Kotebe Metropolitan University
Menelik II Medical and Health Science College

Course Title: Integrated therapeutics III

Course Code:Phar4163

Course ECTS: 7

Lecture notes for Year IV Pharmacy

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INTEGRATED THERAPEUTICS III

PHAR531

(4 Cr Hrs)

ASSEFA M (MSc)

School of Pharmacy

Addis Ababa University

2017

Pharmacotherapy III

- Chapter 1: **Hematological Disorders**
- Chapter 2: **Psychiatric Disorders**
- Chapter 3: **Neurologic Disorders**
- Chapter 4: **Endocrine/metabolic disorders**
- Chapter 5: **Gynecologic and obstetric disorders**
- Chapter 6: **Urological disorders**
- Chapter 7: **Dermatological disorders**

Course objectives

- After completion of this course, students will be able to understand
  - ↳Pathophysiologic processes,
  - ↳Treatment strategies,
  - ↳Monitoring of outcomes

} Hematologic, Psychiatric, Neurologic, Endocrine/ metabolic, Gynecologic/ obstetric, Dermatologic diseases

Teaching Methods

- Illustrated lectures and group discussions
- Individual and group exercise and assignments
- Role plays and case studies

Methods of Assessment:

- Attendance, class activity 20%
- Quiz 10%
- Midterm examination 30%
- Final examination 50%

References

1. Dipiro JT, Talbert RL, Yee GC, et.al. **Pharmacotherapy, A Pathophysiologic Approach.** 10th or later edition.
2. Koda - Kimble MA, Young LY , Kradjan WA, et.al. **Applied Therapeutics, The Clinical Use of Drugs**. 11th or later edition.
3. Kasper, Braunwald, et al. **Harrison's Principles of Internal Medicine**, 20th or later edition

HEMATOLOGIC DISORDERS

CHAPTER ONE

ANEMIA

Learning Objectives

1) Identify common causes of anemia
2) Describe common signs and symptoms of anemia
3) Describe diagnostic evaluation required to determine the etiology of anemia.
4) Recommend a treatment regimen considering the underlying cause and patient-specific variables
5) Monitor the outcomes of pharmacotherapy for the treatment of anemia

Definition

- **Anemia** is a reduction in either the concentration of Hb or RBCs, that results in reduced oxygen-carrying capacity of the blood.
- Anemia is defined by the WHO as Hgb <13 g/dL in men or <12 g/dL in women.
- Anemia can result from
  - Inadequate RBC production,
  - Increased RBC destruction, or
  - Blood loss.
- It can be a manifestation of a host of systemic disorders, such as infection, chronic renal disease, or malignancy.

Epidemiology

- Anemia affects a large part of the world's population.
- According to the WHO, almost **1.6 billion people (25% of the world's population)** are anemic
- Iron deficiency is the leading cause of anemia worldwide, accounting for as many as **50%** of cases

Anemia Classification by RBC Size

- **Macrocytic**
  - Vitamin B_{12} deficiency
  - Folic acid deficiency
- **Normocytic**
  - Recent blood loss
  - Chronic disease.
- **Microcytic**
  - Iron deficiency

Clinical Presentation

- **Symptoms**
  - Decreased exercise tolerance
  - Fatigue
  - Dizziness
  - Irritability
  - Weakness
  - Palpitations
  - Vertigo
  - Shortness of breath
  - Chest pain
  - Neurologic symptoms in vitamin B_{12} deficiency

Clinical Presentation

- **Signs**
  - Tachycardia
  - Pale appearance (most prominent in conjunctivae)
  - Decreased mental acuity
  - Increased intensity of some cardiac valvular murmurs
  - Diminished vibratory sense or gait abnormality in vitamin B_{12} deficiency

Laboratory Tests

- **Hemoglobin**
  - ✓ Male: 14 to 18 g/dL
  - ✓ Females: 12 to 16 g/dL
  - ✍ The amount of Hb per volume of whole blood
  - ✍ Higher value in males: stimulation of RBC production by androgenic steroids,
  - ✍ Lower values in females: result of blood loss during menstruation.
- **Hematocrit**
  - ✓ Males: 39% to 49%
  - ✓ Females: 33 to 43%
  - ✍ The actual volume of RBCs in a unit volume of whole blood (%)
  - ✍ A low Hct indicates a reduction in either the number or the size of RBCs or an increase in plasma volume.

Laboratory Tests

- **Red Blood Cell Count**
  - ✓ **Males: Normal: 4.3 to 5.9 × $10^3/mm^3$**
  - ✓ **Females: Normal: 3.5 to 5.0 × $10^6/mm^3$**
  - ✍ The RBC count is an indirect estimate of the Hb content of the blood;
  - ✍ It is an actual count of RBCs per unit of blood.
- **Red Blood Cell Indices**
  - ✍ Are calculated from the Hb, Hct, and RBC count
  - ✍ Describe the size and Hb content of the RBCs

Laboratory Tests

- **Mean Cell Volume (MCV)**
  - Hct/RBC Count 76 – 100 (in μm^3 or fL
  - Average volume of RBCs
    - **Macrocytic**: size is larger than normal
      - Folic acid and vitamin B_{12} deficiency
    - **Microcytic**: size is smaller than normal,
      - IDA and thalassemia
    - **Normocytic**: size is within normal limits
  - When IDA (decreased MCV) is accompanied by folate deficiency (increased MCV), the overall MCV may be normal

Laboratory Tests

- **Mean Cell Hemoglobin (MCH) (in pg)**
  - Hb/RBC Count
  - Is the amount of Hb in a RBC
  - **Low MCH**: Two morphologic changes, microcytosis and hypochromia, can reduce MCH.
    - A microcytic cell contains less Hb b/se it is a smaller cell
    - A hypochromic cell has a low MCH b/se of the decreased concentration of Hb present in the cell
  - **High MCH**: macrocytosis (e.g., vitamin B_{12} or folate deficiency)

Laboratory Tests

- **Mean Cell Hemoglobin Concentration (MCHC)**
  - **33 – 37 (in g/dL)**
  - Hb/Hct:
  - The concentration of Hgb per volume of cells
  - MCHC is independent of cell size,
    - It is more useful than MCH in distinguishing between **microcytosis** and **hypochromia**
    - A low MCHC indicates hypochromia;
    - A microcyte with a normal Hb concentration will have a low MCH but a normal MCHC.
  - A decreased MCHC is seen most often in IDA.

Laboratory Tests

- **Total Reticulocyte Count**
  - Normal: 1%.
  - An indirect assessment of new RBC production.
  - It reflects how quickly immature RBCs are produced by bone marrow and released into the blood.
  - High reticulocyte count: **acute blood loss** or **hemolysis**
  - A lack of reticulocytosis in anemia indicates: iron deficiency, B_{12} deficiency, anemia of

Laboratory Tests

- **Homocysteine**
  - **Vitamin B_{12}** and **folate** both are required for conversion of **homocysteine** to **methionine**.
  - Increased serum homocysteine may suggest vitamin B_{12} or folate deficiency.
  - Homocysteine levels also can be elevated in patients with vitamin B_6 deficiency, renal failure, hypothyroidism, or a genetic defect in cystathionine β-synthase
- **Methylmalonic Acid**
  - A vitamin B_{12} coenzyme is needed to convert methylmalonyl coenzyme A to succinyl coenzyme A.
  - Patients with vitamin B_{12} deficiency have increased concentrations of serum methylmalonic acid (MMA), which is a more specific marker for vitamin B_{12} deficiency than homocysteine.

Case

- DD, a 58-year-old chronic alcoholic, was hospitalized in a local hospital. A CBC was ordered, and the following RBC indices were noted:
  - MCV, 108 μm3
  - MCH, 38 pg
  - MCHC, 34 g/dL

  How should these indices be interpreted in DD?

Iron-Deficiency Anemia

- Iron deficiency is the most common nutritional deficiency
- Most people lose about 1 mg of iron daily.
- Menstruating women can lose up to 0.6 to 2.5% more per day.
- Pregnancy requires an additional 700 mg of iron
- Blood donation can result in as much as 250 mg of iron loss

Iron-Deficiency Anemia

- Iron is best absorbed in its ferrous (Fe^{2+}) form.
- The normal daily diet contains mainly the ferric (Fe^{3+}) non-absorbed form.
- After iron is ionized by stomach acid and then reduced to the Fe^{2+} state,
  - It is absorbed primarily in the duodenum, and to a smaller extent in the jejunum, via intestinal mucosal cell uptake.
- The daily recommended dietary allowance:
  - 8 mg in adult males and postmenopausal females
  - 18 mg in menstruating females.

Iron-Deficiency Anemia

- **Heme iron**, which is found in meat, fish, and poultry, is about three times more absorbable than the nonheme iron found in vegetables, fruits, dried beans, nuts, grain products, and dietary supplements.
- Gastric acid and other dietary components such as ascorbic acid increase the absorption of nonheme iron.
- Dietary components that form insoluble complexes with iron (**phytates**, **tannates**, and **phosphates**) decrease absorption.
- Phytates, a natural component of grains, brans, and some vegetables, can form poorly absorbed complexes
  - Partially explain the increased prevalence of IDA in poorer countries, where grains and vegetables compose a disproportionate amount of the normal diet.
- Polyphenols bind iron and decrease nonheme iron absorption when large amounts of tea or coffee are consumed with a meal.

Etiology

- Iron deficiency results from prolonged negative iron balance
  - Increased iron demand or hematopoiesis,
  - Increased loss, or
  - Decreased intake/absorption
- Higher risk for iron deficiency include
  - Children younger than 2 years,
  - Adolescent girls,
  - Pregnant/lactating females, and
  - Those older than 65 years

Labs

- Low serum iron and ferritin levels and high TIBC.
  - TIBC >400 mcg/dL suggests IDA, while values <200 mcg/dL usually represent inflammatory disease.
- Hb and Hct fall below normal values,
- A microcytic hypochromic anemia develops (MCV is reduced)

Treatment

- **Desired Outcomes**
  - Reversal of hematologic parameters to normal,
  - Return of normal function and quality of life,
  - Prevention or reversal of long-term complications

Dietary Supplementation

- Iron is best absorbed from meat, fish, and poultry.
  - ✍ These foods as well as certain iron-fortified cereals can help treat IDA.
- **Orange juice** and other **ascorbic acid-rich foods** can be included with meals to increase absorption.
- Milk and tea reduce absorption and should be consumed in moderation.

Oral Iron Preparations

- In most cases of IDA, oral administration of iron therapy with soluble **Fe^{2+}** iron salts is appropriate.
- For patients with IDA, the generally recommended dose is about **150 to 200 mg** of elemental iron daily, usually in two or three divided doses to maximize tolerability
- Iron preferably is administered at least 1 hour before meals because food can interfere with iron absorption.
- Many patients must take iron with food because they experience GI upset when iron is administered on an empty stomach.

Oral Iron Preparations

Iron Salt	Percent Elemental Iron	Common: Formulations and Elemental Iron Provided
Ferrous sulfate	20	60–65 mg/324–325 mg tablet 60 mg/5 mL syrup 44 mg/ 5 mL elixir 15 mg/1 mL
Ferrous sulfate (exsiccated)	30	65 mg/200 mg tablet 50 mg/160 mg tablet
Ferrous gluconate	12	38 mg/325 mg tablet 28–29 mg/240–246 mg tablet
Ferrous fumarate	33	66 mg/200 mg tablet 106 mg/324–325 mg tablet

Oral Iron Preparations

- Adverse reactions to therapeutic doses of iron are
  - Primarily GI in nature and consist of
    - Dark discoloration of feces,
    - Constipation or diarrhea,
    - Nausea
    - Vomiting
  - GI side effects usually are dose related and are similar among iron salts when equivalent amounts of elemental iron are administered.

Parenteral Iron Therapy

- Indications for parenteral iron therapy include
  - Intolerance to oral,
  - Malabsorption, and
  - Long-term nonadherence
  - Patients with significant blood loss
  - CKD patients
  - Cancer patients receiving chemotherapy (on ESAs)
- **Four** different parenteral iron preparations:
  - Iron dextran,
  - Sodium ferric gluconate,
  - Iron sucrose, and
  - Ferumoxytol

Case

- H.P., a 31-year-old woman, is seen in the clinic. Her chief complaints include weakness, dizziness, and epigastric pain. She has a 5-year history of peptic ulcer disease, a 10-year history of heavy menstrual bleeding, and a 15-year history of chronic headaches. She has two children who are 1 and 3 years of age. H.P. is currently taking doxycycline 100 mg QD for acne, ibuprofen 400 mg as needed for headaches, and esomeprazole 40 mg daily. A review of her systems is positive for decreased exercise tolerance. Physical examination reveals a pale, lethargic woman . Her vital signs are within normal limits; her heart rate is regular at 100 beats/minute. Her examination is notable for pale nail beds and splenomegaly.
- Significant laboratory results include the following:
  - Hgb, 8 g/dL, Hct, 26%, Platelet count, 500,000/**μ**L, Reticulocyte count, 0.2%, MCV, 75 fL, MCH, 23 pg/cell, MCHC, 300 g/L, Serum iron, 40 **μ**g/dL, Serum ferritin, 9 ng/mL, TIBC, 450 g/dL, 4+ stool guaiac (normal, negative)

Case

1. What is the cause of H.P.’s anemia?
2. What factors predispose H.P. to anemia?
3. What subjective or objective signs, symptoms, and laboratory tests are typical of H.P. problem?
4. How should H.P. be managed?

Megaloblastic Anemias

- Macrocytosis is caused by abnormal DNA metabolism resulting from vitamin B_{12} or folate deficiency
- It also can be caused by administration of various drugs
  - Hydroxyurea
  - Zidovudine
  - Cytarabine
  - Methotrexate
  - Azathioprine
  - 6-mercaptopurine
  - Cladribine

Megaloblastic Anemias

Vitamin B_{12} Deficiency Anemia

- The three major causes of vitamin B_{12} deficiency are
  - Inadequate intake,
  - Malabsorption syndromes
  - Inadequate utilization
- Inadequate dietary consumption of vitamin B_{12} is rare.
  - It usually occurs only in patients who are strict vegans and their breast-fed infants, chronic alcoholics, and elderly patients who consume a “tea and toast” diet because of financial limitations or poor dentition.
- Decreased vitamin B_{12} absorption can occur with loss of **intrinsic factor** by autoimmune mechanisms (pernicious anemia, in which gastric parietal cells are selectively damaged), chronic atrophic gastritis, or stomach surgery.

Vitamin B_{12} Deficiency Anemia

- Vitamin B_{12} deficiency can cause neurologic and hematologic complications.
- These usually start with bilateral paraesthesia in extremities; deficits in proprioception and vibration
- If not treated, this can progress to ataxia, dementia-like symptoms, psychosis, and vision loss.
- In children prolonged deficiency can lead to poor brain development.
- Patients with unexplained **neuropathies** should be evaluated for vitamin B_{12} deficiency.

Vitamin B_{12} Deficiency Anemia

- **Labs**
  - MCV is elevated >100 fL
  - Low serum vitamin B_{12} level (<150 pg/mL),
  - Low Hct
  - **Elevations in MMA** are more specific for vitamin B_{12} deficiency
  - Homocysteine is also elevated in several other situations including:
    - Folate deficiency
    - Chronic renal disease
    - Alcoholism
    - Smoking
    - Use of steroid or cyclosporine therapy

Vitamin B_{12} Deficiency Anemia

Treatment

- **Goals**
  - Reversal of hematologic manifestations
  - Replacement of body stores
  - Prevention or resolution of neurologic manifestations

Vitamin B_{12} Deficiency Anemia

- 1,000 mcg of **cyanocobalamin** daily IM for 1 week, thereafter weekly for 1 month and monthly thereafter for maintenance.
- Parenteral therapy is preferred for patients exhibiting neurologic symptoms until resolution of symptoms and normalization of hematologic indices
- When patients are converted from the parenteral to the oral form of cobalamin, 1,000 mcg of oral cobalamin daily can be initiated on the due date of the next injection
- B_{12} should be continued for life in pernicious anemia.

Folic Acid Deficiency Anemia

- Major causes of folic acid deficiency include
  - Inadequate intake,
  - Decreased absorption, and
  - Increased folate requirements.
- Poor eating habits make this deficiency more common for elderly patients, teenagers whose diets consist of “junk food,” alcoholics, food faddists, the impoverished, and those who are chronically ill or demented.
- Folic acid absorption may decrease for patients who have malabsorption syndromes or those who have received certain drugs.
- In alcoholics with poor dietary habits, alcohol interferes with folic acid absorption, interferes with folic acid utilization at the cellular level, and decreases hepatic stores of folic acid.

Folic Acid Deficiency Anemia

- Recommended daily allowance
  - Nonpregnant females: 400 mcg
  - Lactating females: 500 mcg
  - Pregnant females: 600 mcg
- Treatment:
  - Folic acid supplementation at a dose of 400 mcg daily is recommended for all women.
  - Women who have previously given birth to offspring with neural tube defects or those with a family history of neural tube defects should ingest 4 mg daily of folic acid.

Anemia of Inflammation

- AI is both ACD and anemia of critical illness
- The onset of anemia of critical illness is quicker, over days, and typically occurs in a hospital setting.
- ACD has a similar mechanism, but it develops over months to years from a chronic condition.

AI

Disease Causing AI

- Chronic disease
  - TB, lung abscess, bronchiectasis
  - HIV
  - Bacterial endocarditis
  - Osteomyelitis
  - UTI
- Chronic inflammation
  - Rheumatoid arthritis
  - SLE
  - IBD
  - Gout
- Malignancy
  - Carcinoma
  - Lymphoma
  - Leukemia
  - Multiple myeloma
- Less common causes
  - Alcoholic liver disease
  - CHF
  - Thrombophlebitis
  - COPD
  - IHD

AI

- Factors that may contribute to anemia in critically ill patients include
  - Sepsis
  - Frequent blood sampling
  - Surgical blood loss
  - Immune-mediated functional iron deficiency
  - Decreased production of endogenous EPO
  - Reduced RBC life span
  - Active bleeding

AI

- **Labs**
  - ✍ Decreased serum iron level,
  - ✍ Serum ferritin level is normal or increased
  - ✍ TIBC is decreased.

AI

- **Treatment**:
  - **Transfusion** (Hb < 7 to 8 g/dL)
  - **ESAs** have been used to stimulate erythropoiesis for patients with AI since a relative EPO deficiency exists for the degree of anemia.
    - Two agents are available: recombinant epoetin alfa and recombinant darbepoetin alfa
    - Dosage:
      - Epoetin alfa: 50 to 100 units per kilogram three times per week
      - Darbepoetin alfa: 0.45 mcg per kilogram once weekly

Follow-Up Evaluation

- Follow up monthly to assess efficacy and tolerance of therapy until resolution of symptoms and Hgb goal achieved.
- Monitor the CBC monthly
- Monitor side effects of therapy
  - Oral iron: nausea, vomiting, abdominal pain, heartburn, constipation, and dark stools
  - Parenteral iron: anaphylaxis (test dose required for iron dextran and observe for 1 hour after), injection-site pain/irritation, arthralgias, myalgias, flushing, malaise, and fever
  - Folic acid: bad taste and nausea, rash, and allergic reactions
  - Vitamin B_{12}: pain and erythema at injection site
  - ESAs: hypertension (monitor blood pressure), thrombosis (eg, deep vein thrombosis/pulmonary embolism, myocardial infarction, cerebrovascular accident, and transient ischemic attack), arthralgias, and headache

Coagulation
and
Platelet Disorders

INHERITED COAGULATION DISORDERS

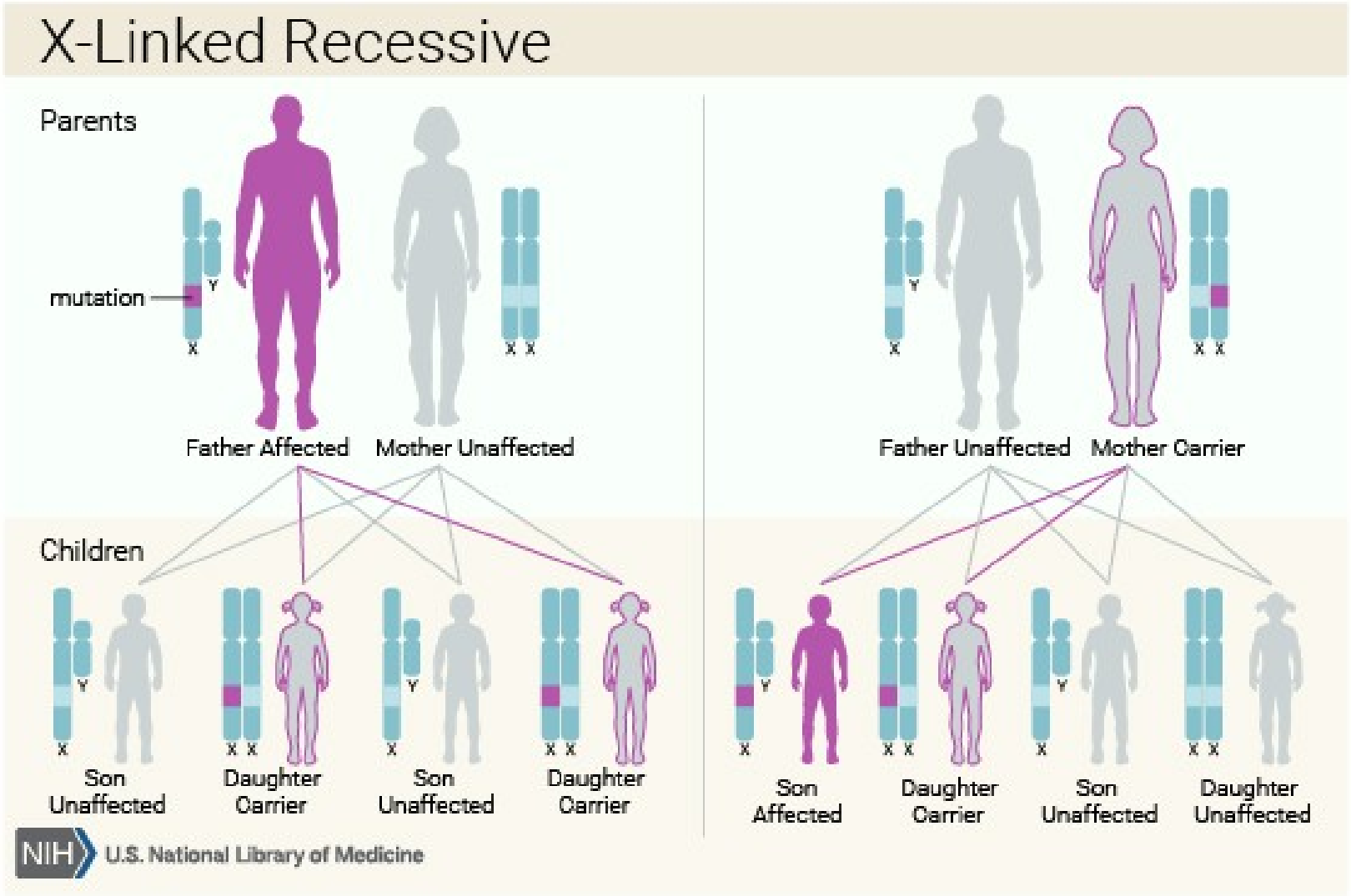
1. Hemophilia

- Hemophilia A and B are coagulation disorders that result from defects in the genes encoding for plasma coagulation proteins.
- **Hemophilia A** (Classic hemophilia)
  - Caused by the deficiency of factor **VIII**
- **Hemophilia B** (Christmas disease)
  - Caused by the deficiency of factor **IX**.
- The incidences of hemophilia A and B are estimated at 1 in 5000 and 1 in 30,000 male births, respectively.
- Both types of hemophilia are evenly distributed across all ethnic and racial groups

Pathophysiology

- The pathophysiology of hemophilia is based on the deficiency of factor VIII or IX inadequate thrombin generation impaired intrinsic-pathway coagulation cascade.
- Factor VIII and IX genes are located on the X chromosome.
- Hemophilias are recessive X-linked diseases.
- Generally, affected males carrying either defective allele on their X chromosome do not transmit the gene to their sons.
- However, their daughters are obligate **carriers**.
- More than 1000 mutations in factor VIII and IX genes have been identified to cause clinical hemophilia.

Pathophysiology



Complications of Hemophilia

	Severe (< 0.01 IU/mL)	Moderate (0.01–0.05 IU/mL)	Mild (> 0.05 IU/mL)
Age at onset	1 year or less	1–2 years	2 years–adult
Neonatal symptoms			
ICH	Usual	Usual	Rare
PCB	Occasional	Uncommon	Rare
Muscle/joint hemorrhage	Spontaneous	Minor trauma	Minor trauma
CNS hemorrhage	High risk	Moderate risk	Rare
Postsurgical hemorrhage (without prophylaxis)	Frank bleeding, severe	Wound bleeding, common	Wound bleeding
Oral hemorrhage	Usual	Common	Common

Signs and Symptoms

- Ecchymoses (palpable/raised)
- Hemarthrosis (especially knee, ankle, and elbow)
- Joint pain
- Joint swelling and erythema
- Decreased range of motion
- Muscle hemorrhage
- Swelling at the site of muscle bleeding
- Pain with motion of affected muscle
- Signs of nerve compression
- Significant anemia from an iliopsoas or thigh bleed
- Oral bleeding with dental extractions or trauma
- Hematuria
- Intracranial hemorrhage (spontaneous or following trauma)
- Excessive bleeding

Laboratory Testing

- Prolonged activated partial thromboplastin time (aPTT)
- Decreased factor VIII or factor IX level
- Normal prothrombin time (PT)
- Normal platelet count
- Normal von Willebrand factor antigen and activity
- Normal bleeding time

Diagnosis

- Male with unusual bleeding
- Family history of bleeding
- Brothers of patients with hemophilia should be screened; sisters should undergo carrier testing
- Prolonged partial thromboplastin time (PTT)
- A decreased FVIII or FIX level

Treatment

- Currently, there is **no** cure for hemophilia A or B.
- The life expectancy of hemophiliacs was only 8 to 11 years in the 1920s and 1930s.
- With the development of effective treatment strategies, life expectancy is currently about 63 to 75 years,
  - Nearly that of the normal population.

Treatment

➲ Desired Outcomes

- ✓ Decrease the number of bleeding episodes per year or bleeding frequency
- ✓ Normalize or improve clotting factor concentrate levels
- ✓ Maintain clinical joint function
- ✓ Maintain quality-of-life measurements

Treatment

- **General Approach to Treatment**
  - Intravenous factor replacement to treat or prevent bleeding is the primary treatment of hemophilia.
  - Primary prophylaxis: the regular administration of factor concentrates with the intention of preventing joint bleeds.
  - The rationale for primary prophylaxis is that individuals with factor levels of greater than **0.02 IU/mL** rarely suffer from spontaneous bleeds and **arthropathy**

Treatment

Nonpharmacologic Therapy

- **Supportive Care:** Rest, ice, compression, elevation (RICE)
- **Surgery:** Surgical arthroscopic synovectomy reduces replacement therapy–resistant disease and repetitive hemarthrosis of a single joint.
  - This procedure removes inflamed joint tissue.
  - Patients may have decreased range of motion after the surgery.
- **Orthotics:** Joint prostheses do not deal with the deformities directly.
  - Orthotics in hemophilia serve as an important supportive measure before or after surgery

Pharmacologic Therapy

Hemophilia A

- Desmopressin
  - Most patients with **mild to moderate** disease and a **minor bleeding** episode can be treated with desmopressin acetate
  - A synthetic analogue of the antidiuretic hormone, ***vasopressin***.
  - Desmopressin causes release of von Willebrand factor (vWF) and factor VIII from endothelial storage sites.
  - Desmopressin increases plasma factor VIII levels by **threefold** to fivefold within 30 minutes.
  - The recommended dose is 0.3 mcg/kg **IV** (in 50 mL of normal saline infused over 15–30 minutes) or **SC** (in < 1.5 mL) or 150 to 300 mcg **intranasally** via concentrated nasal spray, may repeat after 24 hours.

Pharmacologic Therapy

Factor VIII Replacement

- Patients with **severe** hemophilia may receive primary (before the first major bleed) or secondary (after the first major bleed) prophylaxis.
- All hemophiliacs with a major bleed require factor VIII replacement.
- The therapy may include:
  - Recombinant (produced via transfection of mammalian cells with the human factor VIII gene) or
  - Plasma-derived (concentrate from pooled plasma) factor VIII

Pharmacologic Therapy

Hemophilia B

➲Factor IX Replacement

- Hemophilia B therapy may include
  - ✍Recombinant (produced via transfection of mammalian cells
    with the human factor IX gene) or
  - ✍Plasma-derived (concentrate from pooled plasma) factor IX
- Because it is a small protein, the factor IX molecule passes into both the intravascular and the extravascular spaces.
- Therefore, the volume of distribution of recombinant factor IX is twice that of factor VIII.

Pain Associated with Hemophilia

- Pain commonly occurs in patients with hemophilia.
- Acute bleeding episodes and long-term joint destruction are common sources of pain.
- Acetaminophen and opioid analgesics are recommended to control mild to moderate and severe pain, respectively.
- Nonsteroidal anti-inflammatory drugs and aspirin should be avoided if possible, because these drugs bind to platelets and increase the risk of bleeding episodes.
- Cyclooxygenase-2 (COX-2) inhibitors can be used with caution

2. von Willebrand Disease

- von Willebrand disease (vWD) is the most common inherited bleeding disorder caused by a deficiency or dysfunction of vWF
- The disease prevalence is estimated at 30 to 100 cases per million.
- In contrast to hemophilia, the majority of vWD cases are inherited as an autosomal dominant disorder, ensuing equal frequency in males and females.
- Two main functions in hemostasis:
  - to aid platelet adhesion to injured blood vessel walls and
  - to carry and stabilize factor VIII in plasma

Classification of vWD

Phenotype	Mechanism of Disease	Percentage of Cases
Type 1 vWD	**Partial** (mild to moderate) **quantitative** deficiency	70 – 80
Type 2 vWD	**Qualitative** abnormalities of vWF	10 – 30
2A	**Decreased platelet-dependent** vWF function owing to lack of larger multimers	10 – 20
2B	Decreased vWF function due to **increased affinity to platelet GP 1b** and resultant sequestration or loss	5
2M	Defective platelet-dependent vWF functions not associated with multimer defects	Uncommon
2N	Defective vWF binding to **factor**	Uncommon

Clinical Presentation

Symptoms

- Bruising
- Mucocutaneous bleeding
- Epistaxis
- Oral cavity bleeding
- Menorrhagia
- GI bleeding
- Joint and deep tissue bleeding
- Postoperative bleeding

Laboratory Testing

- Low or normal Vwf antigen concentration in plasma (vWF)
- Low or normal factor VIII coagulation assay (FVIII)

Management

Nonpharmacologic Therapy

- Local measures, including pressure and ice, may be used to control superficial bleeding.

Management

- **Desmopressin**
  - Most patients with type 1 vWD (functionally normal vWF) and a minor bleeding episode can be treated successfully with desmopressin,
  - Induces release of factor VIII and vWF from endothelial cells through interaction with vasopressin V2 receptors.
  - A test dose administered at the time of diagnosis

Management

Replacement therapy

- Indications
  - Type 1 patients unresponsive to desmopressin,
  - Patients with type 2 and 3 vWD,
  - Major surgery patients
- Product
  - Plasma-derived virus-inactivated factor VIII concentrates containing vWF

IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

- ITP is one of the most common causes of acquired thrombocytopenia
- Incidence is 1.9 to 6.4 cases per 100,000 persons in children and 3.3 cases per 100,000 in adults.
- ITP is an autoimmune disorder caused by the binding of antibodies (usually immunoglobulin G [IgG]) to platelet surface antigens,

✍Resulting in shortened platelet life span.

IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

- Childhood-onset and adult-onset ITP present very differently.
  - **Adult-onset ITP:**
    - Is generally chronic (> 6 months) and
    - Affects women two to three times more often than men.
  - **Childhood-onset ITP:**
    - Acute in onset
    - Usually follows an infectious illness,
    - Both sexes are equally affected.
    - Resolves on its own within 4 to 6 weeks without major sequelae.

IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

Pathophysiology

- In ITP, IgG autoantibodies bind to platelet-antigen complex and are cleared from the blood via binding to mononuclear phagocytes by macrophage Fcγ receptor
  - ✍Leading to thrombocytopenia.
- Platelet survival time is significantly shorter in patients with ITP (from minutes to 2–3 days compared with normal 7–10 days).
- Sequestration in spleen, liver, and bone marrow is partially
responsible for decreased platelet survival

Clinical Presentation

- **Symptoms**
  - Petechiae
  - Purpura, wet purpura
  - Ecchymoses
  - Cutaneous bleeding
  - Mucosal site bleeding
  - Epistaxis
  - Gingival bleeding
  - Hematuria
  - Menorrhagia
  - Intracranial hemorrhage (rare)

Clinical Presentation

- **Diagnostic Criteria**
  - Platelet count less than 100 × $10^3/mm^3$
  - Otherwise normal CBC with differential
  - Normal reticulocyte count
  - Normal peripheral blood smear (no hemolysis or blast cells)
  - History and physical exam ruling out other possible causes of thrombocytopenia
- **Other Laboratory Testing**
  - Laboratory testing to rule out other courses of thrombocytopenia, such as HCV, HIV, SLE, and others

Treatment

- **Desired outcome**
  - To maintain the platelet count associated with sufficient hemostasis (> 30 × $10^3/mm^3$)
- **General Approach**
  - The initial treatment of children with ITP is controversial because
    greater than 75% to 80% of cases resolve spontaneously irrespective of pharmacologic intervention.
  - Therapy may be considered in children meeting one of the following criteria:
    - Platelet counts less than 10 × $10^3/mm^3$ and mucocutaneous bleeding;
    - Platelet counts less than 30 × $10^3/mm^3$ and moderate systemic or mucosal bleeding; or factors that may increase the risk of bleeding (such as participation in active contact sports increasing risk of head injury)
  - In adults, treatment is indicated when platelet counts are less than 30 × $10^3/mm^3$

Treatment

Glucocorticoids

- Decrease splenic sequestration of antibody-coated platelets, diminish antibody generation by the spleen and the bone marrow, and increase platelet output by the bone marrow.
- In adults, the response rate to oral prednisone (1 mg/kg/day) is 50% to 75%, with patients usually responding within the first 1 to 2 weeks.
- The duration of therapy: **prednisone** therapy for 21 days, followed by a taper.
- High-dose **dexamethasone** (40 mg orally or IV daily) administered for 4 to 8 days.

NEUROLOGIC DISORDERS

Chapter Three

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Seizure and Epilepsy

Objectives

- At the end of this session, the students will be able to:

1. Describe the epidemiology of epilepsy
2. Describe the basic pathophysiology of seizures and epilepsy
3. Differentiate and classify seizure types
4. Recommend an appropriate pharmacotherapeutic regimen with monitoring parameters for the treatment of epilepsy.
5. Determine when and how to discontinue antiepileptic drug therapy.
6. Educate a patient/caregiver on epilepsy and pharmacotherapy for this disorder

Seizure and Epilepsy

- Seizure: a paroxysmal event due to an abnormal, excessive discharges from excessive excitation and synchronization of a population of cortical neurons
- Epilepsy: a clinical condition of recurrent (two or more) seizures due to a chronic, underlying process

Epidemiology

- About 8% of the US population will experience a seizure during their lifetime.
- Epilepsy affects approximately 2 million individuals in the US
- In developing countries, the incidence is higher at 100 to 190 cases per 100,000 persons per year
- New-onset seizures occur most frequently in infants younger than 1 year of age and in adults after age 55

Social Impact

- Restrictions on **driving**
- Fifty percent of patients with epilepsy report **cognitive** and **learning** difficulties.
- Transportation and educational difficulties combine with persistent seizures to cause unemployment (underemployment), and as a result, problems with paying for health care.
- The social **stigma** of embarrassment or **injury** due to seizures in public results in isolation of the patient

Causes of Seizure and Epilepsy

- Seizure is the result of shift in the normal balance of excitation and inhibition with in the CNS
- Adolescence and young adult
  - Head trauma
  - Drug intoxication and withdrawal*
- Older adult
  - Stroke
  - Brain tumor
  - Acute metabolic disturbances*
  - Neurodegenerative

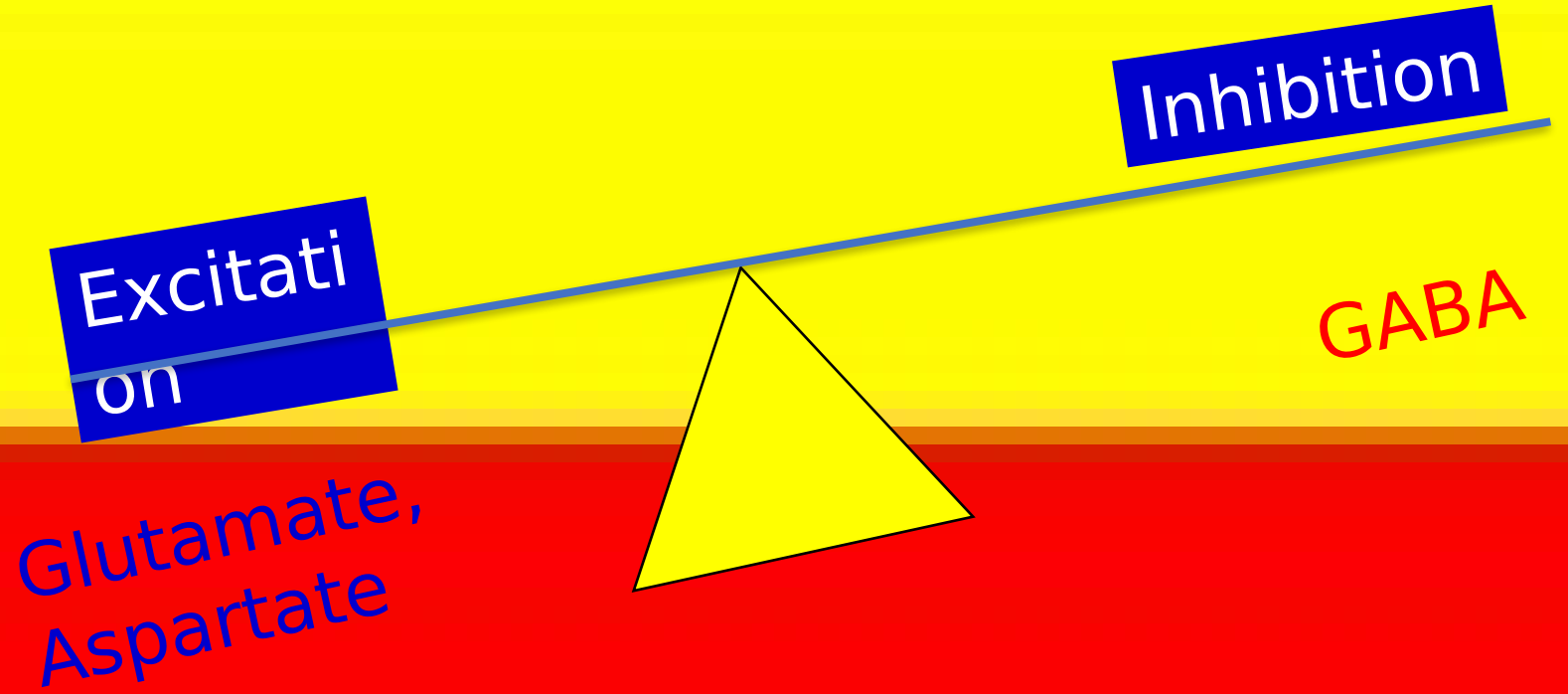
Factors that precipitate seizures

- Hyperventilation can precipitate absence seizures.
- Sleep, **sleep deprivation**, sensory stimuli, and **emotional stress**
- Hormonal changes occurring around the time of menses, puberty, or pregnancy
- Theophylline, alcohol, high-dose phenothiazines, antidepressants (maprotiline or bupropion), and street drug use

Pathophysiology

- Seizures result from **excessive excitation** or in the case of absence seizures from **disordered inhibition** of a large population of cortical neurons
- Reflected on EEG as a sharp wave or spike.
- Initially, a small number of neurons fire abnormally
- Normal membrane conductance and inhibitory synaptic currents break down, and excess excitability spreads,
  - Either locally to produce a focal seizure or more widely to produce a generalized seizure.

Pathophysiology



Normal CNS Function: Excitation and Inhibition

- **Excitation**
  - Ionic: inward Na^{+}, Ca^{++} currents
  - Neurotransmitter: glutamate, aspartate

- **Inhibition**
  - Ionic: inward Cl^{-}, outward K^{+} currents
  - Neurotransmitter: GABA

Pathophysiology

- There are multiple mechanisms that might contribute to synchronous hyperexcitability, including:

(a) Alterations in the distribution, number, type, and biophysical properties of ion channels in the neuronal membranes;

(b) Biochemical modifications of receptors;

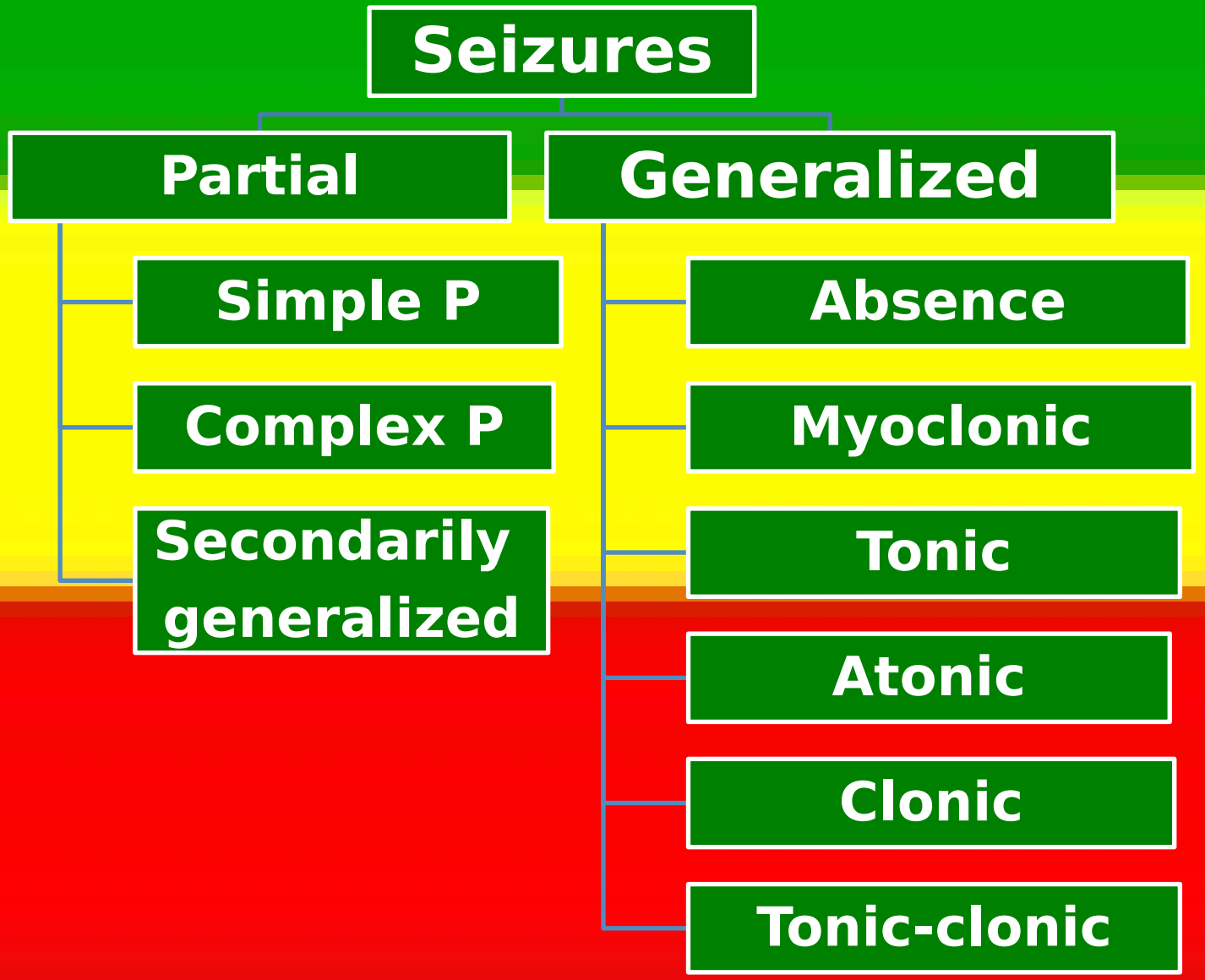
(c) Modulation of second messaging systems and gene expression;

(d) Changes in extracellular ion concentrations;

(e) Alterations in neurotransmitter uptake and metabolism in glial cells;

(f) Modifications in the ratio and function of inhibitory circuits.

Classification of Seizure



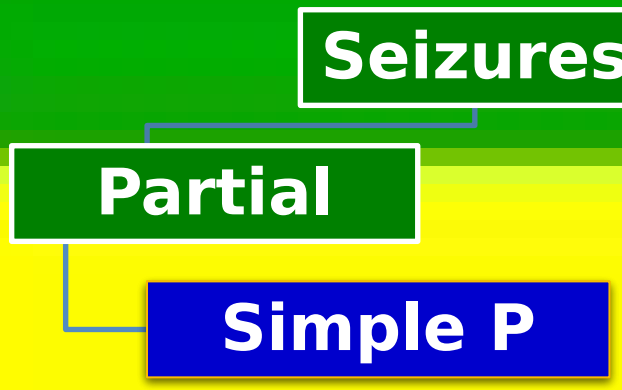
Partial Seizure

Seizures

Partial

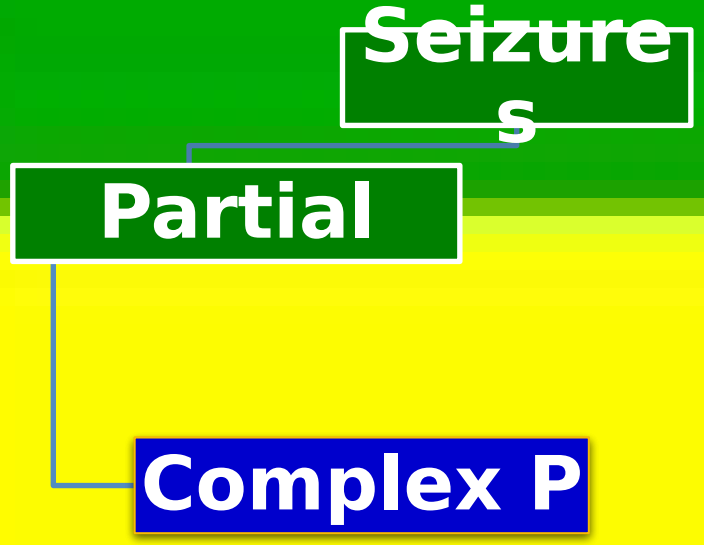
- Begin in one hemisphere of the brain
- Result in an asymmetric motor manifestation.

Simple Partial Seizure



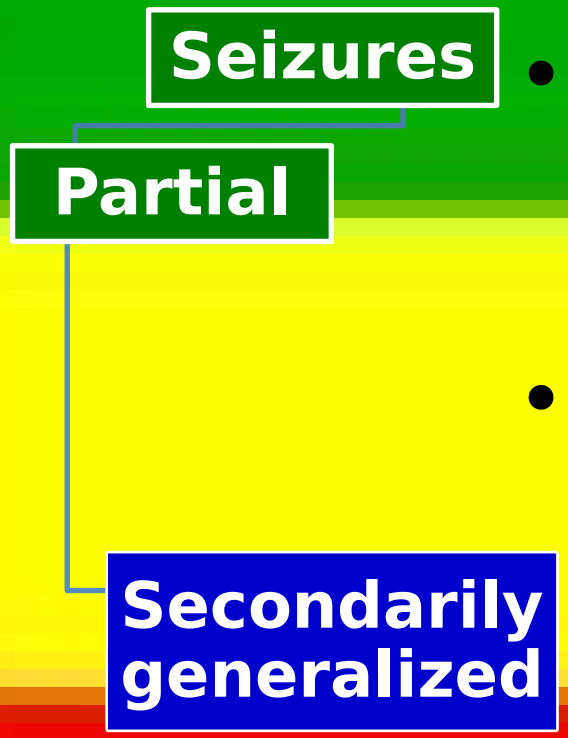
- With no loss of consciousness
- Manifest as alterations in motor functions, sensory or somatosensory (auras) symptoms, or automatisms.

Complex Partial Seizure



- With impairment of consciousness
- Simple partial onset followed by impairment of consciousness – with or without automatisms
- Impaired consciousness at onset – with or without automatism
- Are amnestic to these events
- Duration: <2min

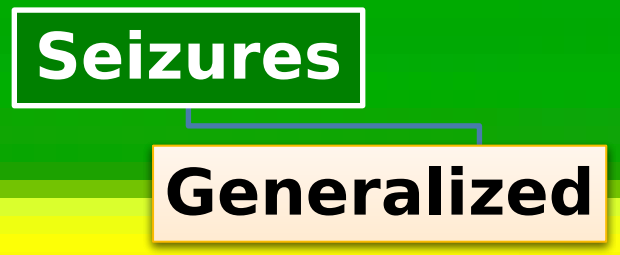
Secondary Generalized Partial Seizure



- Partial onset evolving to generalized tonic-clonic seizures
- Duration: 1-3 minutes

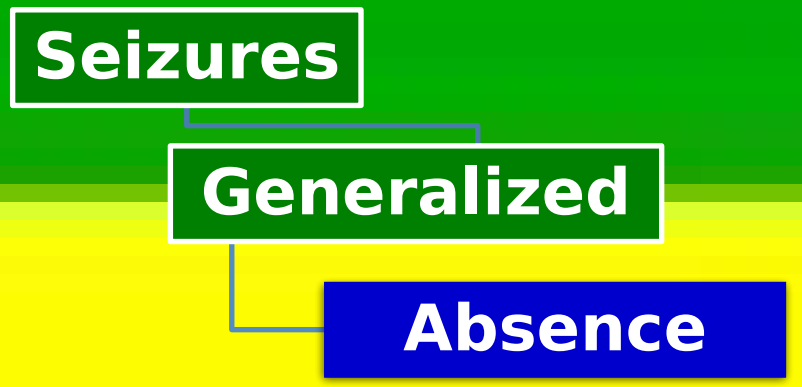
Generalized Seizure

- Involvement of both hemispheres.
- Motor manifestations are bilateral
- There is a loss of consciousness.



