serotonin and norepinephrine.
2. SSRIs and SNRIs have little effect on acetylcholine, or histamine systems.
3. Because of this selectivity, SSRIs and SNRIs cause fewer side effects and are safer in overdose, in the elderly, and in pregnancy than heterocyclics or MAOIs.
4. SNRIs may work more quickly (e.g., in 2–3 weeks) and cause fewer sexual side effects than SSRIs.

Selective serotonin reuptake inhibitors (SSRI)

- a. Most widely used antidepressants
- b. No effect on NE or dopamine, very selective blockage of reuptake of serotonin
- c. Fewest adverse effects of any antidepressants currently available, also the largest selling
- d. Adverse effects:
 - i. GI upset
 - ii. CNS Excitation: headache, anxiety, insomnia
 - ii. Anorgasmia and delayed orgasm in 30-50% of patients
 - iii. **Serotonin syndrome**: Medical emergency, potentially fatal
(This could happen if SSRIs were taken with drugs that increase serotonin level as Lithium, Tryptophan, Tramadol.)
- Associated with: high doses, MAOI and SSRI combo, MAOI and synthetic narcotic combo
- Symptoms: general restlessness, myoclonus, fever, sweating, insomnia, nausea, diarrhea, cramps, seizures, delirium
- Treatment: remove causative agent, stop SSRIs, give cyproheptadine
- e. Drugs from this class
 - i. Fluoxetine: longest half-life
 - ii. Sertraline
 - iii. Paroxetine
 - iv. Fluvoxamine: approved for OCD
 - v. Citalopram
 - vi. Escitalopram

Heterocyclic Agents

1. HCAs block reuptake of norepinephrine and serotonin at the synapse. Some also block reuptake of dopamine. Ex. Amitriptyline, Imipramine, Clomipramine, Nortriptyline, Desimpramine

a. These agents also block muscarinic acetylcholine receptors, resulting in anticholinergic effects (e.g., dry mouth, blurred vision, urine retention, constipation); they are contraindicated in patients with glaucoma.

b. Histamine receptors also are blocked by heterocyclic agents, resulting in antihistaminergic effects (e.g., weight gain and sedation).

2. Other adverse effects include cardiovascular effects, such as orthostatic hypotension, tachycardia, and QT prolongation, and neurologic effects, such as tremor, may lower seizure threshold, weight gain (as Amitriptyline), and sexual dysfunction.

3. Heterocyclics are dangerous in overdose

-because they can cause heart block, tachycardia, seizures, glaucoma and arrhythmia.

2. Avoid during first trimester

MAOIs

1. MAOIs inhibit the breakdown of neurotransmitters by monoamine oxidase in the brain in an irreversible reaction.
2. These agents may be particularly useful in the management of atypical depression and treatment resistance to other agents.
3. A major drawback of using MAOIs is a potentially fatal reaction when they are taken in conjunction with certain foods or medications. This reaction occurs because
 - a. MAO metabolizes tyramine, a pressor, in the gastrointestinal tract.
 - b. If MAO is inhibited, ingestion of tyramine-rich foods (e.g., aged cheese, beer, wine, broad beans, beef or chicken liver, and smoked or pickled meats or fish) or sympathomimetic drugs (e.g., ephedrine, methylphenidate [Ritalin], phenylephrine, pseudoephedrine) can increase tyramine levels.
 - c. Increase in tyramine can cause elevated blood pressure, sweating, headache, and vomiting (i.e., the noradrenergic or hypertensive crisis), which in turn can lead to stroke and death.

MAOIs

4. Other adverse effects of MAOIs are similar to those of the heterocyclics, including danger in overdose.

5. The serotonin syndrome

a. MAOIs and SSRIs or HCAs used together as well as MAOIs used along with serotonergic analgesics such as meperidine or tramadol can cause a potentially fatal drug–drug interaction, the serotonin syndrome.

b. This syndrome is characterized by high fever, autonomic instability, headache, seizures, delirium, nausea, diarrhea, vomiting, and muscular rigidity.

c. To avoid this reaction, the recommended washout period for an SSRI or an HCA before starting an MAOI is 2 weeks.

We need 5 weeks in the case of fluoxetine

Atypical antidepressants

Mirtazapine

a. Stimulates NE and 5-HT release

b. Blocks 5-HT₂ and 5-HT₃ receptors

- They are also alpha-2 receptor antagonist, which increases the release of norepinephrine

a. Side effects: somnolence (60%), increased appetite, weight gain

Bupropion (NDRI)

a. Weak inhibitor of dopamine, modest effect on NE, no effect on 5-HT reuptake

b. No anticholinergic effect

c. Little cardiac depressant effect

d. Increased risk of seizures

e. Less sexual effects or weight gain

f. Side effects: appetite suppressant, agitation, insomnia

g. Approved for smoking cessation

MOOD STABILIZERS

A. Lithium (carbonate and citrate)

1. Lithium is a mood stabilizer used to treat and prevent both the manic and depressive phases of bipolar disorder.
2. It may be used also to increase the effectiveness of antidepressant agents in depressive illness and to control aggressive behavior.
3. Adverse effects of chronic use of lithium include:
 - a. congenital abnormalities (particularly of the cardiovascular system e.g., Ebstein's anomaly)
 - b. hypothyroidism
 - c. tremor
 - d. renal dysfunction leading to diabetes insipidus
 - e. cardiac conduction problems
 - f. gastric distress
 - g. mild cognitive impairment
4. Lithium takes 2–3 weeks to work. Antipsychotics or benzodiazepines rather than lithium are therefore the initial treatment for psychotic symptoms in an acute manic episode.
5. Because of potential toxicity, blood levels of lithium must be maintained at 0.8–1.2 mEqL.