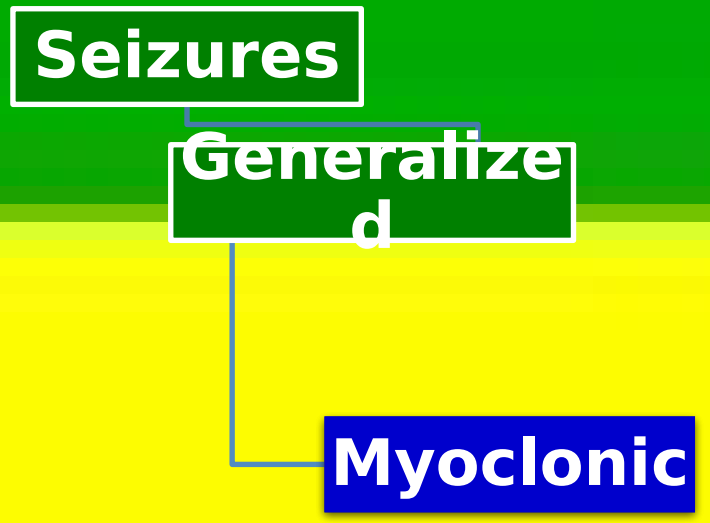
Absence S

- A sudden onset, interruption of ongoing activities, a blank stare, and possibly a brief upward rotation of the eyes.
- Young children-adolescence
- Duration: 3-20 seconds



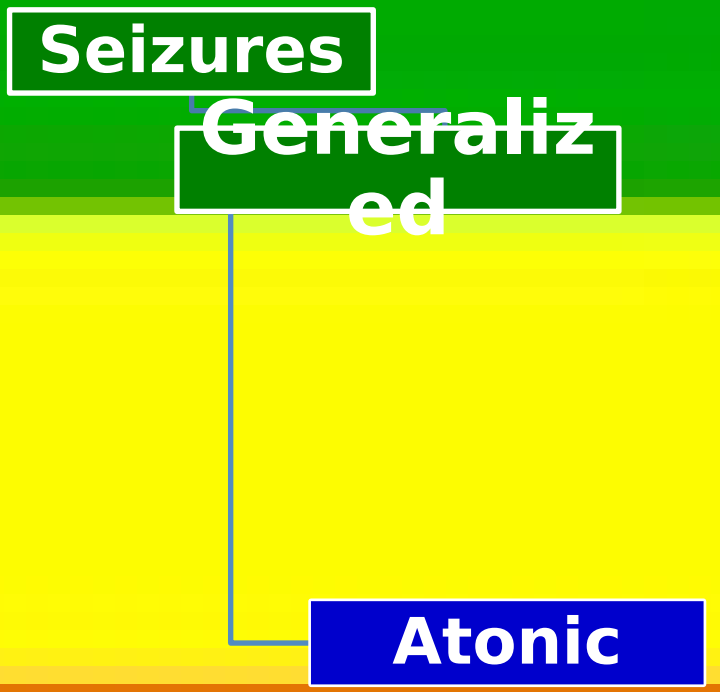
Generalized Myoclonic Seizure

- Brief shock-like muscular **contractions** of the face, trunk, and extremities



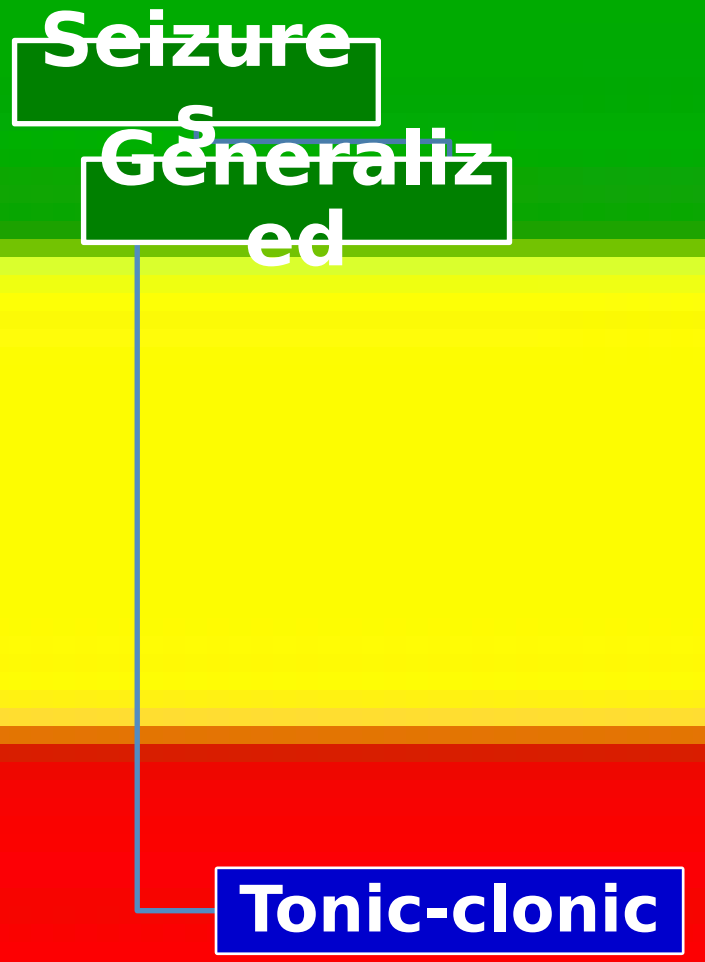
Atonic Seizure

- A sudden **loss of muscle tone**
- A head drop, the dropping of a limb, or a slumping to the ground



Generalized Tonic – Clonic Seizure

- Sudden sharp tonic contraction of muscles followed by a period of rigidity and clonic movements.
- During the seizure, the patient may **cry** or **moan**, lose sphincter control, bite the tongue, or develop cyanosis.
- After the seizure, the patient may have altered consciousness, drowsiness, or confusion for a variable period of time (**postictal period**) and frequently goes into a deep sleep.
- Tonic and clonic seizures can occur separately.
- Duration: 30-120 sec



TREATMENT

- **Desired Outcome**
  - Complete elimination of seizures
  - Optimal quality of life with a seizure-free state.
  - Balance between efficacy and side effects

General Approach

- Treatment of underlying conditions that cause or contribute to the seizures,
- Avoidance of precipitating factors
- Suppression of recurrent seizures by prophylactic therapy with AEDs or surgery, and
- Addressing a variety of psychological and social issues.

Treatment of Underlying Conditions

- Treatment of metabolic disturbance such as an abnormality of serum electrolytes or glucose
- Avoidance of drugs that caused the seizure (e.g., theophylline) or illicit drug use (e.g., cocaine)
- Appropriate treatment of underlying lesions (a structural CNS lesion such as a brain tumor, vascular malformation, or brain abscess)

Avoidance of Precipitating Factors

- Patient who has seizures in the setting of sleep deprivation should obviously be advised to maintain a normal sleep schedule
- Modify alcohol drinking habits
- Stress reduction techniques such as physical exercise, meditation, or counseling

Initiation of AED

- Antiepileptic drug therapy should be started in any patient with **recurrent seizures**
- Whether to initiate therapy in a patient with a single seizure is controversial.
  - ✓ Risk factors associated with recurrent seizures include the following:
    1) Abnormal neurologic examination,
    2) Seizures presenting as status epilepticus,
    3) Postictal Todd's paralysis,
    4) Strong family history of seizures, or
    5) An abnormal EEG.
  - ✓ Patients with one or more of these risk factors should be treated

SELECTION OF ANTIEPILEPTIC DRUGS

- Older medications such as phenytoin, valproic acid, carbamazepine, and ethosuximide are generally used as first-line therapy for most seizure disorders since,
  - They are as effective as recently marketed drugs and
  - Significantly less expensive.
- Most of the new drugs are used as add-on or alternative therapy.
- In addition to efficacy, factors influencing the choice of an initial medication include the **convenience of dosing** (e.g., once daily versus three or four times daily) and **potential side effects.**

Partial Seizures

- **Carbamazepine**, **phenytoin**, or **lamotrigine** is currently the initial drug of choice
  - Phenytoin has long half-life (once or twice daily dosing compared to two or three times daily dosing for carbamazepine and lamotrigine)
  - Phenytoin shows properties of **saturation kinetics**, such that small increases in phenytoin doses above a standard maintenance dose can precipitate marked side effects (acute phenytoin toxicity)
  - Long-term use of phenytoin has untoward **cosmetic effects** (e.g., hirsutism, coarsening of facial features, and gingival hypertrophy), and effects on bone metabolism

Partial Seizures

- Carbamazepine can cause **leukopenia**, **aplastic anemia**, or **hepatotoxicity**
- Lamotrigine causes skin rash during the initiation of therapy (can lead to Stevens-Johnson syndrome), risk can be reduced by slow introduction and titration.
- Lamotrigine must be started slowly when used as add-on therapy with valproic acid, since valproic acid inhibit its metabolism, thereby substantially prolonging its half-life.
- Valproic acid also rarely causes reversible bone marrow suppression and hepatotoxicity, and laboratory testing is required to monitor toxicity

Generalized Seizures

- **Valproic acid** is currently the best initial choice for the treatment of primarily generalized, tonic-clonic seizures.
- **Lamotrigine**, followed by carbamazepine and phenytoin, are suitable alternatives.
- Valproic acid is also particularly effective in absence, myoclonic, and atonic seizures and is therefore the drug of choice in patients with generalized epilepsy syndromes having **mixed seizure** types.
- Both carbamazepine and phenytoin can worsen certain types of generalized seizures, including absence, myoclonic, tonic, and atonic seizures

Generalized Seizures

- Ethosuximide is a particularly effective drug for the treatment of uncomplicated absence seizures, but it is not useful for tonic-clonic or partial seizures.
- Ethosuximide rarely causes bone marrow suppression, so that periodic monitoring of blood cell counts is required.
- **Lamotrigine** appears to be effective in epilepsy syndromes with mixed, generalized seizure types

Selection of Antiepileptic Drugs

Generalized Tonic Clonic	Focal	Absence	Myoclonic, Atonic
First Line			
Lamotrigine Valproic acid	Lamotrigine Carbamazepine Oxcarbazepine Phenytoin Levetiracetam	Valproic acid Ethosuximide Lamotrigine	Valproic acid Lamotrigine Topiramate
Alternatives			
Phenytoin Carbamazepine Oxcarbazepine Topiramate Phenobarbital Primidone Felbamate	Topiramate Valproic acid Gabapentin Exogabine Phenobarbital Primidone Felbamate	Lamotrigine Clonazepam	Clonazepam Felbamate Clobazam

Phenytoin (Dilantin)

- Principal uses: grand mal, focal onset
- Dose: 300 – 400 mg/d (3 – 6mg/kg, adult; 4 – 8 mg/kg, child); qd-bid
- Adverse Effects:
  - Neurologic: Dizziness, diplopia, ataxia, confusion, incoordination
  - Systemic: gum hyperplasia, lymphadenopathy, hirsutism, osteomalacia, facial coarsening, skin rash
- Drug interaction: Level ↓d by INH, sulfonamides, fluoxetine; Level ↑d by enzyme inducing drugs

Carbamazepine (Tegretol, Carbatrol)

- Principal Uses: tonic-clonic, focal onset
- Dose: 600 – 1800 mg/d (15 – 35 mg/kg, child); bid – qid
- Adverse Effects:
  - Neurologic: Dizziness, diplopia, ataxia, Vertigo
  - Systemic: Aplastic anemia, leukopenia, GI irritation, hepatotoxicity, hyponatremia
- Drug interaction: Level ↓d by erythromycin, INH, cimetidine, fluoxetine; Level ↑d by

Valproic acid (Depakene, Depakote)

- Principal Uses: Tonic-clonic, absence, atypical absence, myoclonic, focal-onset
- Dose: 750– 2000 mg/d (20– 60mg/kg); bid – qid
- Adverse Effects:
  - ✓Neurologic: sedation, ataxia, tremor
  - ✓Systemic: Hepatotoxicity, thrombocytopenia, GI irritation, wt gain, transient alopecia
  - ✓Drug interaction: Level ↓d by enzyme inducing drugs

Lamotrigine (Lamictal)

- Principal Uses: Focal-onset, Tonic-clonic, Atypical absence, Myoclonic
- Dose: 150– 500 mg/d bid
- Adverse Effects:
  - ✓Neurologic: Dizziness, diplopia, sedation, ataxia, headache
  - ✓Systemic: Skin rash, Stevens-Johnson syndrome
- Drug interaction: Level □d by enzyme inducing drugs, level increased by valproic acid

Ethosuximide (Zarontin)

- Principal Uses: Absence Seizure (petit mal)
- Dose: 750– 1250 mg/d (20-40 mg/kg); qd-bid
- Adverse Effects:
  - Neurologic: Ataxia, Lethargy, Headache
  - Systemic: GI irritation, skin rash, bone marrow suppression

Gabapentin (Neurontin)

- Principal Uses: focal onset
- Dose: 900 – 2400 mg/d; tid-qid
- Adverse Effects:
  - Neurologic: Sedation, dizziness, ataxia, fatigue
  - Systemic: GI irritation, weight gain, edema

Topiramate (Topamax)

- Principal Uses: Focal-onset, tonic-clonic
- Dose: **200– 400 mg/d; bid**
- Adverse Effects:
  - Neurologic: Psychomotor slowing, sedation, speech or language problems, fatigue, paresthesias
  - Systemic: Renal stones (avoid use with other carbonic anhydrase inhibitors), weight loss
- Drug interaction: Level decreased by enzyme inducing drugs

Phenobarbital (Luminol)

- Principal Uses: Focal-onset, tonic-clonic
- Dose: 60– 180 mg/d (1– 4 mg/kg adult); (3– 6 mg/kg, child); qd
- Adverse Effects:
  - Neurologic: Sedation, ataxia, confusion, dizziness, decreased libido, depression
  - Systemic: Skin rash
- Drug interaction: Level increased by valproic acid, phenytoin

MONITORING OF THERAPY

- Most anticonvulsant drugs need to be introduced relatively slowly to minimize side effects
- Patients should expect that minor side effects such as mild sedation, slight changes in cognition, or imbalance will typically resolve within a few days
- Monitoring of serum antiepileptic drug levels
- If seizures continue despite gradual increases to the maximum tolerated dose and documented compliance, then it is necessary to switch to another AED
- This is usually done by **maintaining the patient on the first drug while a second drug is added.**

WHEN TO DISCONTINUE THERAPY

- It is reasonable to attempt withdrawal of therapy after 2 years in a patient who meets all of the following criteria:
  (1) Complete medical control of seizures for 1 to 5 years;
  (2) Single seizure type, either partial or generalized;
  (3) Normal neurologic examination, including intelligence;
  (4) Normal EEG.
- In most cases it is preferable to reduce the dose of the drug gradually over 2 to 3 months.
- Most recurrences occur in the first 3 months after discontinuing therapy,

Epilepsy and Pregnancy

- The most concerning effects are found with the use of valproic acid
  - Associated with a risk of major congental malformations that is 3.5 to 4 times that of offspring from nonepileptic women, especially if taken during the first trimester of pregnancy
  - These effects are dose-dependent
- Risk factors for malformations
  - Higher AED doses
  - Higher AED serum concentrations
  - Polytherapy (especially polytherapy with valproate), and a
  - Family history of birth defects

Epilepsy and Pregnancy

- Teratogenic effects may possibly be prevented by adequate folate intake,
- Prenatal vitamins with folic acid (0.4-5 mg/day) are recommended for women of child-bearing potential who are taking AEDs.
- Higher folate doses should be used in women with a history of a previous pregnancy with a neural tube defect or taking valproic acid

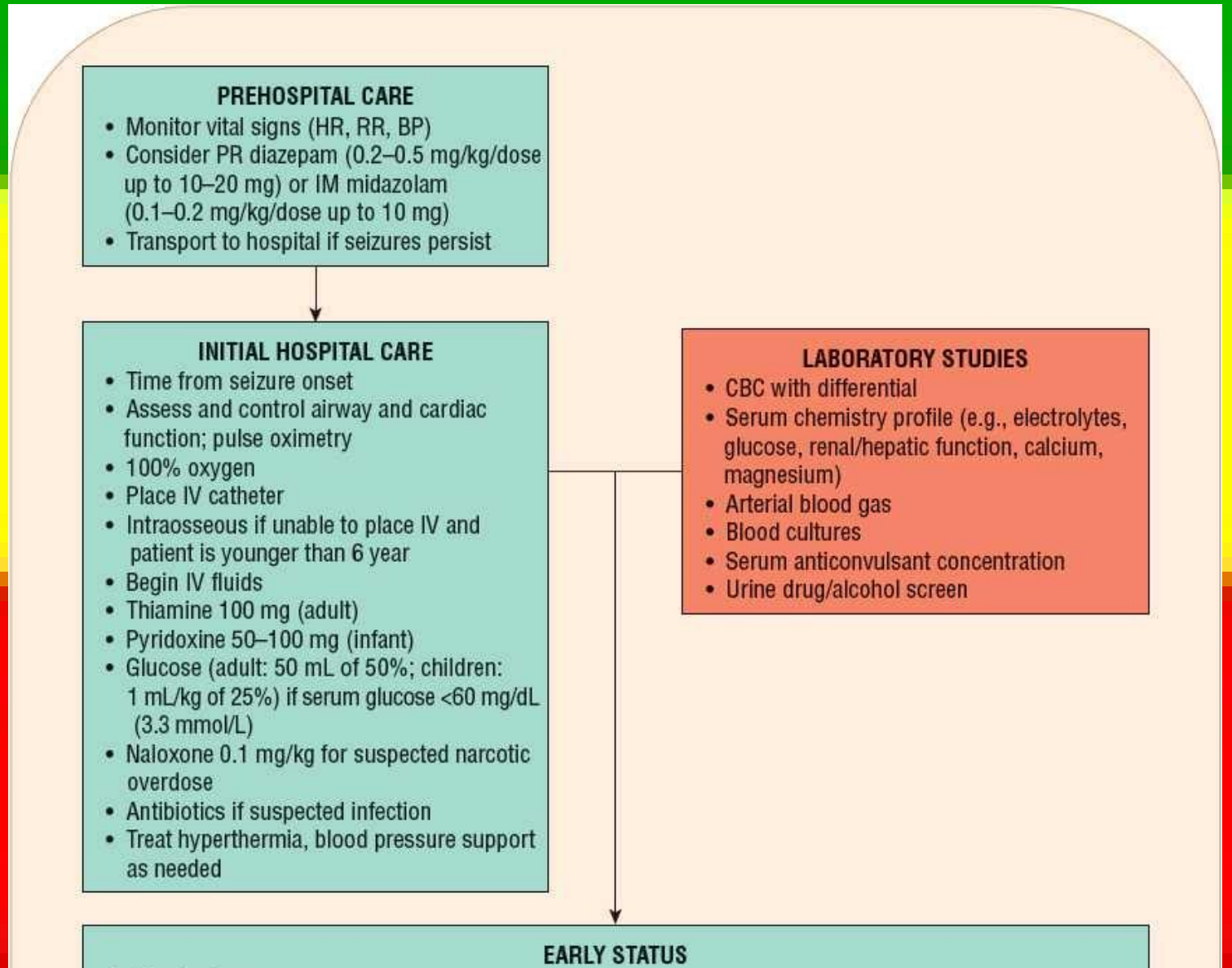
Status Epilepticus

- SE is defined as continuous seizure activity lasting more than 5 minutes or two or more seizures without complete recovery of consciousness.
- **Refractory status epilepticus** (RSE) is unresponsive to emergent (first-line) or urgent (second-line) therapy
- SE can present as nonconvulsive status epilepticus (NCSE) or
  generalized convulsive status epilepticus (GCSE).
  - NCSE is characterized by persistent impaired consciousness **without clinical seizure activity** and is diagnosed with electroencephalography (EEG).
  - GCSE is characterized by full-body motor seizures and involves the entire brain

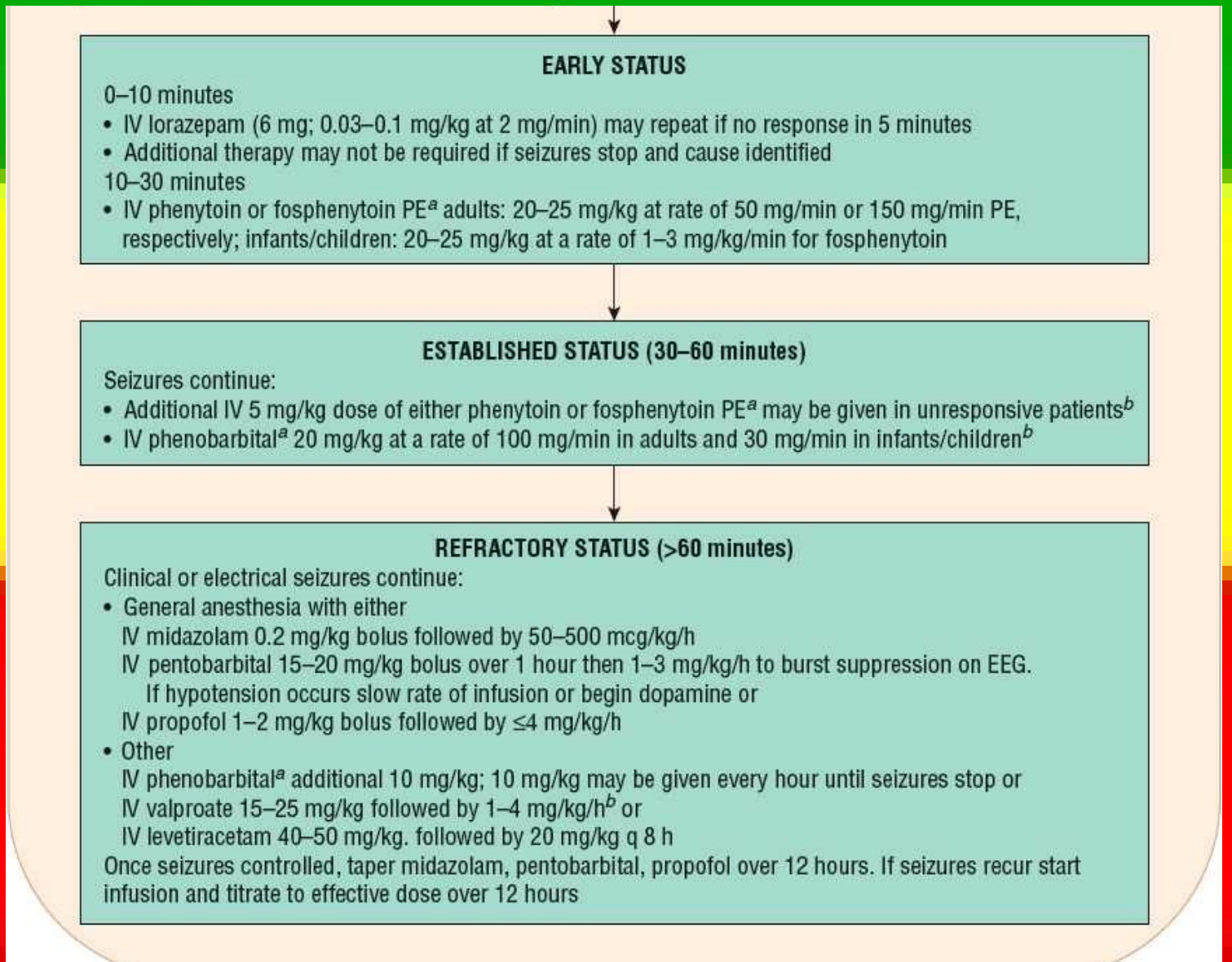
Etiology

- Causes of SE include
  - Metabolic disturbances (eg, hyponatremia, hypernatremia, hyperkalemia, hypocalcemia, hypomagnesemia, hypoglycemia);
  - Central nervous system (CNS) disorders, infections, injuries;
  - Hypoxia;
  - Drug toxicity (theophylline, isoniazid, cyclosporine, cocaine).
  - Preexisting epilepsy: anticonvulsant withdrawal or sub-therapeutic levels
  - Chronic alcoholism (withdrawal seizures), CNS tumors, and strokes.

Algorithm for the treatment of SE



Algorithm for the treatment of SE



PSYCHIATRIC DISORDERS

CHAPTER TWO

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SCHIZOPHRENIA

Definitions

- **Psychosis** is a difficult term to define and is frequently misused, not only in the newspapers and movies and on television, but unfortunately among mental health professionals as well.
- Psychosis can be considered to be a set of symptoms in which a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others are impaired.

Disorders in which psychosis is a defining feature

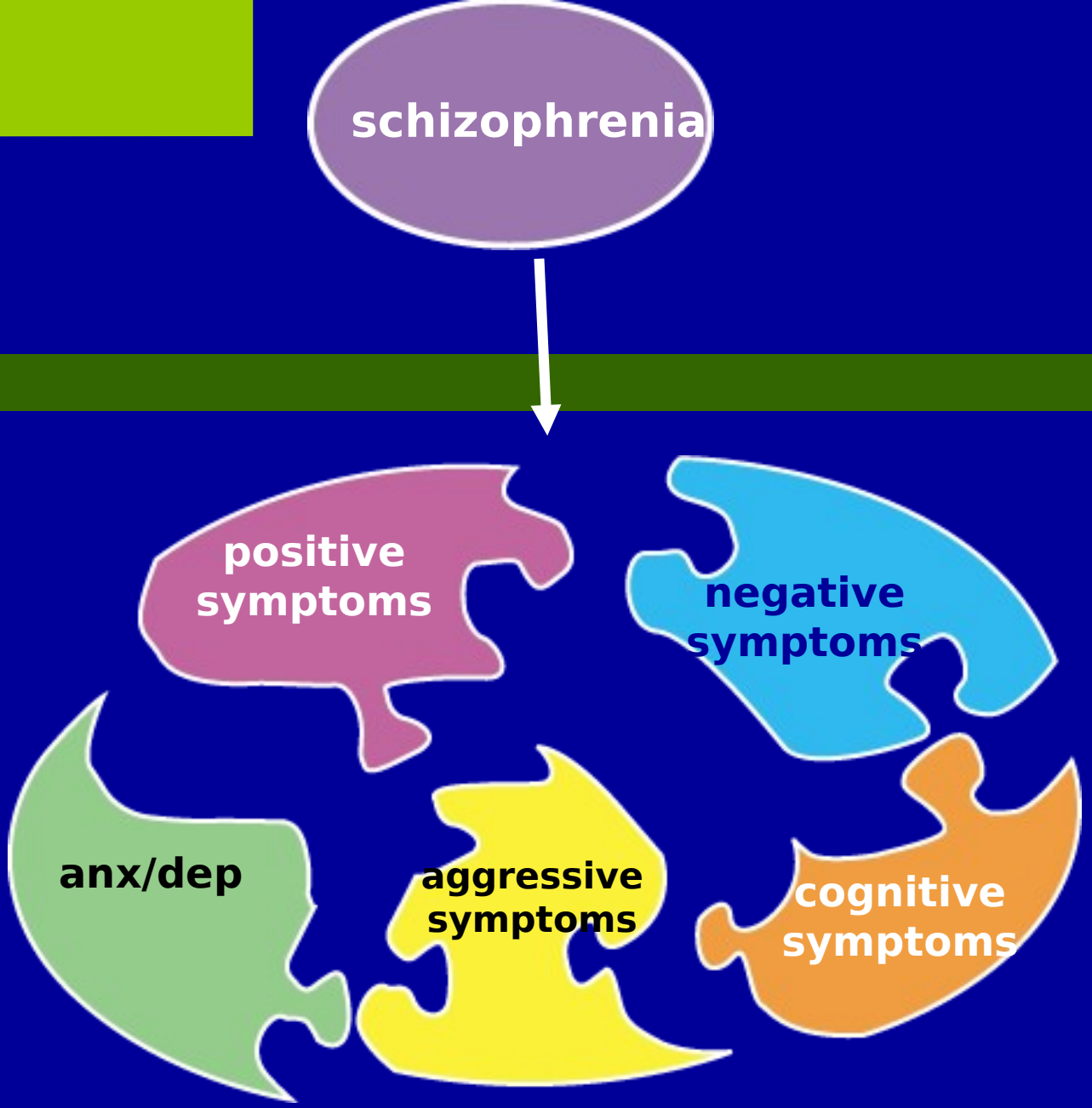
- Schizophrenia
- Substance induced psychotic disorders
- Schizophreniform Disorder
- Schizoaffective Disorder
- Delusional Disorder
- Brief Psychotic Disorder
- Shared Psychotic Disorder
- Psychotic Disorder due to general medical condition

Disorders in which psychosis is an associated feature

- Mania
- Depression
- Cognitive Disorders
- Alzheimer Dementia

SCHIZOPHRENIA

- Two (or more) of the following, each present for a significant portion of time during a 1 – month period
  - ✓Delusions,
  - ✓Hallucinations,
  - ✓Disorganized speech,
  - ✓Grossly disorganized or catatonic behavior, or
  - ✓Negative symptoms.
- ❖Continuous signs of the disturbance persist for at least 6 months


schizophrenia
positive symptoms
negative symptoms
anx/dep
aggressive symptoms
cognitive symptoms

Positive Symptoms

- Delusions
- Hallucinations
- Disorganized speech
- Disorganized or catatonic or agitated behavior

Positive Symptoms

- **Delusions:**
  - ✓ **Persecutory:** False belief that one's self or others are being persecuted, watched or conspired against by others.
  - ✓ **Delusion of control:** False belief that ones thoughts, feelings or behaviors are controlled by an outside force.
  - ✓ **Delusions of guilt or sin:** False belief that one has committed a terrible act.
  - ✓ **Somatic delusions:** False belief that ones appearance or part of one's body is diseased or altered.

Positive Symptoms

- **Delusion (continued)**
  - ✓ **Grandiose delusions :** False belief that one has “special” power or that “supernatural knowledge”
  - ✓ **First Rank symptoms:** These are
  - (a) *Thought insertion (*experience of thoughts being put into one’s mind);
  - (b) *Thought broadcasting (*experience of one’s thoughts being known to others)
  - (c) *Thought withdrawal (*experience of thoughts being removed from one’s mind)

Positive Symptoms

- **Hallucinations:**
  - ✓ Auditory hallucinations: the patient experiences hearing voices from outside which will tell him to “do certain things” or two or more voices talking among each other commenting about the patient.
  - ✓ Visual hallucinations: It is rare in functional psychoses like schizophrenia, however some schizophrenics do experience “seeing things” which are not there.
- **Thought disorder:**
  - Looseness of association; incoherence;

COGNITIVE SYMPTOMS

- Incoherence
- Loose associations
- Neologisms
- Impaired attention & impaired information processing
- Impaired verbal fluency (finding words to express your thoughts and feelings-Semantic memory)
- Problems with serial learning
- Impairment in vigilance for executive functioning (decision making; mental flexibility)
- Impaired working and secondary (storage)

Negative Symptoms

- **A**ffective flattening
- **A**logia
- **A**volition
- **A**nhedonia
- **A**ttentional impairment

Aggressive Symptoms

- Overt hostility
- Self-injurious behavior
- Sexual acting out
- Suicide
- Arson or other property damage

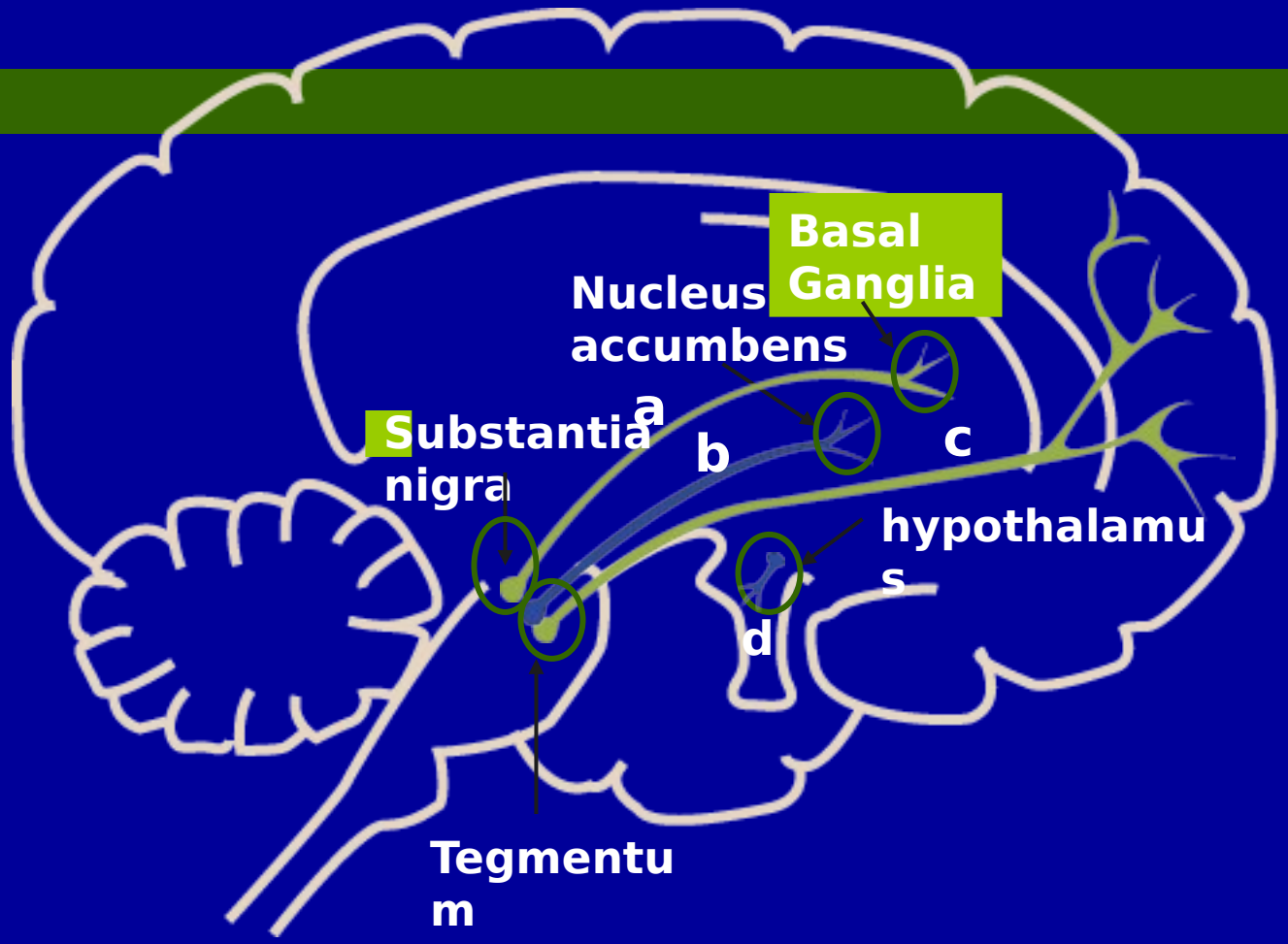
Depressive & Anxious Symptoms

- Depressed mood
- Anxious mood
- Guilt
- Tension
- Irritability
- Worry

Four key Dopamine Pathways and the biological basis of Schizophrenia

1. The Mesolimbic Dopamine Pathway
2. The Mesocortical Pathway
3. The Nigrostriatal Pathway
4. The Tubero infundibular Pathway

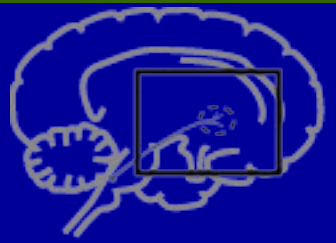
DOPAMINE PATHWAYS

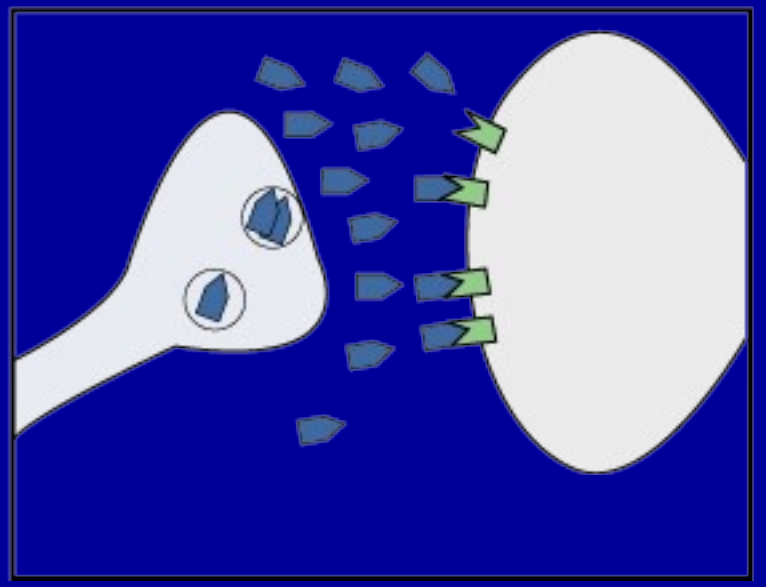


1. The Mesolimbic Dopamine Pathway

- It projects from dopaminergic cell bodies in the ventral tegmental area of the brainstem to axon terminals in limbic areas of the brain, such as the nucleus accumbens.
- It is thought to have an important role in emotional behaviors.
- Hyperactivity of the mesolimbic dopamine pathway hypothetically accounts for **positive symptoms** of schizophrenia.

Mesolimbic over activity = positive symptoms



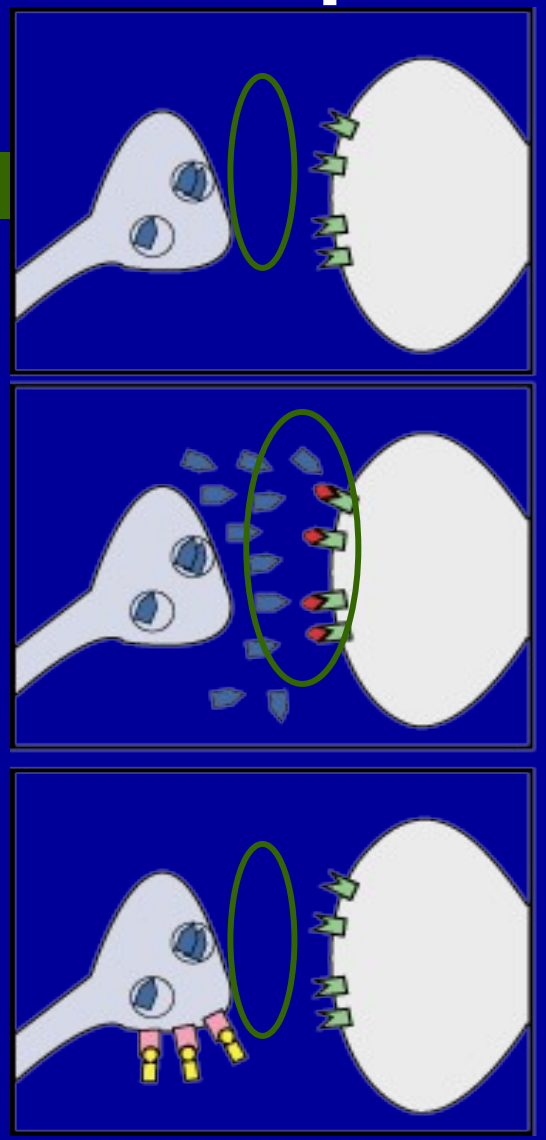




2. Mesocortical Dopamine Pathway

- It also projects from the midbrain ventral tegmental area to axons of the frontal cortex especially to *dorsolateral prefrontal cortex.*
- It mediates the **negative** and **cognitive symptoms** in schizophrenia.
- It has been implicated in aspects of learning & memory.
- Dopamine antagonists can worsen negative symptoms of schizophrenia.

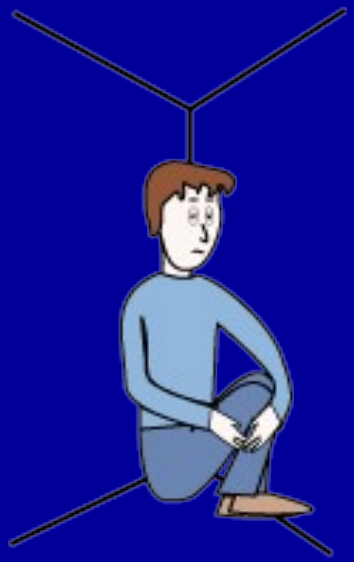
Mesocortical pathway



Primary dopamine deficiency

=

D2 receptor blockade



Secondary dopamine deficiency

increase in negative symptoms

3. Nigrostriatal Pathway

- It projects from dopaminergic cell bodies in the substantia nigra of the brainstem via axons terminating in the basal ganglia or striatum.
- **Deficiencies in DA** this pathway cause movement disorders, like Parkinson's disease, which is characterized by rigidity, akinesia, or bradykinesia, and tremor.
- DA deficiency in the basal ganglia also can produce akathisia and dystonia.
- **Hyperactivity of DA** in the nigrostriatal pathway is thought to underlie various hyperkinetic movement disorders, such as chorea, dyskinesias, and tics
- Chronic blockade of DA 2 receptors in this pathway may result in a hyperkinetic movement disorder known as *Tardive*

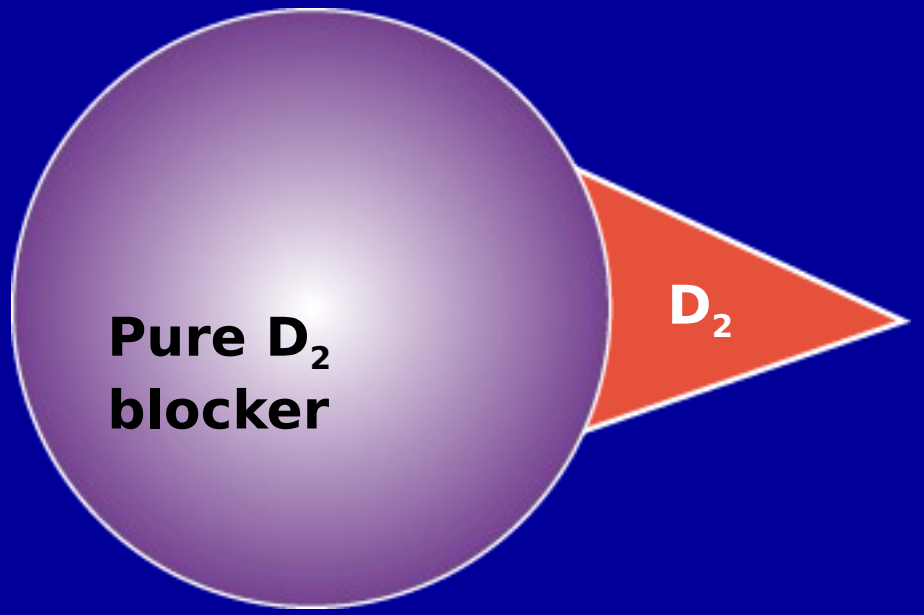
4. Tuberoinfundibular Dopamine Pathway

- It projects from the hypothalamus to the anterior pituitary
- It regulates prolactin secretion into the circulation.
- **Dopamine inhibits prolactin secretion**.
- Post-synaptic D2 receptor blockade by antipsychotic drugs increase prolactin secretion which produces galactorrhea, amenorrhea, sexual dysfunction, depression and osteoporosis.

ANTIPSYCHOTIC AGENTS

- Conventional Antipsychotic Drugs
- Atypical Antipsychotic Drugs

Conventional Antipsychotic Drugs



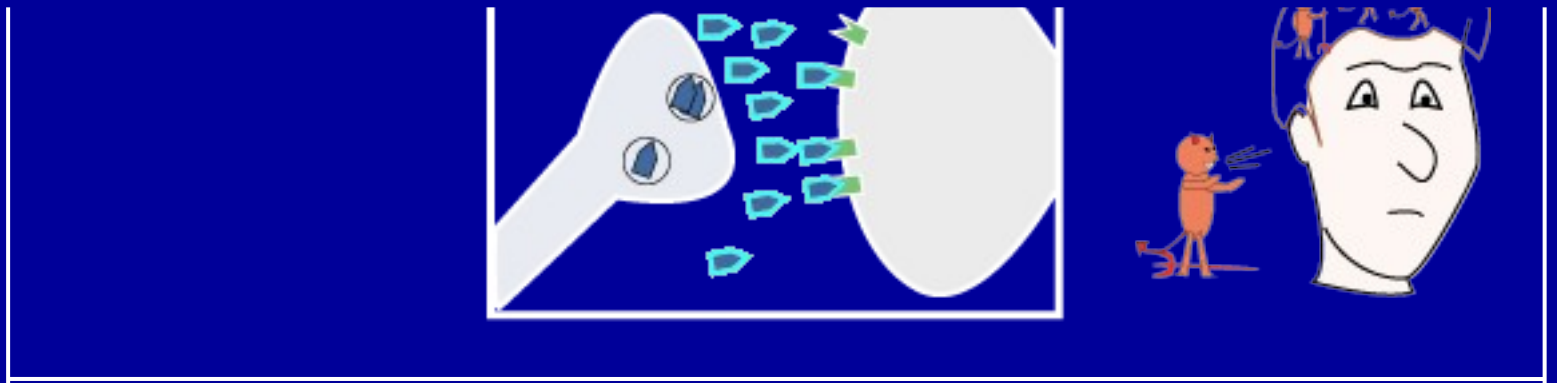
Conventional Antipsychotics

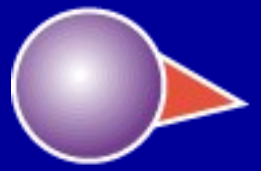
Generic name	Daily Oral Dose
Chlorpromazine (Thorazine)	200-1500
Fluphenazine (Prolixin)	2-20
Haloperidol (Haldol)	2-20
Loxapine (Loxitane)	20-200
Mesoridazine (Serentil)	50-400
Molindone (Moban)	20-150
Perphenazine (Trilafon)	4-48
Thiorizadine (Mellaril)	200-800
Thiothixene (Navane)	2-30
Trifluoperazine (Stelazine)	5-50

Conventional Antipsychotic Drugs

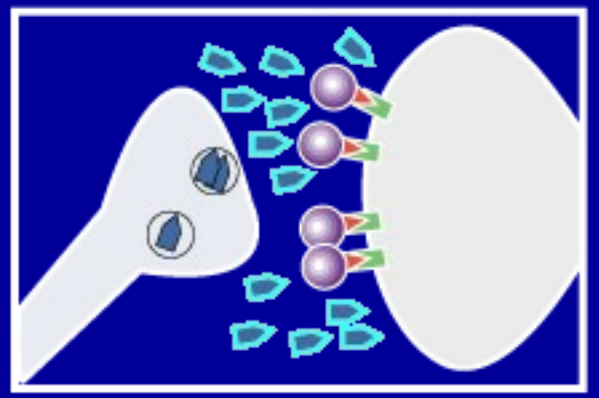
- The earliest effective treatments for schizophrenia and other psychotic illnesses arose from serendipitous clinical observations rather than from scientific knowledge of the neurobiological basis of psychosis or the mechanism of action of effective antipsychotic agents.
- Thus, the first antipsychotic drugs were discovered by accident in the 1950s when a putative antihistamine (**chlorpromazine**) was serendipitously observed to have antipsychotic effects when tested in schizophrenic patients.

Blockade of postsynaptic dopamine 2 receptors by a dopamine 2 antagonist acting in the mesolimbic dopamine pathway is hypothesized to mediate the antipsychotic efficacy of the antipsychotic drugs and their ability to diminish or block positive symptoms.



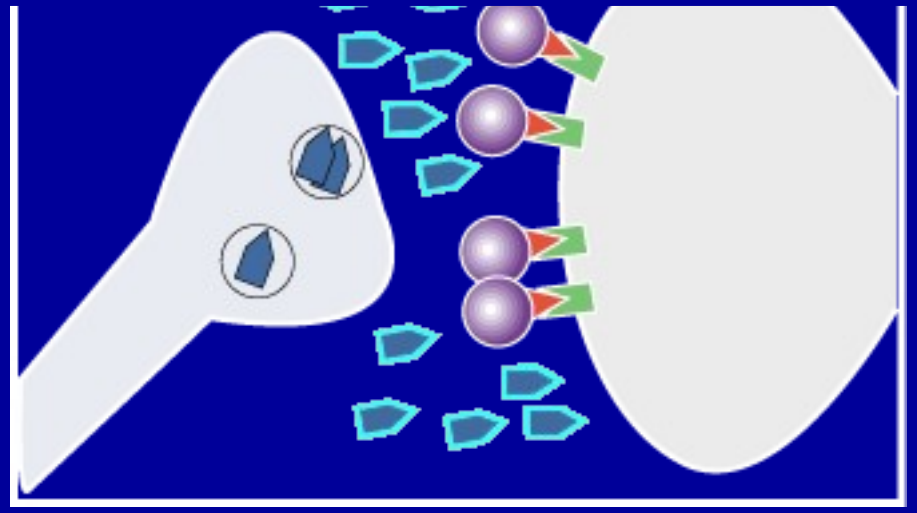


Pure D2 blocker

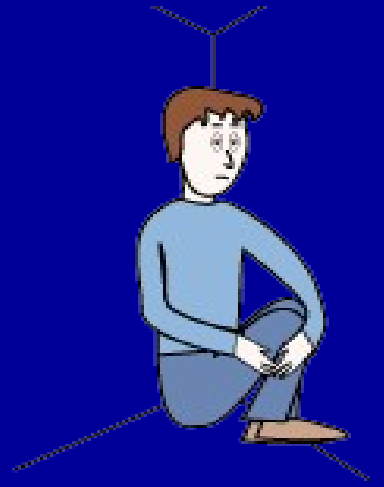




When postsynaptic dopamine 2 receptors are blocked by dopamine 2 antagonist acting in the **mesocortical dopamine pathway**, this can cause emotional blunting and cognitive problems that mimic the **negative symptoms** of schizophrenia. If a patient already has these symptoms before treatment, medication with drugs that block these receptors can make their negative symptoms worse.

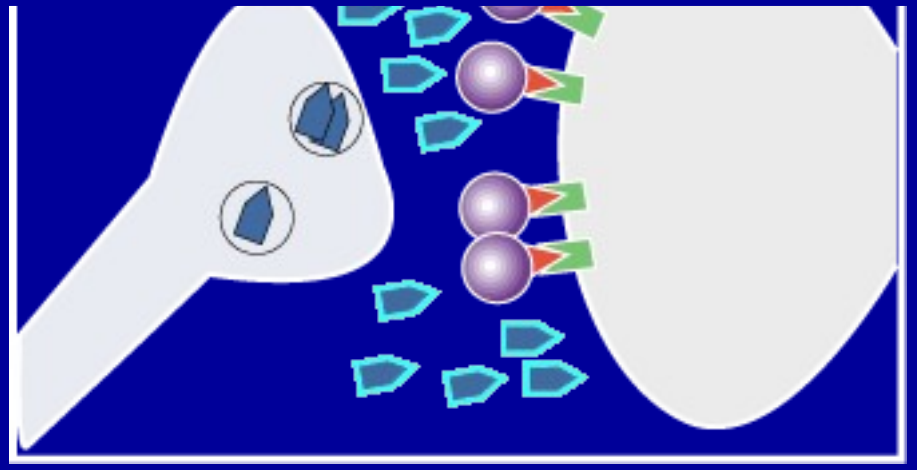


Mesocortical Pathway



Increase in negative symptoms

When dopamine 2 receptors are blocked by dopamine 2 antagonists in the nigrostriatal pathway, it produces disorders of movement like those in Parkinson's disease. Since the nigrostriatal pathway projects to the basal ganglia, a part of the so-called extrapyramidal nervous system, side effects associated with blockade of dopamine 2 receptors there are sometimes called extrapyramidal symptoms (EPS).



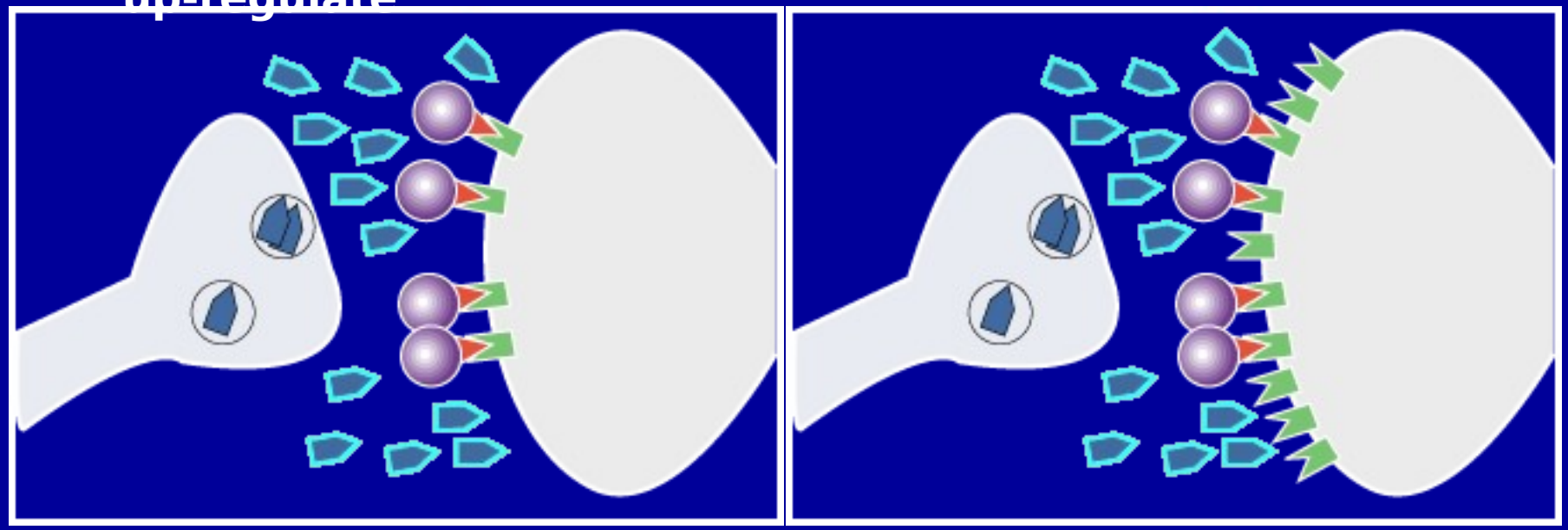
Nigrostriatal pathway



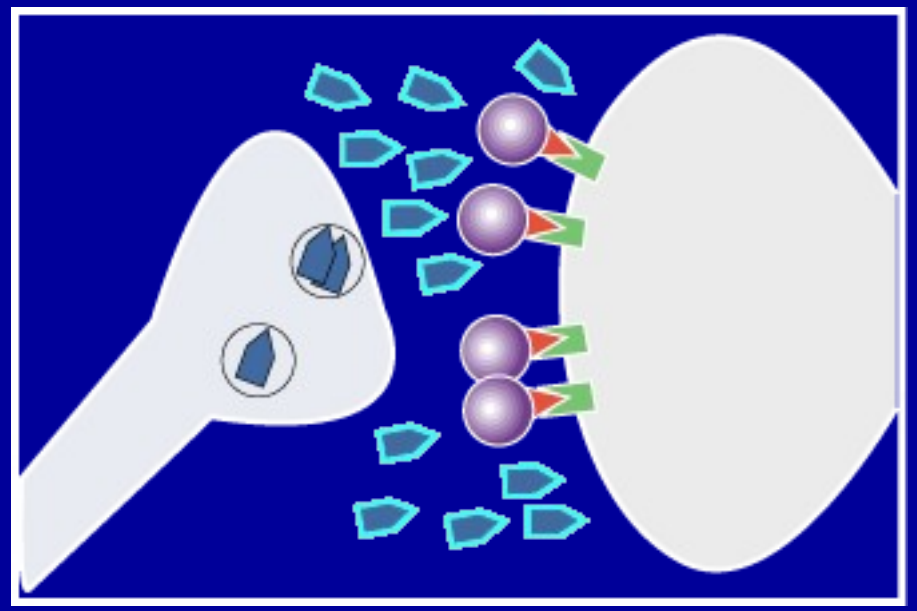
EPSs

Blockade of receptors in the nigrostriatal dopamine pathway causes them to up-regulate

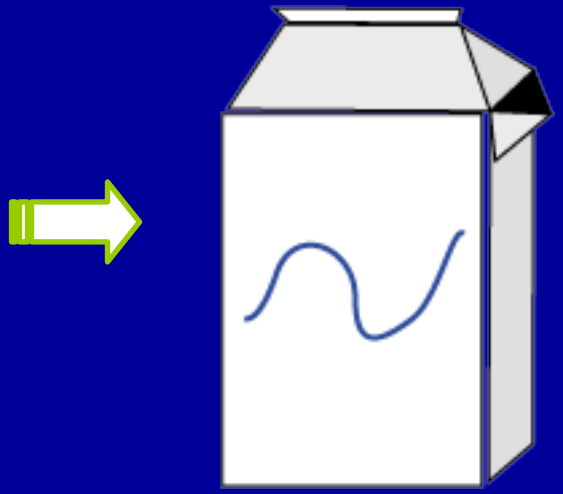
This up-regulation may lead to tardive dyskinesia



The **tuberoinfundibulardopamine pathway** controls prolactin secretion. When dopamine 2 receptors in this pathway are blocked by dopamine 2 antagonists, prolactin levels rise, sometimes so much so that women may begin lactating inappropriately, a condition known as **galactorrhea**.

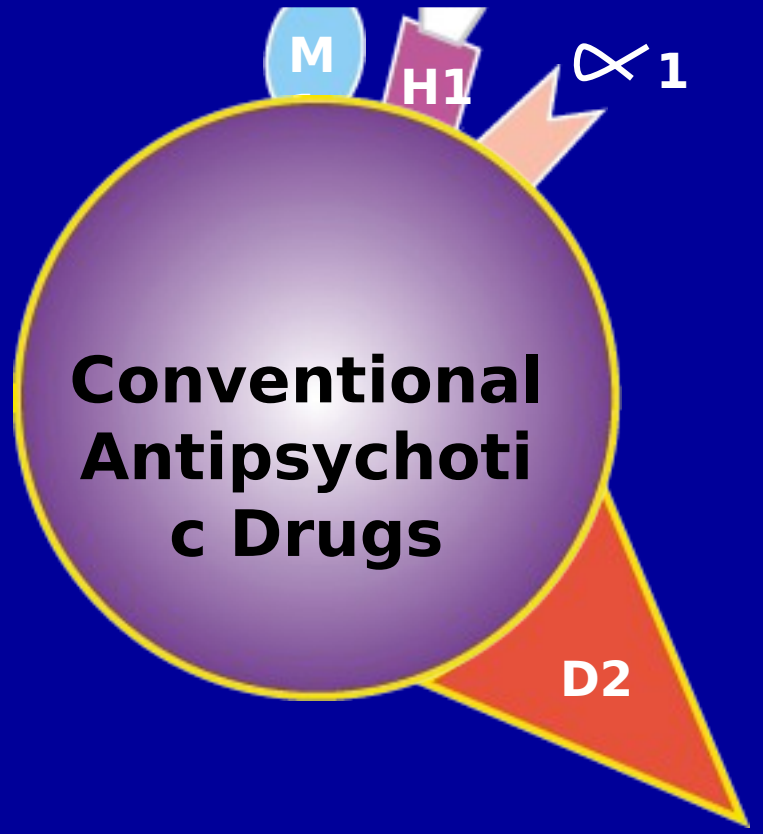


Tuberoinfundibular pathway



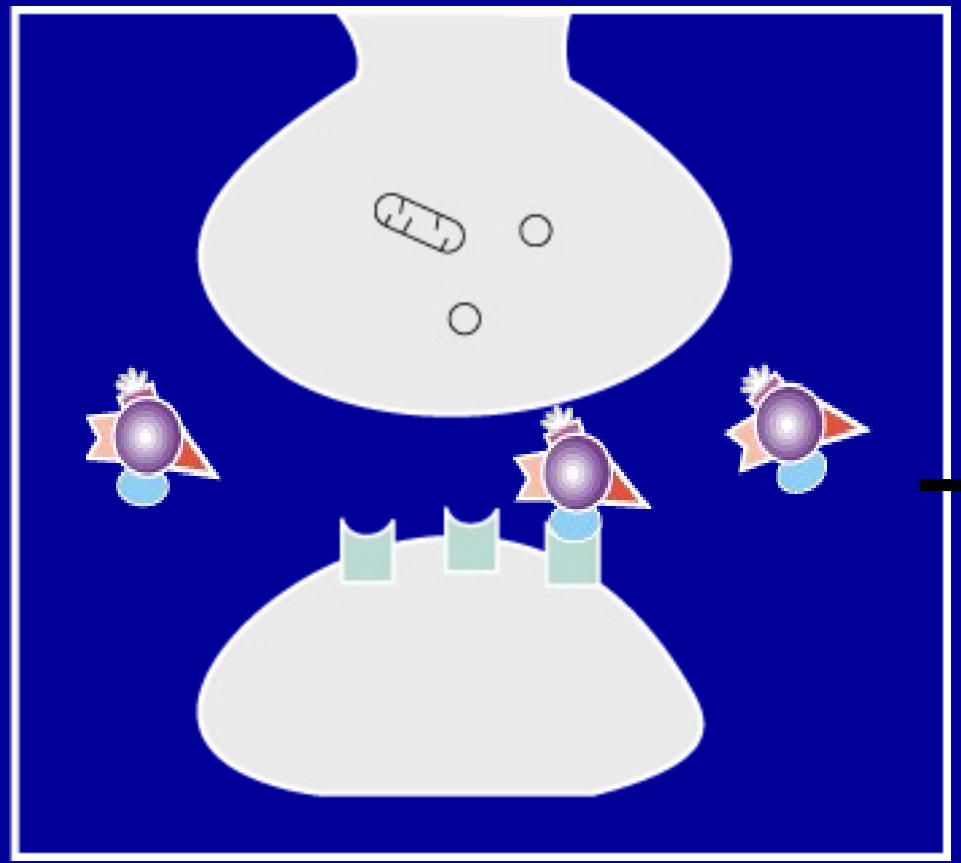
Prolactin levels rise

Conventional antipsychotic drugs have at least four actions: blockade of dopamine 2 receptors (D2); blockade of muscarinic cholinergic receptors (M1); blockade of alpha 1 adrenergic receptors (alpha 1); and blockade of histamine receptors (antihistaminic actions; [H1]).



Side Effects

M1 Inserted



constipation



blurred vision



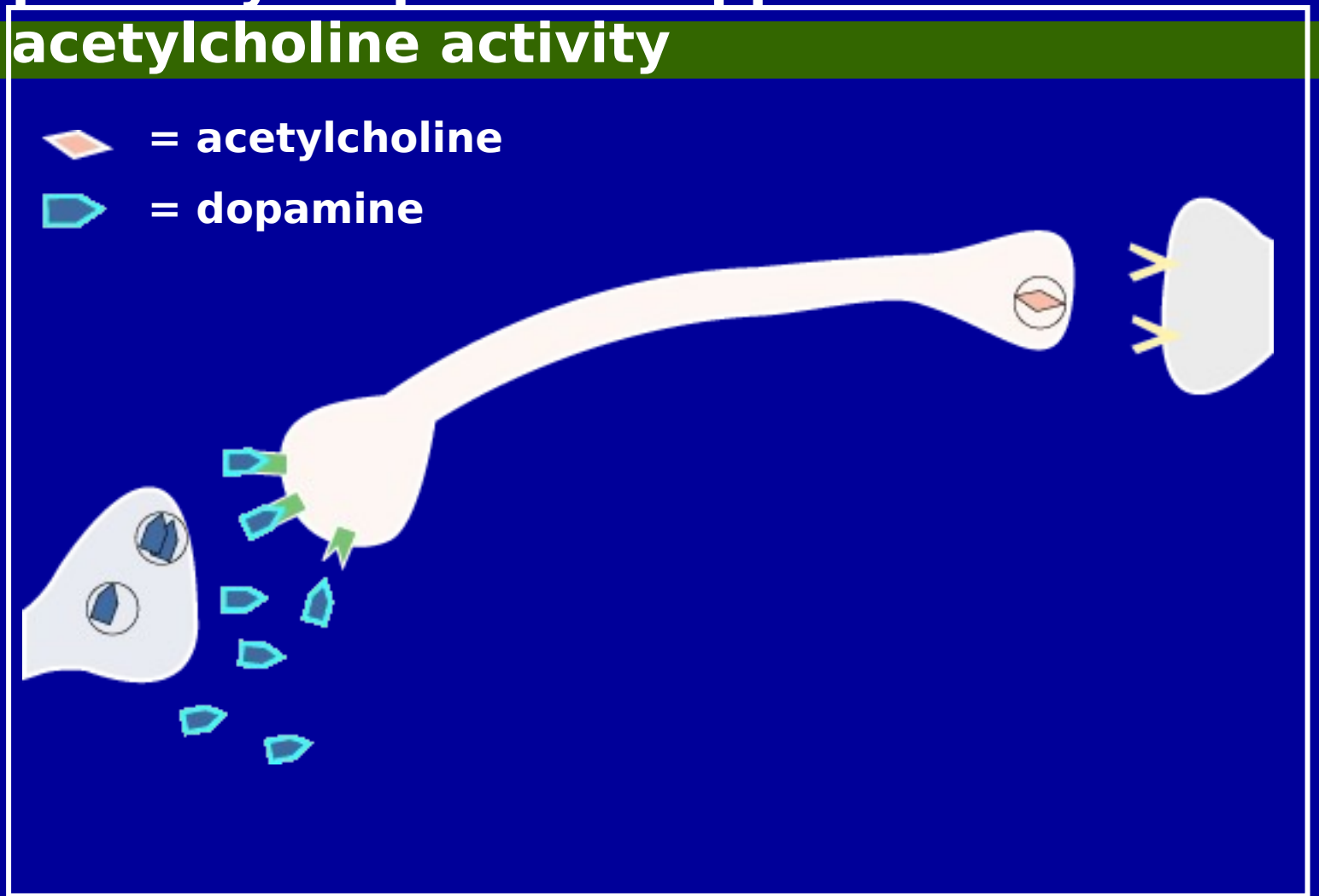
dry mouth



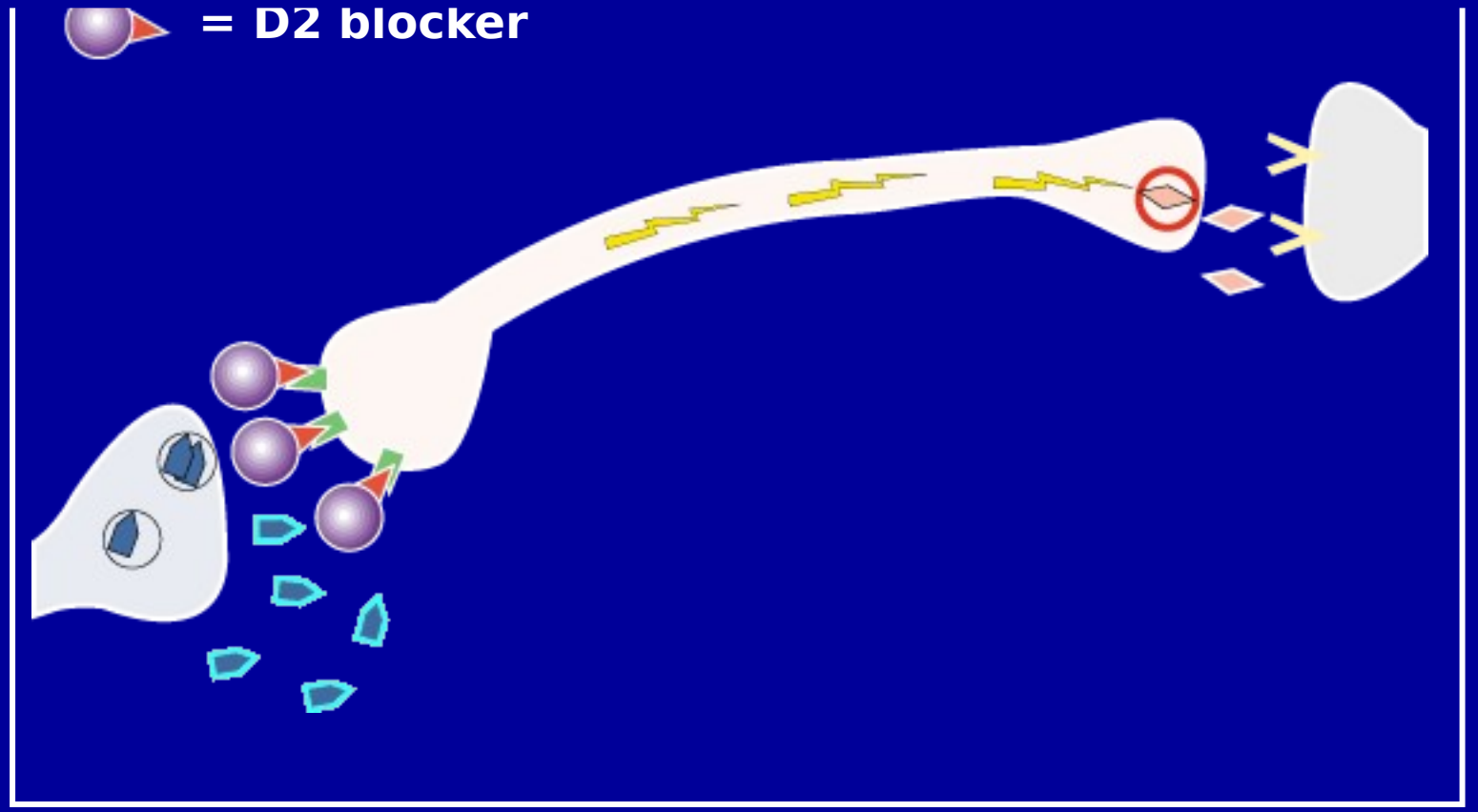
drowsiness



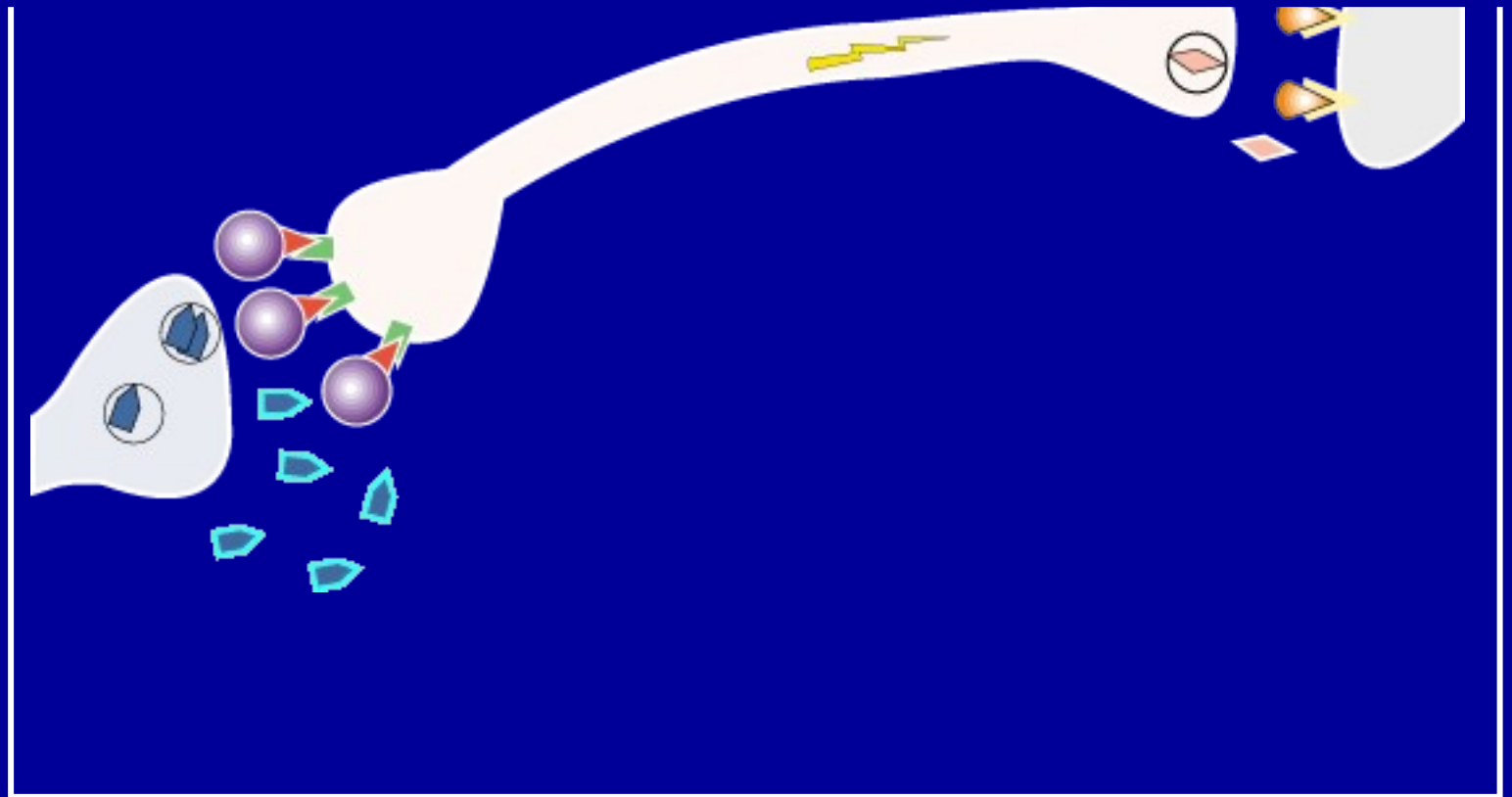
Dopamine & Acetylcholine have a reciprocal relationship in the nigro-striatal dopamine pathway. Dopamine suppresses acetylcholine activity



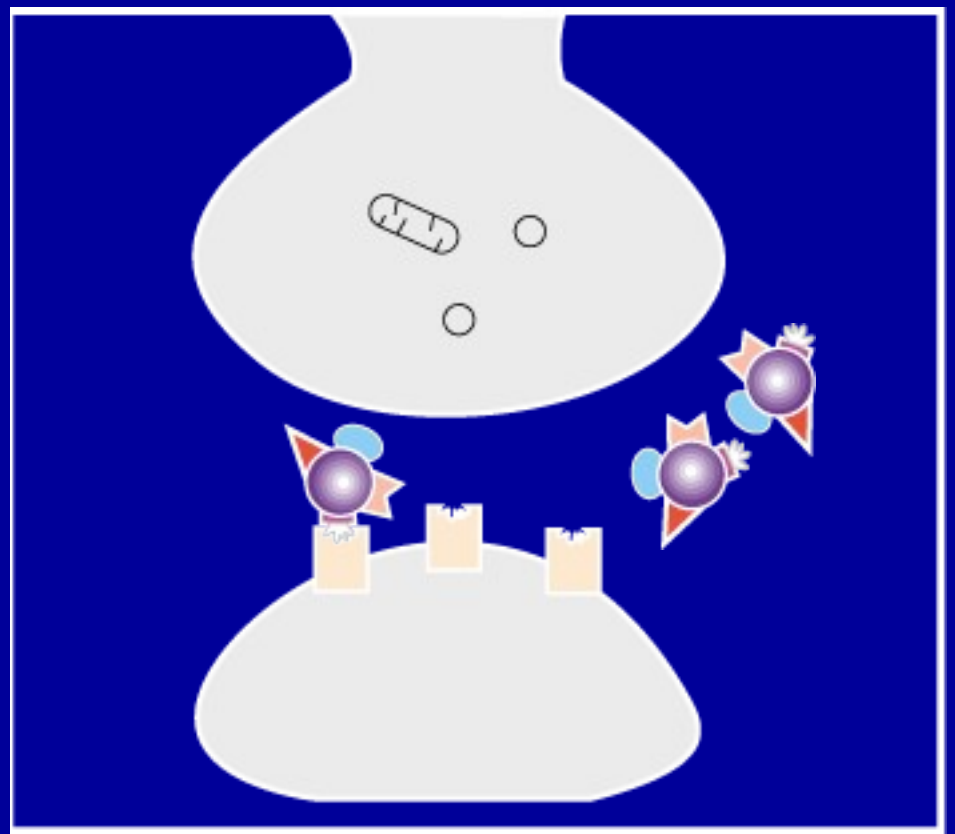
As dopamine normally suppresses acetylcholine activity, removal of dopamine inhibition causes an increase in acetylcholine activity. Thus, if dopamine receptors are blocked, acetylcholine becomes overly active. This is associated with the production of extrapyramidal symptoms (EPS)



One compensation for the overactivity of acetylcholine that occurs when dopamine receptors are blocked is to block the acetylcholine receptors with an anticholinergic agent. Thus, anticholinergics overcome excess acetylcholine activity caused by removal of dopamine inhibition when dopamine receptors are blocked by conventional antipsychotics



H1 Inserted



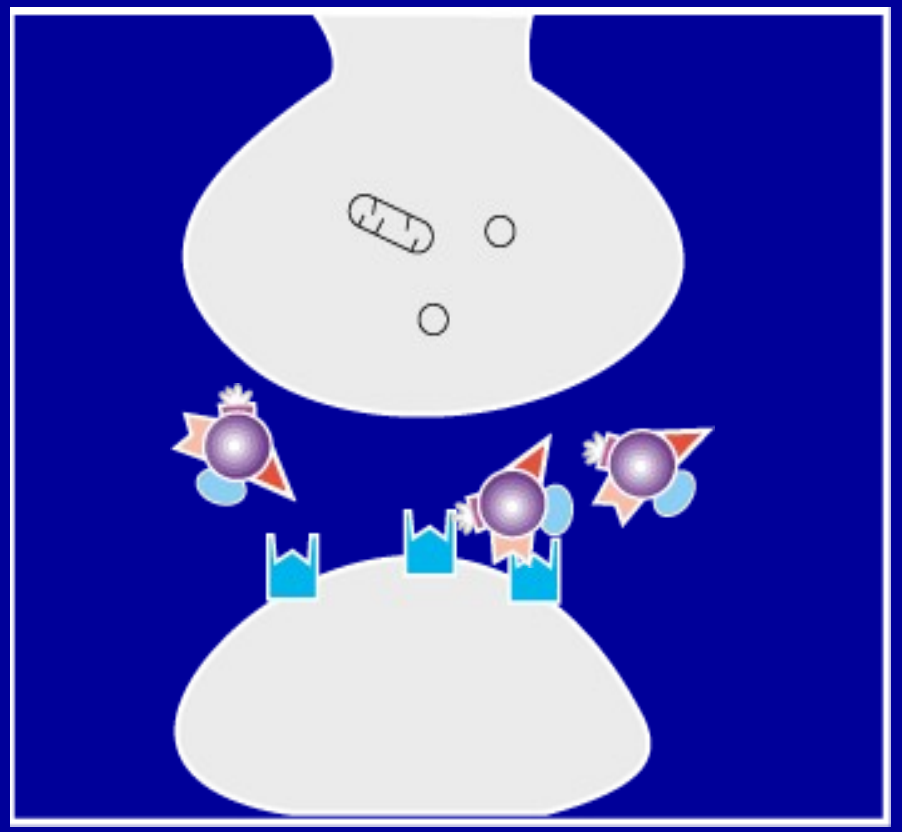
drowsiness





weight gain

1 Inserted





dizziness

decreased blood pressure

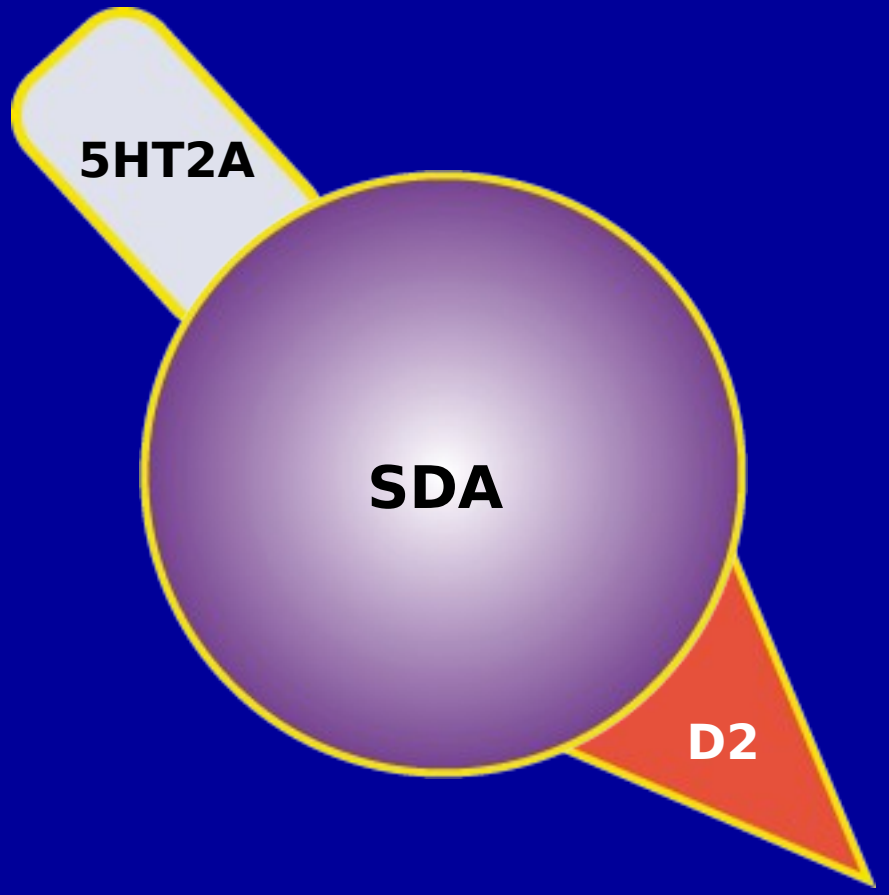


drowsiness

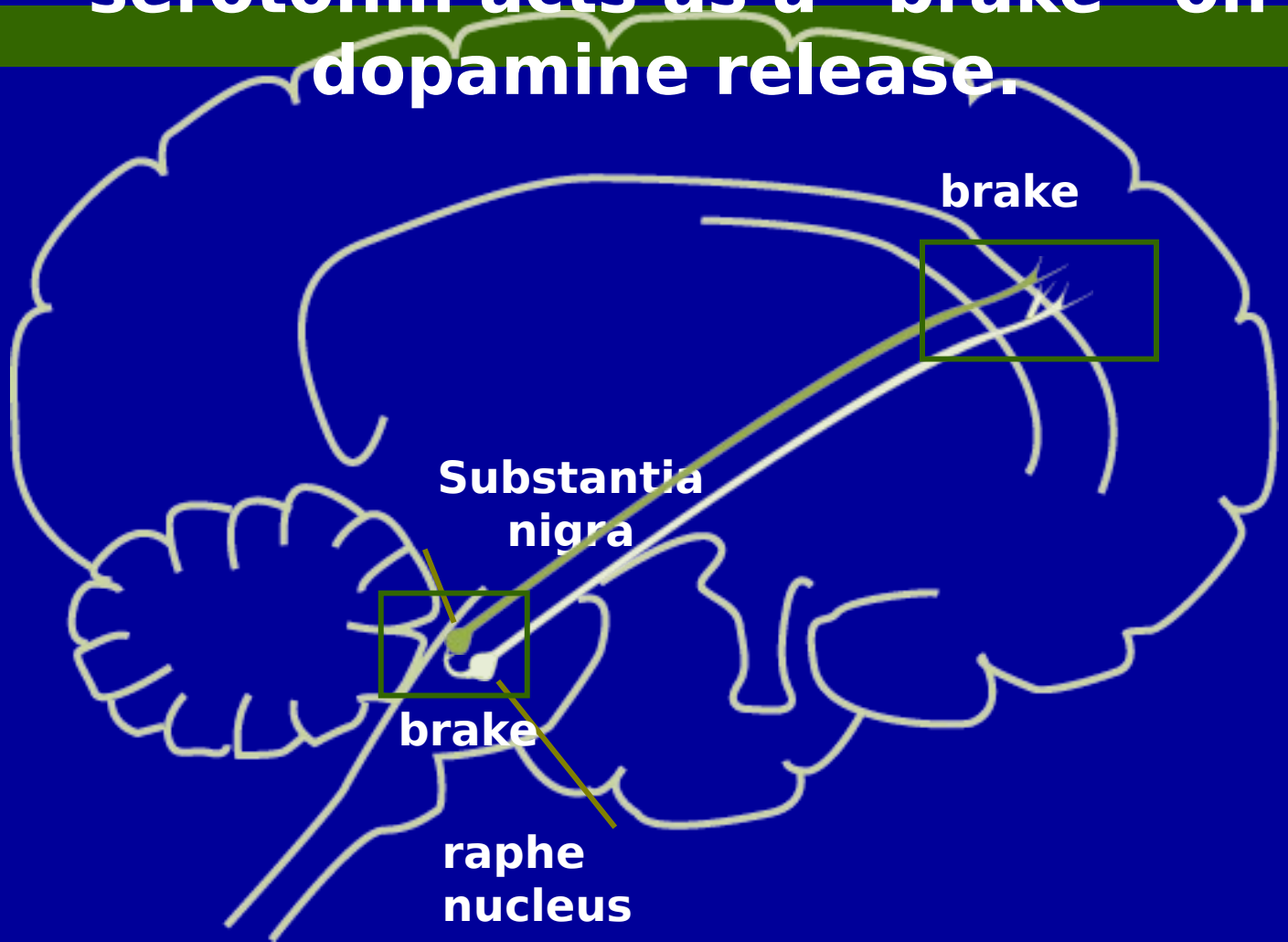
Depot Injections

- Long-acting depot inj are used for maintenance therapy especially when compliance with oral treatment is unreliable
- However, depot inj of conventional antipsychotics may give rise to a higher incidence of EPS than oral preparations
  - Fluphenazine decanoate (Modecate®) every 2 weeks
  - Haloperidol decanoate every 4 weeks

Atypical Antipsychotic Drugs



5HT-DA Interactions: Serotonin inhibits dopamine release, thus the release of serotonin acts as a “brake” on dopamine release.



Serotonin-Dopamine Antagonism

- Atypical antipsychotic is defined in part by the clinical properties that distinguish such drugs from conventional antipsychotics.
- Atypical antipsychotics

(1) Have stronger antagonism of 5-HT2 receptors than D2-dopamine receptors

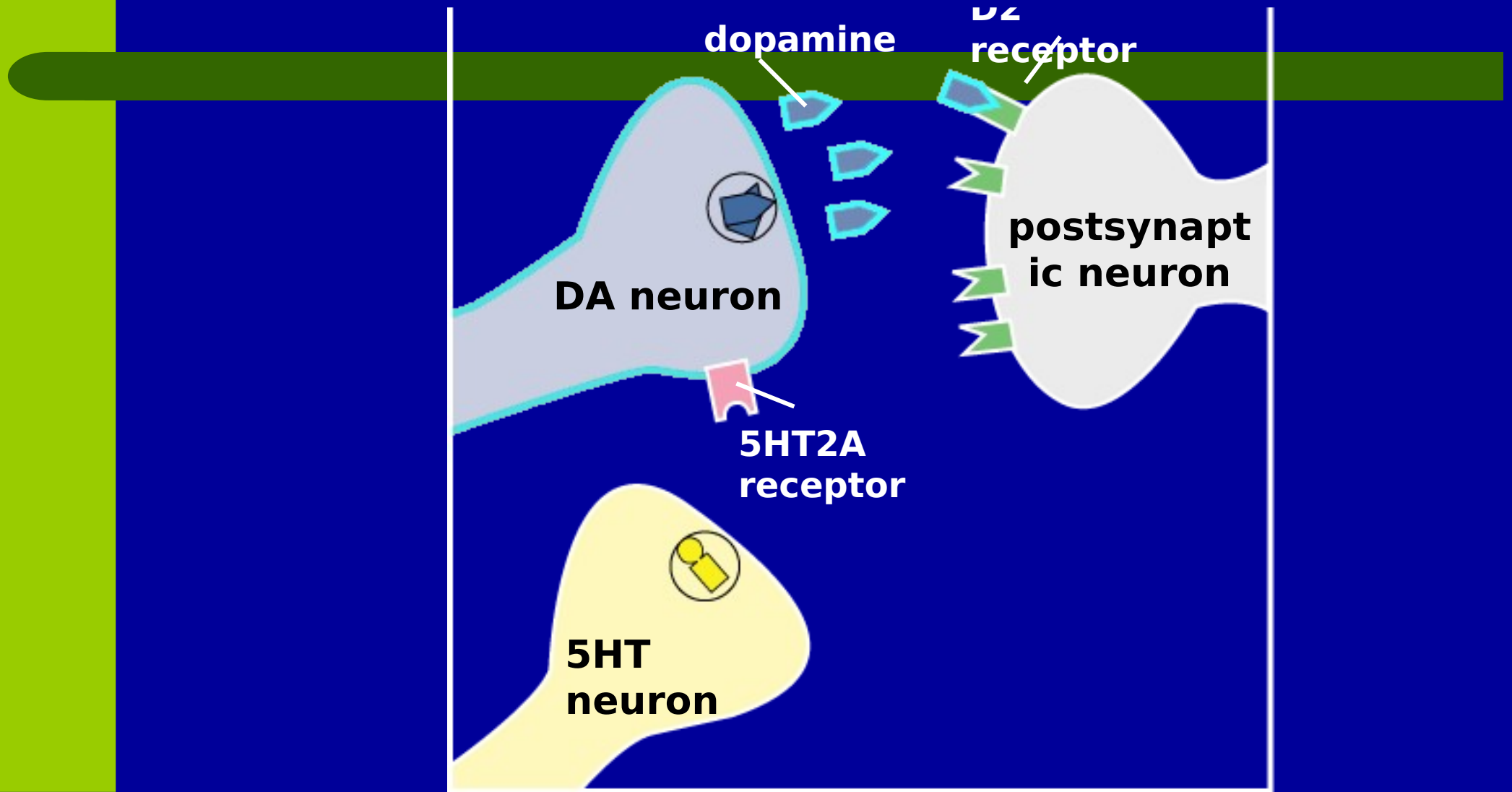
(2) Cause fewer EPS than conventional antipsychotics

(3) Improve negative symptoms

(4) Improve positive symptoms as well as do conventional antipsychotics.

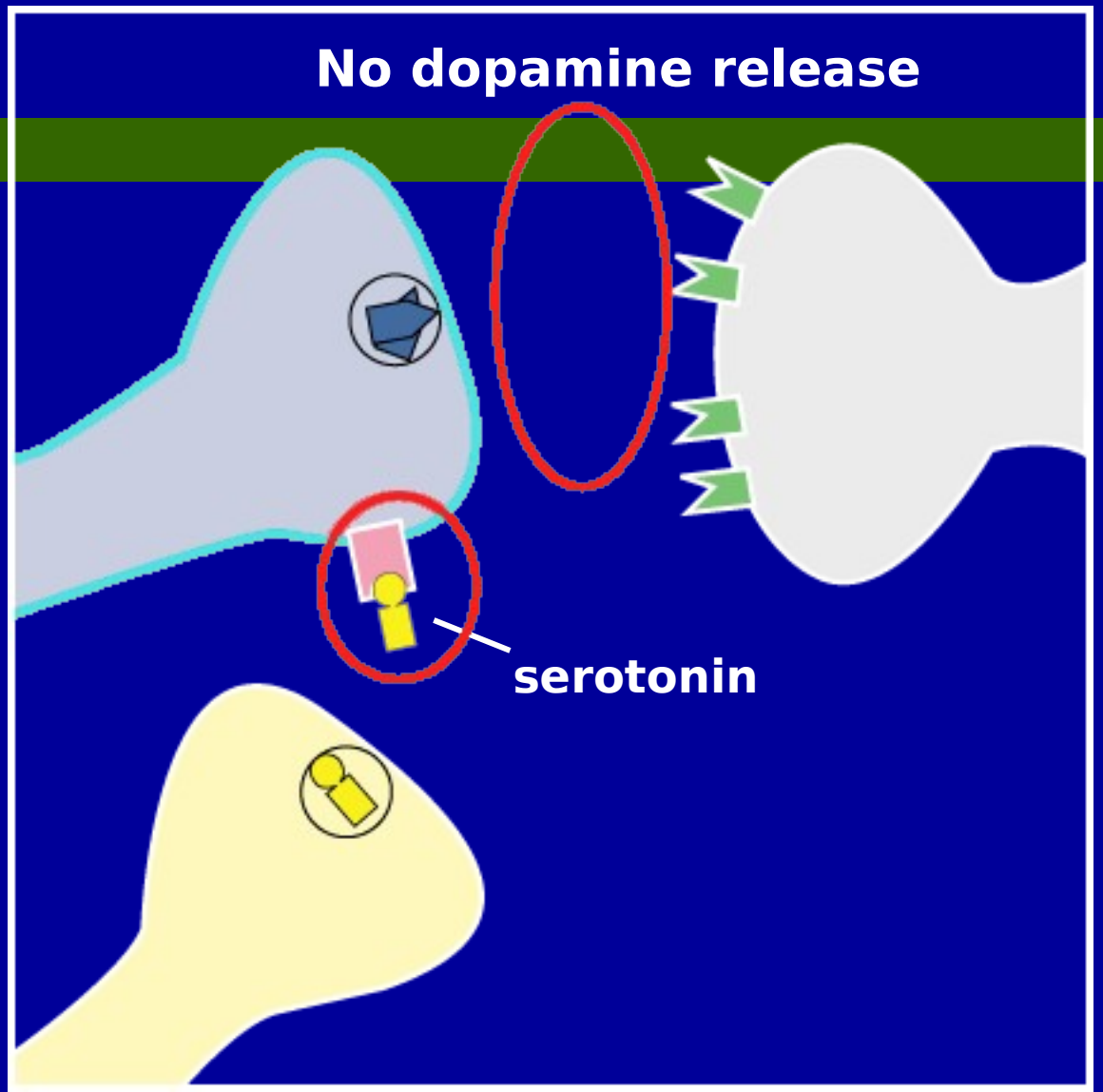
NIGROSTRIATAL

Serotonin regulation of dopamine release



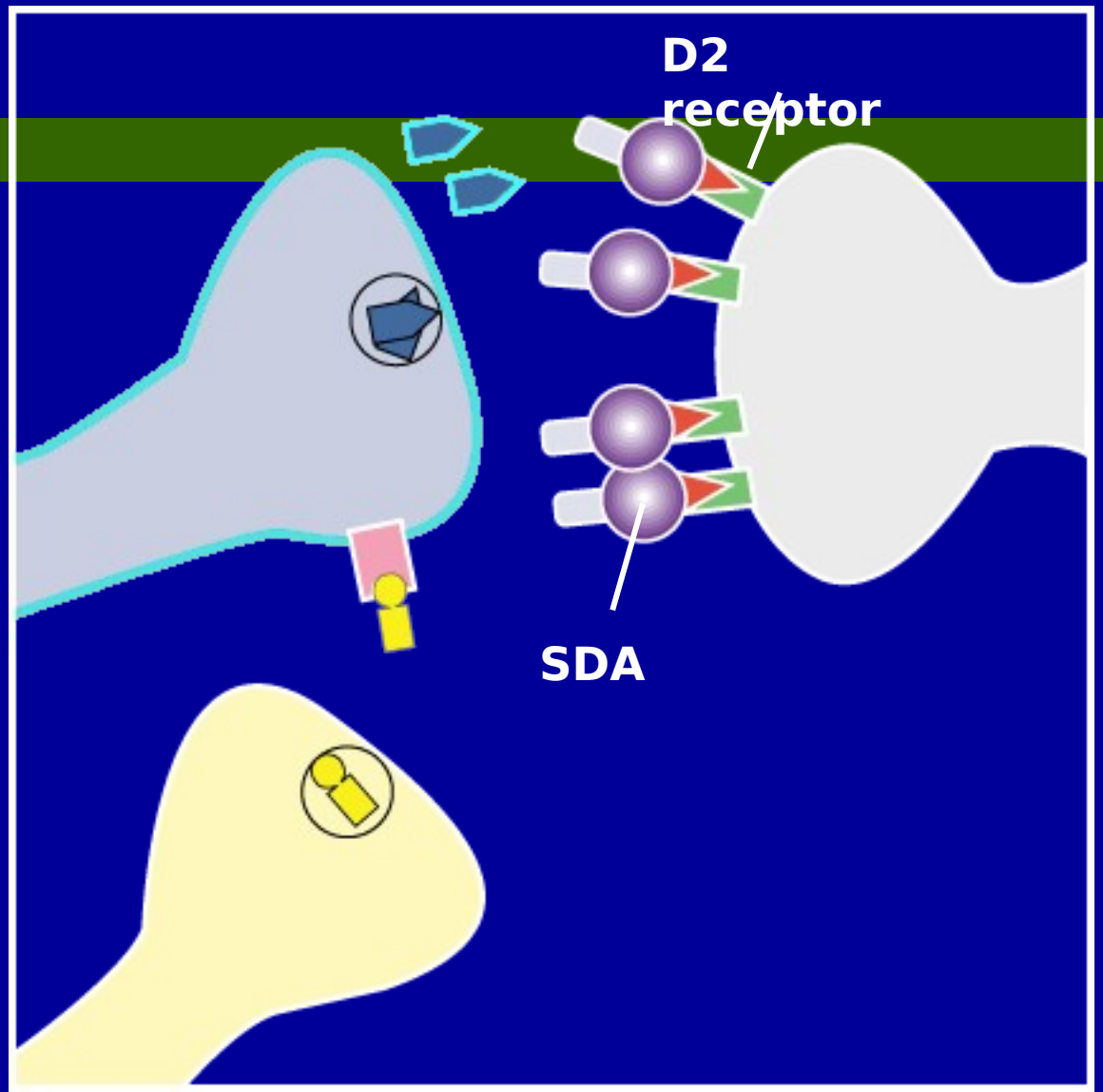
NIGROSTRIATAL PATHWAY

Dopamine release is being inhibited by 5HT



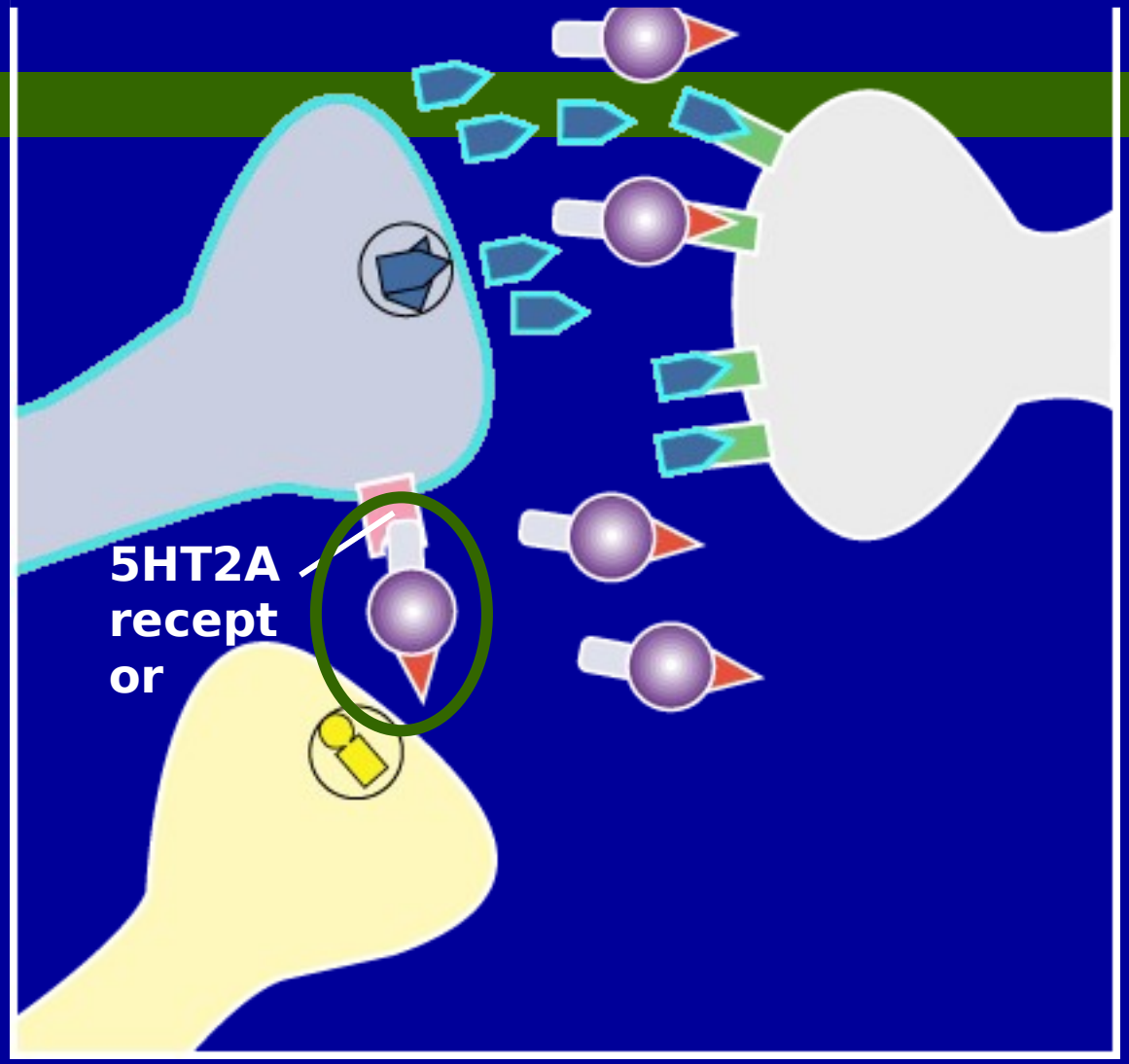
Dopamine release is being inhibited by 5HT

NIGROSTRIATAL PATHWAY



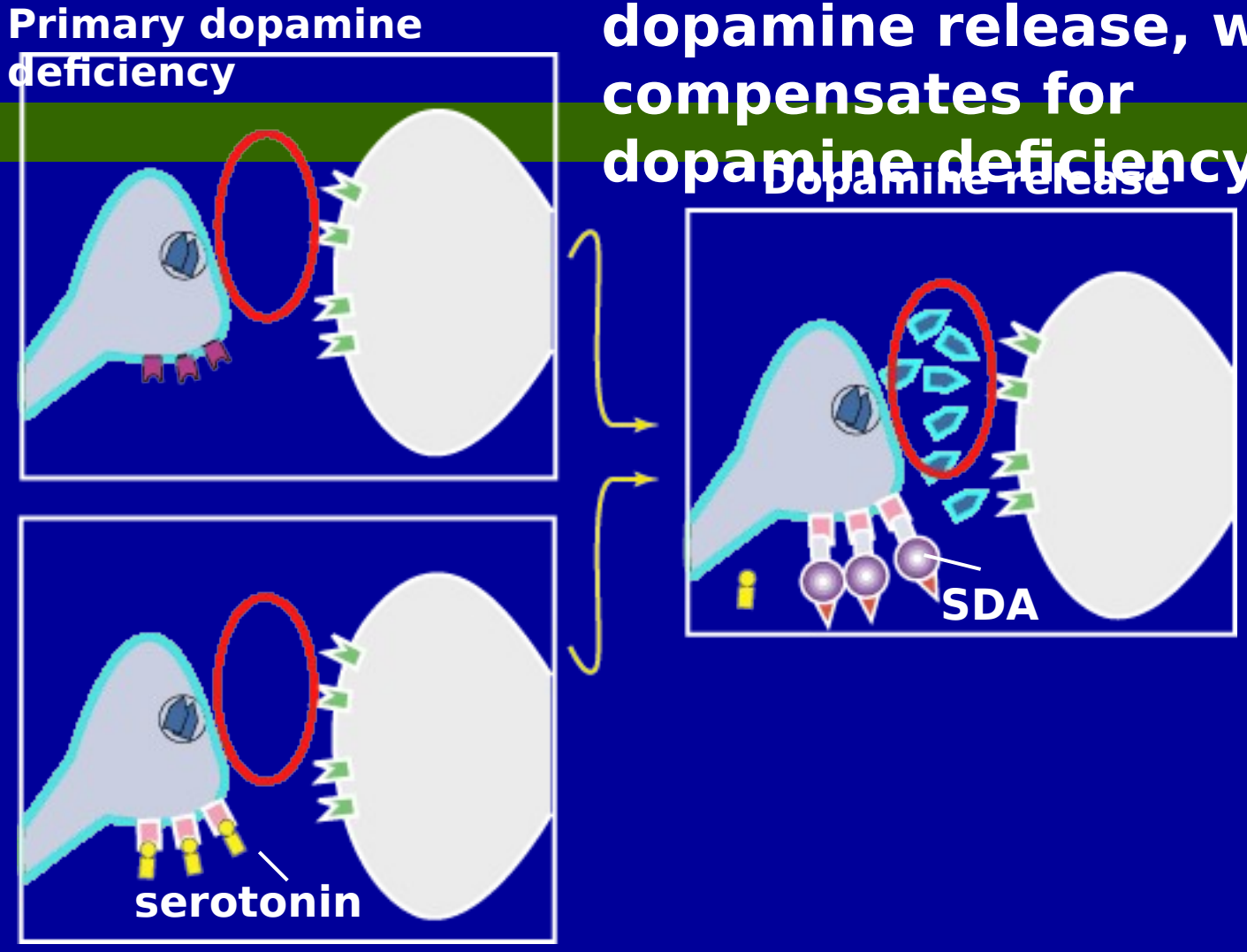
NIGROSTRIATAL PATHWAY

Blocking 5HT2A reverse D2 blockers in the striatum, causing little EPS.