MOOD STABILIZERS

B. Anticonvulsants: carbamazepine (Tegretol), oxcarbamazepine (Trileptal), valproic acid (Depakene, Depakote), and others

1. Anticonvulsants are also used to manage bipolar disorder, particularly rapid cycling bipolar disorder (i.e., more than four episodes annually), and mixed episodes (mania and depression occurring concurrently).

2. Carbamazepine may be associated with severe adverse effects, such as aplastic anemia and agranulocytosis.

3. Valproic acid may be particularly useful for treating bipolar symptoms resulting from cognitive disorders and for prophylaxis of migraine headaches.

4. Adverse effects of valproic acid include gastrointestinal and liver problems, congenital neural tube defects (e.g., spina bifida), and alopecia (hair loss).

5. Other anticonvulsant agents that appear to have mood-stabilizing effects include lamotrigine, gabapentin, topiramate, and tiagabine.

C. Atypical antipsychotics are also indicated in the management of bipolar disorder.

ANTI ANXIETY AGENTS

A. Benzodiazepines (BZs) (as alprazolam or diazepam)

1. BZs activate binding sites on the γ -aminobutyric acid A (GABA_A) receptor, thereby decreasing neuronal and muscle cell firing. (GABA agonists)
2. These agents have a short, intermediate, or long onset and duration of action and maybe used to treat disorders other than anxiety disorders.
3. Their characteristics of action are related to their clinical indications and their potential for abuse; for example, short-acting agents are good hypnotics (sleep inducers) but have a higher potential for abuse than longer acting agents.
4. BZs commonly cause sedation but have few other adverse effects in adults.
5. Tolerance and dependence may occur with chronic use of these agents.
6. Flumazenil is a BZ receptor antagonist that can reverse the effects of BZs in cases of overdose or when BZs (e.g., midazolam [Versed]) are used for sedation during medical or surgical procedures.

Non-benzodiazepines

B. Non-benzodiazepines

1. Buspirone (BuSpar), an azaspirodecanedione, is not related to the BZs.

a. In contrast to BZs, buspirone is nonsedating and is not associated with dependence, abuse, or withdrawal problems.

Affects serotonin, not GABA (Buspirone acts as an agonist of the serotonin 5-HT_{1A} receptor with high affinity)

b. It is used primarily to treat conditions causing chronic anxiety, in which BZ-dependence can become a problem (e.g., generalized anxiety disorder).

c. Buspirone takes up to 2 weeks to work and may not be acceptable to patients who are accustomed to taking the fast-acting BZs for their symptoms.

Non-benzodiazepines

2. Zolpidem, zaleplon, eszopiclone, and ramelteon are short-acting agents used primarily to treat insomnia. Like the BZs, the first three of these agents act on the GABA A receptor. In contrast, ramelteon is a selective melatonin agonist.

3. Antihypertensives such as b-blockers (block both α_1 - and β_2 -adrenergic receptors) such as propranolol (Inderal) and α_2 -adrenergic receptor agonist such as clonidine decrease autonomic hyperarousal and are used to treat symptoms of anxiety (e.g., tachycardia), particularly in patients with social phobias such as fear of public speaking.

Electroconvulsive Therapy (ECT)

A. Uses of electroconvulsive therapy (ECT)

1. ECT provides rapid, effective, safe treatment for some psychiatric disorders.

a. It is most commonly used to treat major depressive disorder that is refractory to antidepressants.

b. ECT may be indicated also for serious depression when rapid symptom resolution is imperative because of psychotic symptoms or suicide risk.

c. ECT is particularly useful for treating depression in the elderly because it may be safer than long-term use of antidepressant agents. It also may be used to treat depression during pregnancy.

2. The mechanism of action of ECT is not known but may be related to alteration of neurotransmitter function in a manner similar to that of treatment with psychoactive agents.

Electroconvulsive Therapy (ECT)



B. Administration

1. ECT involves the induction of a generalized seizure, lasting 25–60 seconds, by passing an electric current across the brain.
2. Prior to seizure induction, the patient is premedicated (e.g., with atropine), then administered a short-acting general anesthesia (e.g., methohexital) and a muscle relaxant (e.g. succinylcholine) to prevent injury during the seizure.
3. Improvement in mood typically begins after a few ECT treatments. A maximum response to ECT is usually seen after 5–10 treatments given over a 2–3-week period. 90% show some immediate improvement .

C. Problems associated with ECT

1. The major adverse effects of ECT are memory problems.
2. Increased intracranial pressure or recent (within 2 weeks) myocardial infarction is relative contraindication for ECT.
3. The mortality rate associated with ECT is very low and is comparable to that associated with the induction of general anesthesia.

The End