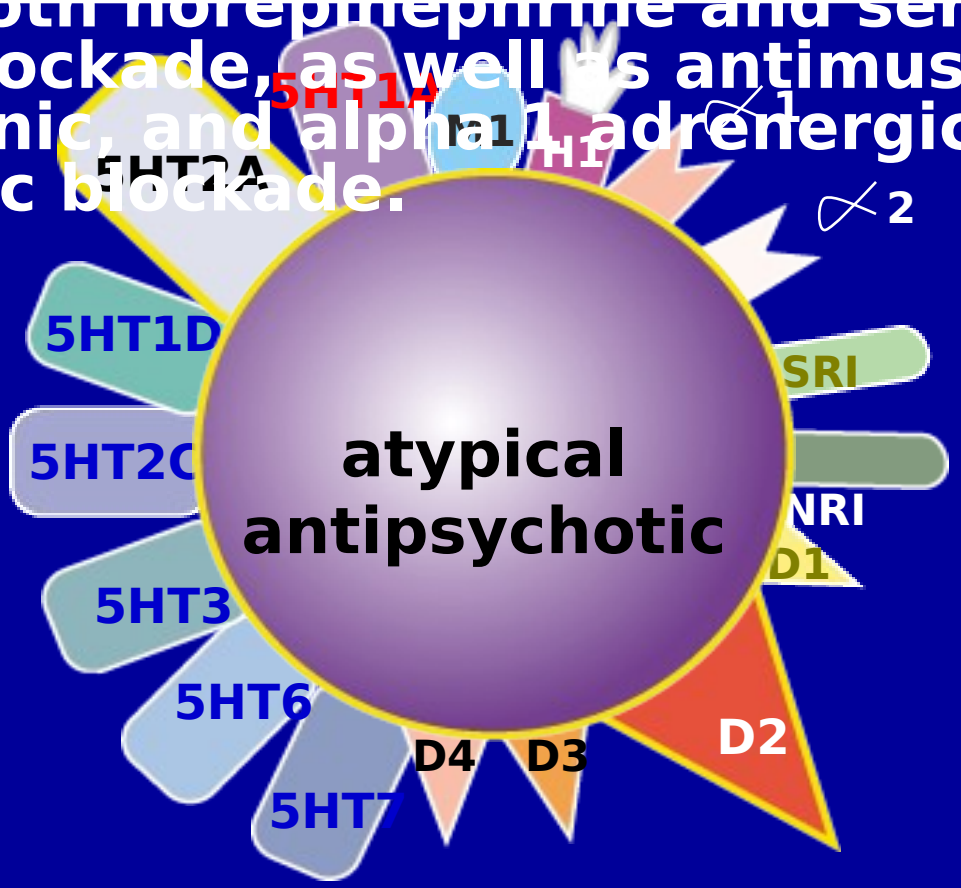


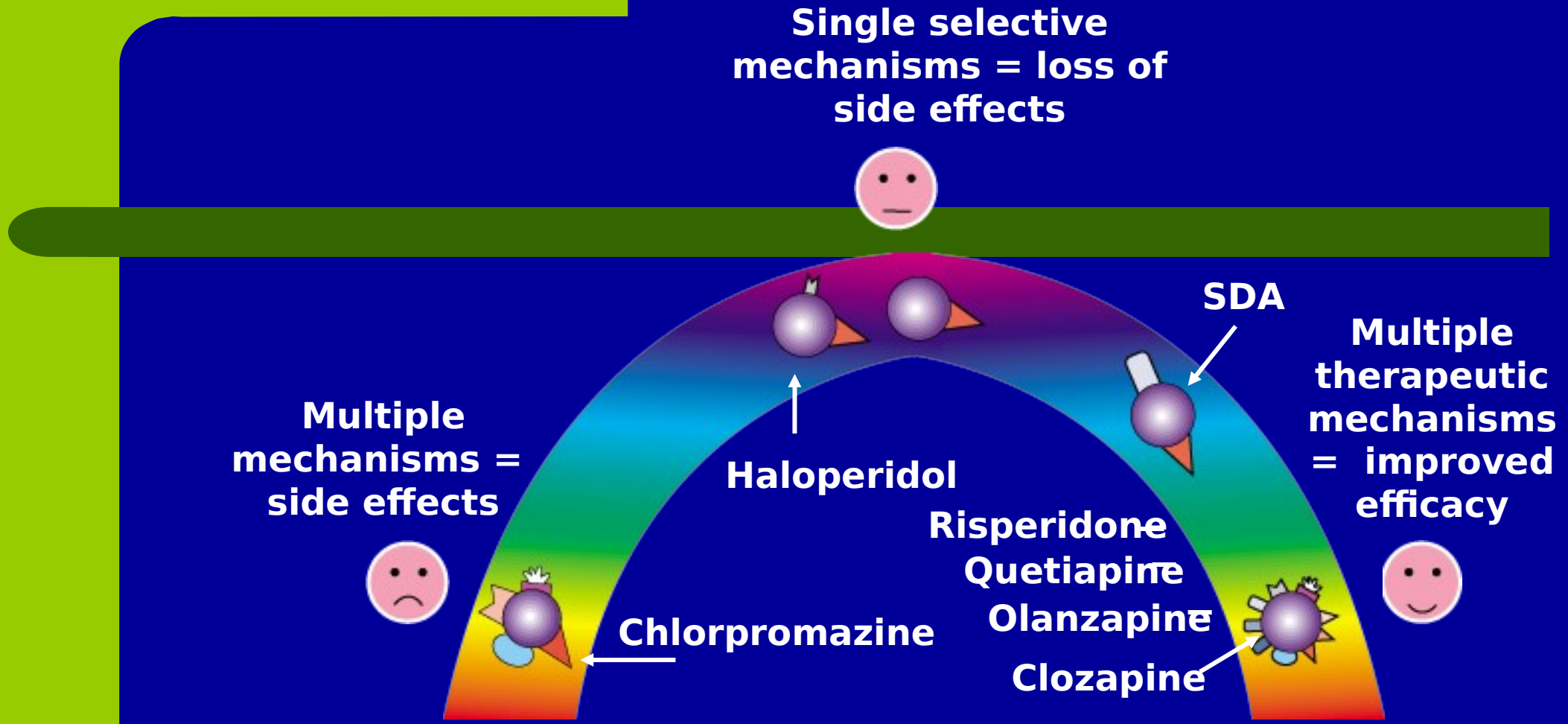
MESOCORTICAL PATHWAY

Blockade of 5HT2A receptors with an atypical antipsychotic leads to dopamine release, which compensates for dopamine deficiency.

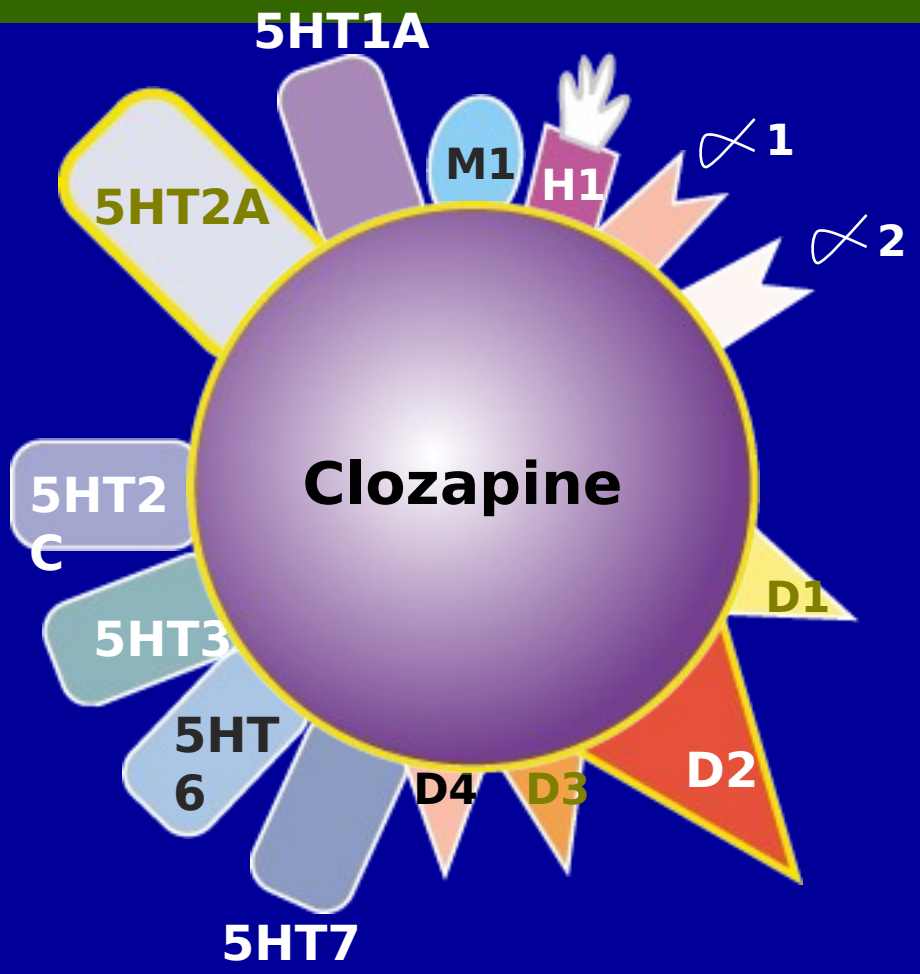


Beyond the SDA concept: Beyond antagonism of serotonin 2A and dopamine 2 receptors, some agents in this class interact with multiple other receptor subtypes for both dopamine and serotonin, including 5HT1A, 5HT1D, 5HT2C, 5HT3, 5HT6, 5HT7, and D1, D3, and D4. Other neurotransmitter systems are involved as well, ~~including both norepinephrine and serotonin~~ reuptake blockade, as well as antimuscarinic, antihistaminic, and alpha 1 adrenergic plus alpha 2 adrenergic blockade.




Single selective mechanisms = loss of side effects
SDA
Multiple therapeutic mechanisms = improved efficacy
Multiple mechanisms = side effects
Haloperidol
Risperidone
Quetiapine
Olanzapine
Chlorpromazine
Clozapine

Clozapine


5HT1A
M1
H1
α1
α2
5HT2A
Clozapine
5HT2C
D1
5HT3
5HT6
D4
D3
D2
5HT7

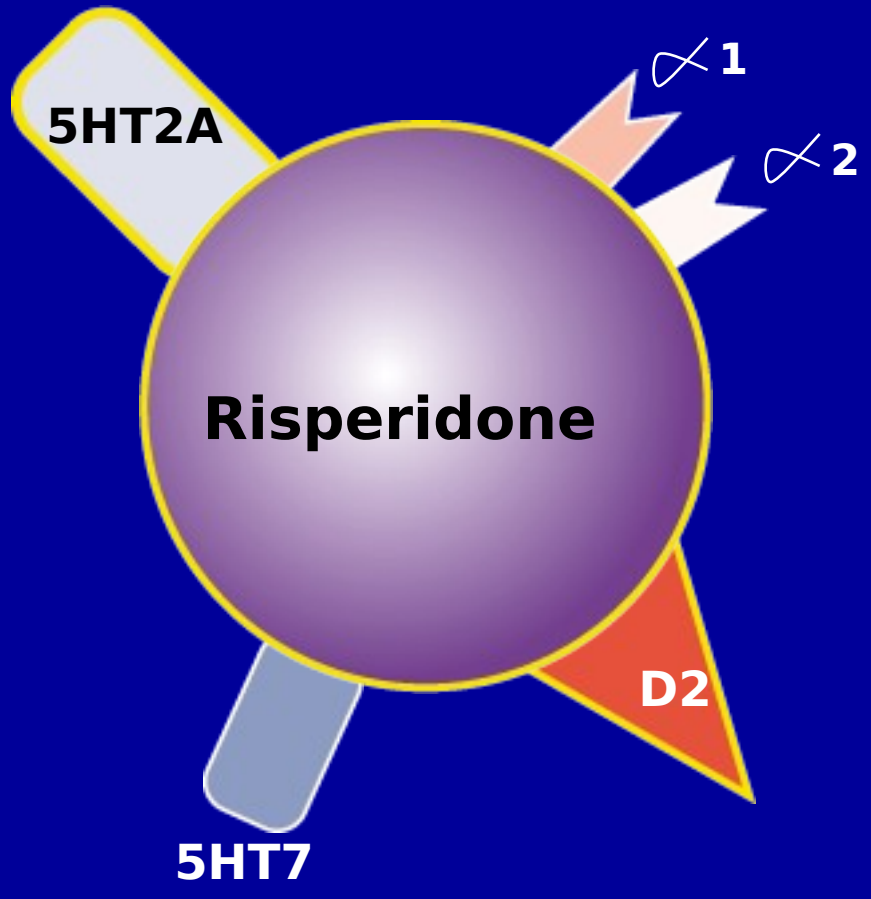
Clozapine

- Is considered the prototype of the atypical antipsychotic.
- It is a weak antagonist of the D2 receptor but appears to be a potent antagonist of the D4 receptor and 5HT2 receptors.
- Is indicated for treatment resistant schizophrenia and for patients who have **tardive dyskinesia**.
- It is also associated with the risk of a life-threatening **agranulocytosis** which occurs in 0.5 to 2% of patients.
- It also entails an increased risk of **seizures**, especially at high dose.

Clozapine

- The most common other adverse effects associated with clozapine treatment are sedation, fatigue, sialorrhea, weight gain, and at times fever.
- Dosage: start 25 mg once or twice daily and then raise the dosage to 300 mg by increasing the dose by 25 mg every 4 or 5 days.
- The usual effective treatment range is 400 to 500 mg a day.
- Lab monitoring: weekly WBCs for the first 6 months and then every 2 weeks. Clozapine should be discontinued if the granulocyte count is less than 1000 per mm^3.

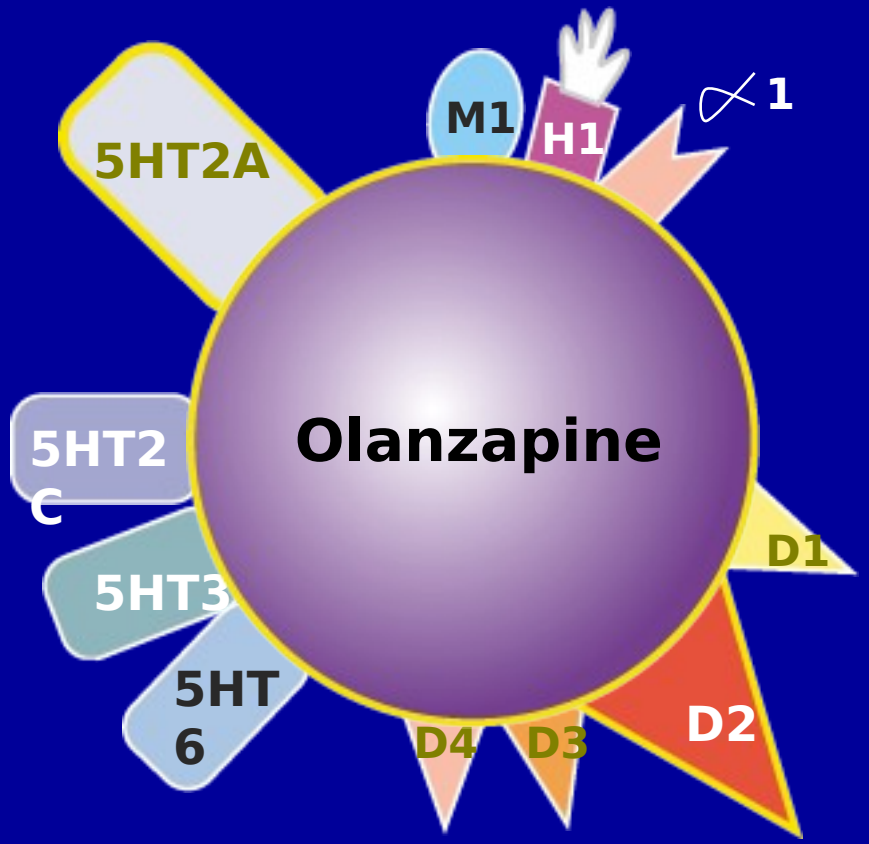
Risperidone



Risperidone

- It has the simplest pharmacologic profiles and comes closest to an SDA
- It is atypical at lower doses but can become more “conventional” at high doses in that EPS can occur.
- It has favored uses, not only in schizophrenia at moderate doses but also for conditions in which low dose of typical antipsychotics have been used in the past (for elderly pts and children)
- The major adverse events are somnolence, fatigue, orthostatic dizziness, tachycardia, weight gain, sexual dysfunction, rhinitis and nausea.

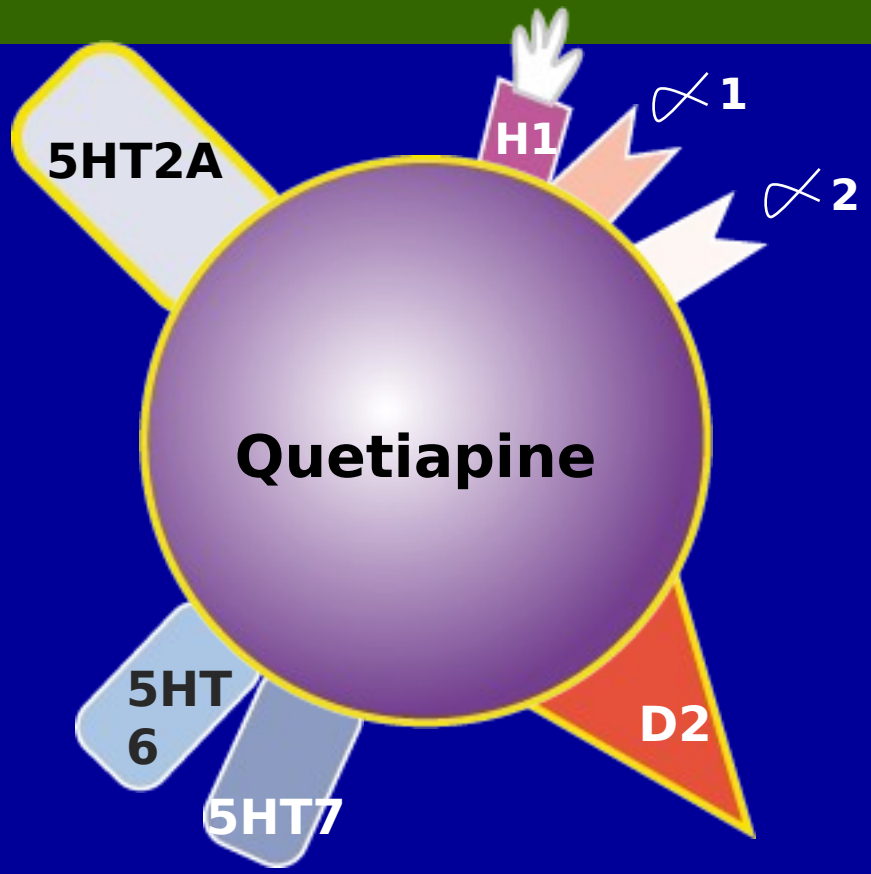
Olanzapine



Olanzapine

- It has a chemical structure related to clozapine.
- It is atypical because it lacks EPS not only in smaller dosage but also at higher dosage.
- **It lacks the extreme sedating properties of clozapine**.
- It is associated with **weight gain** because of its antihistaminic and serotonin 2C antagonist properties.
- It is highly effective in the treatment of the negative symptoms because of its antagonism on 5HT2A receptors on the dopamine neurons.
- It is the first antipsychotic medication which has been approved for the treatment of acute mania and maintenance of bipolar disorder in USA.

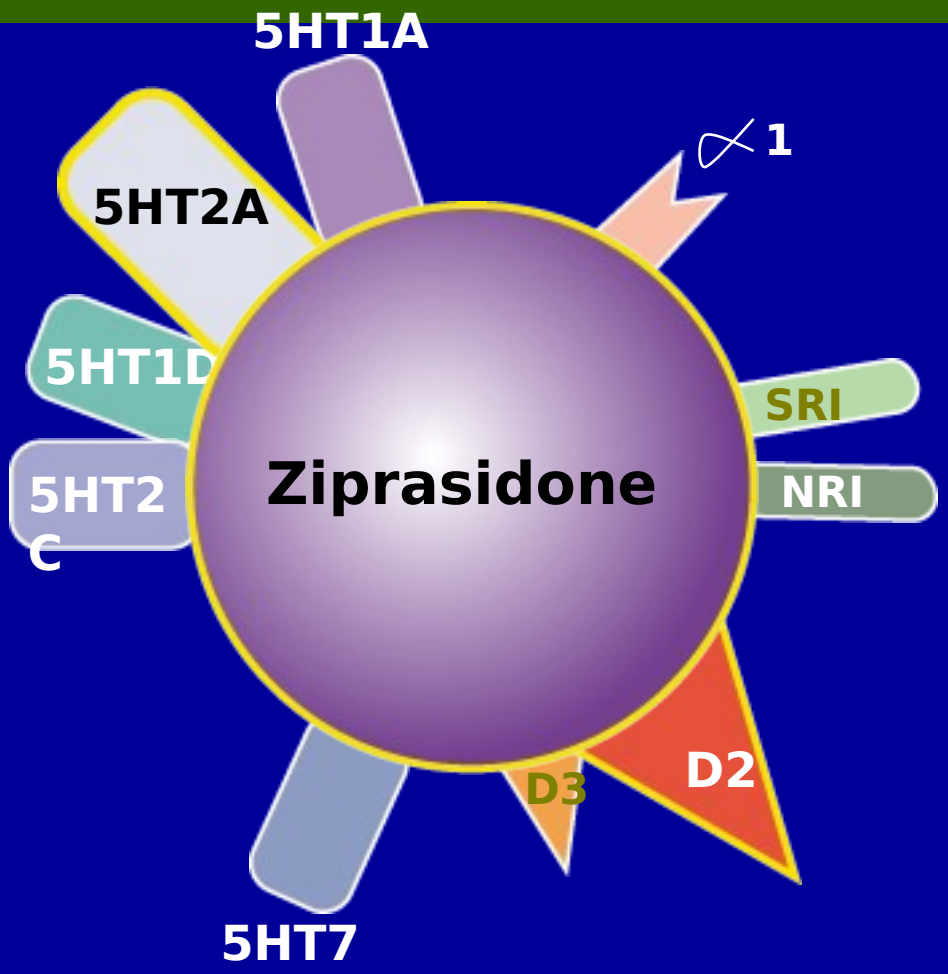
Quetiapine



Quetiapine

- No EPS
- Implicated in the development of new-onset type-2 diabetes.
- No report of tardive dyskinesia or prolactin elevation.
- Dose range 75-800mg

Ziprasidone



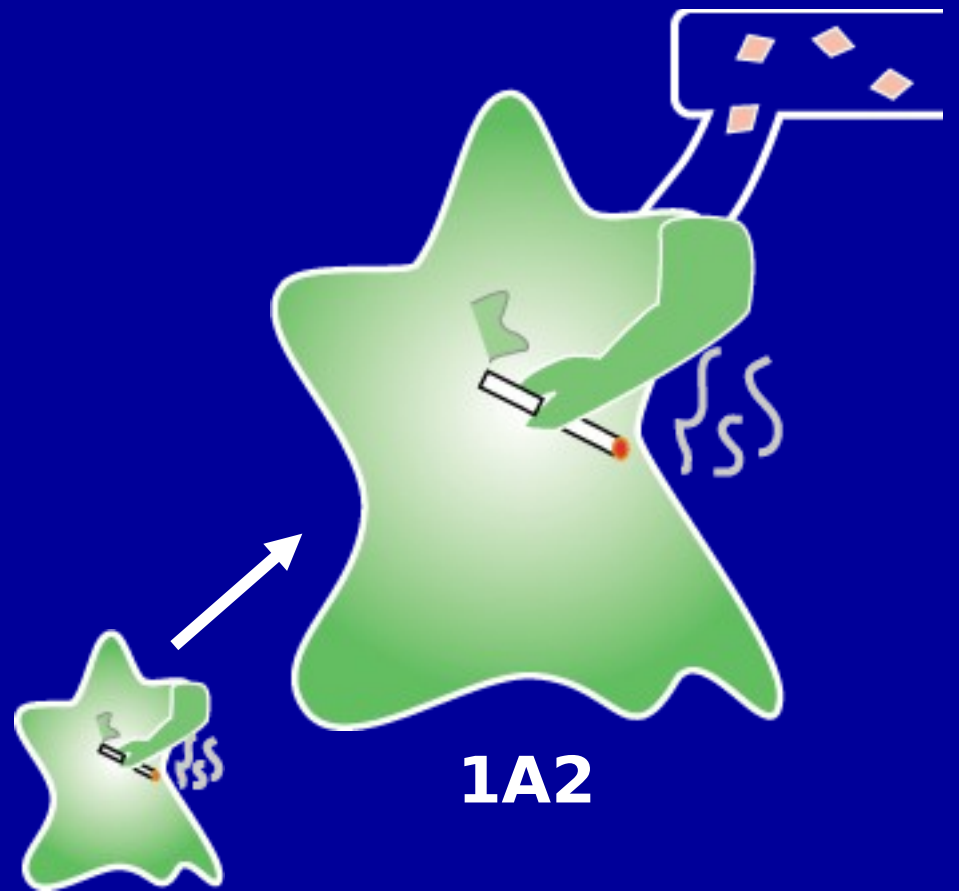
Ziprasidone

- The recommended adult starting dose of oral ziprasidone is 20 to 40 mg twice daily,
- Doses up to 240 mg/day are well tolerated.
- Side effects include mild sedation early in treatment, nausea, weakness, nasal congestion, and mild QT prolongation

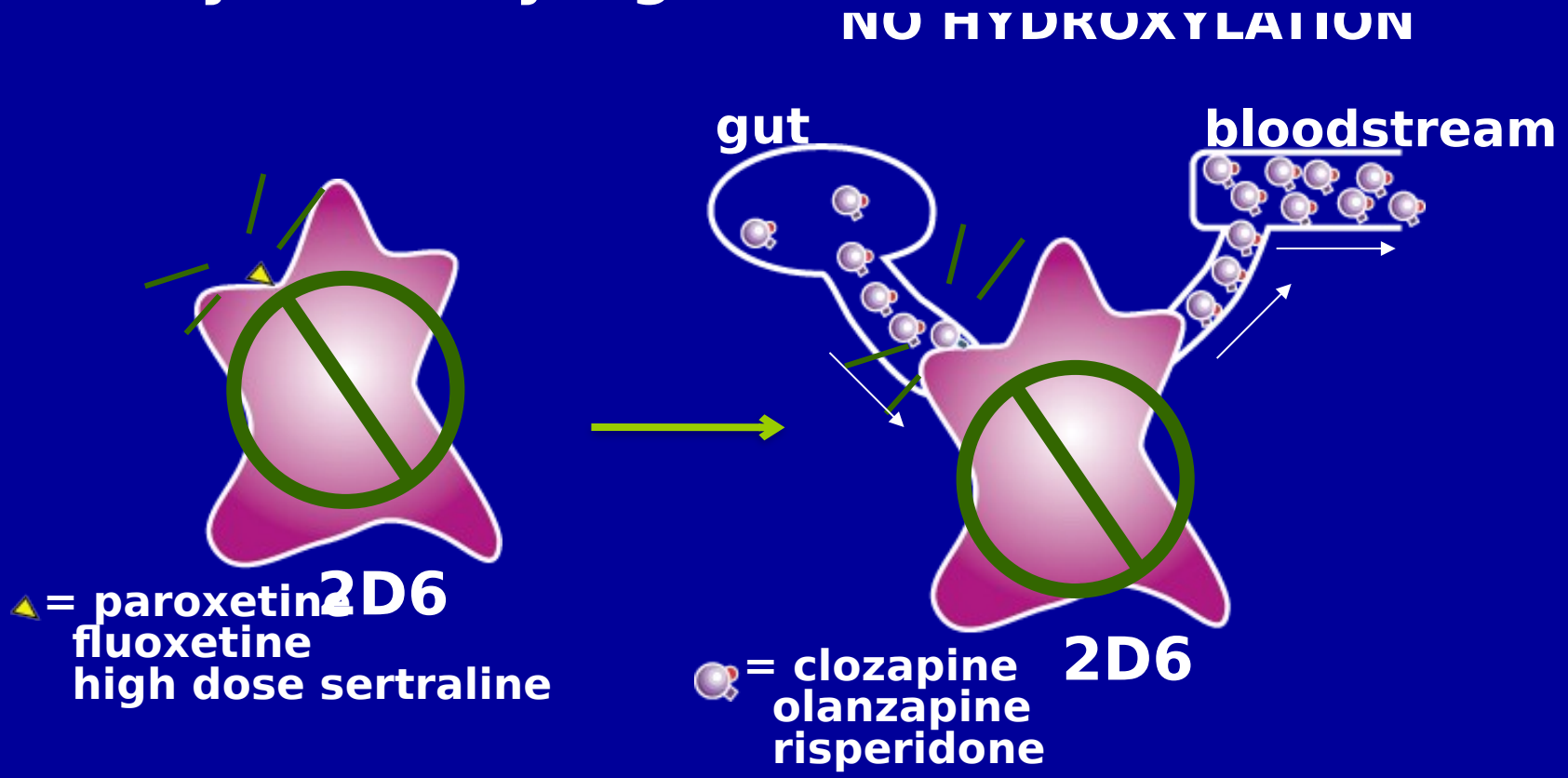
Aripiprazole (Abilify®)

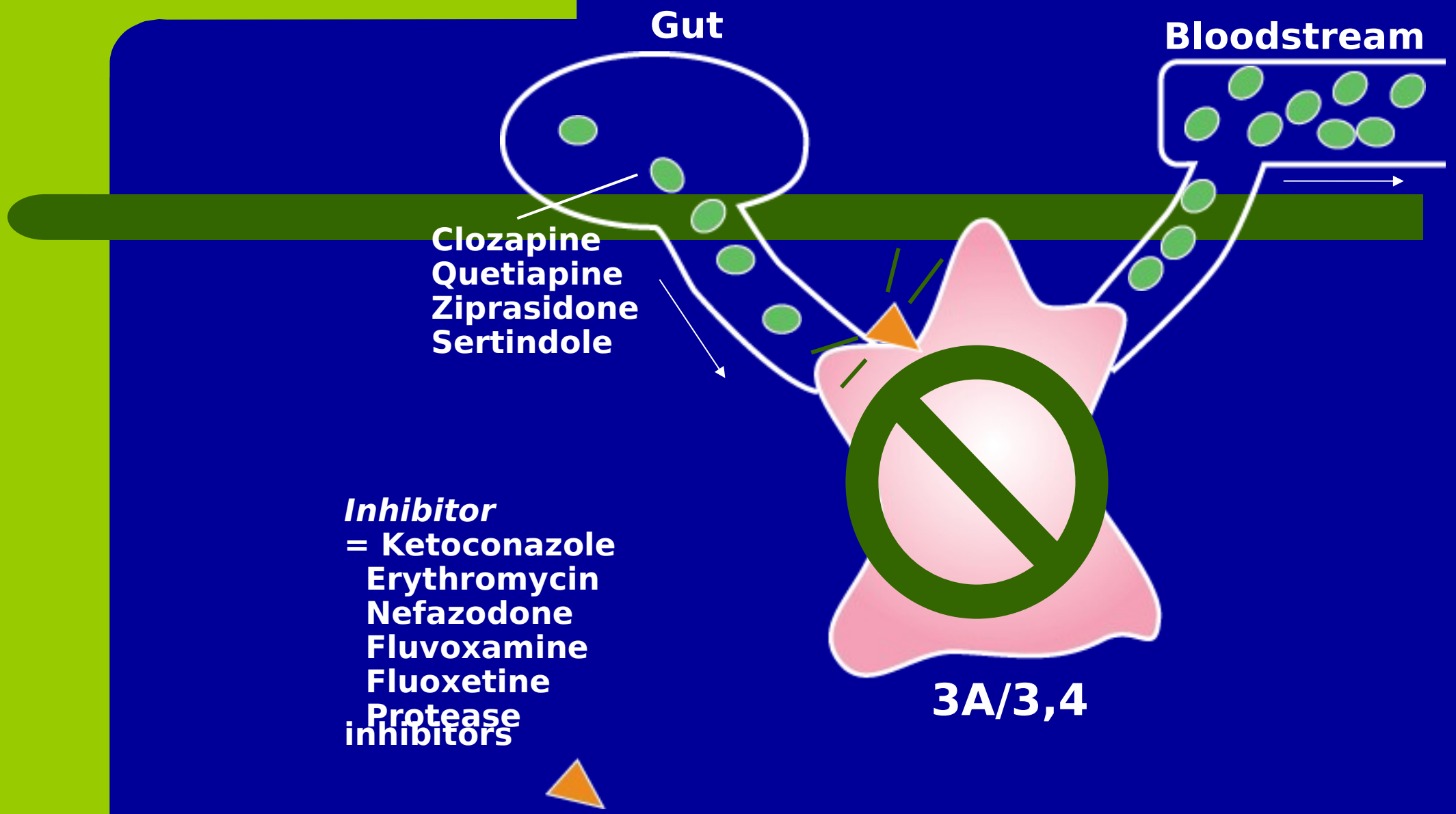
- Aripiprazole acts as a partial agonist at dopamine D2 receptors.
- The drug is also a partial agonist at serotonin 5HT1a receptors, but an antagonist at 5HT2a, H1, and alpha-1-adrenergic receptors.
- Dose: 10 to 30 once daily
- The most common side effects of aripiprazole are headache, nausea, vomiting, insomnia, tremor, and

Cigarette smoking, quite common among schizophrenics, can induce the enzyme CYP450 1A2 and lower the concentration of drugs metabolized by this enzyme, such as olanzapine and clozapine. Smokers may also require higher doses of these drugs than nonsmokers.

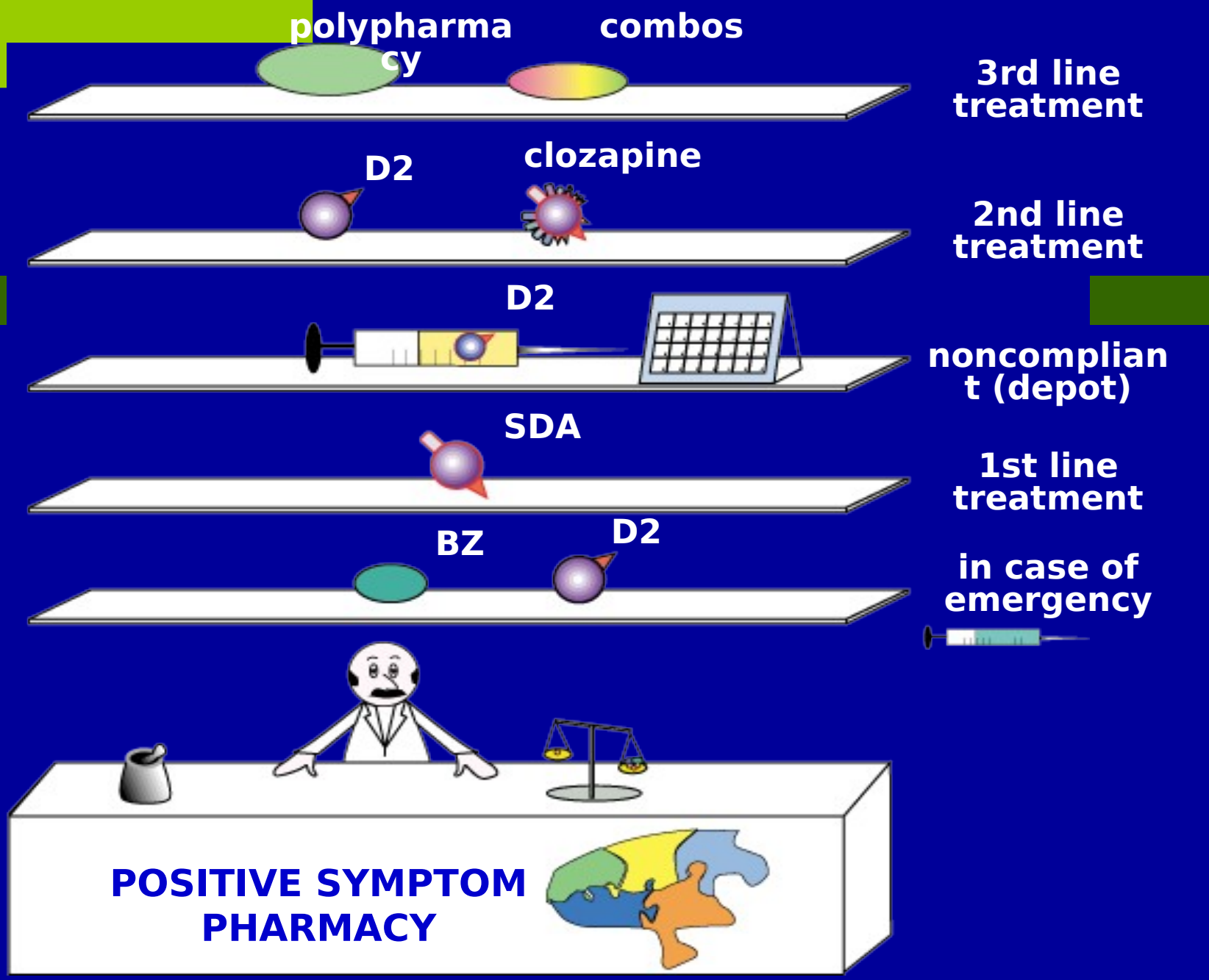


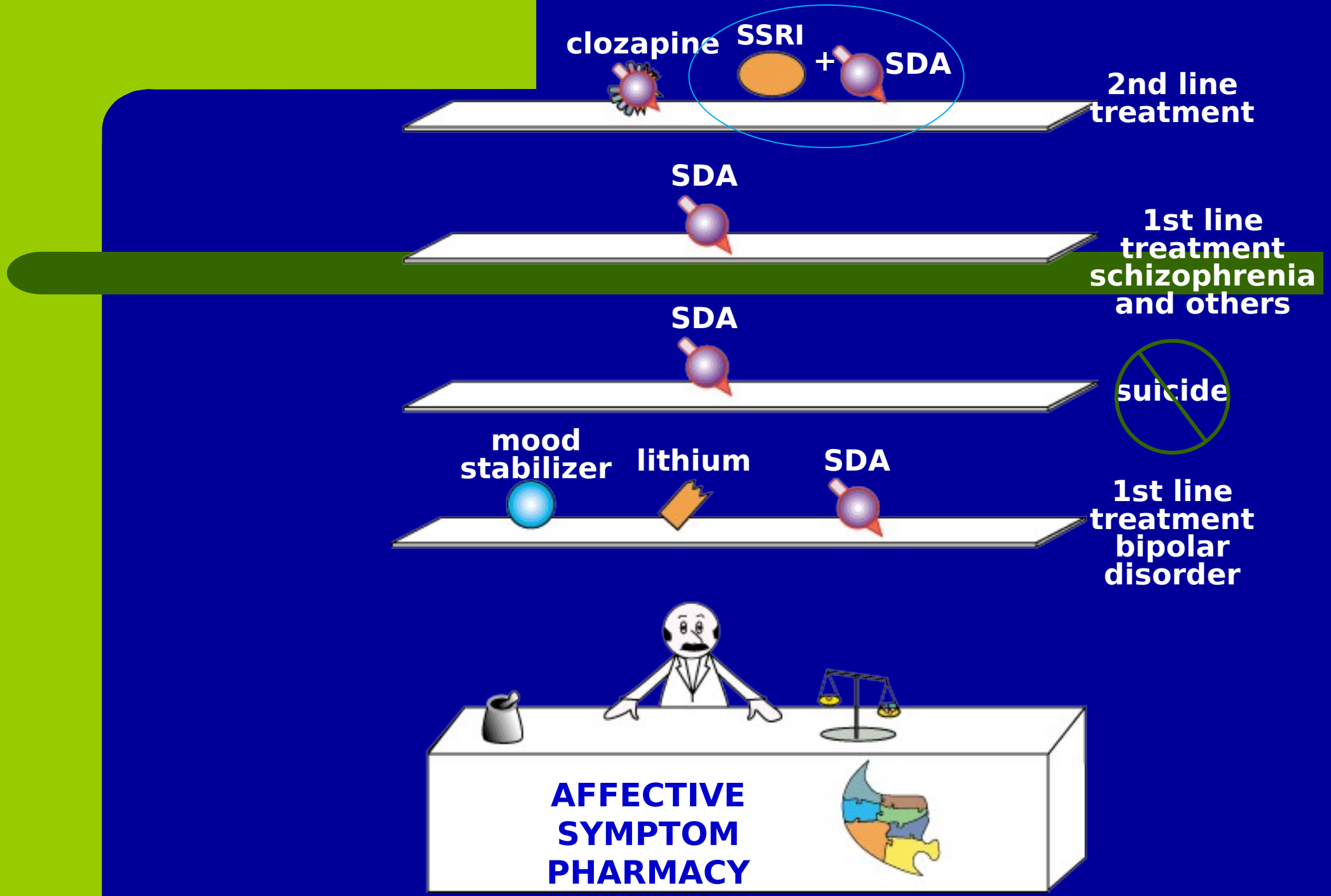
Several antidepressants are inhibitors of CYP450 2D6 and could theoretically raise the levels of 2D6 substrates such as risperidone, olanzapine, and clozapine. However, this is not usually clinically significant.

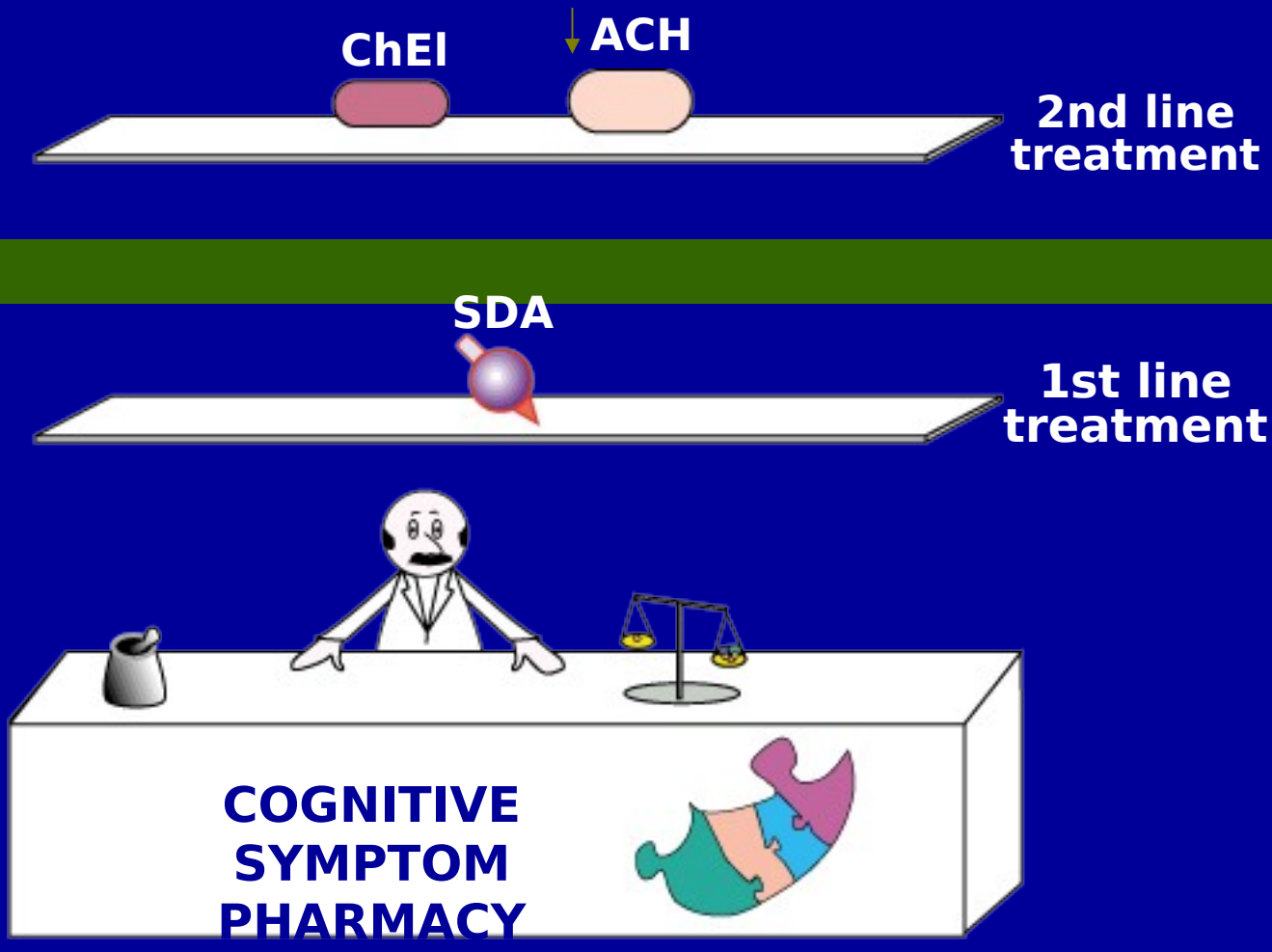


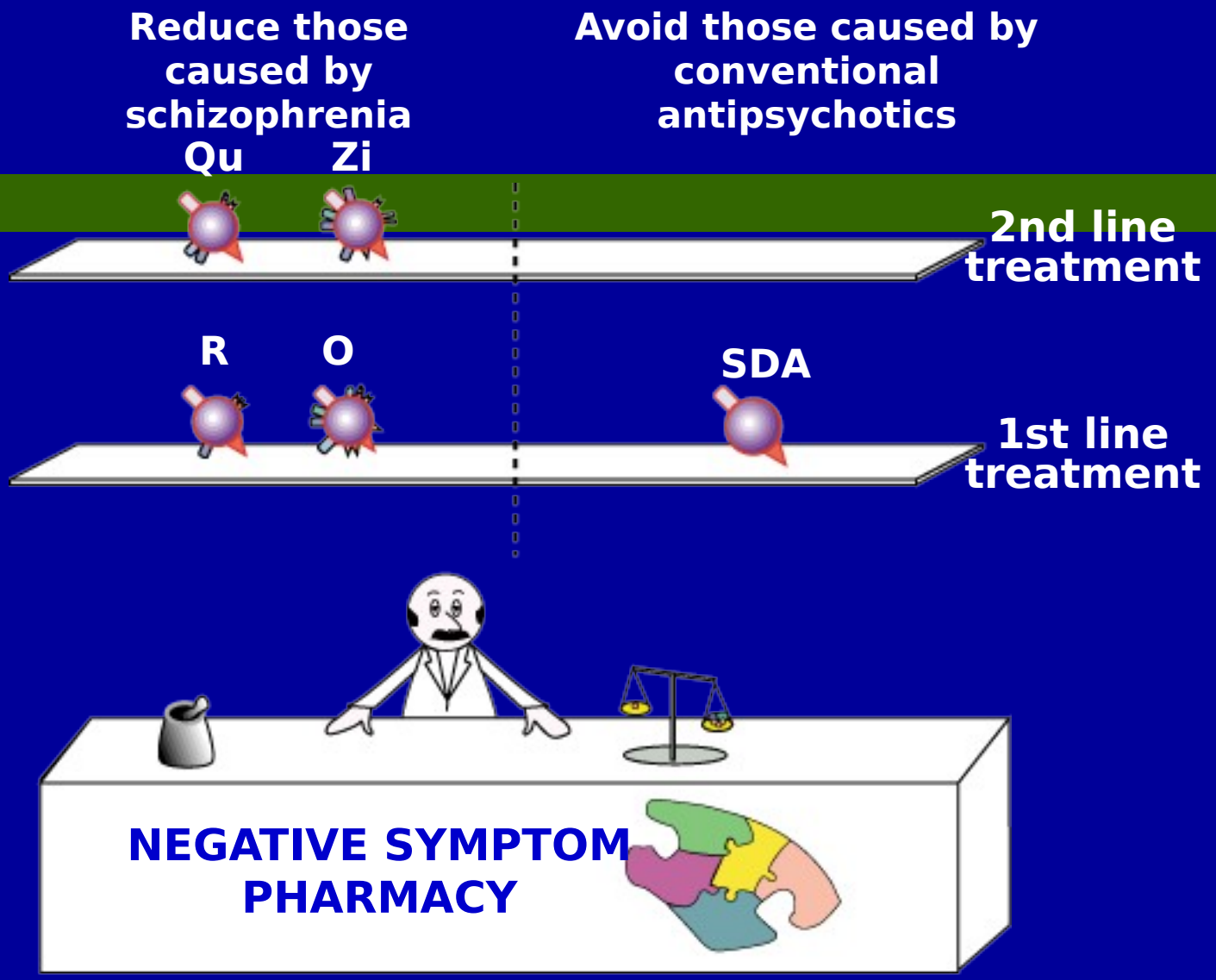


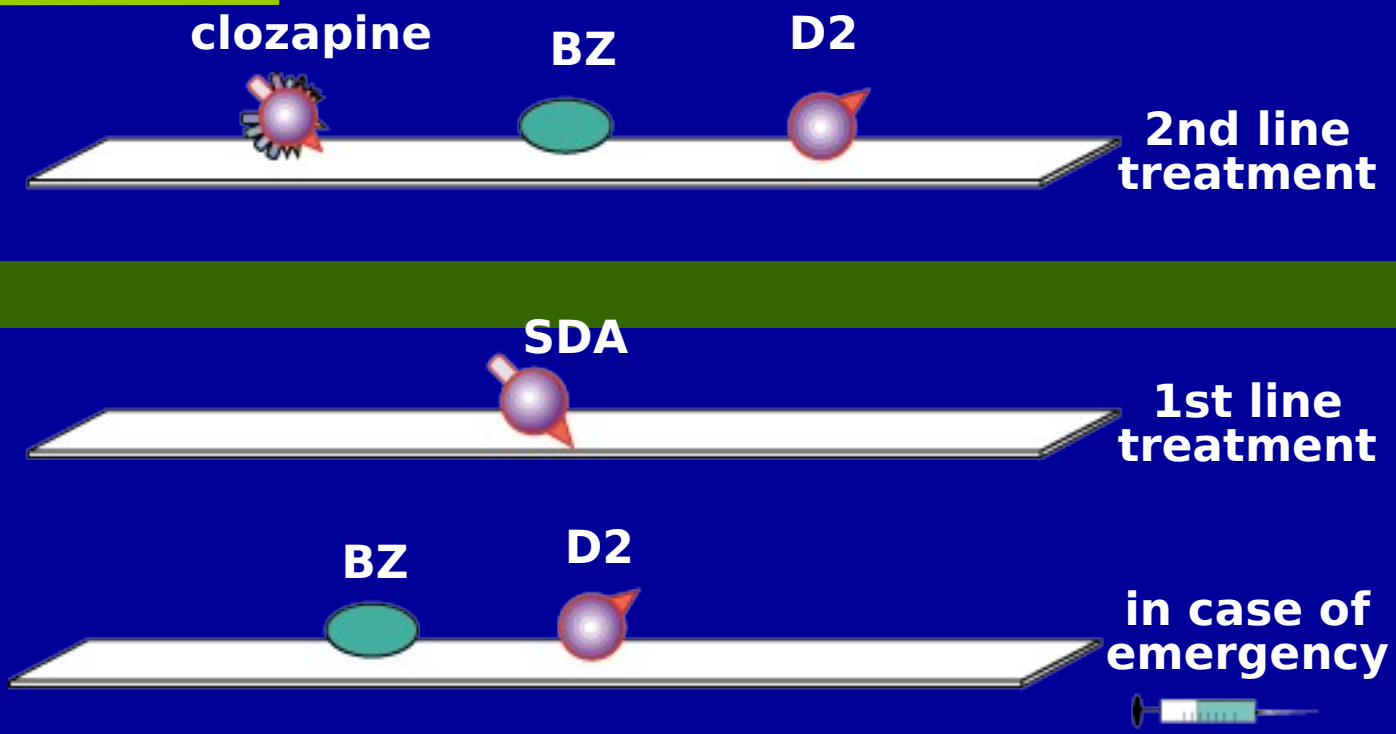
Inhibitor
= Ketoconazole
Erythromycin
Nefazodone
Fluvoxamine
Fluoxetine
Protease inhibitors


polypharmacy
combos
3rd line treatment
D2
clozapine
2nd line treatment
D2
noncomplian t (depot)
SDA
1st line treatment
BZ
D2
in case of emergency
POSITIVE SYMPTOM PHARMACY


clozapine
SSRI
+
SDA
2nd line treatment
SDA
1st line treatment schizophrenia and others
SDA
suicide
mood stabilizer
lithium
SDA
1st line treatment bipolar disorder
AFFECTIVE SYMPTOM PHARMACY


ChEI
ACH
2nd line treatment
SDA
1st line treatment
COGNITIVE
SYMPTOM
PHARMACY


Reduce those caused by schizophrenia
Qu
Zi
Avoid those caused by conventional antipsychotics
2nd line treatment
R
O
SDA
1st line treatment
NEGATIVE SYMPTOM PHARMACY


clozapine
BZ
D2
2nd line treatment
SDA
1st line treatment
BZ
D2
in case of emergency
AGGRESSIVE
SYMPTOM PHARMACY

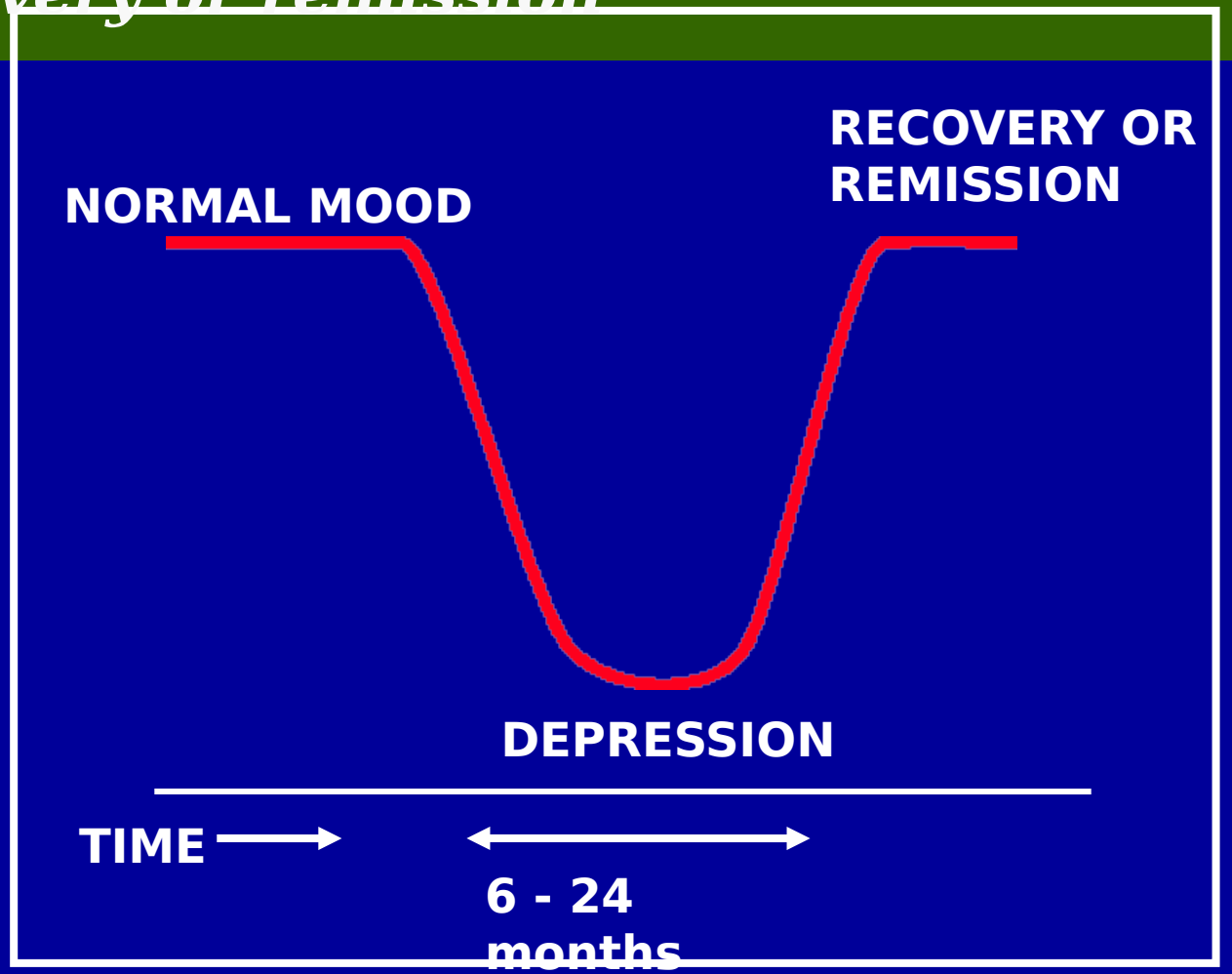
DEPRESSION

Epidemiology

- Life-time prevalence is about 15% although in women it is as high as 25%
- Depression occurs in all age, racial, ethnic, and socioeconomic groups.
- Prevalence of depression is more in medically ill patient than the general population.

EPISODE OF DEPRESSION

***Depression** is **episodic**, with untreated episodes commonly lasting 6 to 24 months, followed by recovery or remission*



Forms of Primary Depression

- Major Depression
  - ✓Unipolar
  - ✓Bipolar
- Dysthymia

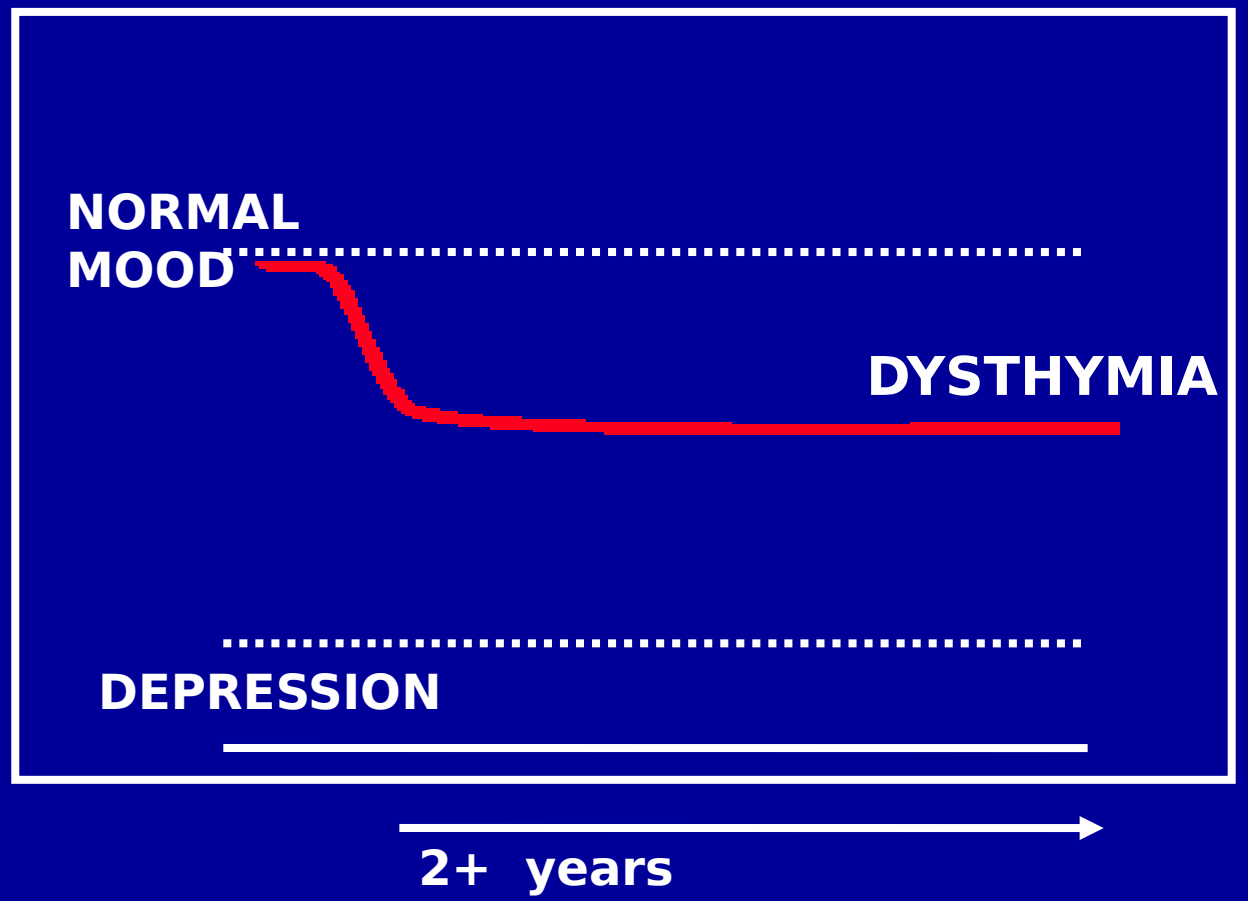
Diagnostic Features of MDD

- Depressive episodes lasting at least 2 weeks
- Not attributable to other organic factors
- Absence of hypomania or mania

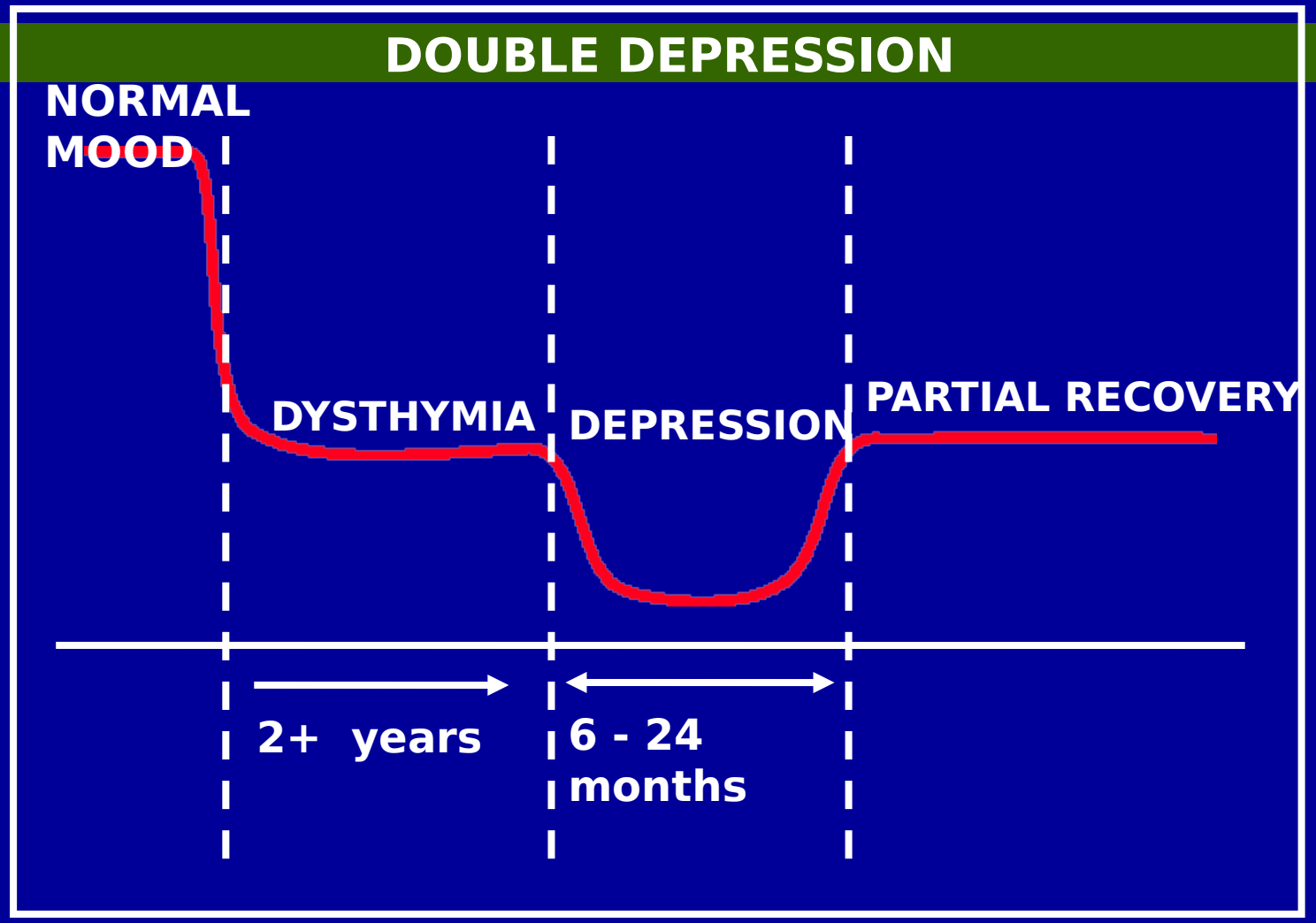
Typical symptoms of MDD

- Depressed mood most of the day, almost everyday (feels sad or empty, appears tearful)
- Loss of interest or pleasure in usual activities (anhedonia)
- Decreased energy or increased fatigability
- Loss of confidence or self-esteem
- Unreasonable feelings of guilt, feelings of worthlessness
- Recurrent thoughts of death or suicide
- Complaints of diminished ability to think or concentrate
- Change in psychomotor activity, with agitation or retardation

***Dysthymia** is a low-grade but very chronic form of depression, which lasts for more than 2 years.*



Double depression *is a syndrome characterized by oscillation between episodes of major depression and periods of partial recovery or dysthymia.*



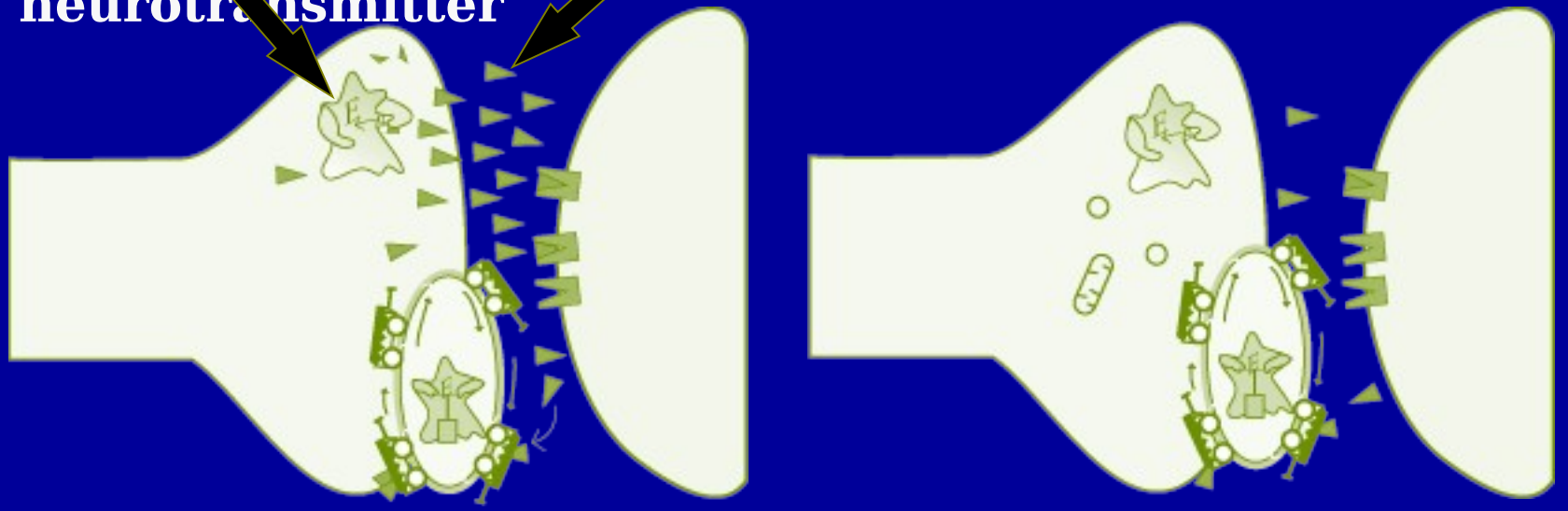
Etiology & Pathogenesis of Depression

- Neurobiological factors:
  - ✓Family, twin & adoption studies
  - ✓Neurotransmitter dysregulation
- Psychosocial factors
  - ✓Social stressors as precipitators
- Developmental factors:
  - ✓Early stressful life events

Monoamine Hypothesis

MAO enzyme destroying neurotransmitter

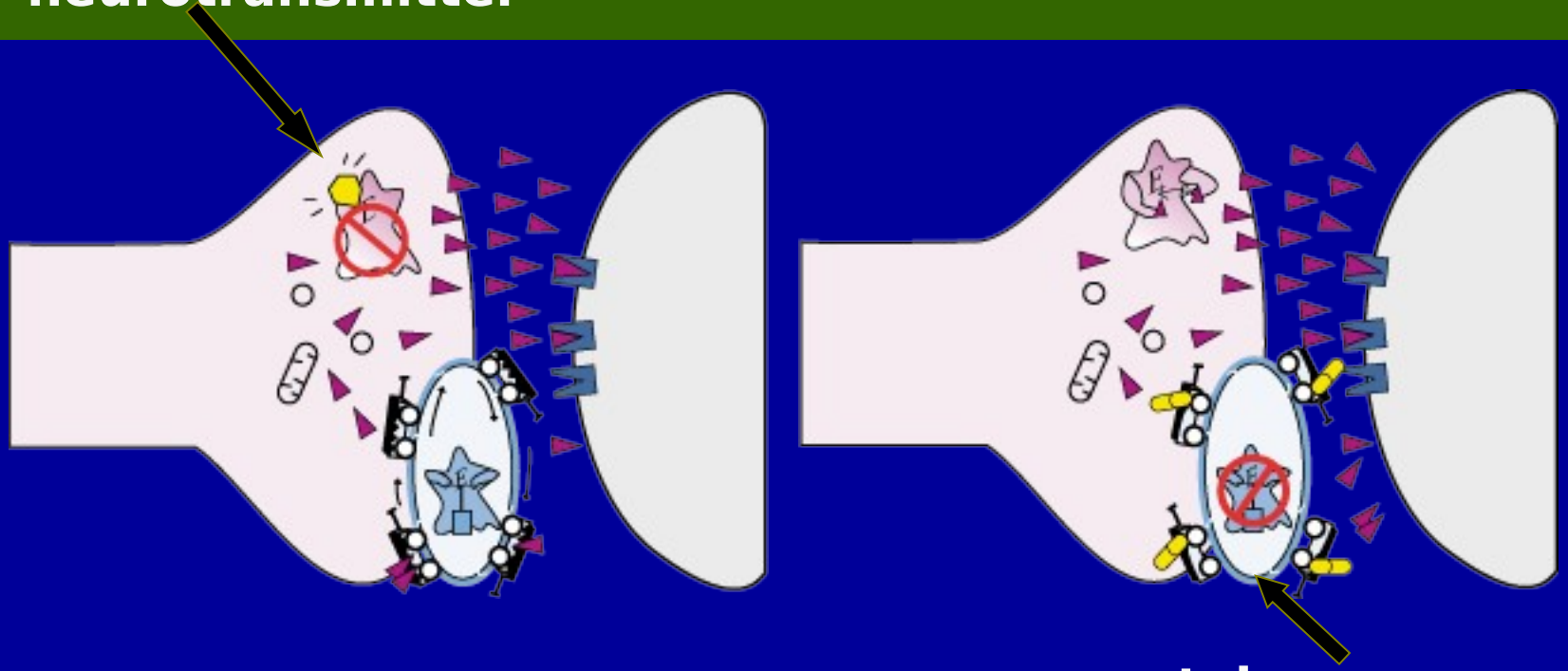
monoamine neurotransmitter



NORMAL STATE: no depression

DEPRESSION: caused by neurotransmitter deficiency

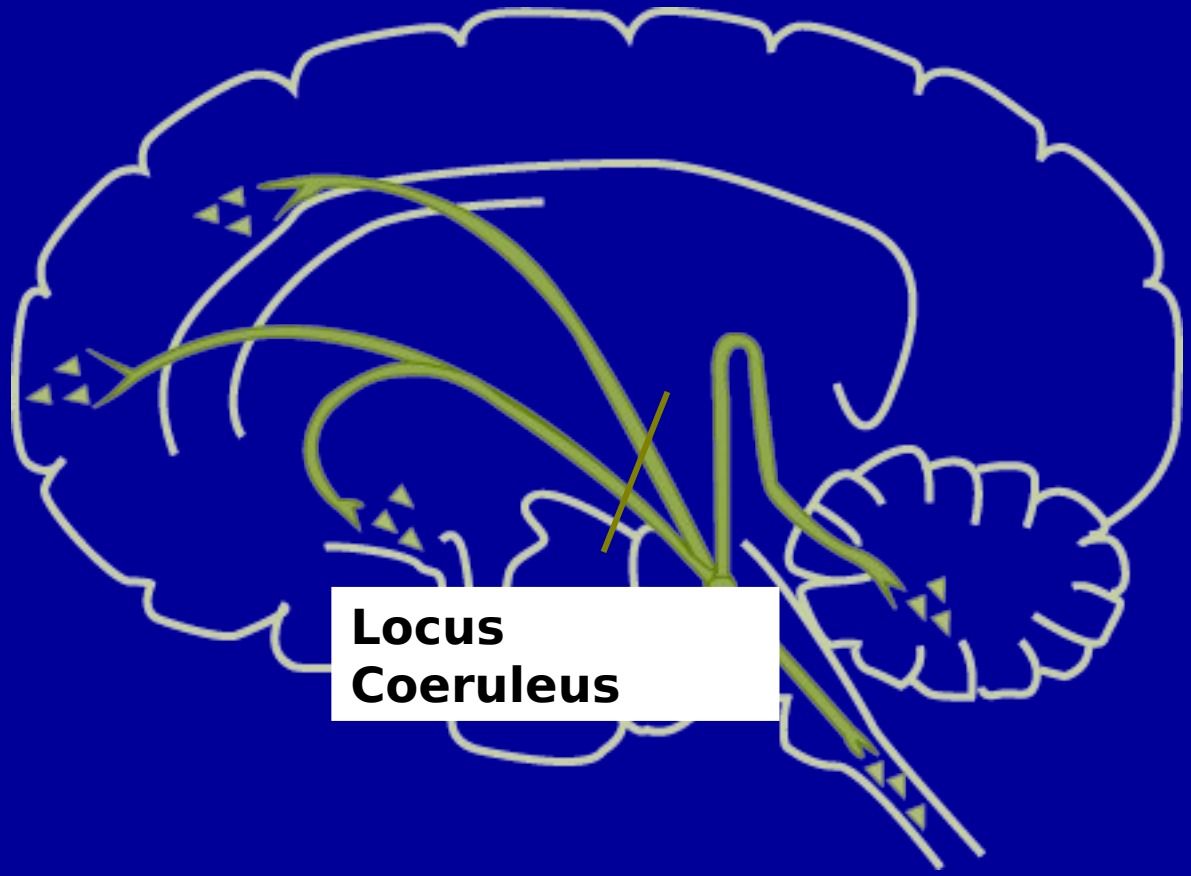
MAO inhibitor blocks the enzyme from destroying monoamine neurotransmitter



Increase in neurotransmitters causes return to normal state

reuptake pump blocked by antidepressant

Norepinephrine Pathways



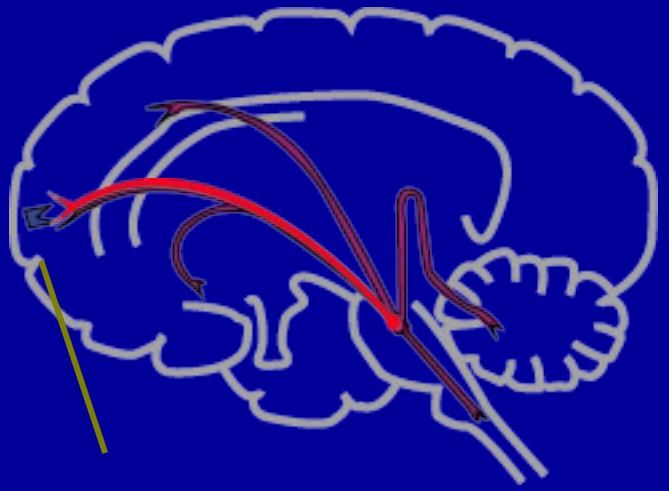
Norepinephrine Pathways

- Most of the cell bodies for noradrenergic neurons in the brain are located in the brainstem in an area known as the **locus coeruleus**.
- This is the **headquarters** for most of the important noradrenergic pathways mediating behavior and other functions such as cognition, mood, emotions, and movements.
- Malfunction of the locus coeruleus is hypothesized to underlie disorders in which mood and cognition intersect, such as depression, anxiety, and disorders of attention and information processing.

Norepinephrine Pathways

Frontal 1

Depression



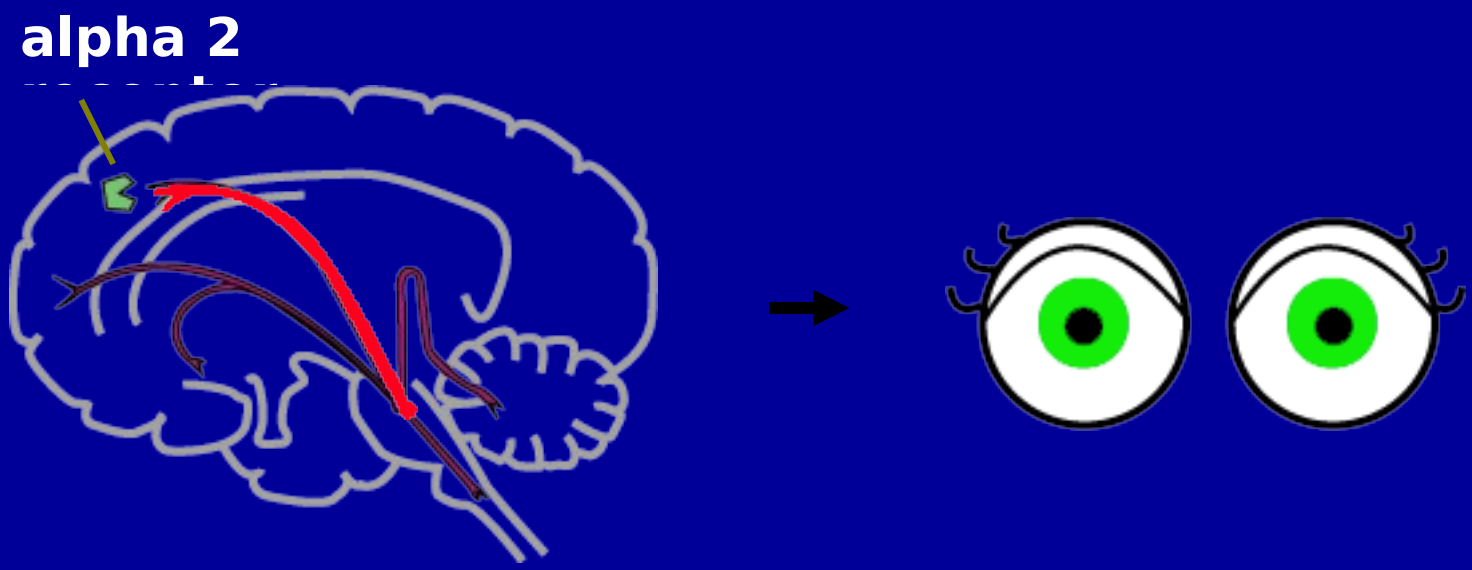


beta 1 receptor

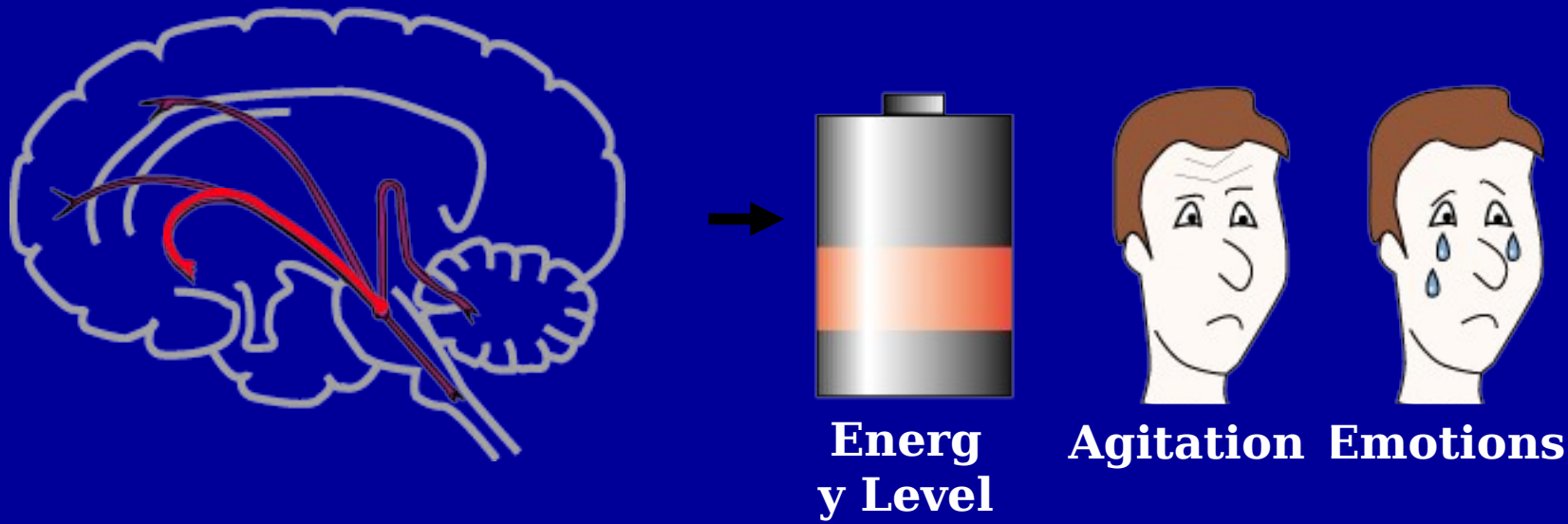
Some noradrenergic projections from the locus coeruleus to frontal cortex are thought to be responsible for the regulatory actions of norepinephrine on <u>mood</u>. Beta 1 postsynaptic receptors may be important in transducing noradrenergic signals regulating mood in

Other noradrenergic projections from the locus coeruleus to frontal cortex are thought to mediate the effects of norepinephrine on attention, concentration, and other cognitive functions, such as working memory and the speed of information processing. Alpha 2 postsynaptic receptors may be important in transducing postsynaptic signals regulating attention in postsynaptic target neurons.

Frontal 2 **Attention**



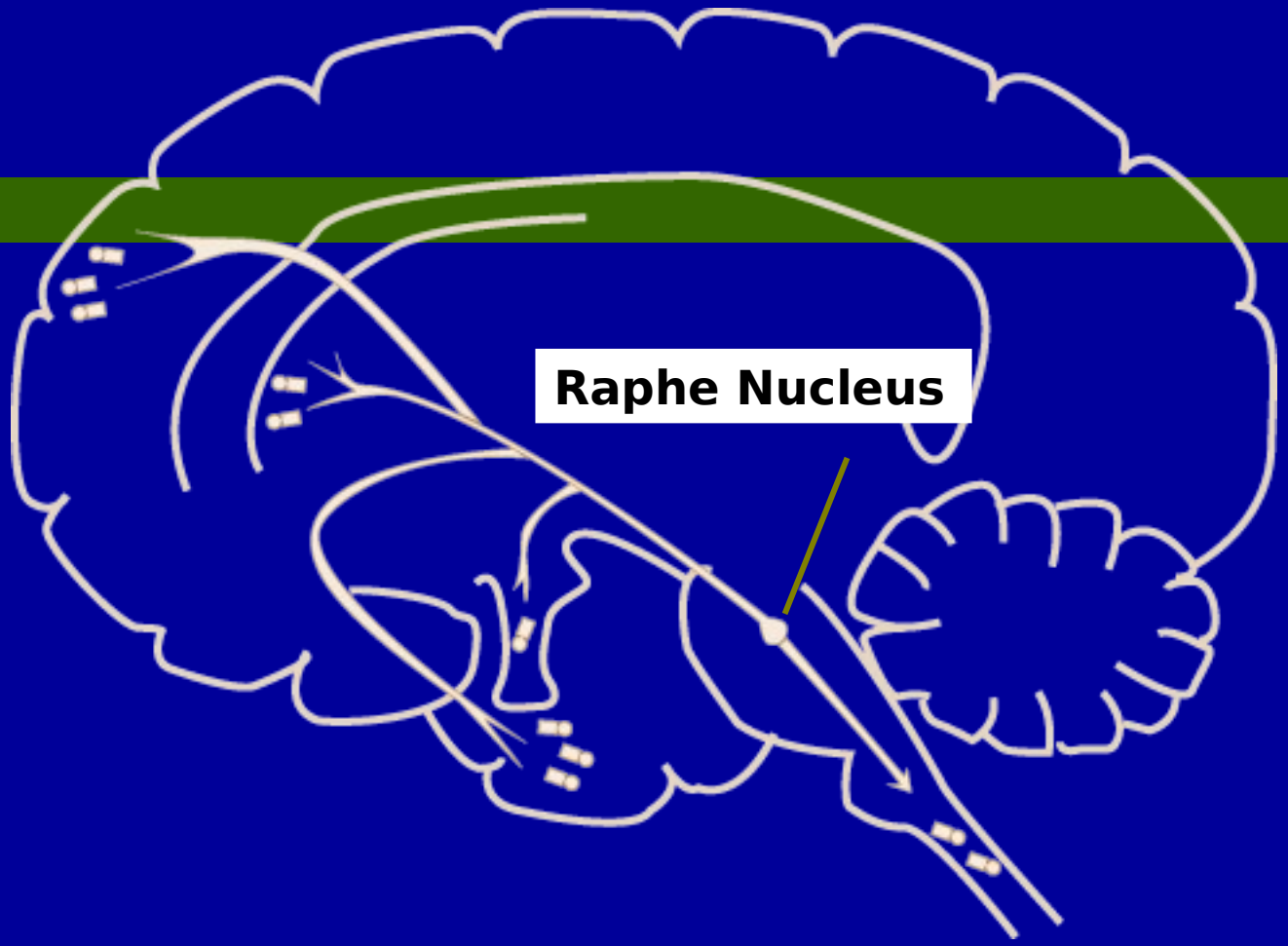
The noradrenergic projection from the locus coeruleus to limbic cortex may mediate <u>emotions</u>, as well as <u>energy</u>, <u>fatigue</u>, and <u>psychomotor</u> <u>agitation</u> or psychomotor <u>retardation</u>



Serotonin Pathways

- In addition to the 5HT transporter, there is a key presynaptic 5HT receptor (the 5HT1D receptor) and another key presynaptic receptor, the alpha 2 noradrenergic heteroreceptor.
- This organization allows 5HT release to be controlled not only by serotonin but also by NE, even though the 5HT neuron does not itself release norepinephrine.

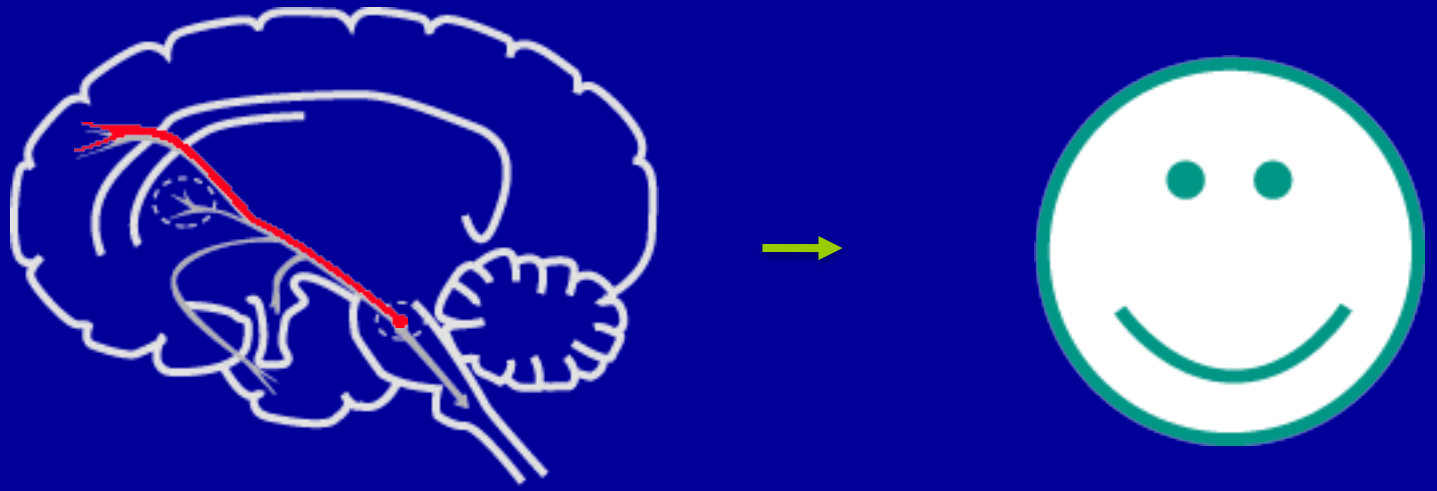
Serotonin Pathways



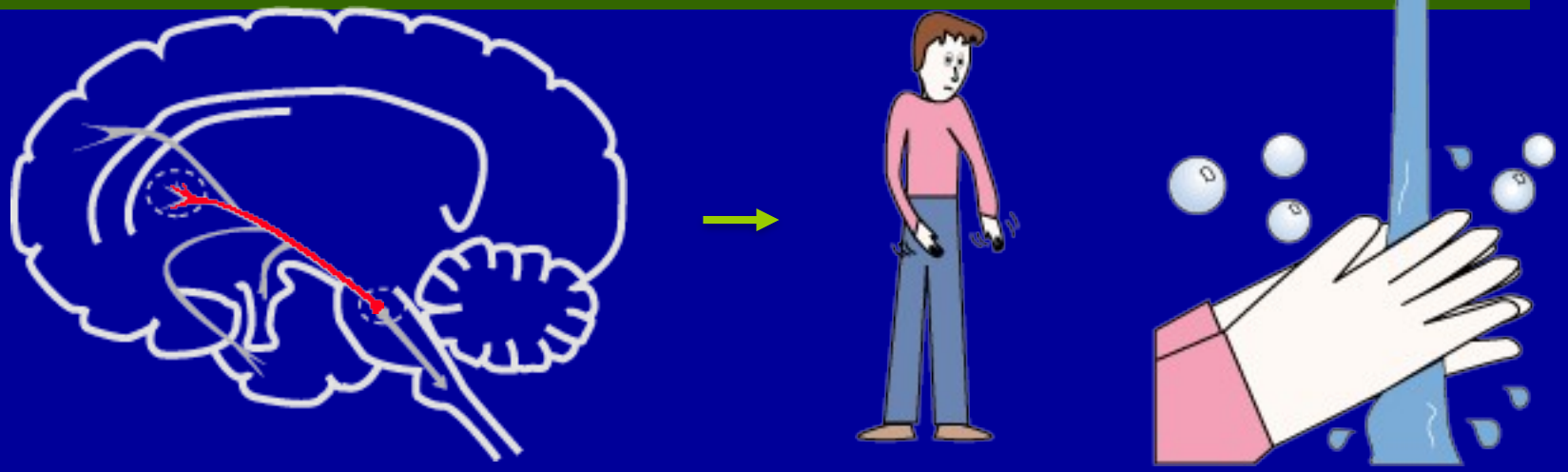
The headquarters for the cell bodies of serotonergic neurons is in the brainstem area called the <u>raphe nucleus.</u>

Serotonergic projections from raphe to <u>frontal cortex</u> may be important for regulating <u>mood</u>.

Frontal Cortex → **Mood**



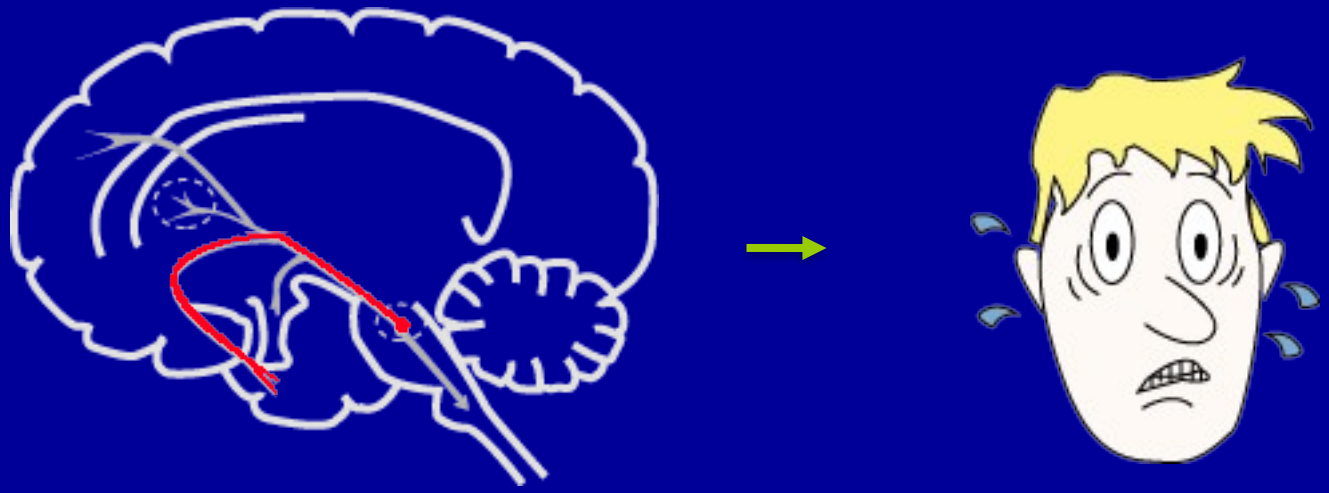
Basal Ganglia **Akathisia/ Agitation** **OCD**



Serotonergic projections from raphe to basal ganglia may help control movements as well as obsessions and compulsions

Limbic

Anxiety



Serotonergic projections from raphe to <u>limbic areas</u> may be involved in <u>anxiety</u> and <u>panic</u>.

Hypothalamus



Appetite/ bulimia



Serotonergic projections to the <u>hypothalamus</u> may regulate <u>appetite and eating behavior</u>.

Sleep Centers

Insomnia

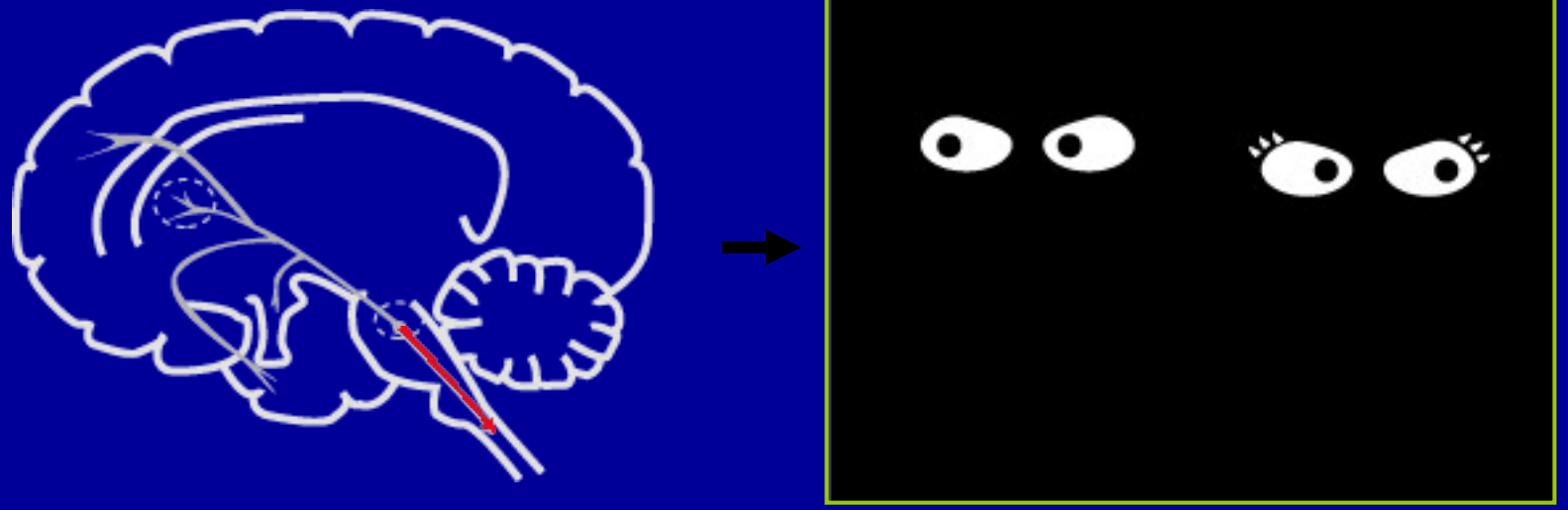




Serotonergic neurons in brainstem <u>sleep centers</u> regulate <u>sleep</u>, especially slow-wave sleep

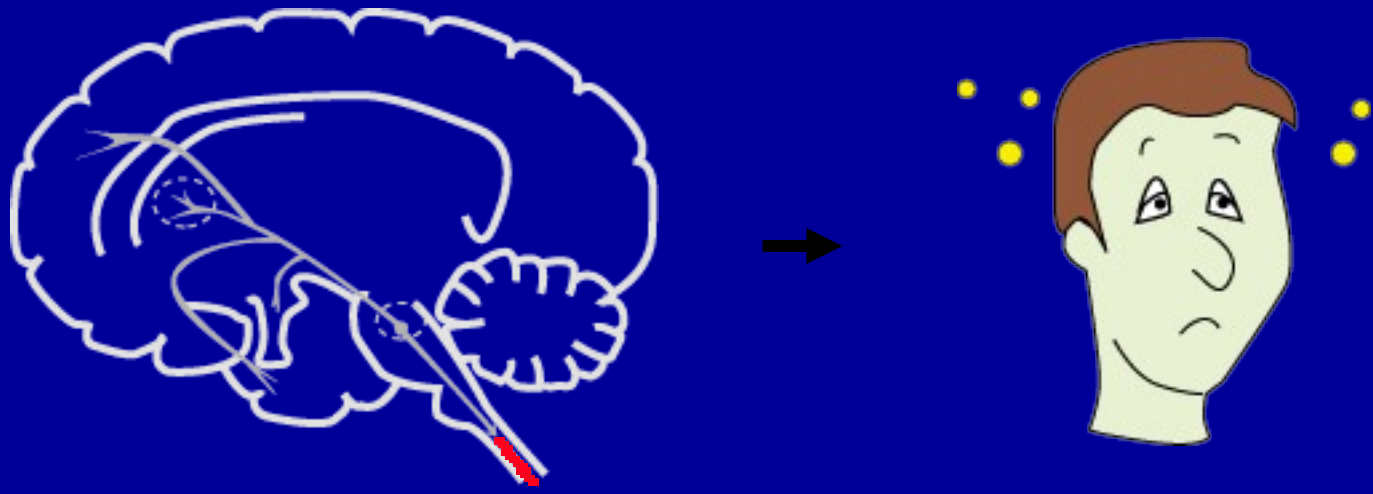
Serotonergic neurons descending down the spinal cord may be responsible for controlling certain spinal reflexes that are part of the sexual response, such as orgasm and ejaculation.

Spinal Cord → **Sexual Dysfunction**



Brainstem Vomiting Center

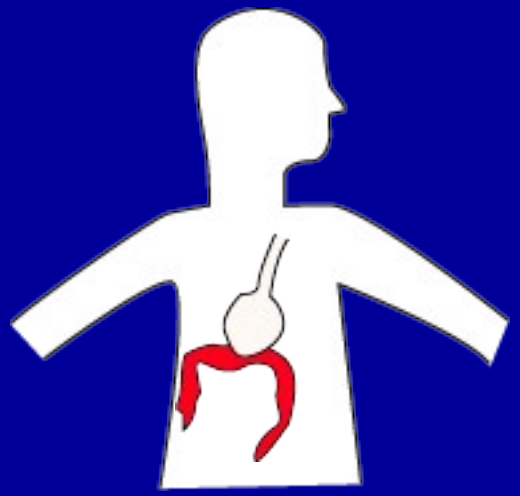
Nausea and vomiting



The chemoreceptor trigger zone in the brainstem can mediate vomiting, especially via 5HT3 receptors

Peripheral 5HT3 and 5HT4 receptors in the gut may regulate appetite as well as other gastrointestinal functions, such as gastrointestinal motility.

Gut

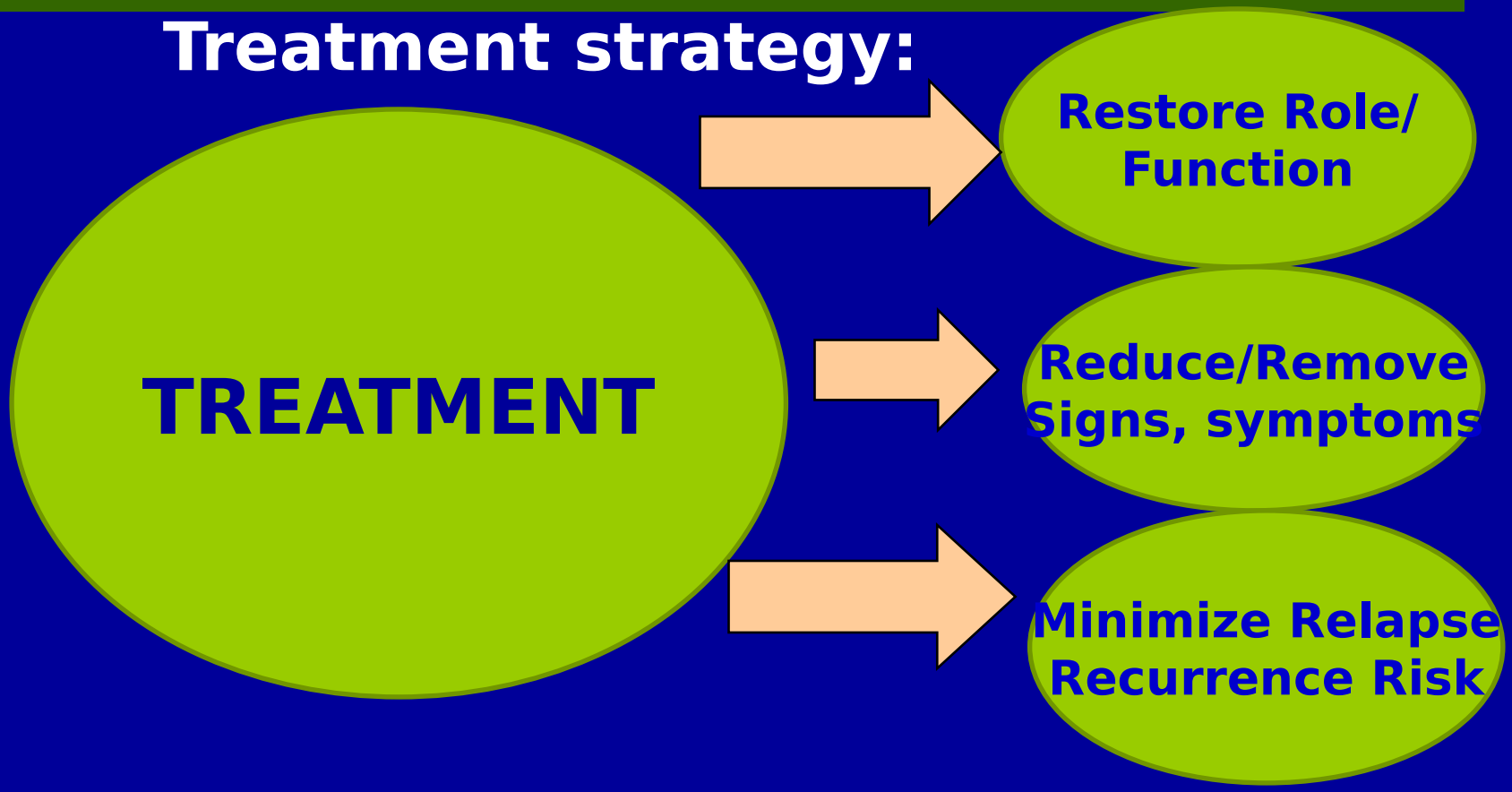


GI cramps/Diarrhea

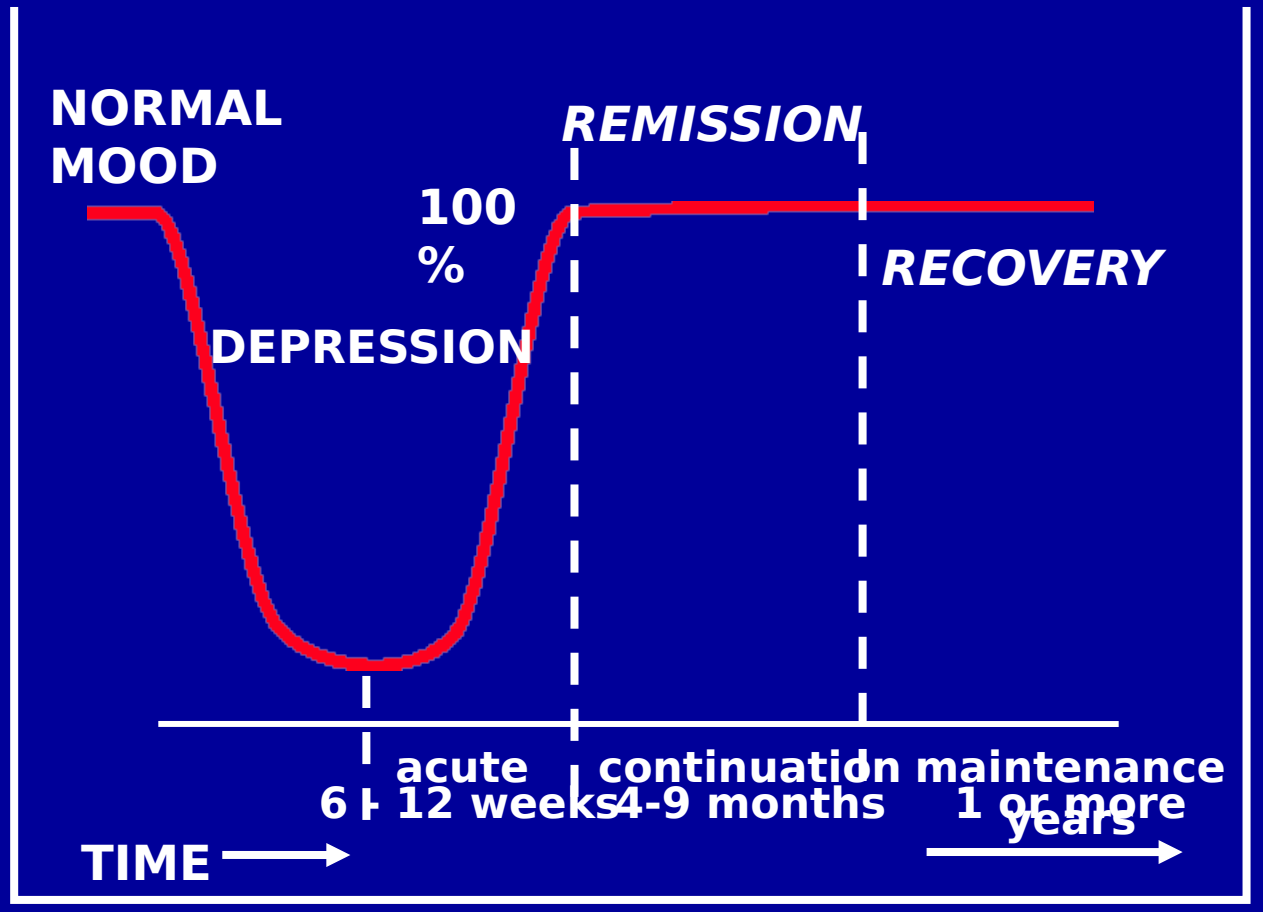


Treatment Goal for Depression

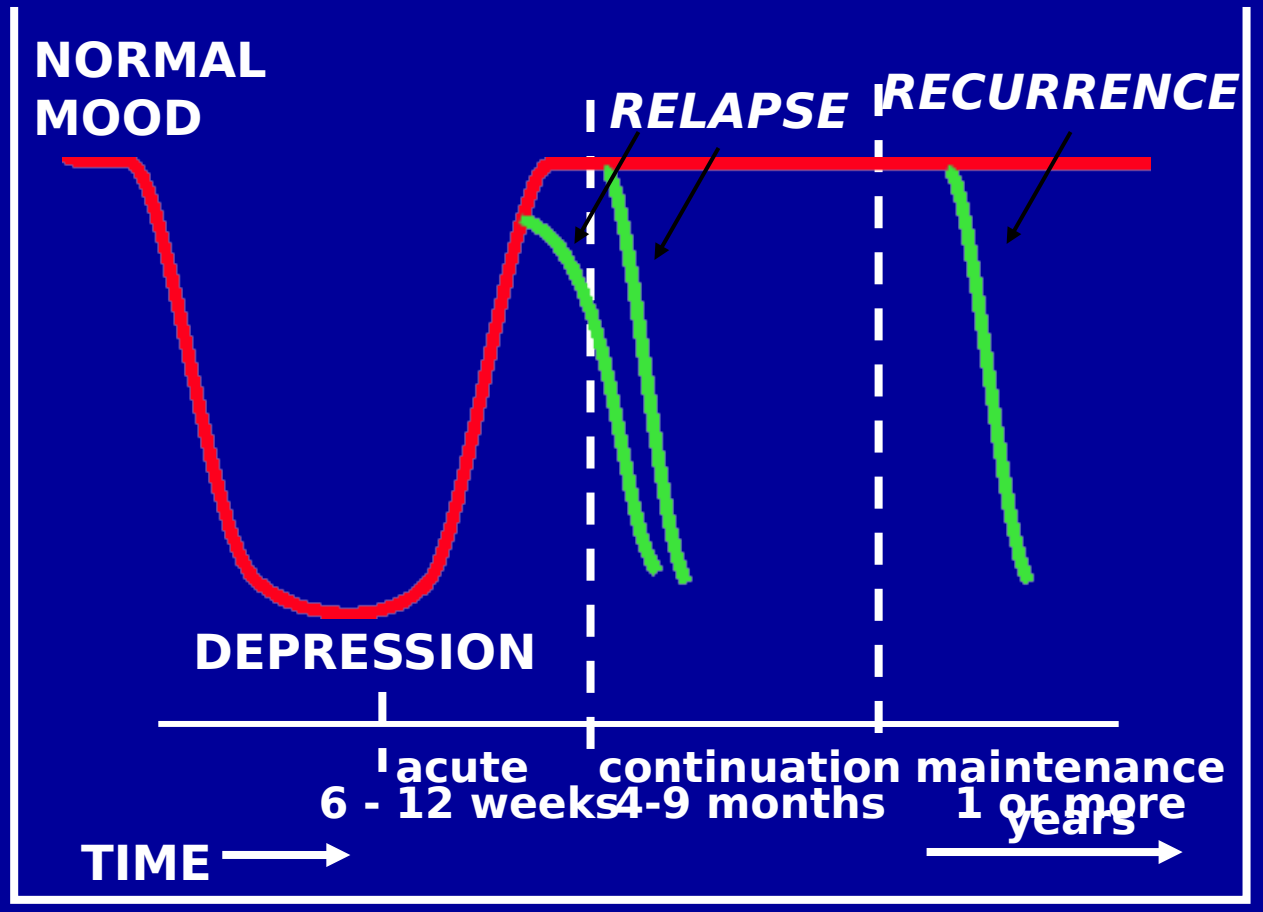
Treatment strategy:



When treatment of depression results in removal of essentially all symptoms, it is called remission for the first several months, and then recovery if it is sustained for longer than 6 to 12 months. Such patients are not just better – they are well.



When depression returns before there is a full remission of symptoms or within the first several months following remission of symptoms, it is called a relapse. When depression returns after a patient has recovered, it is called a recurrence.



Classes of antidepressants

TCA'S

- **Amitriptyline**
- **Clomipramine**
- **Desipramine**
- **Imipramine**
- **Nortriptyline**

MAOIs

- **Isocarboxazid**
- **Phenelzine**
- **Tranylcypromine**

SSRIs

- Citalopram
- Escitalopram
- Fluoxetine
- Paroxetine
- Sertraline
- Fluvoxamine

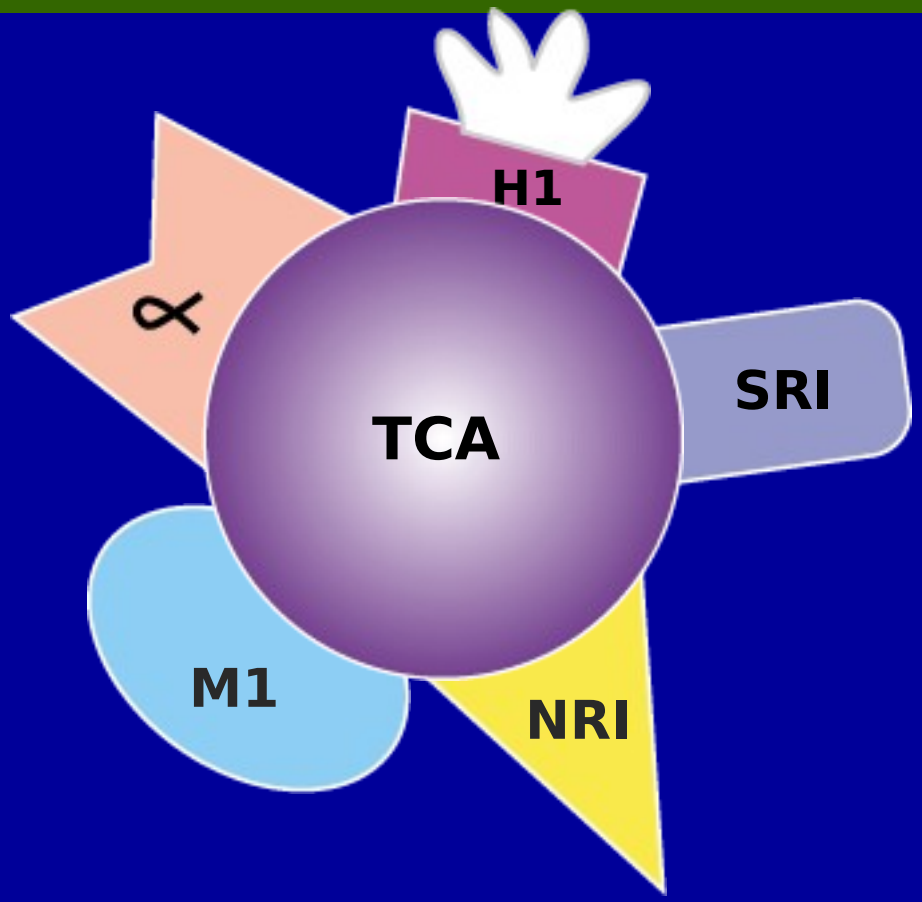
SNRI

- Venlafaxin

Other agents

- **Amoxapine**
- **Bupropion**
- **Mirtazapine**
- **Nefazodone**

Tricyclic Antidepressant (TCA)



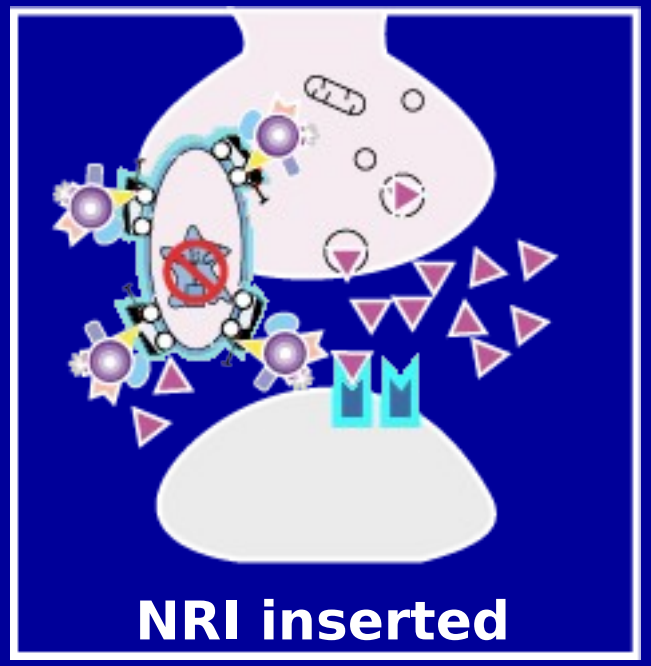
TCAs

- The TCAs were discovered during the search for new and safer antipsychotic agents.
- The first among these was imipramine.
- The TCAs have a high affinity for many CNS receptors including muscarinic, cholinergic, histaminergic, alpha-adrenergic, as well as serotonin & norepinephrine transporters
- The antidepressant effect of the TCAs is attributed to their inhibition of NE & 5-HT



SRI inserted

depression lifts



NRI inserted

depression lifts

TCAs

- Side Effects:
  - Dry mouth, urinary retention, constipation, tachycardia, & blurred vision (anticholinergic)
  - Sedation & weight gain (antihistaminic)
  - Can cause cardiac conduction delays, particularly first-degree atrioventicular and bundle branch block.
  - Orthostatic hypotension attributed to blockade of alpha adrenergic receptors
  - Less common side effects are sexual dysfunction

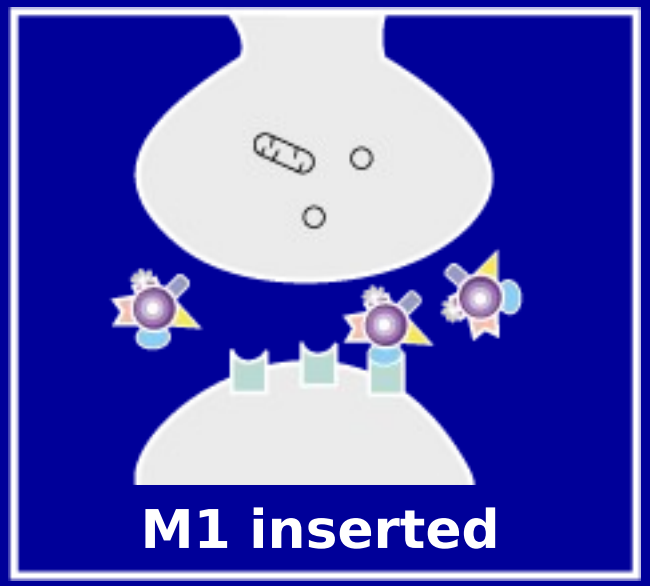


weigh
t gain



drowsiness





constipation



blurred vision

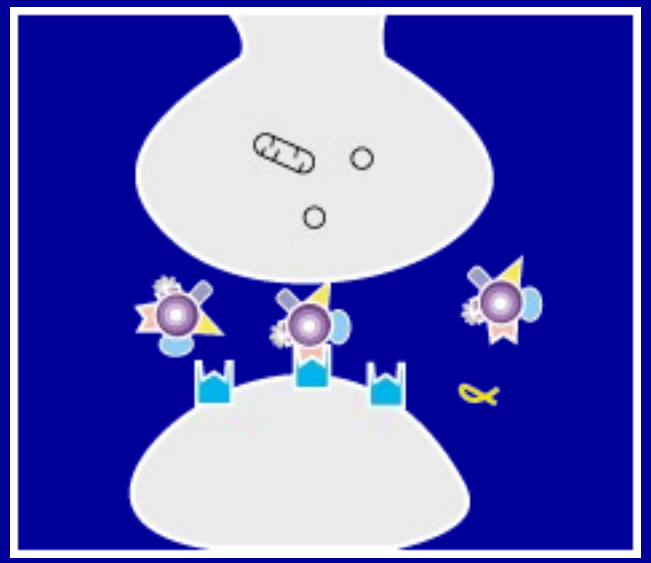


dry
mouth



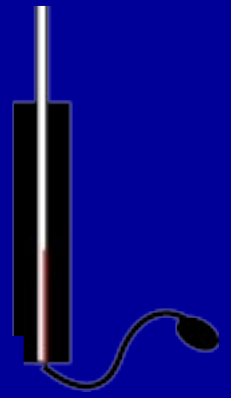
drowsiness





decreased blood pressure





dizziness

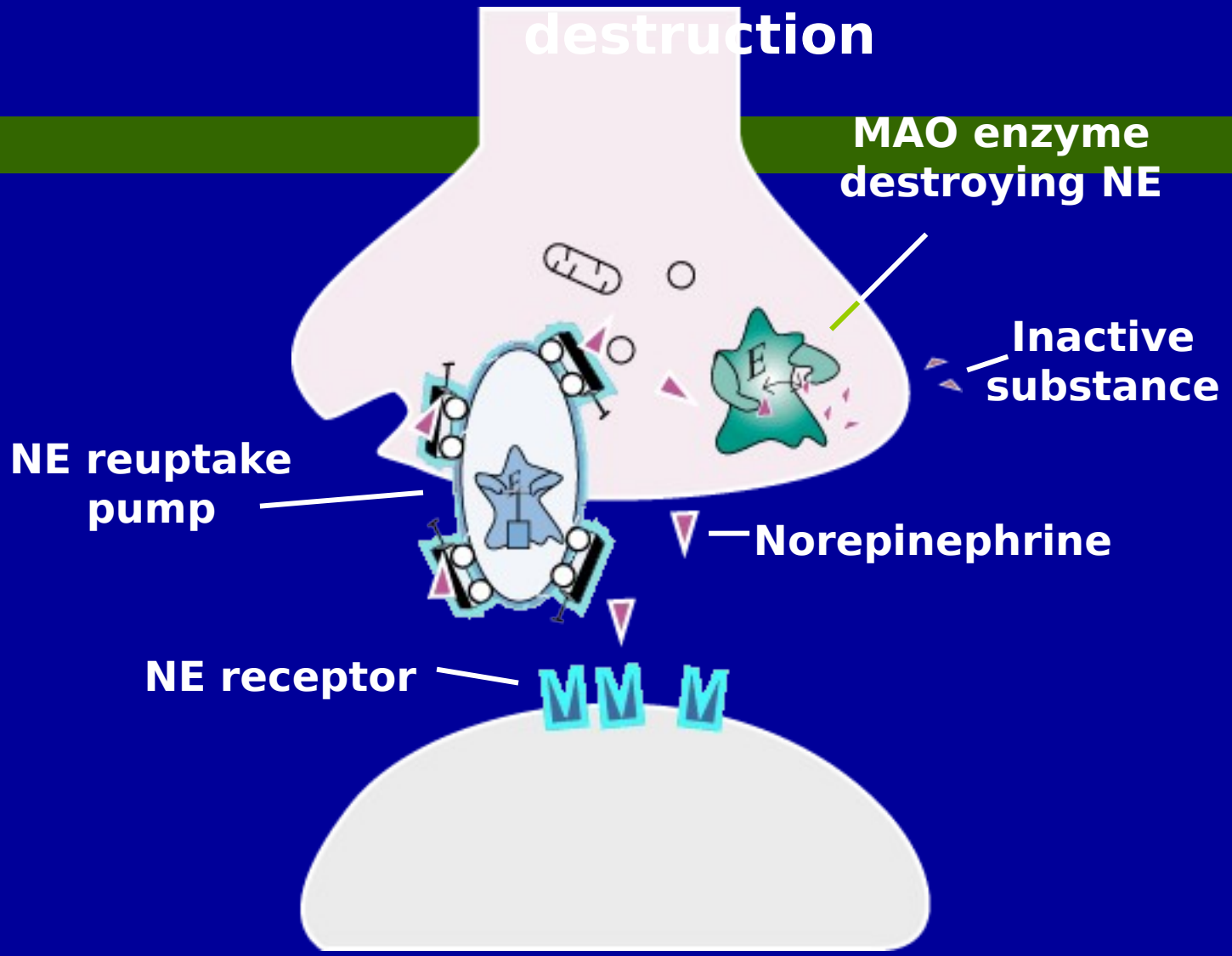
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TCAs

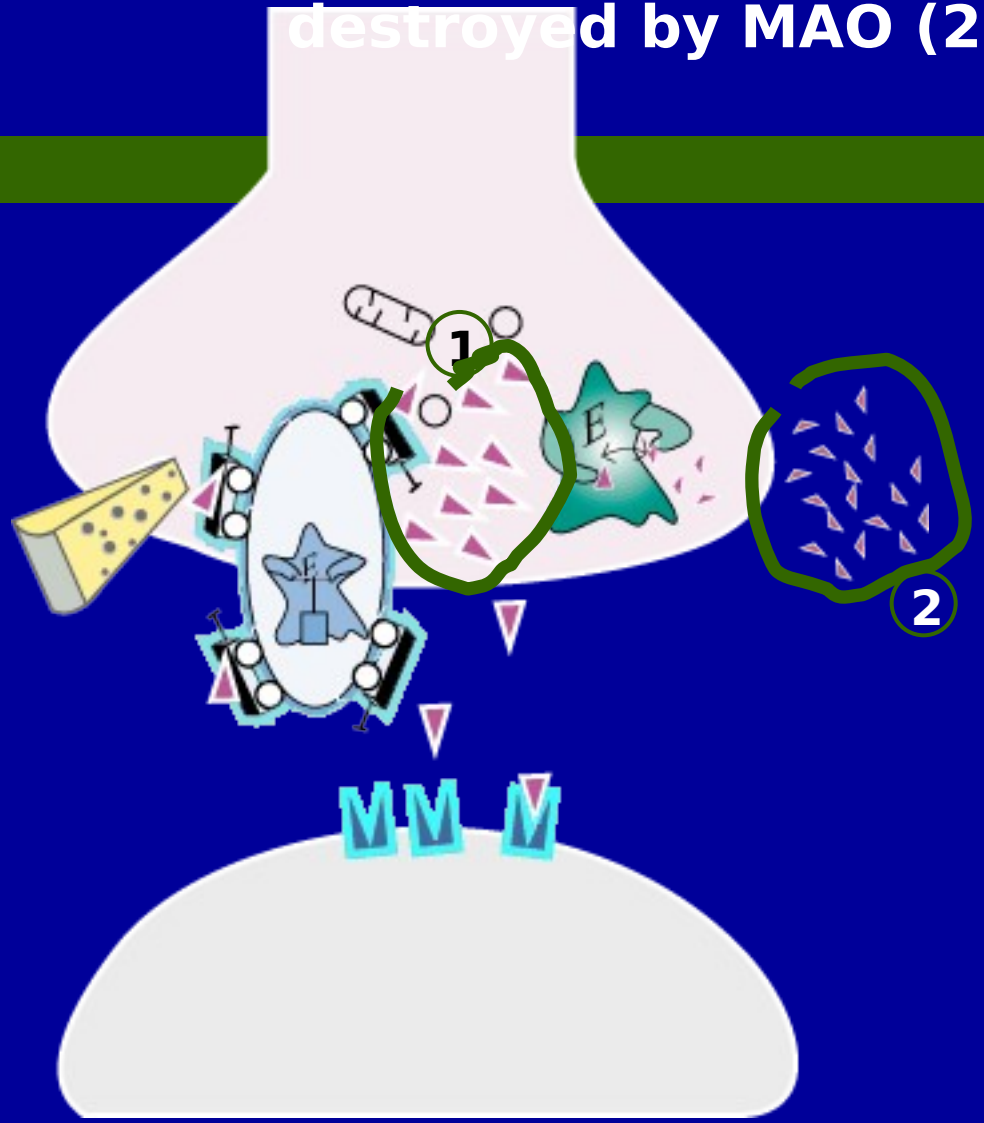
Examples	Initial dose	Max dose
Amitriptyline	30–75 mg	300mg
Clomipramine	10 mg daily	250mg
Doxepin	75 mg daily	300mg
Imipramine	75 mg daily	300mg
Nortriptyline	75 mg daily	150mg
Trimipramine	50 mg daily	300mg

Monoamine Oxidase Inhibitors

Normal NE production and destruction



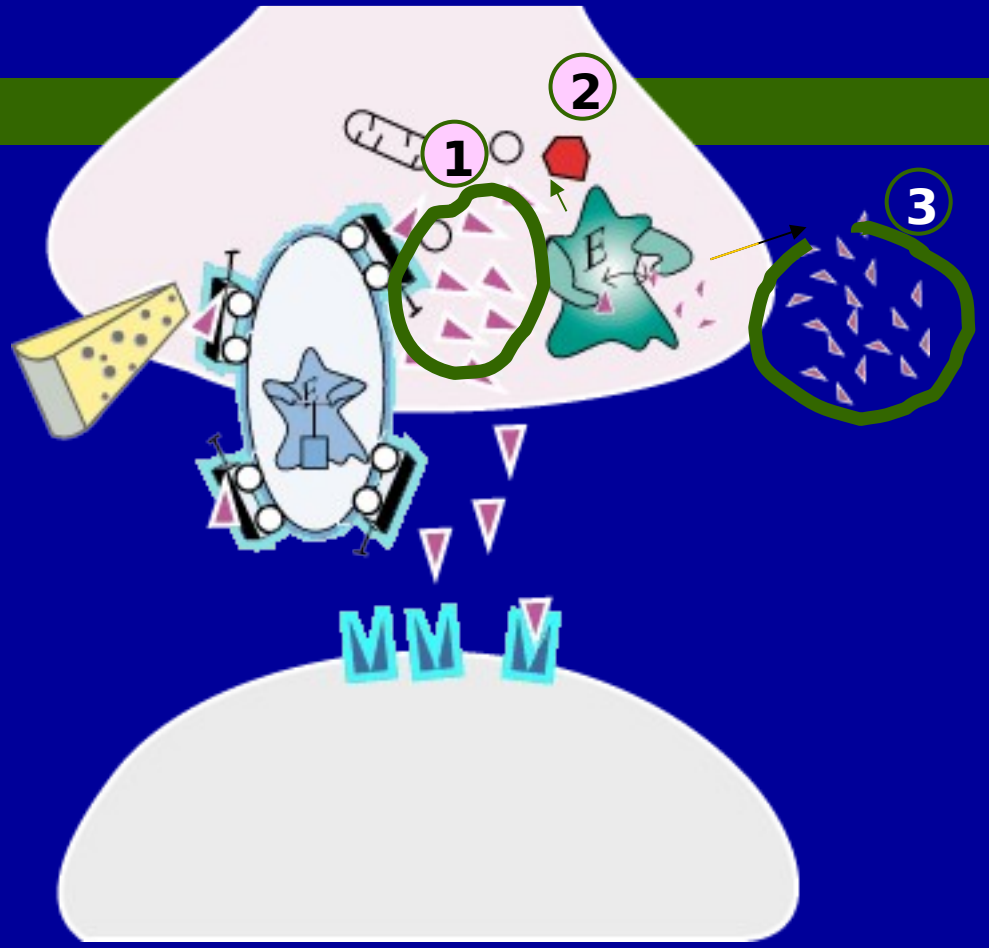
Tyramine, as in cheese, increases the release of NE (1), and the excess is destroyed by MAO (2)



Here, the tyramine increases the release of NE (1) and the irreversible MAO-inhibitor causes MAO enzyme to stop destroying NE (2). This increase in NE can lead to dangerous elevations of blood pressure (3).



In the case of a reversible inhibitor of MAO (1), the NE released by tyramine can displace the RIMA (2), allowing for normal destruction of the extra NE (3).



Monoamine Oxidase Inhibitors

- The action of MAOI is to increase the availability of the monoamine neurotransmitter NE, DA, and 5-HT by blocking their metabolism.
- The classical MAOI are non-selective & irreversible (Phenelzine, Tranylcypromine, & Isocarboxazid)
- The newer ones are selective and reversible
  - Reversible inhibitor of MAO-A (Moclobemide)
  - Selective inhibitor of MAO-B (Deprenyl)
- Despite their efficacy, their clinical use has been limited due to the life threatening “hypertensive crisis” when they are ingested with certain food or medications (tyramine, sympathomimetics etc.

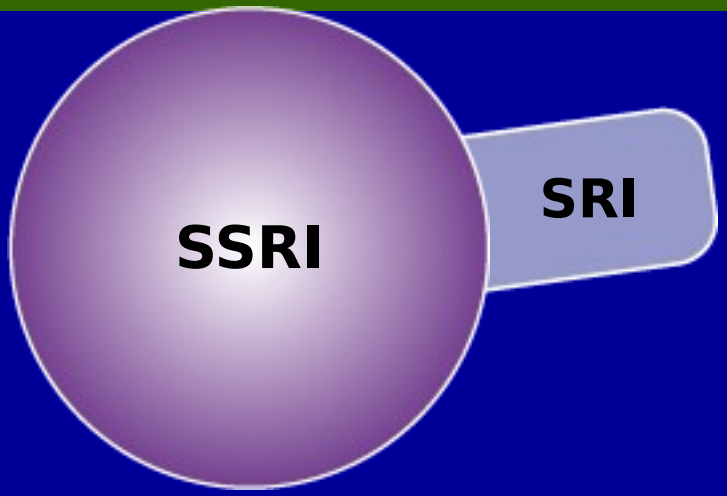
MAOI

- Another untoward drug-drug interaction is the so called serotonin syndrome if it is co-administered with SSRIs, TCAs & some of the newer antidepressant.
- Other side effects of MAOI include dizziness, orthostatic hypotension, suppression of REM sleep, weight gain & sexual dysfunction.
- Moclobemide is reversible, selective MAO type A inhibitor, was found to be very

MAOIs

Examples	Initial dose	Max dose
Phenelzine	15 mg 3 times daily	30mg TID
Isocarboxazid	30 mg daily	60mg daily
Tranylcypromine	10 mg twice daily	30mg
Moclobemide	300 mg daily	600mg

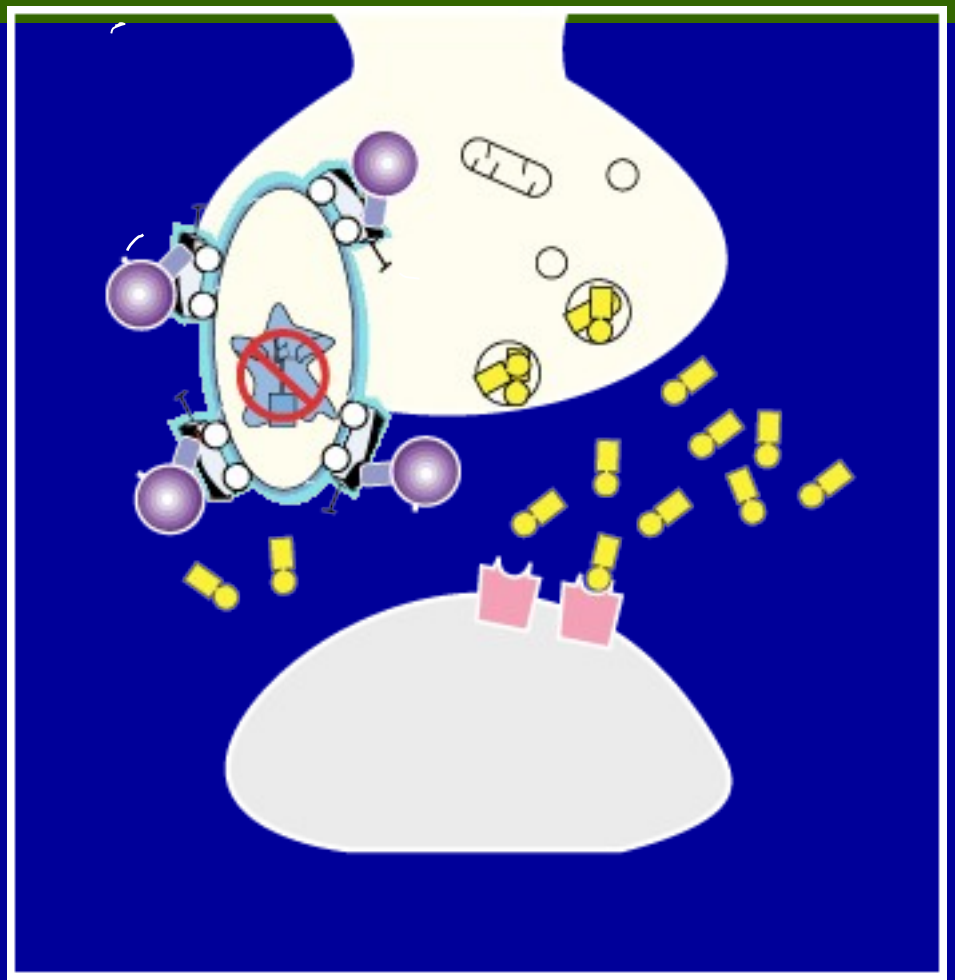
Selective Serotonin Reuptake Inhibitors (SSRI)



SSRI

- First introduced in 1988 (Prozac)
- 6 SSRIs are (in order of release): fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, & escitalopram
- Efficacious like other antidepressants (TCAs etc.)
- Disinhibition of serotonergic neurotransmission in the pathway from midbrain raphe to prefrontal cortex could hypothetically help mediate the antidepressant effects of SSRIs.
- Disinhibition of the pathway from midbrain raphe to Basal ganglia mediate the therapeutic actions of SSRIs in OCD.

SSRI ACTION



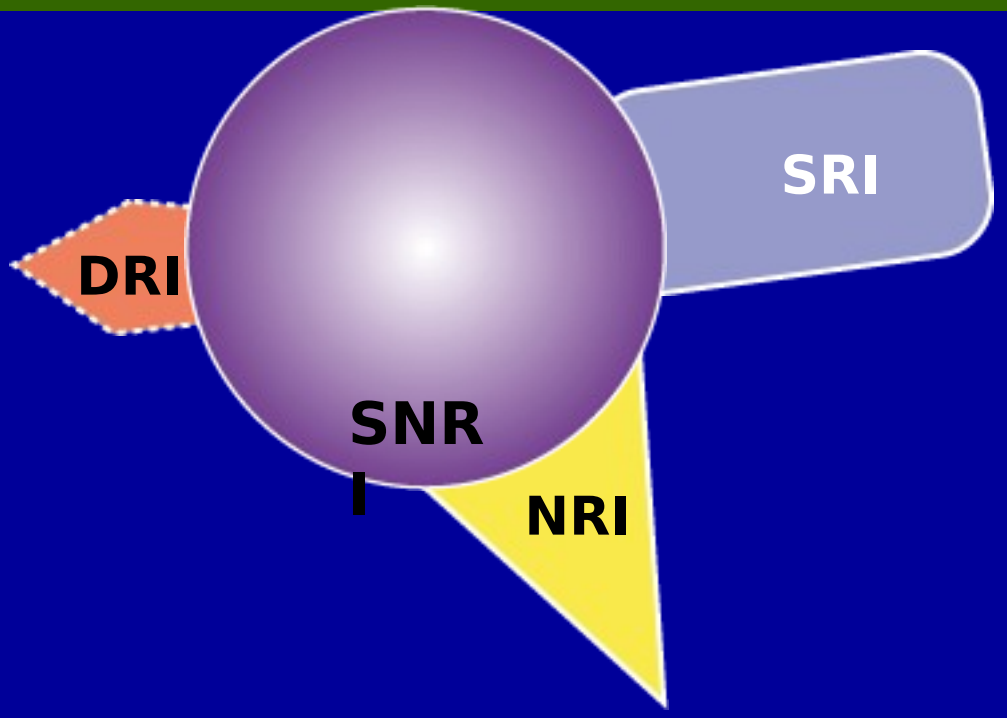
SSRIs

Examples	Initial dose	Max dose
Citalopram	20 mg daily	40 mg daily
Escitalopram	10 mg daily	20 mg daily
Fluoxetine	20 mg daily	60 mg daily
Fluvoxamine	50 mg daily	300 mg daily
Paroxetine	20 mg daily	50 mg daily
Sertraline	50 mg daily	200 mg daily

Norepinephrine & Dopamine Reuptake inhibitor

- Bupropion is the prototypical agent of the NE & dopamine reuptake inhibitors.
- Boosts norepinephrine & dopamine in the synapse
- It is used also as augmenting agent
- Most common side effects include anxiety, agitation, decreased appetite & insomnia.
- The most dangerous side effect of bupropion is its increase in seizure risk
- The half-life of bupropion is 14 hrs and maximum dosage is 450 mg/day
- Other applications of bupropion are for ADHD & treatment of smoking cessation.

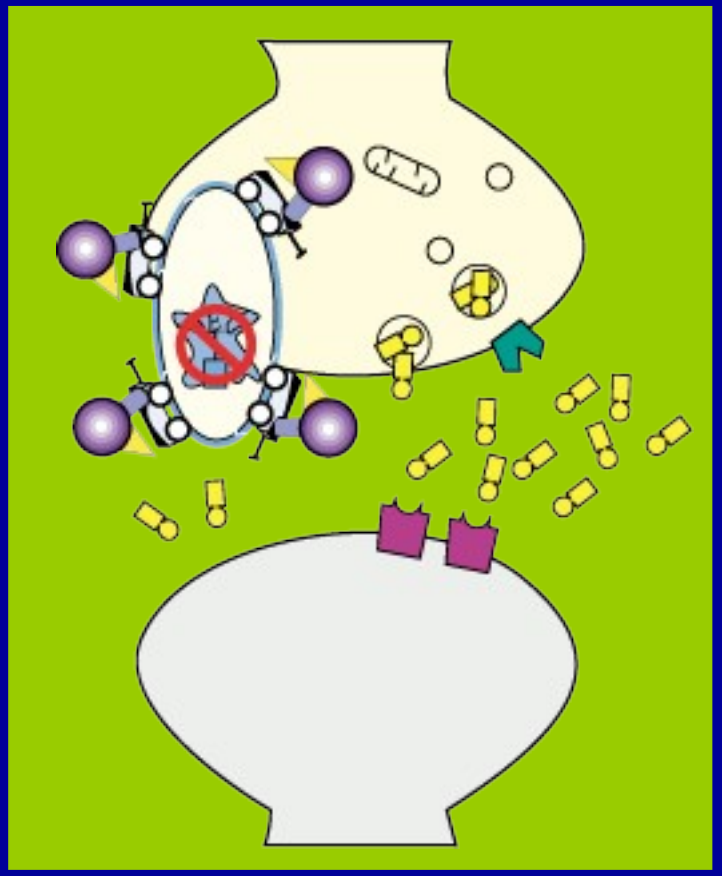
Selective Noradrenergic Reuptake Inhibitors (SNRI)

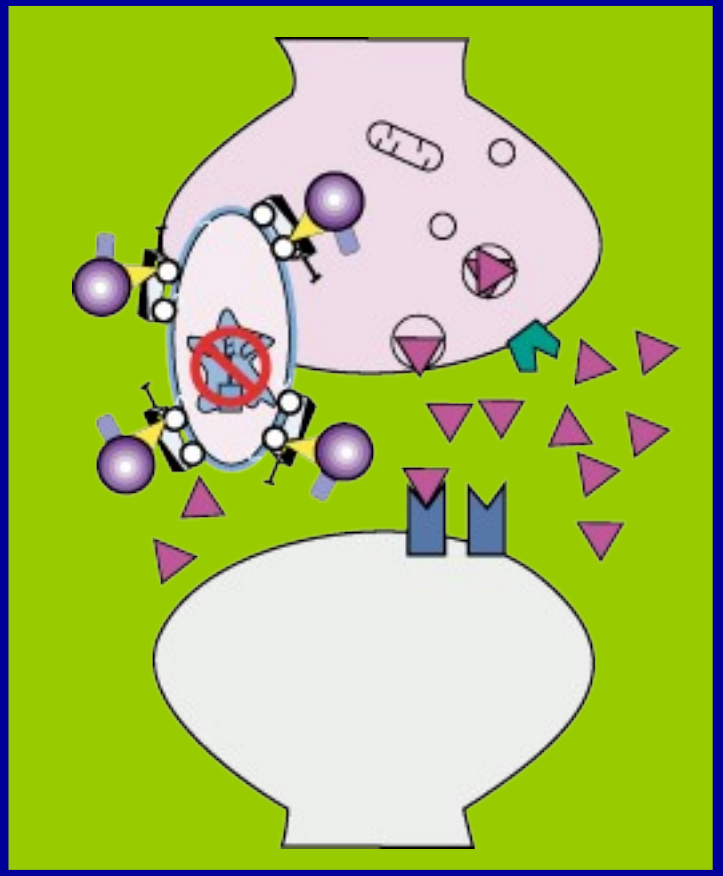


SNRI

- The first truly selective noradrenergic reuptake inhibitor (NRI) is reboxetine
- It provides selective noradrenergic reuptake inhibition greater than serotonin reuptake inhibition but without the undesirable binding properties of the TCA

SNRI ACTIONS





Serotonin & Norepinephrine Reuptake Inhibitors

- Venlafaxine (Effexor) is the only dual action SNRI marketed.
- Was found to be superior in efficacy over SSRIs
- It does not have affinity for muscarinic, cholinergic, histaminic or alpha-adrenergic receptors.
- At higher dosage it also acts as a dopamine reuptake inhibitor.
- Its half-life is 5 hrs with its active metabolite having 11 hrs. The dose range is from 75 – 375mg
- The most common side effects are nausea, anorexia, insomnia, and nervousness.

Bipolar Disorder

Bipolar disorder

- Over the course of bipolar disorder, *four* different kinds of mood episodes can occur:

1. Mania (manic episode):

- Mania often begins with a pleasurable sense of heightened energy, creativity, and social ease-feelings that can quickly escalate out of control into a full-blown manic episode.
- People with mania typically lack insight, deny anything is wrong, and angrily blame

- In a manic episode, the following symptoms are present *for at least 1 week*, associated with impaired functioning:
- Feeling or appearing unusually "high," euphoric, or irritable

***Plus at least four* (and often almost all) of the following:**

- Needing ***little sleep*** yet having great amounts of energy
- Talking so ***fast*** that others can't follow the speech
- Having racing thoughts
- Being so ***easily distracted*** that ***attention shifts between many topics*** in just a few minutes
- Having an ***inflated feeling of power, or importance***
- ***Doing things without concern*** about possible bad consequences such as spending too much money, inappropriate sexual activity, making foolish business investments.

2. Hypomania (hypomanic episode).

- Hypomania is a milder form of mania with similar but less severe symptoms and less impairment.
- The individual may have an elevated mood, feel better than usual, and be ***more productive***.
- These episodes often feel good and the onset for hypomania may even cause people *to stop their medication*.

3. Depression (major depressive episode).

- The symptoms of depression are present for at *least 2 weeks* associated with impaired functioning.
- Severe depressions may be accompanied by hallucinations or delusions.

4. Mixed Episode.

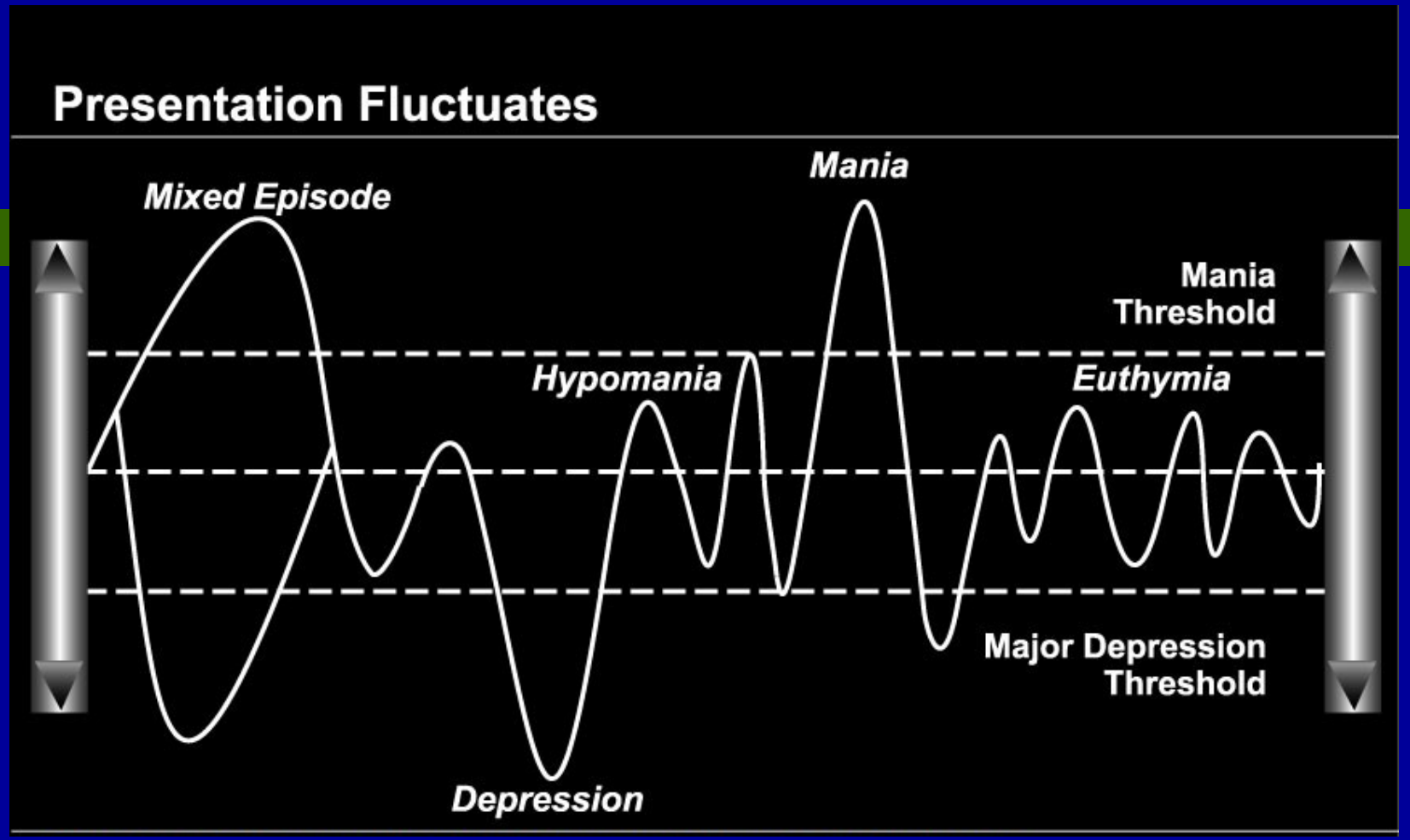
- During such an episode symptoms of both mania and depression occur at the same time or alternating frequently during the day.

Bipolar Disorder: Diagnostic Criteria

- **Bipolar I Disorder:**
  - ✓The essential feature is its clinical course that is characterized by the occurrence of one or more **manic** or mixed episodes.
- **Bipolar II Disorder:**
  - ✓Presence or history of at least one major depressive episode
  - ✓Presence or history of at least one hypomanic episode.
  - ✓There has never been a manic or mixed episode.

Bipolar Disorder: Diagnostic Criteria

- ***Rapid Cycling Bipolar Disorder:***
  - ✓ When a person has at *least four episodes per year*, in any combination of manic, hypomanic, mixed, or depressive episodes.


Presentation Fluctuates
Mixed Episode
Mania
Mania Threshold
Hypomania
Euthymia
Major Depression Threshold
Depression

Bipolar Disorder: Origin, recognition & treatment

- The occurrence rate in men & women is similar, the life-time prevalence of bipolar disorder to be 1.6% & 1.3% respectively.
- Bipolar disorder in female patients has been associated with relatively ***predominant depressive***, rather than manic, features.
- Period of onset appears to be during adolescence (15-19)
- The life time risk of death by suicide is approx. 19%.

Bipolar Disorder: Etiology

- **Genetics*:***
  - ✓ Family linkage studies have shown that bipolar disorder is substantially genetical.
  - ✓ Concordance rates for bipolar disorder have been estimated to be up to 90% for monozygotic twins & 14% for dizygotic twins.

Bipolar disorder: Pathophysiology

- It is probably mediated through multiple NT pathways and biological interactions.
- Several neurotransmitters including **NE**, **dopamine**, **glutamate**, & **GABA** have been implicated in bipolar disorder to some degree (L-dopa, amphetamine, & *cocaine* have been found to precipitate mania in non-bipolar individuals)
- Hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA) has been documented in bipolar disorder

Bipolar Disorder: Neuroanatomy

- Two studies using MRI found indications of *bilateral amygdala enlargement* with no change in the hippocampus
- Using computerized tomography scans significant *enlargement of the lateral and third ventricles was* found. Ventricle size was also associated with *cerebellar atrophy* in manic patients.
- *Decreased metabolism in the pre-frontal cortex* was also associated in bipolar

Bipolar Disorder: Treatment

- **Pharmacological:**
  - Medications have been shown to be effective in the treatment of bipolar disorders.
  - Currently there are several mood stabilizers
    - Lithium, sodium valproate, olanzapine , risperidone, quetiapine, ziprasidone, aripiprazole, and lamotrigine
  - Unapproved but have substantial controlled data are: Carbamazepine,

Bipolar disorder: treatment

- **Lithium**:
  - It was first reported in 1949 as having antimanic agent.
  - Has been in use for bipolar disorder since mid-60’s.
  - It is more effective than placebo but not better than VPA & carbamazepine.
  - It was also found that it was effective in preventing episodes of mania & depression.
  - Mechanism of action involves modifying the

Bipolar Disorder: Lithium

- Lithium is a salt and it is excreted entirely by the kidney
- It is not protein bound and is not metabolized. As a result it is distributed in the total body water.
- Change in hydration & renal function affects the Li. level
- Thiazide diuretics increase the level of Li up to 50% (although furesomide is not)
- NSAID, ACE inhibitors also can increase the Li level.
- Side effects include: *polyuria*, *polydypsia*, *increased weight*, *cognitive dulling* (decreased memory, poor concentration, & confusion), *tremor, sedation, lethargy, impaired coordination, GI problems, hair loss, leuckocytosis, acne & edema.*
- Long term side effects are: hypothyroidism, and kidney damage.

Bipolar Disorder: Lithium

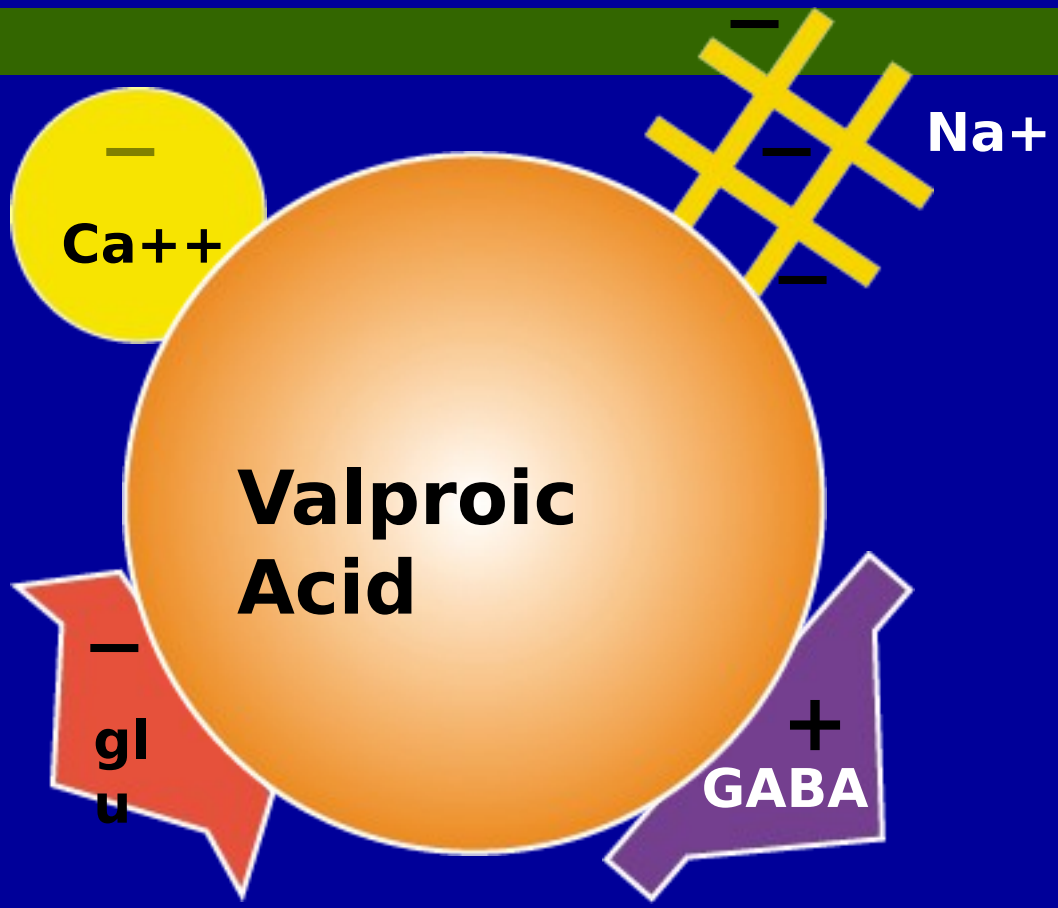
- Idiosyncratic side effect is *psoriasis vulgaris*.
- Fetal exposure has high risk of developing congenital defect *polyhydraminos, premature delivery* and *thyroid abnormalities*.
- Has a narrow therapeutic window and as a result it can be toxic even in a therapeutic dosage.
- Treatment for toxicity is supportive i.e. *fluid maintenance*, *gastric lavage* & possibly *hemodyalsis*.

Bipolar Disorder: Lithium

- Initiating treatment:
  - Medical workup including CBC, comprehensive metabolic chem. (electrolytes, kidney function, TFTs), pregnancy test
  - Start with 300 mg po tid and check the level after 24 hrs.
  - Check the serum level

Bipolar Disorder: *Valproate*

- Is an anti-epileptic drug for a long period of time.
- Its exact mechanism of action is unknown, however it is considered that it might *inhibit the sodium & calcium channel function* & thereby *boosting the GABA inhibitory action* as well as *reduce glutamate excitatory action.*
- It is extensively metabolized by the liver & is also highly protein bound.
- Toxicity can happen by co-administering with highly protein-binding drugs (e.g. *aspirin*).

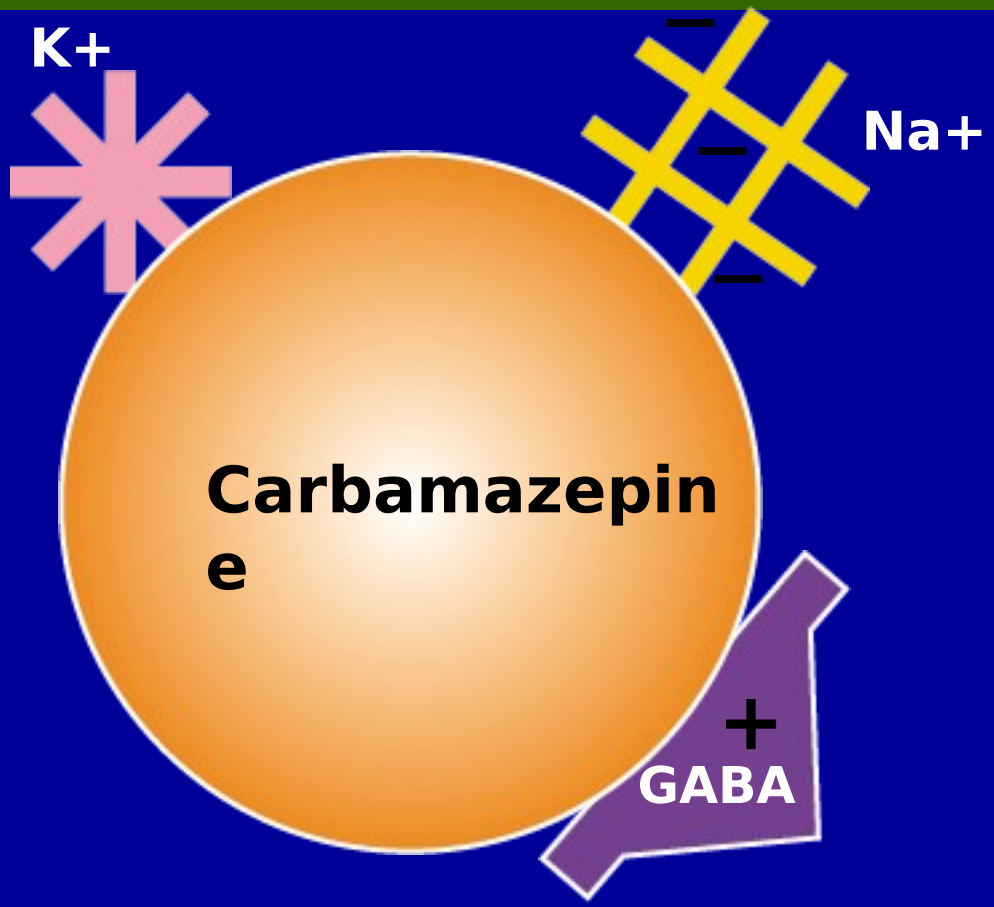

−
Na+
−
−
−
Ca++
Valproic
Acid
−
gl
u
+
GABA

Bipolar Disorder: *Valproate*

- Numerous studies have shown that Valproate is very efficacious in the treatment of *acute mania*.
- It also works well in certain bipolar groups (rapid cycling, comorbid sub. abuse)
- It is even more efficacious when administered concomitantly with other mood stabilizers.
- Its efficacy in the treatment of acute bipolar depression has not been fully examined. However, patients who

Bipolar Disorder: Valproate

- Side effects include: sedation, GI distress, benign hepatic transaminase elevation, weight gain, hair loss, and rarely acute pancreatitis (in children), & polycystic ovary disease.
- Use in pregnancy has been associated in neural tube defects in the fetus.
- Dosing: 1) in mild forms, start with 250 mg po tid and increase the dosage as needed till the patient stabilizes. 2) in acute mania: load the patient up to 20mg/kg/day.
- Therapeutic serum levels are from 50-125mcg/ml
- Fluoxetine increases its plasma level while tegretol decreases its plasma level. Inhibits the metab. of TCA


K+
Na+
Carbamazepin
e
+
GABA

Bipolar Disorder: Carbamazepine

- Has not been approved by the FDA
- Evidence of its effectiveness in acutely manic bipolar patient has been demonstrated in 19 studies to date.
- Comparison studies between lithium and carbamazepine showed that carbamazepine to be as or *more effective*.

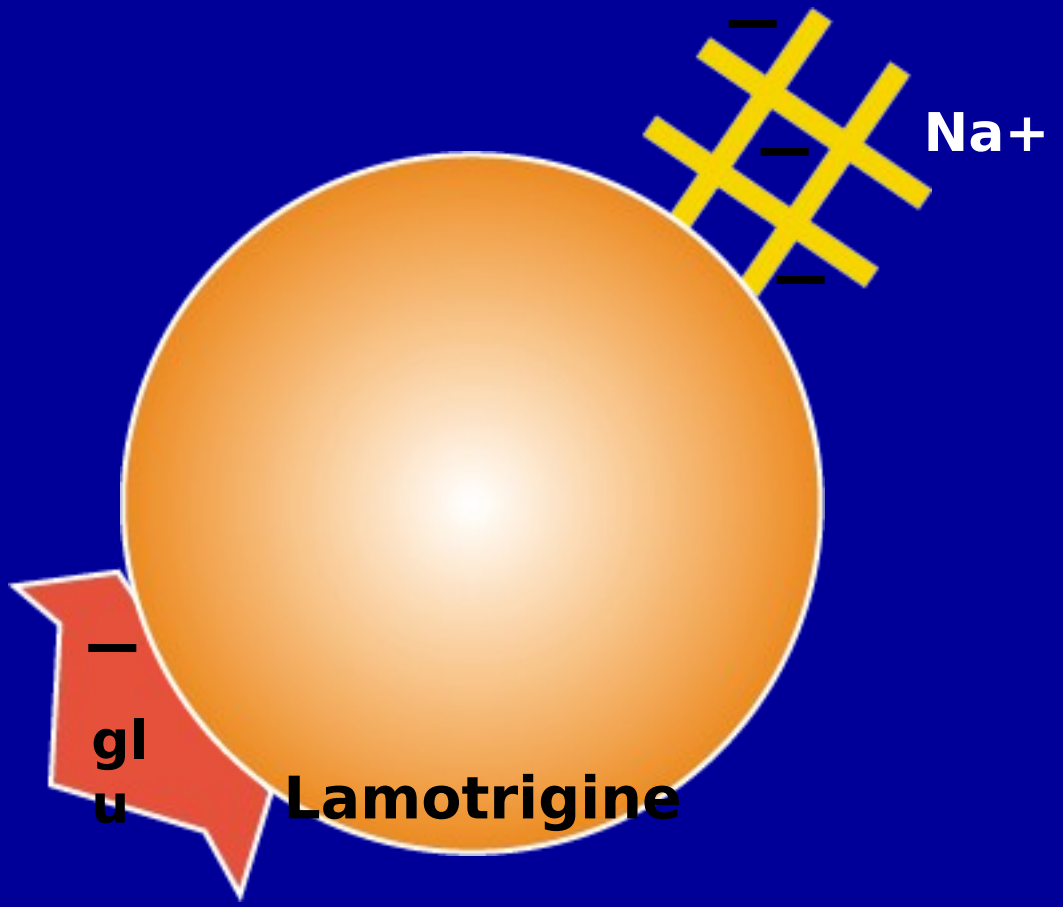
Bipolar Disorder: Carbamazepine

- It is highly protein bound
- It is metabolized by the liver and it has a property of inducing its metabolism, thereby decreasing its half-life (from 18-55 to 5-26 hrs)
- Decrease the plasma level TCAs neuroleptics, benzos (with the exception of clonazepam)
- Its level can be increased by erythromycin, calcium channel blockers (verapamil)
- Common side effects include: diplopia, fatigue, nausea, and ataxia.
- Other infrequent side effects are skin rashes, mild leukopenia, hyponatremia, & thrombocytopenia

Bipolar disorder: Carbamazepine

- Rare but dangerous side effects include hepatic failure, exfoliative dermatitis (Steven-Johnson syndrome), agranulocytosis, & aplastic anemia.
- Initiating treatment:
  - Check CBC, LFT
  - Start with 200 mg po tid as patient tolerates and increase up to maximum 1800mg /day.
  - Check serum level & it should be between 4-15mg/ml

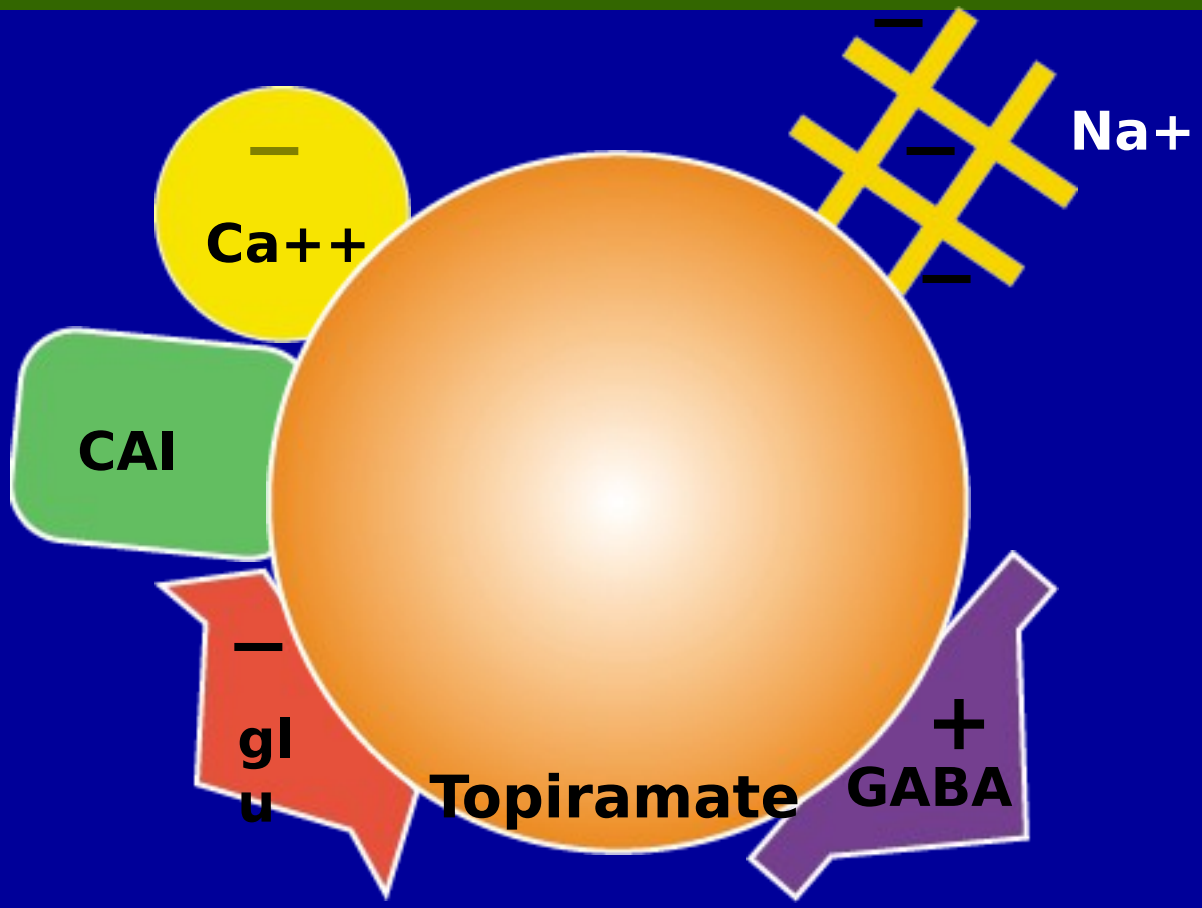
Bipolar Disorder: Lamotrigine



Bipolar Disorder: Lamotrigine

- Is approved as anticonvulsant
- It is effective in the treatment of bipolar depression.
- Side effects include: dizziness, diplopia, ataxia, blurred vision, nausea somnolence and tremor.
- Rare but very serious include: leukopenia, agranulocytosis, hepatic or multi-organ failure

Bipolar Disorder: Topiramate



Bipolar Disorder: Antipsychotic agents

- **Olanzapine** is the only agent that has been approved for the treatment of bipolar disorder.
- Olanzapine combined with *fluoxetine* also has been to relieve bipolar depression
- The most common side effects are: somnolence, dry mouth, dizziness and weight gain
- Recently it has been associated with *hyperglycemia* & *hyperlipidemia*

BIPOLAR COMBOS

1ST line monotherapy	Lithium, Valproic Acid
2ND line monotherapy	atypical antipsychotics
3RD line monotherapy	Carbamazepine, GABApentin, Lamotrigine, Topiramate
atypical combo	Li or Valproic Acid + atypical antipsychotics
benzo “assault weapon” combo	Li or Valproic Acid + benzodiazepine
neuroleptic “nuclear weapon” combo	Li or Valproic Acid + Neuroleptic
mood stabilizer combo	2 or more mood stabilizers
antidepressant combo	antidepressant + mood stabilizer or atypical antipsychotic

ANXIETY DISORDERS

Generalized Anxiety Disorder

Epidemiology:

- Lifetime Prevalence: ~ 5%
- 25% in anxiety disorder clinics
- F:M = 2:1
- Age of onset: 15-25 years
- 50% start before age 20

Etiology:

- Unknown

Biological Factors

- Possibly occipital lobe - highest concentration of benzo receptors.
- Possibly limbic system, basal ganglia or frontal cortex.
  - Speculation: Abnormal serotonin regulation; sub sensitivity of alpha2 adrenergic receptors.
- Other research involves NE, Glutamate, CK

Etiology:

Genetics:

- 50% concordance in monozygotic, 15% in dizygotic twins.
- Family, relative risk: 6
- May have increased rates in 1st degree relatives (25%)

Psychosocial:

- Incorrect perception of dangers due to:
  - ✓ Selective attention to negative details
  - ✓ Distorted information processing
  - ✓ Negative view of personal coping skills.
- Anxiety is due to an unresolved and unconscious

Clinical Features

- Excessive anxiety/worry on most days for >6 months of several events/activities.
- Difficulties controlling the worry.

At least 3:

- ✓ Blank mind/difficulty concentrating
- ✓ Energy low/easily fatigued
- ✓ Sleep disturbance
- ✓ Keyed up/restless/on edge
- ✓ Irritability
- ✓ Muscle tension (can be headaches, shakiness…)

Treatments

Psychological Treatment

- Evidence supporting CBT
  - ✓ CBT better than: no treatment or non-specific psychological treatment.
  - ✓ Benefits comparable to antidepressants.
  - ✓ CBT good individually or in group setting.
  - ✓ CBT benefits are maintained 6 mth – 2 yrs.
- Supportive therapy
  - ✓ Reassurance and comfort

Pharmacologic Treatments

First line:

- SSRI's: Paroxetine, Escitalopram, Sertraline
- Venlafaxine

Second Line:

- Benzodiazepines: lorazepam, diazepam, alprazolam and bromazepam
  - Clonazepam has a lower potential for rebound anxiety.
  - Usually given for 2-6 weeks with 1-2 wks of tapering.
  - May be used for severe agitation/severe anxiety.
  - Not much better than placebo after 4-6 wks of treatment

Pharmacologic Treatments

Buspirone (5HT1A partial agonist)

- Less effective than venlafaxine.
- As effective as benzos but may not be as good in pts who previously used benzos
- May start by combining the two and tapering off benzo
- Especially helpful for “chronic psychological anxiety”
- Takes 2-3 wks to have effect.

Pharmacologic Treatments

- Imipramine
  - Superior to placebo and similar to benzo Second line due to side-effects
- Pregabalin
  - More effective than placebo and as effective as benzo
- Propranolol: may be helpful for somatic symptoms
  - It does not treat the underlying condition;

Panic Disorder

Epidemiology:

- Life-time Prevalence:
  - ✓ Panic Attacks: 15%
  - ✓ Panic Disorder: 5%
  - ✓ Agoraphobia: 5% (2-6%)
- 1/3 -1/2 of PD pts have agoraphobia.
- M:F =1:2-3
- Onset usually among teen/young adults.
- Mean age of onset 25 (17-35)
- Onset after 40: secondary to medical/substances

Panic Disorder

Social and other factors:

- Recent divorce/ separation
- 60% of women with PD had sexual abuse.
- Double risk of suicide attempts than pts with other psych illnesses; 20 x risk of those without a psych illness.
- 80% first seen at primary care/ER

Etiology

Genetics:

- First degree relative will get PD: 8x more likely
- 1/2-3/4 have no relative affected.
- Twin studies suggest 40% heritability.

Biological theories:

- Abnormal brain autonomic nervous and noradrenergic systems.
  - ✓ Increased sympathetic tone
  - ✓ Slow adaptation to repeated stimuli
  - ✓ Excessive response to moderate stimuli

Etiology

Neurotransmitter abnormalities:

Dysregulation - 5HT, NE, GABA

- Limbic system - anticipatory anxiety (responds to relaxation, breathing and benzodiazepines)
- Cortex – prefrontal cortex in phobic avoidance.

Serotonin (in median raphe n.): postsynaptic 5HT hypersensitivity.

NE at the locus ceruleus

GABA: Attenuated inhibitory GABA-ergic transmission in parts of the brain (amygdala, midbrain, hypothalamus).

Clinical Features

- Recurrent panic attacks – at least 2.
- One or more attacks has been followed by 1 month or more:
  - ✓ Persistent concern of a future attack.
  - ✓ Worry about consequence of the attack.
  - ✓ Significant change in behavior related to the attack.
- Presence or absence of agoraphobia

Clinical Features

Other Features:

- Increased use of health-care visits…
- Increased cardiopulmonary co-morbidity
- Its course tends to be a chronic that fluctuates.

Common agoraphobic situations: Crossing a bridge, vehicles, leaving home.

- Can decrease if with trusted person.
- Patients seek help more often than those with other disorders

Medical illnesses considered as differential diagnosis

- Hyperthyroidism
- Hyperparathyroidism
- Pheochomocytoma
- Hypoglycemia
- CNS illness (neoplasm, vestibular dysfunction)
- Arrhythmia
- Asthma.

Treatment

Psychological

- Cognitive Behavior Therapy (CBT)
  - ✓ Exposure
  - ✓ Cognitive restructuring
  - ✓ Relaxation training

Pharmacotherapy

First line

- Any SSRI: Fluoxetine, Paroxetine and Sertraline
- Venlafaxine

Second Line:

- TCA: Clomipramine > Imipramine
- Benzodiazepines: Alprazolam or clonazepam

Third Line:

- MAOI/RIMA
  - ✓ Phenelzine
  - ✓ Moclobemide conflicting results

Social Anxiety Disorder

Epidemiology

- Incidence: 3% of population.
- Lifetime prevalence: 8-12%
- M:F=2:3
- Onset rare after age 25.
- Usually seek help for MDD, subs abuse
- Patients are often: less educated, low SES, Unmarried

Etiology

Behavioural Factors:

- Anxiety arouses with naturally frightening stimuli along with a second neutral stimulus.
- When the frightening and neutral stimuli occur together frequently the neutral stimuli can then provoke anxiety by itself.
- In phobias, attenuation of the response to stimulus does not occur.
- Operant conditioning: the person learns to avoid the anxiety provoking stimulus.

Biological Factors: Dysregulation of serotonin

Clinical Features

- Excessive fears of humiliation or embarrassment in social settings
- Example: speaking in public, “shy bladder”, and speaking to a date.
- Generalized social phobia - chronic and disabling condition characterized by a phobic avoidance of most social situations

Treatments

Psychological Treatment:

CBT:

- An established treatment.
- Associated with sig improvement in SAD.
- Major components: education, cognitive restructuring and exposure. Often also has social skills training and relaxation procedures.

Pharmacotherapy

First Line:

- SSRI: Paroxetine, Sertraline, Fluvoxamine, Escitalopram
- Venlafaxine

Second Line:

- Citalopram
- Benzodiazepines: Clonazepam, alprazolam or Bromazepam
  - Efficicacy reported similar to SSRI or CBT and superior to placebo.
- Anticonvulsants: Gabapentin and Pregablin
- Phenelzine

SLEEP DISORDERS

SLEEP CYCLES

- Sleep is measured with a polysomnograph, which measures
  - Brain activity (electroencephalogram [EEG])
  - Eye movement (electro-oculogram), and
  - Muscle tone (electromyogram).
- It takes the average person 15 to 20 minutes to fall asleep; this is the sleep latency.
- Sleep is divided into two phases:
  - Non-rapid eye movement (NREM) sleep
  - Sleep and rapid eye movement (REM) sleep.

SLEEP CYCLES

- NREM sleep consists of four sleep stages, named stage 1 through stage 4
- From wakefulness, sleep typically progresses quickly through stages 1 and 2
- During stages 3 and 4 NREM, both metabolic activity and brain waves slow, **deep sleep**
- REM sleep involves a dramatic physiologic change from NREM sleep, to a state in which the brain becomes electrically and

SLEEP CYCLES

- Characteristics of REM sleep
  - Autonomic instability
    - ✓ Increased HR, BP, and RR
    - ✓ Increased variability in HR, BP, and RR
    - ✓ Appears similar to an awake person on EEG
  - Tonic inhibition of skeletal muscle tone leading to paralysis
  - Rapid eye movements.
  - Dreaming.
  - Relative poikilothermia (cold-bloodedness).
  - Penile tumescence or vaginal lubrication.
  - Reduced sensitivity to sounds

SLEEP DISORDERS

- It is a significant problem in 10% of medical out patients.
- It is associated with:
  - ✓ Significant morbidity.
  - ✓ Poor daytime functioning
  - ✓ Injuries or deaths from motor vehicle accidents.

SLEEP DISORDERS

- **Four Major Symptoms:**
  1. Insomnia
  2. Hypersomnia
  3. Parasomnia
  4. Sleep-wake Schedule Related Problems.

INSOMNIA

- A difficulty in initiation or maintenance of sleep OR
- Non restorative sleep.
- Associated with significant distress or impairment.
- C.C- ‘not enough sleep’ ‘feeling tired’
- MSE- moderate impairment of concentration and psychomotor function.

INSOMNIA

- **Transient insomnia:** can occur in response to situational stressors.
- Treatment:
  - ✓ Patient education.
  - ✓ Emotional support.
  - ✓ Attention to proper sleep hygiene.
  - ✓ Short term use of Benzodiazepines.
- **Persistent insomnia:** requires identification and treatment of the underlying problem.

INSOMNIA

- **Primary insomnia:**
  - ✓ Occurs independent of any known physical or mental condition.
  - ✓ May begin in childhood .
  - ✓ Insomnia should occur for at least one month.
- **Insomnia secondary to medical condition:**
  - ✓ Pain of any source
  - ✓ Prostatism, esophageal reflux, etc.

INSOMNIA

- **Insomnia secondary to substance abuse:**
  - ✓ Use of any stimulants.
  - ✓ Withdrawal of sedating substances .
- **Insomnia due to psychiatric problems:**
  1. Mood or anxiety disorders.
  2. Patients with character disorders.
     - ✓ Increased trouble falling asleep once angered resulting in self reinforcing negative cycle.
     - ✓ Demand for large doses of sedatives which can result drug dependence.

TREATMENT OF INSOMNIA

Non-pharmacologic:

- **Behavioral**: relaxation; meditation.
  - sleep restriction therapy.
- **Psychotherapy**: to reduce emotional distress.
- **Life style alterations:**
  - ✓ Regular aerobic exercise.
  - ✓ Omitting alcohol, caffeine and cigarettes.
  - ✓ Avoid heavy meal before bed.
  - ✓ Sleep hygiene.

Rules for Proper Sleep Hygiene

- Use the bed for sleeping only!
- Avoid eating, reading, or watching TV in bed.
- Keep a regular bed time and wake up time including on weekends.
- Avoid naps
- Avoid evening stimulation.
- Leave the bed and bed room if unable to fall asleep after 15min. And read or perform a quiet activity (no TV!) ; return to bed only when sleepy.

TREATMENT OF INSOMNIA

Medications:

- **Sedating antidepressants:**
  - Amitriptyline, paroxetine, trazodone.
  - For patients with concomitant *anxiety* or *affective* disorders.
- **Long term use of benzodiazepines:**
  - Controversial - needs caution
  - Avoid in patients with past or current history of alcohol or substance abuse, personality disorders, and sleep related breathing disorders.

TREATMENT OF INSOMNIA

- **Buspirone**: may be effective in those with *anxiety* or *sleep apnea*.
- **Sedating antihistamines:**
  - Can be used as alternatives to benzodiazepines.
  - May cause delirium in the elderly or in those with a compromised nervous system.

HYPERSOMNIA

- Falling asleep inappropriately during the day or prolonged episodes of deep sleep.

A. **Primary Hypersomnia**:
   - Excessive somnolence occurring for at least one month.
   - No evident cause on evaluation.
   - Long sleepers.

   Treatment:
   - **Stimulants: amphetamines**.
   - **SSRIs**.

HYPERSOMNIA

B. **Narcolepsy**:

- Excessive day time sleepiness
- Abnormal manifestations of REM sleep.
- At least 3 months duration.

- Classic ***tetrad*** of narcolepsy:

1. ***Sleep attacks-*** irresistible usually brief, refreshing episodes of sleep (usu. 2-6 times per day).

NARCOLEPSY

2. **Cataplexy**: a sudden bilateral loss of muscle tone.
   - Often involves the knees.
   - Sometimes the arms, jaw, face etc.
   - No impairment of consciousness.
   - Triggered by *strong emotions*.
   - It may last seconds to minutes.

NARCOLEPSY

3. ***Sleep paralysis***- episodes of total muscular paralysis at sleep onset or awakening.
   - Patients are awake but unable to move a muscle.
   - If it lasts longer than few seconds it may be distressing.
4. ***Hypnagogic and Hypnopompic hallucinations***
   - Vivid visual or auditory perceptual experiences

NARCOLEPSY

- **Etiology*:***
  - Abnormality of the REM inhibiting mechanisms.
- **Prevalence*:***
  - 0.02-0.16%
  - Onset is usually the second decade.
  - A third of patients have family history of excessive daytime sleepiness.

NARCOLEPSY

- ***Treatment***:
  - ✓ Prophylactic *naps* help to reduce the amount of medication required.
  - ✓ *Stimulants*- increase day time alertness.
  - ✓ *Antidepressants*- control REM related phenomena like cataplexy, sleep paralysis…
  - ✓ *Benzodiazepines*- as adjunct may consolidate nocturnal sleep.

SLEEP APNEA (breathing related sleep disorder)

- **Apnea**: a complete cessation of respiration for more than 10 sec.
- **Hypopnea**: a minimum of one-third reduction in air flow.
- **Sleep apnea**: more than *five* episodes of apnea or hypopnea per hour of sleep.
- Reduces the quality of nocturnal sleep by causing frequent arousals.

SLEEP APNEA
(breathing related sleep disorder)

- **Central**: no effort is made by the person.
- **Obstructive**: cessation of respiration despite efforts leads to loud snorts and snores.
  - ✓ Patients may complain of morning headache, mental dullness and irritability.
- **Mixed type**: the most common type of sleep apnea.

SLEEP APNEA
(breathing related sleep disorder)

Treatment*:*

- Lose weight if obese.
- Avoid alcohol and sedatives.
- Continuous positive airway pressure.
- Uvulopalatoplasty or tracheostomy if CPAP fails.
- *SSRIs* and *heterocyclics* may help by suppressing REM sleep and decrease apneic periods.

PARASOMNIAS

Nightmare Disorder

- Long frightening dreams from which persons awaken scared.
- Almost always occur during REM sleep and late in the night.
- It is sometimes associated with periods of stress and illness.
- TCAs may help by suppressing REM sleep
- Benzodiazepines can also be used

PARASOMNIAS

Sleep Terror Disorder

- Usually seen in children.
- More common in boys than girls and tends to run in families.
- ? Minor abnormality in the temporal lobe.
- Closely related to ***sleep walking***.

PARASOMNIAS

It is characterized by:

- An arousal in the first third of the night during stages 3 &4.
- Begins with a panicky scream and accompanied by intense anxiety.
- The persons have no memory of the event.

PARASOMNIAS

Treatment of sleep terror:

- Investigation of stressful family situations.
- Individual or family therapy.
- Low dose *diazepam* at bed time.

PARASOMNIAS

Sleep Walking Disorder

- Peak age 12; boys; family history.
- A sequence of complex behaviors occurring in the first third of the night during stages 3 &4.
- The person is expressionless and is unresponsive to others.
- There is *amnesia* for the event.

Rx:- measures to prevent injury.

- drugs that suppress stages 3 & 4 sleep.

SLEEP PARALYSIS

- An isolated or Familial type.
- 25-35% of all people experience at least once in a life time.
- INCUBUS or MARE

“one who leaps on, crushes or oppresses”

- Complaints could be:
  - ✓ Inability to move the body at sleep onset or up on awakening
  - ✓ Inability to speak or cry out.
  - ✓ Associated hypnagogic hallucination may be present

SLEEP PARALYSIS

- The episode is often terminated by a sound or a touch on the body.
- People feel that someone is in the room with them.
- Some experience that something is sitting on their chest and may feel impending death from suffocation.
- Treatment:- reassurance
  - sleep hygiene
  - antidepressants

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Diagnostic Criteria for ADHD

- Persistent symptoms of inattention and/or hyperactivity/impulsivity
- Onset of symptoms before age 7
- Impairment in 2 or more settings (e.g., school, work, home)
- Evidence of clinically significant impairment in social, academic, or occupational functioning
- Symptoms not a result of other disorders

ADHD: Core Symptom Areas

Inattention

Impulsivity/Hyperactivity

DSM-IV Diagnostic Criterion: Symptoms for ADHD

Inattention

- Is careless
- Has difficulty sustaining attention in activity
- Does not listen
- Does not follow through with tasks
- Is disorganized
- Avoids/dislikes tasks requiring sustained mental effort
- Loses important items
- Is easily distracted
- Is forgetful in daily activities

DSM-IV Diagnostic Criterion: Symptoms for ADHD

Hyperactivity

- Squirms and fidgets
- Cannot stay seated
- Runs/climbs excessively
- Cannot play/work quietly
- Is on the go/driven by a motor
- Talks excessively

Impulsivity

- Blurts out answers
- Cannot wait turn
- Intrudes/interrupts others

ADHD: Subtypes

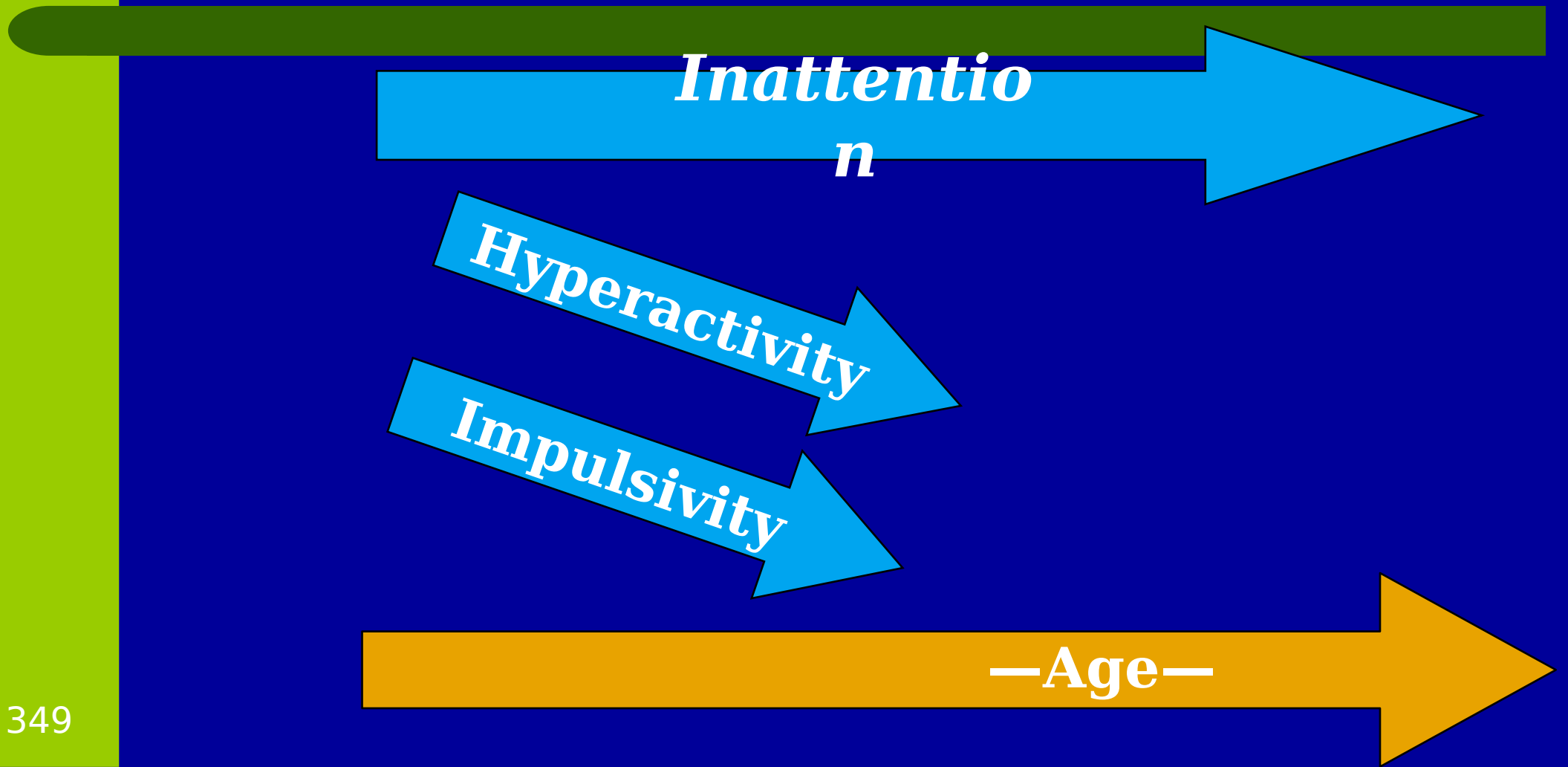
- ADHD Predominantly Inattentive Type
  - Criteria met for inattention but not for impulsivity/hyperactivity
- ADHD Predominantly Hyperactive-Impulsive Type
  - Criteria met for impulsivity/hyperactivity but not for inattention
- ADHD Combined Type
  - Criteria are met for both inattention and







ADHD: Course of the Disorder



Progression of Executive Functions from Childhood to Adulthood

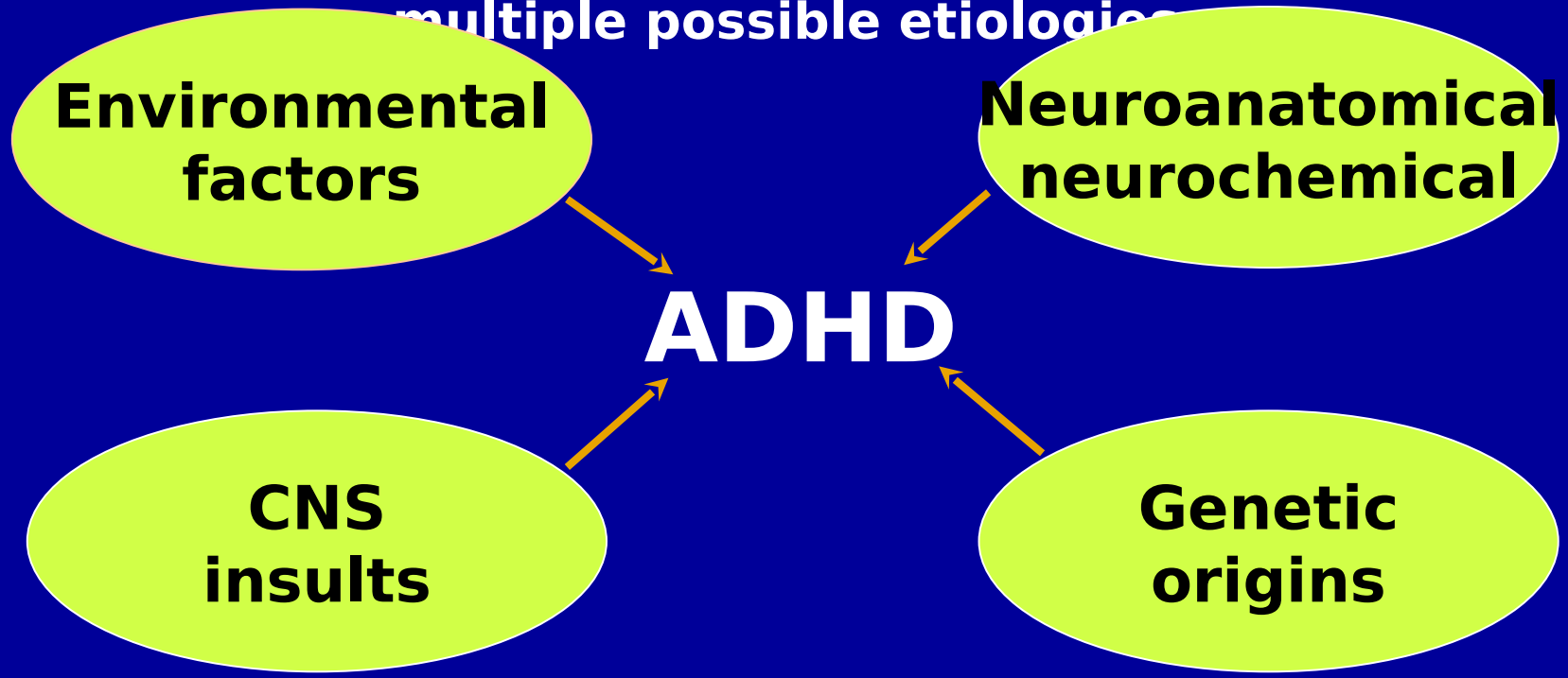
- **Early childhood**
  - Simple responses to limited demands in a protective environment
- **Late childhood into adulthood**: executive functions become more important
  - Juggling competing tasks, independence, organization, and planning

Comorbidities in Children with ADHD

Comorbidities	Range
Anxiety disorder	8%– 30%
Conduct disorder	8%– 25%
Oppositional-defiant disorder	45%– 64%
Affective disorder	15%– 75%
Tic disorder	8%– 34%
Mania/hypomania	0%– 22%
Learning/academic problems	10%– 92%

ADHD: Etiology

ADHD is a heterogeneous behavioral disorder with multiple possible etiologies



Pathophysiology of ADHD

- Specific etiology unknown
  - Combination of environmental and genetic factors
  - Average heritability of up to 90%
- Neuroimaging has revealed anomalies (both volume and metabolic activity) in the frontal cortex and basal ganglia
  - Dysfunction of prefrontal cortex is fundamental to symptoms of ADHD
- Biochemical basis is not fully known
  - ?Alterations in cortical-striatal neurotransmission

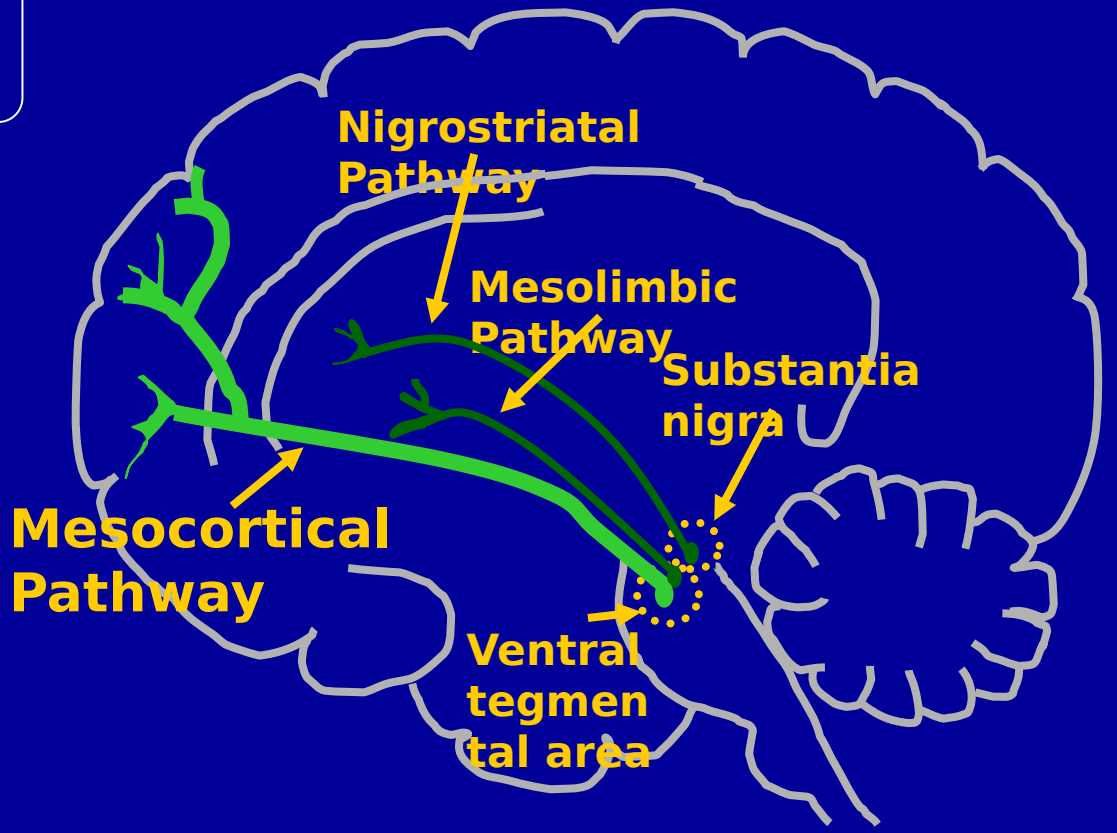
Neurochemistry of ADHD

- Both dopaminergic (DA) and noradrenergic (NE) systems are strongly implicated in the pathophysiology of ADHD.
- Maximal effectiveness may be produced by those agents that act on both the DA and the NE neurotransmitter systems.
- Stimulants potentiate the actions of both dopamine and norepinephrine in the synapse.

DA Neurotransmission Relative to ADHD

Dopamine

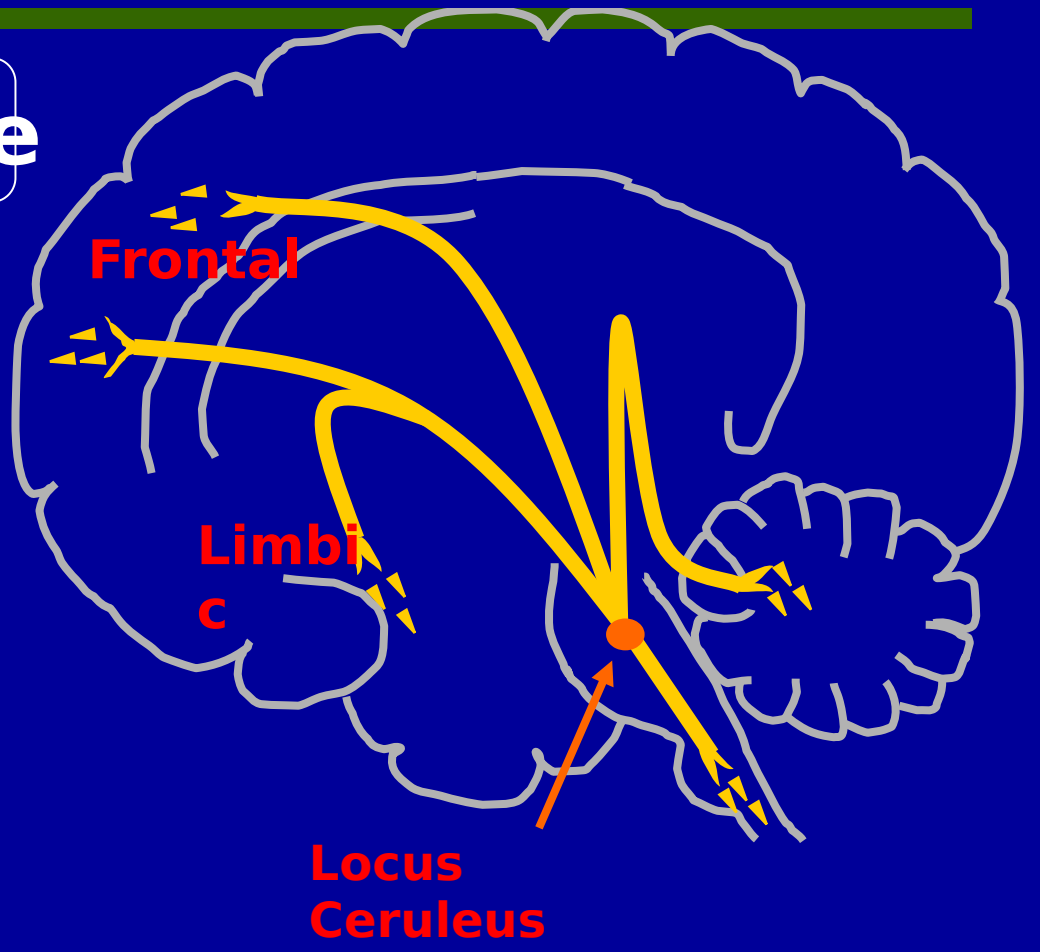
- Enhances signal
- Improves attention
  - Focus
  - Vigilance
  - On-task behavior
  - On-task cognition



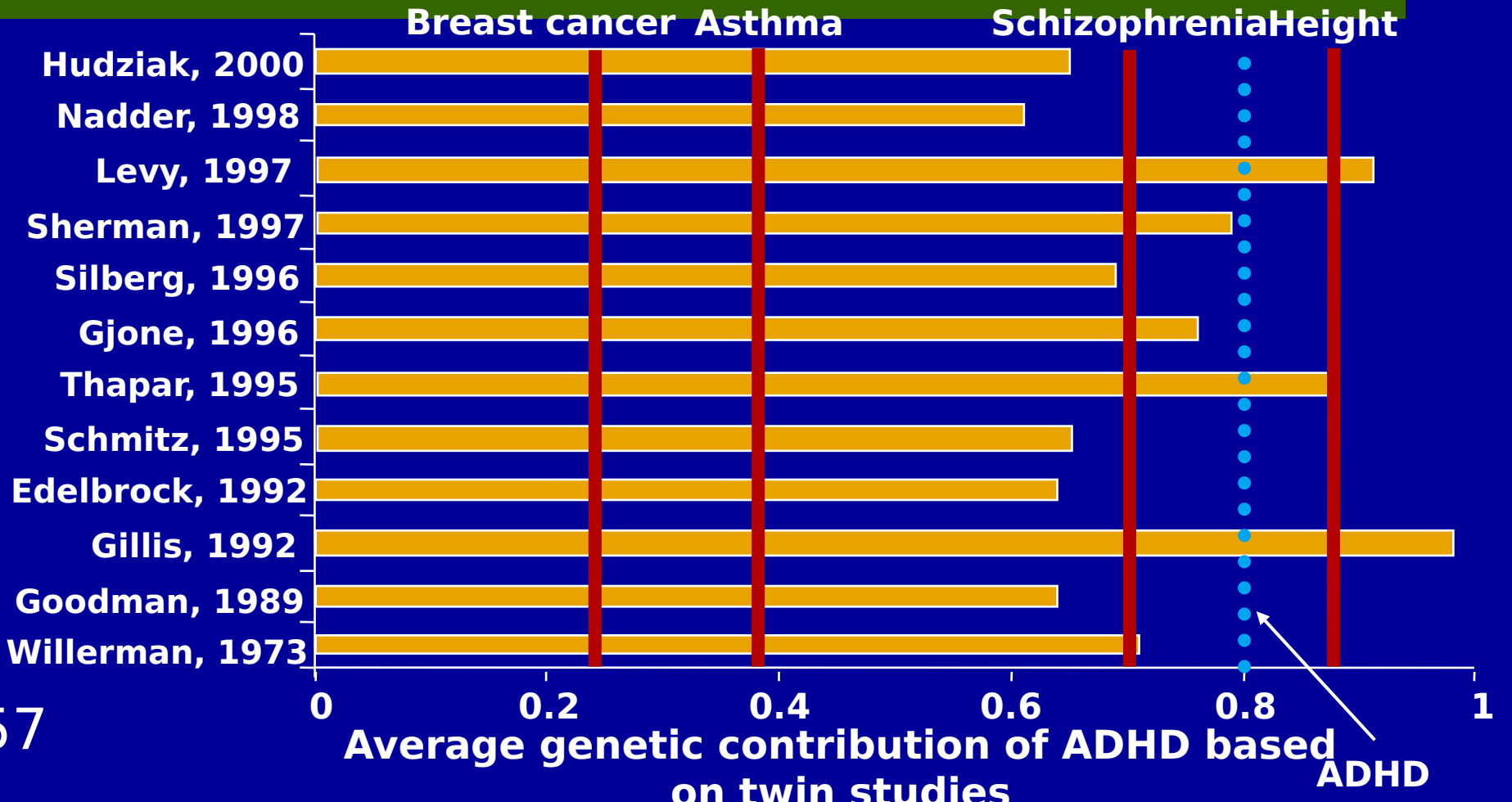
NE Neurotransmission Relative to ADHD

Norepinephrine

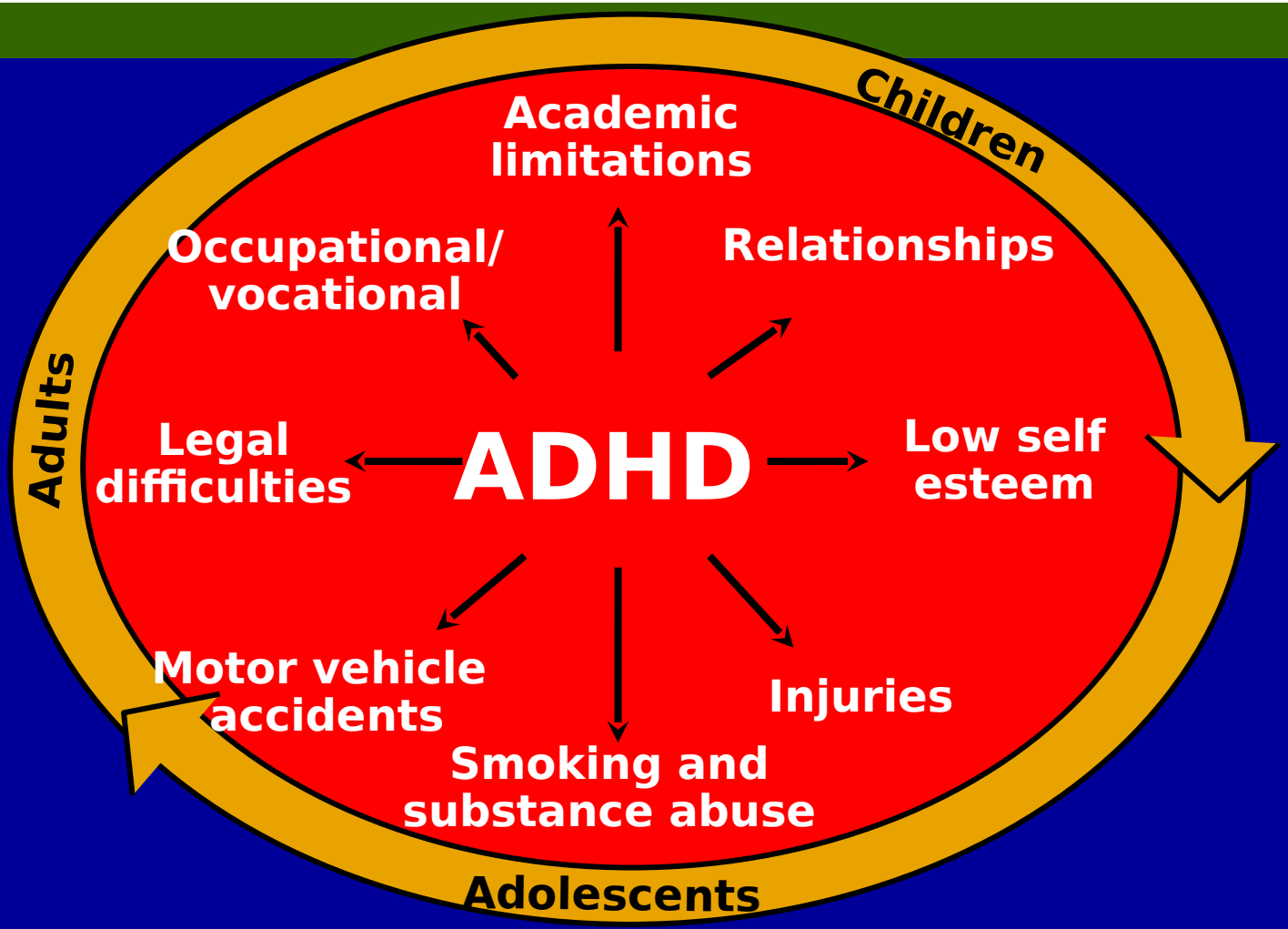
- Dampens noise
- Enhances executive operations
- Increases inhibition



Twin Studies Show ADHD Is a Genetic Disorder



Potential Areas of Impairment



ADHD May Result in Performance Limitations

- Despite similar educational levels and IQ scores, non-medicated adults with ADHD display:
  - Significantly more academic difficulty in school (25% repeat a grade)
  - Lower levels of occupational advancement

ADHD Affects Socialization

- Children are stigmatized by their behavior
  - **Disruptive behavior**
    - Troublemakers
      - Bad
      - sportsmanship
    - Excessive talking
      - Cannot sit still
    - Unfocused, not responsive to others
      - Impulsive
      - aggression
  - **Immaturity and impulsiveness**
    - Center of attention
      - Breaks the rules
    - Blurting out answers
      - Peer rejection
- Adolescents continue to demonstrate social problems
  - Poor participation in group activities
  - Few friends
  - Vulnerable to antisocial groups, drug abuse

ADHD Treatment Strategies

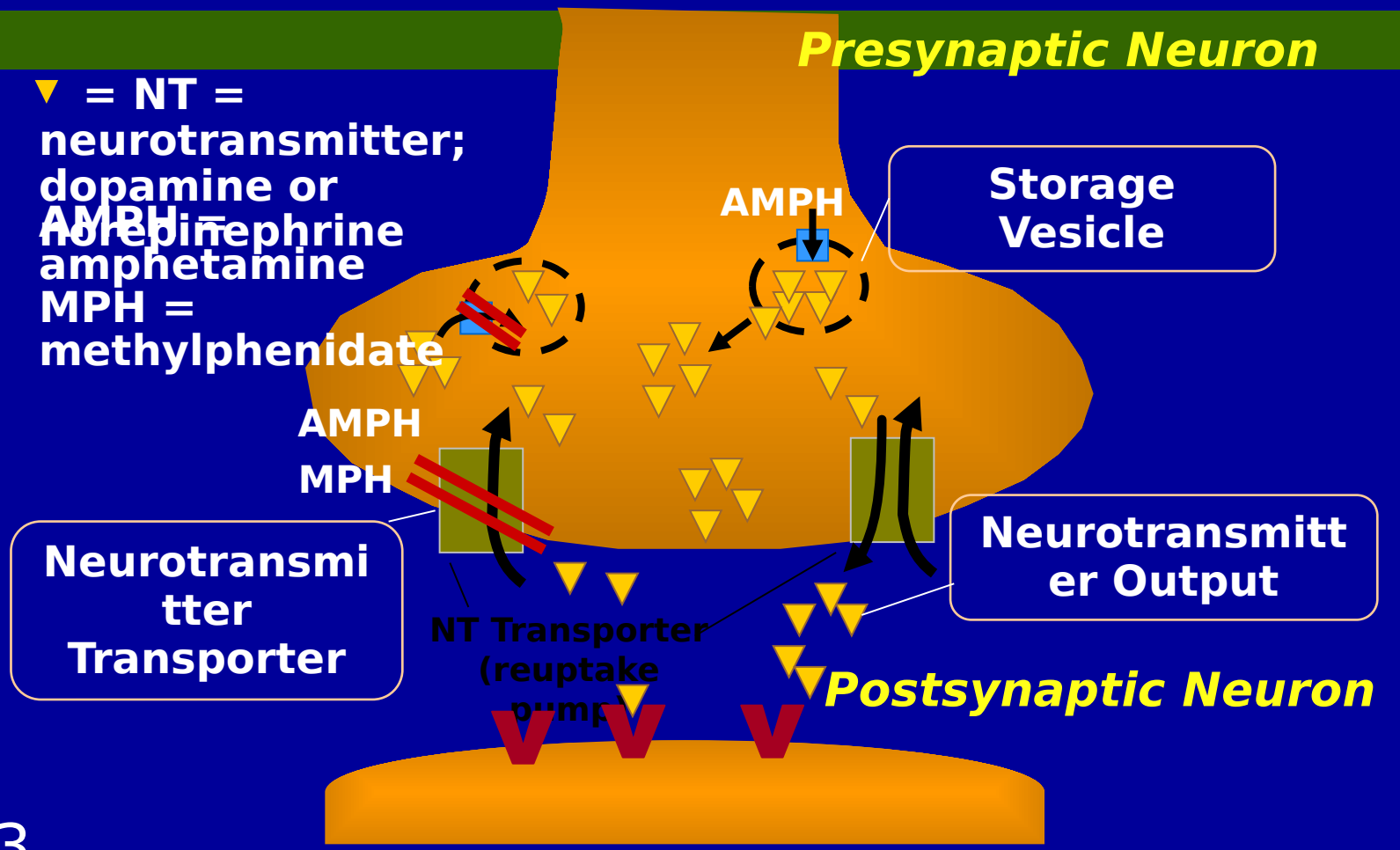
Three Components of ADHD Treatment

- Education
- Psychosocial interventions
- Pharmacotherapeutic interventions

New Stimulant Formulations

- Focalin™: a refined form of Ritalin®, isolating only the effective isomer
- Ritalin® LA: **once-daily** formulation of Ritalin® (**Methylphenidate**) that mimics BID dosing and duration and designed to last the school day (8-9 hours)
- Adderall XR™: extended-release formulation of mixed amphetamines (**Amphetamine-dextroamphetamine**) that mimics **BID** dosing (12 hours)
- Metadate® CD: **methylphenidate** formulation designed to mimic **BID** duration (8-9 hours)

Stimulants Proposed Mechanism of Action



Stimulants: Potential Side Effects

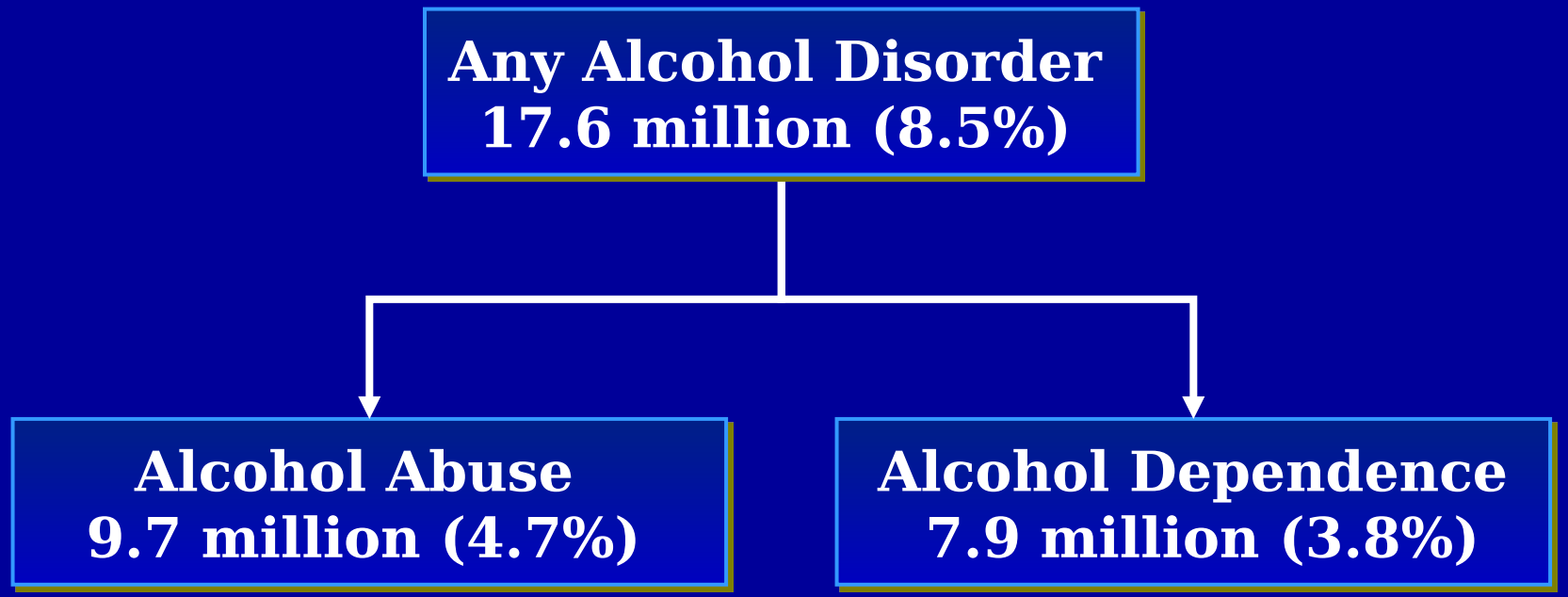
- Appetite loss, abdominal pain
- Insomnia
- Nervousness
- Mild increase in pulse, blood pressure
- Psychiatric effects, irritability, dysphoria, and rebound

(Effects occurring in >5% of patients and >placebo)

Controversies: growth deficits, tic exacerbation, seizures, abuse

Alcohol Related Disorders

Prevalence of Alcohol Use



Defining the “Standard Drink”

- A standard drink = 14 g ethanol
  - 12 oz of regular beer or cooler (5% alcohol)
  - 5 oz of table wine (12% alcohol)
  - 1.5 oz of hard liquor (40% alcohol, 80 proof)
  - The average person metabolizes about 1 standard drink per hour



Alcohol Abuse

Maladaptive pattern of alcohol use leading to clinically significant impairment or distress, manifested within a 12-month period by at least 1 of the following:

1. Failure to fulfill role obligations at work, school, or home
2. Recurrent use in hazardous situations
3. Legal problems related to alcohol
4. Continued use despite alcohol-related social or interpersonal problems

Alcohol Dependence

Maladaptive pattern of alcohol use leading to clinically significant impairment or distress, manifested within a 12-month period by at least 3 of the following:

2. Withdrawal
3. Loss of control over amount of alcohol consumed
4. Preoccupation with controlling drinking
5. Preoccupation with drinking activities
6. Impairment of social, occupational, or recreational activities
7. Use is continued despite persistent problems related to drinking

Physiological Dependence

- Alcohol dependence accompanied by tolerance (criterion 1) and/or withdrawal (criterion 2)
- More severe clinical course
- Potentially higher risk for immediate general medical problems
- Higher relapse rate

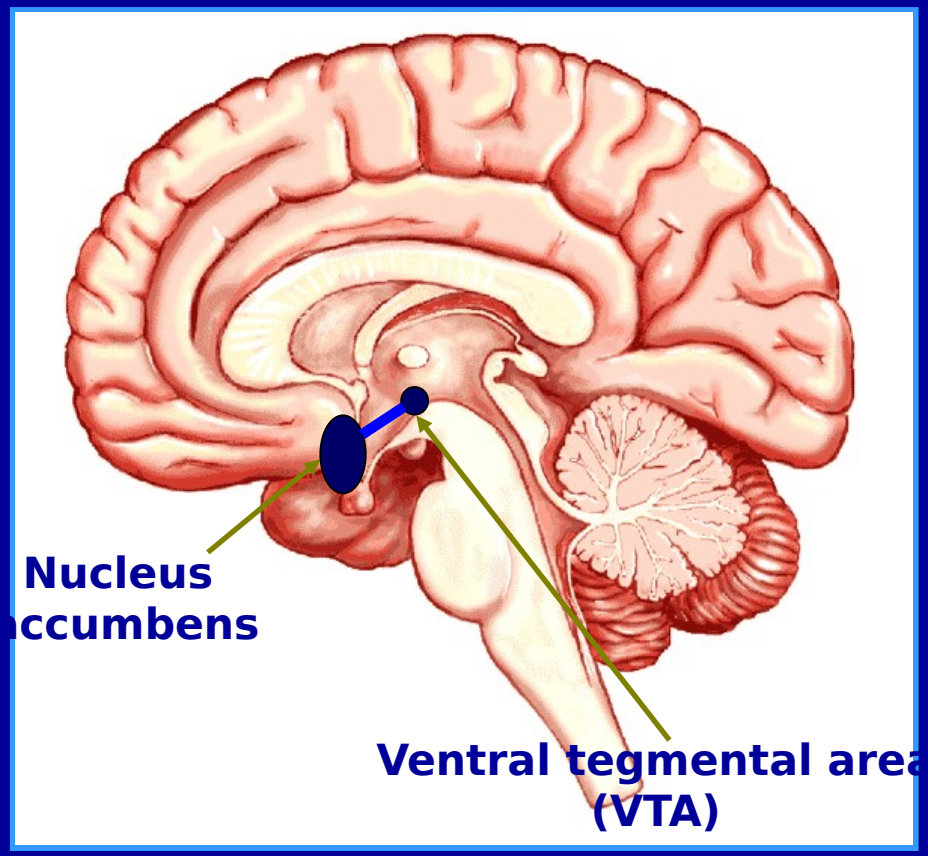
Sign & Symptoms, Early Stage Alcoholism

- Physical
  - Dyspepsia, gastritis, elevated liver enzyme levels, glucose intolerance, hyperlipidemia, impotence, intermittent diarrhea, labile refractory hypertension, macrocytosis, recurrent or minor injuries, sleep disorders, vague abdominal complaints
- Psychological
  - Anxiety, depressed mood
- Others
  - Marital and family problems, victim or

Sign & Symptoms, Chronic Alcoholism

- Physical
  - Cardiomyopathy, delirium tremens,
  - Hepatitis, cirrhosis, malnutrition, pancreatitis,
  - Parotid swelling, periodontal disease
  - Recurrent trauma, seizure,
  - Testicular atrophy,
  - Wernicke-Korsakoff syndrome
- Others
  - Alienation from friends and family
  - Arrest for intoxication
  - Incarceration
  - Financial problems
  - Job loss

Brain Reward Pathways



- The VTA-nucleus accumbens pathway is activated by all drugs of dependence including alcohol
- This pathway is important not only in drug dependence, but also in essential physiological behaviors such as

Effects of Alcohol on Neural Circuits : Glutamate system



Alcohol Free

CNS Equilibrium

Acute Alcohol Effect

- **Inhibits NMDA receptors**
- **Effect: ↓ anxiety, ↑ sedation**

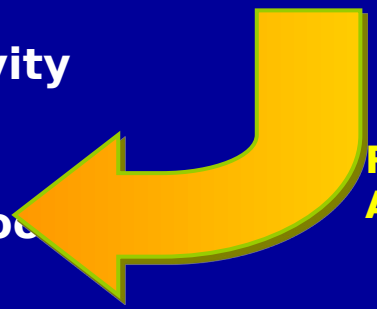


Adaptation

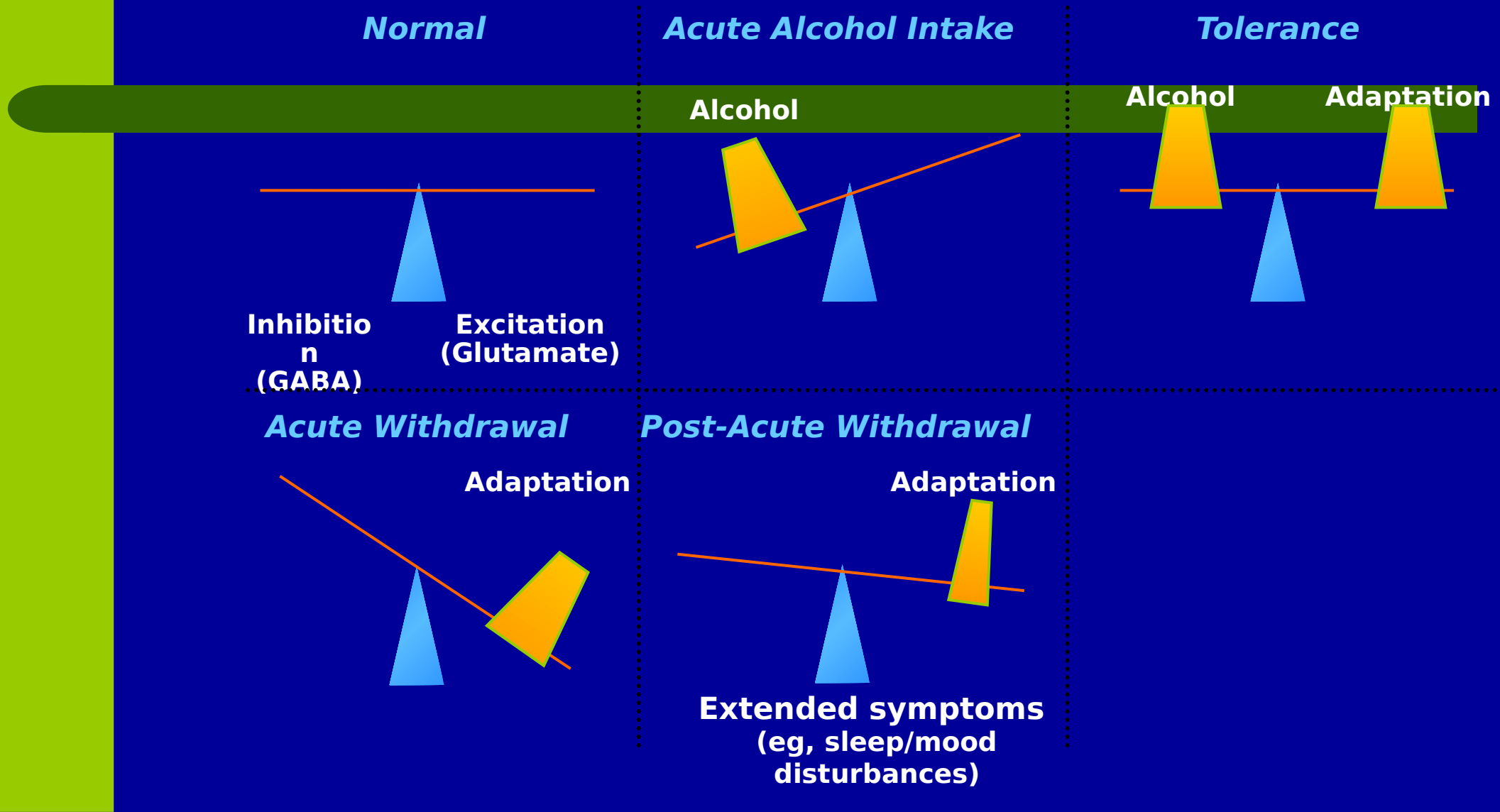
- **# and/or function of NMDA receptors on neurons**
- **Balances acute alcohol effect**
- **Effect: tolerance, dependence**

Withdrawal

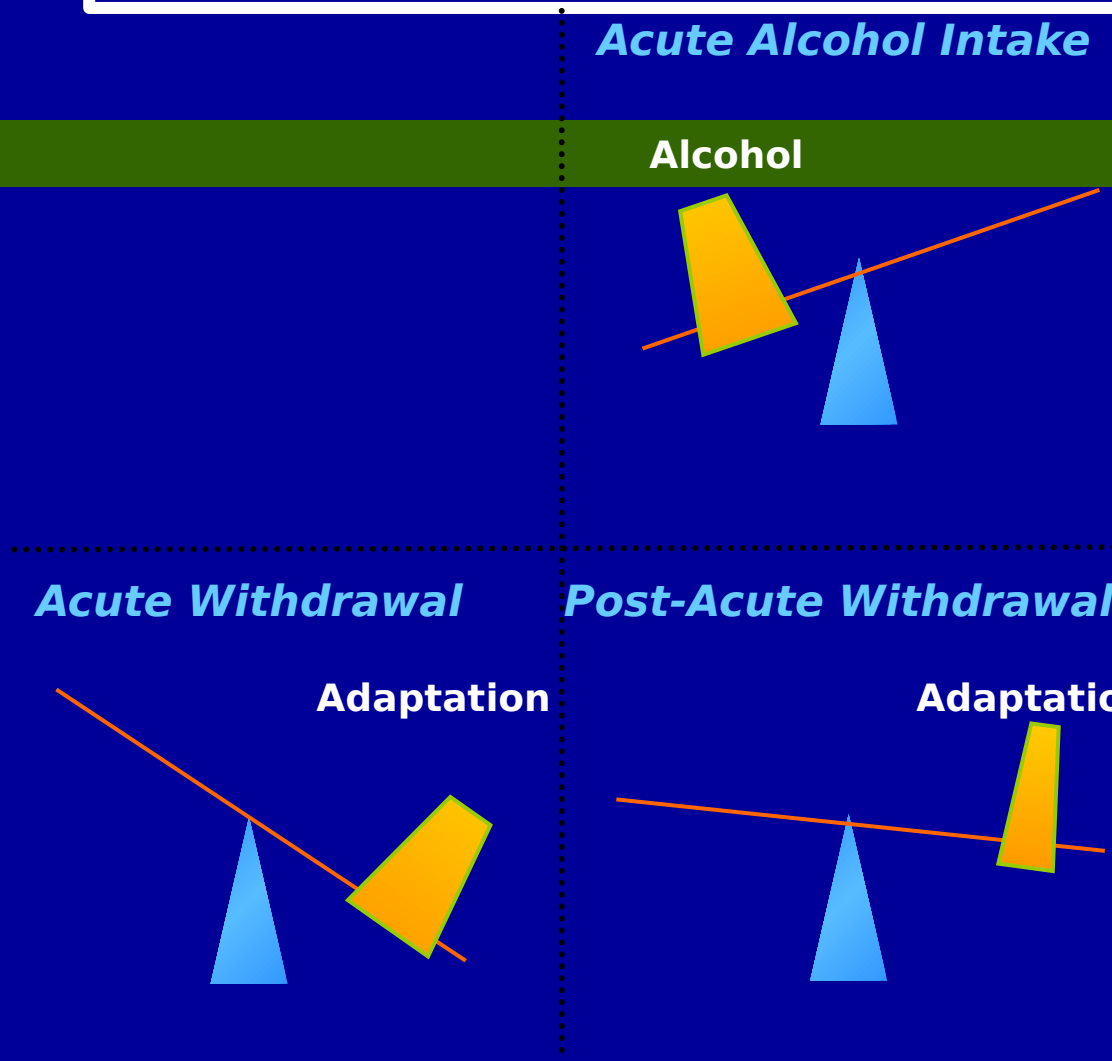
- **Increased glutamatergic activity**
- **Effect: - *Acute:* dysphoria, hallucinations**
  - *Post-acute:* sleep/mo disturbances



Features of Alcohol Dependence



Pharmacological Motives for Drinking



Positive Reinforcement:
Reward

Negative Reinforcement:
Avoidance of withdrawal

Absorption:

- About 10% of consumed alcohol is absorbed from the stomach, with the remainder absorbed from the intestine.
- Peak blood plasma concentrations of alcohol is reached in 30 to 90 minutes depending whether it is taken with food or not.
- Absorption is rapid with high percent alcohol.
- The rate of absorption also has a direct bearing on the intoxication response.
- Alcohol is uniformly dissolved in the water of the body.

Metabolism:

- About 90% of absorbed alcohol is metabolized through oxidation in the liver; the remaining 10% is excreted by the kidneys & lungs.
- It is metabolized by two enzymes:
  - Alcohol dehydrogenase (ADH) & Aldehyde dehydrogenase.
  - ADH catalyzes the conversion of alcohol into acetaldehyde.
- Women have a lower ADH content than men which may account for women's tendency

Behavioral Effects:

- Thought, judgment and restraint may be loosened or disrupted by 0.05% of BAL.
- Voluntary motor actions becomes clumsy with BAL of 0.1%
- At 0.2% BAL the function of the entire motor area of the brain is depressed.
- At 0.3% a person is commonly confused or becomes stuporous.
- At 0.4 to 0.5% a person is in a coma.

Other physiological effects:

- **Liver**: accumulation of fats and proteins, resulting in the appearance of fatty liver (on physical exam it is palpated as enlarged liver).
  - Chronic use of alcohol predisposes to the development of alcoholic hepatitis and hepatic cirrhosis
- **GI system**: long term heavy drinking esophagitis, gastritis, achlorhydria, and gastric ulcers.
  - Pancreatitis, pancreatic insufficiency and pancreatic cancer are also associated with heavy alcohol use.
  - Vitamin B deficiency due to poor dietary habits.

Delirium Tremens

- DT is also associated with alcohol withdrawal.
- It is a medical emergency that can result in significant morbidity and mortality.
- They may be assaultive, suicidal or act out secondary to their hallucinations or delusions. DT occurs within one week of cessation of drinking.
- The features include:
  - Tachycardia, diaphoresis, fever, anxiety, insomnia, hypertension, perceptual distortions (visual or tactile hallucinations), fluctuating levels of psychomotor activity.
  - Treatment should include: IV lorazepam (0.1mg/kg at 2mg/min

Alcohol-induced Amnestic Disorder

- Wernicke’s syndrome (acute) and Korsakoff’s syndrome (a chronic condition)
  - Wernicke's encephalopathy (WE) is a common, acute neurologic disorder caused by thiamine deficiency.
    - It is manifested by a clinical triad of encephalopathy, oculomotor dysfunction, and gait ataxia
  - Korsakoff's syndrome (KS) is a late, neuropsychiatric manifestation of Wernicke's encephalopathy (WE) in which there is a striking disorder of selective anterograde and retrograde amnesia

- Alcohol-induced psychotic disorder:
  - the most common hallucinations are auditory
- Fetal Alcohol syndrome:
  - is the result of exposing fetuses to alcohol in utero.
  - Children who have fetal alcohol syndrome exhibit: microcephaly,

Alcohol Detoxification: Inpatient protocol

- Patient should be admitted to a detox. unit
- Give Librium (chlordiazepoxide) 50 mg po qid and valium (diazepam) 10 mg po tid for 24 hrs.
- And then give Librium 25 – 100mg po Q6 hrs with symptoms and signs of alcohol withdrawal
- Give thiamine 100mg po bid to tid.
- Check vital signs every 4hrs

Pharmacotherapies for Alcohol Dependence

Disulfiram

- Inhibits aldehyde dehydrogenase
- When taken with alcohol, ↑ [acetaldehyde] leads to nausea, dizziness, headache, flushing
- Decreases desire to drink
- Poor tolerability profile

Naltrexone

- Opioid antagonist
- Binds to opioid receptors, thus blocking alcohol reward pathways

Thank You

Q?

PARKINSON’S DISEASE

Definition

- Parkinsonism is a progressive neurological disorder of muscle movement, characterized by
  - ✓Tremors,
  - ✓Muscular rigidity,
  - ✓Bradykinesia (slowness in initiating and carrying out voluntary movements), and
  - ✓Postural and gait abnormalities.
- Result from a reduction of dopaminergic transmission within the basal ganglia

Epidemiology

- Its peak age of onset is in the 60s (range is 35 to 85 years)
- Familial clusters of autosomal dominant and recessive forms of PD comprise 5% of cases
- Risk factors include:
  - A positive family history
  - Male gender
  - Head injury
  - Exposure to pesticides
  - Consumption of well water
  - Rural living

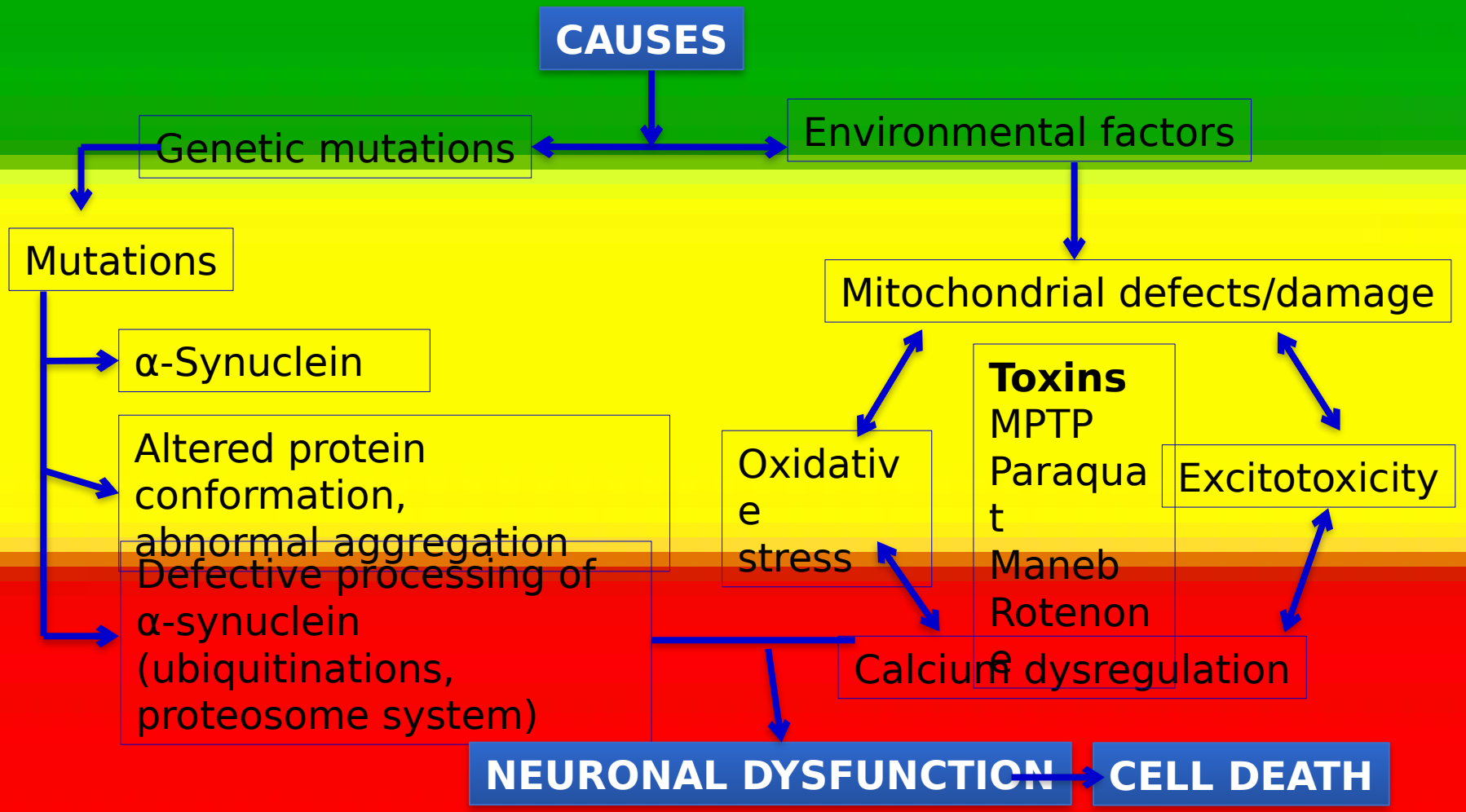
Etiology

- True etiology is unknown
- Genetics
  - In cases with age of onset 50 years
- Toxins:
  - Intrinsic: free radicals produced by the metabolism of dopamine and melanin
  - Extrinsic: synthetic pesticides

Pathophysiology

- Loss of SNc neurons and
- Presence of Lewy bodies (neuronal cytoplasmic filamentous aggregates composed of the presynaptic protein α-synuclein) in the remaining SNc neurons.

Pathophysiology



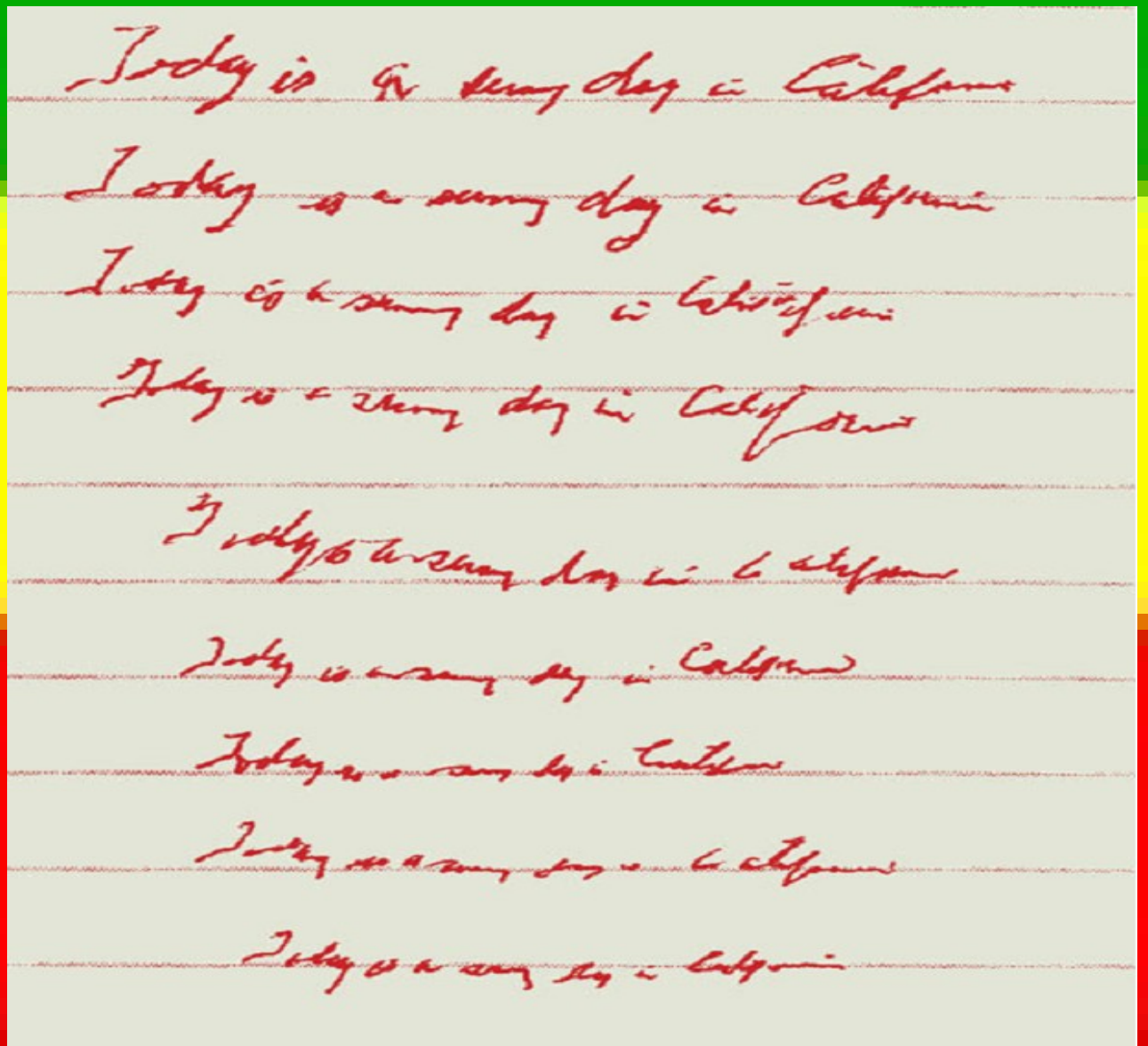
Clinical Presentation

- Motor Feature
- Non-Motor Features

Clinical Presentation

- **Motor Features:**
  - **Bradykinesia**:
    - The most disabling feature: interfere with daily living such as walking, rising from a chair, turning in bed, dressing.
    - Decreased manual dexterity and handwriting (micrographia).
    - Soft speech (hypophonia) and sialorrhea
  - **Tremor**
    - Appears unilaterally, first distally, involving the digits and wrist
    - Spreads proximally, ipsilaterally, and occasionally to the leg before crossing to the other side after a year or more.
    - It may appear later in the lips, tongue, and jaw but spares the head.

Micrographia



Clinical Presentation

- **Motor features:**
  - **Dystonia**:
    - involving the distal arm or leg may occur early in the disease
    - Especially in younger patients.
  - Gait disturbance:
    - Shuffling short steps and a tendency to **turn en bloc** is a prominent feature
  - Abnormalities of balance and posture
    - Flexion of the head, stooping and tilting of the upper trunk, and a tendency to hold the arm in a flexed posture while walking are common,
    - Contributing to falls and injuries and leading to major morbidity and mortality

Clinical Presentation

- Non-Motor Features
  - ✍Include
    - Depression and anxiety,
    - Cognitive impairment,
    - Sleep disturbances,
    - Sensory abnormalities and pain,
    - Loss of smell (anosmia), and
    - Disturbances of autonomic function.

TREATMENT

- Goal of therapy:
  - Improve motor and nonmotor symptoms
  - Preservation of function and ability to perform activities of daily living;
  - Improvement of mobility;
  - Minimization of adverse effects and treatment complications

Anticholinergic

- Dopamine tonically inhibits acetylcholine neurons in the striatum
  - The degeneration of nigrostriatal dopamine neurons results in a relative increase of striatal cholinergic interneuron activity.
  - This increased cholinergic activity (caused by dopamine depletion) contribute to the tremor of PD
- Benztropine and trihexyphenidyl are considered effective against tremor

Anticholinergic

- Use of anticholinergic agents is limited
  - Intolerable side effects, necessitating dosage reduction or drug discontinuation.
  - Common adverse effects include:
    - Blurred vision, confusion, constipation, dry mouth, memory difficulty, sedation, and urinary retention

Generic Name	Trade Name	Dosage Range (mg/day)
Benztropine	Cogentin	0.5 – 4
Trihexyphenidyl	Artane	1 – 6

Amantadine

- Inhibit of glutamatergic N-methyl-D-aspartate (**NMDA**) receptors
- Administered 300 mg/day in divided doses
- Amantadine is eliminated renally and a reduced dose should be administered when renal dysfunction is present
  - 100 mg/day with creatinine clearances of 30 to 50 mL/min,
  - 100 mg every other day for creatinine clearances of 15 to 29 mL/min, and
  - 200 mg every 7 days for creatinine clearances of less than 15 mL/min and patients on hemodialysis).

Amantadine

- Common side effects: confusion, dizziness, dry mouth, and hallucinations.
  - The elderly are particularly prone to develop confusion.
- Uncommonly: livedo reticularis, a diffuse mottling of the skin occurs in the upper or lower extremities and often accompanied by lower-extremity edema.

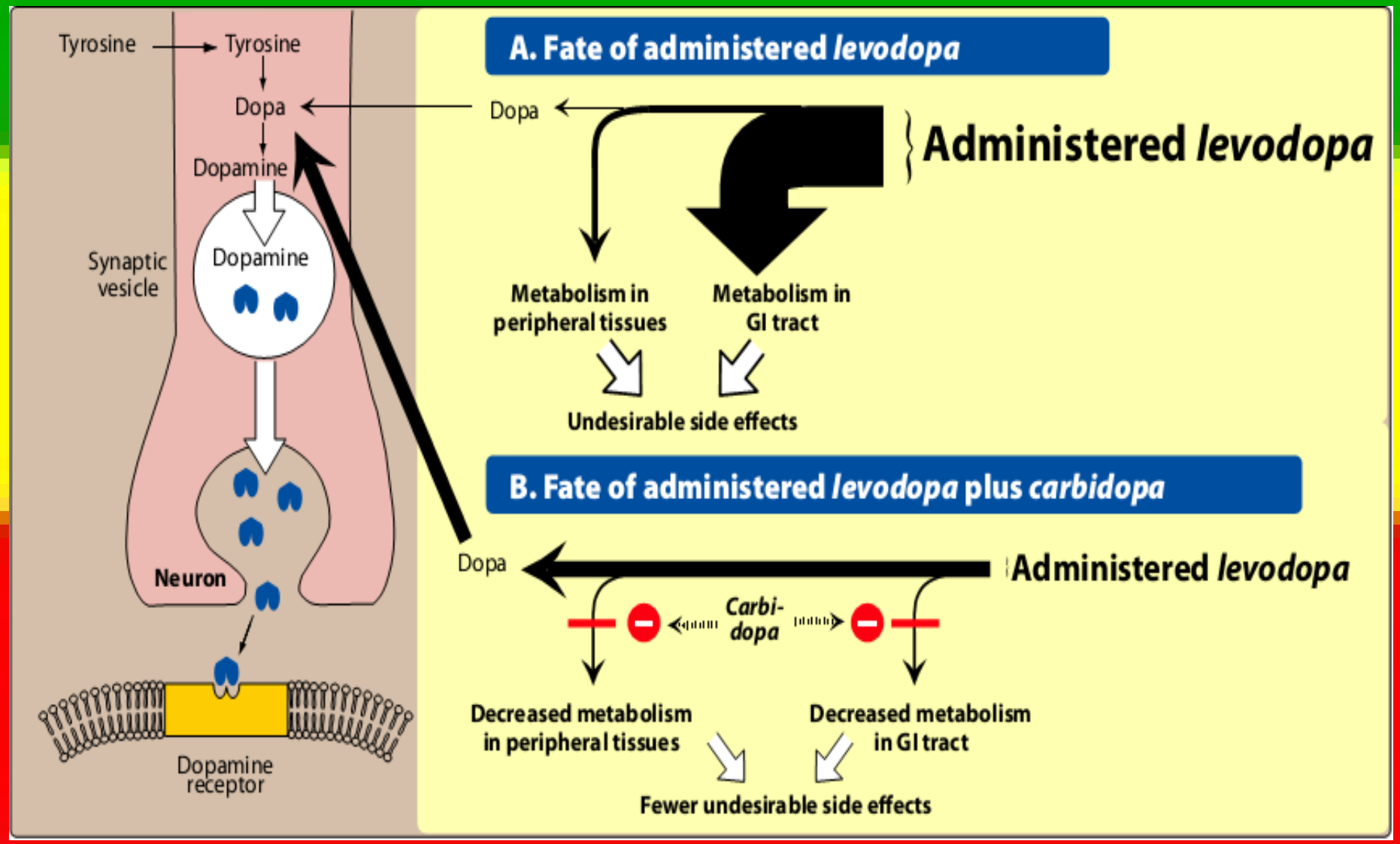
Levodopa and carbidopa

- Levodopa is a metabolic precursor of dopamine
- It restores dopaminergic neurotransmission in the corpus striatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra.
- Dopamine itself does not cross the blood-brain barrier, but its immediate precursor, levodopa, is actively transported into the CNS and is converted to dopamine in the brain
- Large doses of levodopa are required, because much of the drug is decarboxylated to dopamine in the periphery, resulting in side effects that include nausea, vomiting, cardiac arrhythmias, and hypotension.

Levodopa and carbidopa

- Carbidopa, a dopa decarboxylase inhibitor, diminishes the metabolism of levodopa in the GIT and peripheral tissues, thereby increasing the availability of levodopa to the CNS.
- The addition of carbidopa lowers the dose of levodopa needed by four- to fivefold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine.

Synthesis of dopamine from levodopa in the absence and presence of carbidopa



Levodopa and carbidopa

- **Adverse effects**
  - Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone of the medulla
  - Mydriasis
  - Visual and auditory hallucinations
  - Abnormal involuntary movements (dyskinesias)

Levodopa and carbidopa

- **Dose**:
  - ❖Initially 100 mg (with carbidopa 25 mg) 3 times daily, increased by 50–100 mg (with carbidopa 12.5–25 mg) daily or on alternate days according to response, up to 800 mg (with carbidopa 200 mg) daily in divided doses
- **Breast-feeding**: Levodopa may suppress lactation. It is present in milk – avoid.

Motor Complications of L-Dopa

- **End-of-Dose Wearing Off**
  - ✓ Related to the increasing loss of neuronal storage capability for dopamine as well as the short halflife of L-dopa.
  - ✓ Initially, exogenous L-dopa is taken up by the remaining presynaptic neurons, converted to dopamine, and stored in synaptic vesicles.
  - ✓ With progressive loss of presynaptic neurons, storage capacity, and synthesis of endogenously derived dopamine, patients become more dependent on exogenous L-dopa.

Motor Complications of L-Dopa

- With advancing PD, the duration of action of a single carbidopa/L-dopa dose progressively shortens, and in some cases may produce benefits for as little as 1 hour.
- As a result, carbidopa/L-dopa needs to be given more frequently so as to minimize daytime off episodes and to maximize on time.
- **Solution:**
  - Increase frequency of carbidopa/L-dopa doses; or
  - Add either COMT inhibitor or MAO-B inhibitor or dopamine agonist

Motor Complications of L-Dopa

- **“Delayed-On” and “No-On” Response.**
  - Can be a result of delayed gastric emptying or decreased absorption in the duodenum.
  - Solution:
    - Give carbidopa/L-dopa on empty stomach;
    - Use carbidopa/L-dopa ODT;
    - Avoid carbidopa/L-dopa CR;
    - Use apomorphine subcutaneous

Freezing

- “**Freezing**,” or a sudden, episodic inhibition of lower extremity motor function, may occur and will interfere with ambulation and increase the risk of falls.
- Patients may report that their “feet are stuck to the floor” and that they have difficulty initiating steps (start hesitation) or turns (turn hesitation)
- Solution:
  - Increase carbidopa/L-dopa dose;
  - Add a dopamine agonist or MAO-B inhibitor;
  - Utilize physiotherapy along with assistive walking devices or sensory

Dyskinesias

- Involuntary movements involving usually the neck, trunk, and lower/upper extremities
- Are associated with peak striatal dopamine levels (peak dose dyskinesia)
- Solution:
  - Provide smaller doses of carbidopa/L-dopa; add amantadine

Selegiline

- Selegiline selectively inhibits **MAO Type B** (which metabolizes dopamine) at low to moderate doses but does not inhibit MAO Type A (which metabolizes nor-epinephrine and serotonin)
- By, thus, decreasing the metabolism of dopamine, selegiline has been found to increase dopamine levels in the brain.
- Therefore, it enhances the actions of levodopa when these drugs are administered together.
- Selegiline substantially reduces the required dose of levodopa
- Side effects: severe hypertension at higher dose, insominia

Dopamine-receptor agonists

- This group of anti-Parkinson compounds includes **bromocriptine**, an ergot derivative, and newer, nonergot drugs, ropinirole, pramipexole, and rotigotine.
- These agents have durations of action longer than that of levodopa and, thus, have been effective in patients exhibiting fluctuations in their response to levodopa.

Bromocriptine

- Bromocriptine, a derivative of the vasoconstrictive alkaloid, ergotamine, is a dopamine-receptor agonist
- Hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent
- Dose: Initially 1 mg daily, increased by increments of 0.5–1 mg at 7 or 14 day intervals; max. 3 mg daily

HEADACHE DISORDERS

Objectives

- Upon completion of this session, you will be able to:

1. Differentiate types of headache syndromes based on clinical features.
2. Recommend nonpharmacologic measures for headache treatment and prevention.
3. Determine when the pharmacologic treatment of headache is indicated.
4. Construct individualized treatment regimens for the acute and chronic management of headache syndromes.
5. Monitor headache treatment to ensure its safety, tolerability, and efficacy

Introduction

- Headache is one of the most common complaints encountered by healthcare practitioners (>1% of visits to physicians' offices or ED).
- One of the top 10 presenting complaints in ambulatory medical care
- Headache can be symptomatic of a distinct pathologic process or can occur without an underlying cause
- Primary Headache:
  - MIGRAINE HEADACHE
  - TENSION-TYPE HEADACHE

Migraine Headache

Migraine

- The prevalence of migraine varies considerably by age and gender.
- **Before the age of 12 years**, migraine is more common in boys than in girls, but prevalence increases more rapidly in girls after puberty.
- **After age 12**, females are two to three times more likely than males to suffer from migraine.
- Prevalence is highest in both men and women between the **ages of 25 and 45 years**.

ETIOLOGY AND PATHOPHYSIOLOGY

Vascular hypothesis:

- The **migraine aura** is caused by intracerebral arterial vasoconstriction that is followed by reactive extracranial vasodilation and associated headache
- Migraine pain is believed to result from activity within the trigeminovascular system
- Activation of trigeminal sensory nerves triggers the release of vasoactive neuropeptides, including calcitonin gene-related peptide (CGRP), neurokinin A, and substance P, from perivascular axons.
- The released neuropeptides interact with dural blood vessels to promote vasodilation and dural plasma extravasation, resulting in neurogenic inflammation

ETIOLOGY AND PATHOPHYSIOLOGY

- Genetic factors: 50% heritability in monozygotic twins
- Serotonin (5-hydroxytryptamine [5-HT]): important mediator of migraine headache in decreasing pain.

CLINICAL PRESENTATION

- Phases of migraine attach:
  - Premonitory symptoms
  - Aura
  - Migraine headache

Premonitory Symptoms

- Experienced by approximately 20% to 60% of migraineurs in the hours or days **before** the onset of headache
- Previously popular terms prodrome and warning symptoms
  - ✓Neurologic symptoms (phonophobia, photophobia, hyperosmia, and difficulty concentrating)
  - ✓Psychological (anxiety, depression, euphoria, irritability, drowsiness, hyperactivity, and restlessness)
  - ✓Autonomic (polyuria, diarrhea, and constipation), and
  - ✓Constitutional symptoms (stiff neck, yawning, thirst, food cravings, and anorexia)

Aura

- Complex of positive and negative **focal neurologic symptoms** that precedes or accompanies an attack, is experienced by approximately 31% of migraineurs on some occasions.
- The aura typically evolves over 5 to 20 minutes and lasts less than 60 minutes.
- Headache usually occurs within 60 minutes of the end of the aura.
- Occasionally, aura symptoms begin at the onset of headache or during the attack.
- The aura is most often visual and frequently affects half the visual field.

Auras:

- Visual auras include:
  - Positive features: scintillations, photopsia, teichopsia, or fortification spectrum) and
  - Negative features: scotoma, hemianopsia.
- Sensory and motor aura symptoms,
  - Paresthesias or numbness involving the arms and face, dysphasia or aphasia, weakness, and hemiparesis

Migraine headache phase

- Occur at any time of the day or night but occurs most often in the **early morning hours** on awakening
- Pain is usually gradual in onset, peaking in intensity over a period of minutes to hours and lasting between 4 and 72 hours in adults
- Pain can occur anywhere in the face or head but most often involves the **frontotemporal** region
- Headache is typically **unilateral** and **throbbing** or **pulsating** in nature

Migraine headache phase

- GI symptomes:
  - During an attack, as many as 90% of migraineurs experience nausea, and emesis occurs in approximately one-third of patients
- Systemic symptoms:
  - Anorexia, food cravings, constipation, diarrhea, abdominal cramps, nasal stuffiness, blurred vision, diaphoresis, facial pallor, and localized facial, scalp, or periorbital edema

Resolution phase

- Characterized by feeling tired, exhausted, irritable, or listless.
- Impaired concentration may continue, as well as scalp tenderness or mood changes

TREATMENT

- Goals of long-term migraine treatment
  1. Reduce migraine frequency, severity, and disability
  2. Improve quality of life
  3. Prevent headache
  4. Avoid escalation of headache medication use
  5. Educate and enable patients to manage their disease
  6. Reduce headache-related distress and psychological symptom

Goal of therapy

- Goals for acute migraine treatment
  1. Treat migraine attacks rapidly and consistently without recurrence
  2. Restore the patient’s ability to function
  3. Minimize the use of backup and rescue medications
  4. Optimize self-care for overall management
  5. Be cost-effective in overall management
  6. Cause minimal or no adverse effects

GENERAL APPROACH

- Pharmacotherapeutic management of migraine can be acute (e.g., symptomatic or abortive) or preventive (prophylactic)
- **Abortive** or **acute therapies** can be:
  - Migraine-specific: ergots and triptans
  - Nonspecific: analgesics, antiemetics, NSAIDs, and corticosteroids
- Nonspecific agents for **mild to moderate headache** while reserving migraine-specific medications for more **severe attacks.**

GENERAL APPROACH

- The absorption and efficacy of orally administered drugs can be compromised by the gastric stasis or nausea and vomiting that often accompany migraine.
- **Pretreatment with antiemetic agents** or the use of non oral treatment (e.g., suppositories, nasal sprays, or injections) is advisable when nausea and vomiting are severe
- The frequent or excessive use of acute migraine medications can result in a pattern of increasing headache frequency and drug consumption known as **medication-overuse headache** (or rebound headache)

GENERAL APPROACH

- Medication overuse is one of the most common causes of chronic daily headache
- Discontinuation of the offending agent leads to a gradual decrease in headache frequency and severity and a return of the original headache characteristics
- Recommend limiting use of acute migraine therapies to 2 or 3 days per week to avoid the development of medication-misuse headache

GENERAL APPROACH

- **Preventive migraine therapies** are administered on a daily basis to reduce the frequency, severity, and duration of attacks and improve responsiveness to symptomatic migraine therapies
- Preventive therapy also may be administered preemptively or intermittently when headaches recur in a **predictable pattern** (e.g., exercise-induced migraine or menstrual migraine).

GENERAL APPROACH

- Preventive therapy should be considered in
  - Recurring migraines that produce significant disability
  - Frequent attacks requiring symptomatic medication more than twice per week with the risk of developing rebound headache;
  - Symptomatic therapies that are ineffective, contraindicated, or produce serious side effects;
  - Uncommon migraine variants that cause profound disruption and/or risk of permanent neurologic injury (e.g., hemiplegic migraine, basilar migraine, and migraine with prolonged aura);

Nonpharmacologic Therapy

- Application of ice to the head and periods of rest or sleep, usually in a dark, quiet environment
- Headache diary
- Relaxation therapy, cognitive therapy

Acute Migraine Management

- Analgesics and NSAIDs
- Opiate Analgesics
- Antiemetics
- Miscellaneous Nonspecific Medications
- Ergot Alkaloids and Derivatives
- Serotonin Receptor Agonists (Triptans)

Analgesics and NSAIDs

- First-line choice for treatment **of mild to moderate** migraine attacks
- Of the NSAIDs, aspirin, ibuprofen, naproxen, and the combination of acetaminophen plus aspirin and caffeine have demonstrated the most consistent evidence of efficacy
- Acetaminophen alone is not generally recommended for migraine because the scientific support is not optimal
- Suppository analgesic preparations and intramuscular ketorolac are also options when nausea and vomiting are severe.

Analgesics and NSAIDs

Analgesic/NSADs	Dosage
Acetaminophen	1,000 mg at onset; repeat every 4–6 hours as needed
Acetaminophen 250 mg/aspirin 250 mg/caffeine 65 mg	2 tablets at onset and every 6 hours
Aspirin	500–1000 mg every 4–6 hours
Ibuprofen	200–800 mg every 6 hours
Naproxen sodium	550–825 mg at onset; can repeat 220 mg in 3–4 hour
Diclofenac	50–100 mg at onset; can repeat 50 mg in 8 hours

Opiate Analgesics

- Narcotic analgesic drugs (e.g., meperidine, butorphanol, oxycodone, and hydromorphone) are effective but generally should be reserved for patients with **moderate to severe** infrequent headaches
  - Whom conventional therapies are contraindicated or as “rescue medication” after patients have failed to respond to conventional therapies
- Frequent use of narcotic analgesics can lead to the development of dependency and rebound headache

Antiemetics

- A single dose of an antiemetic, such as metoclopramide or chlorpromazine administered 15 to 30 minutes before ingestion of oral abortive migraine medications is often sufficient

Miscellaneous Nonspecific Medications

- ***Corticosteroids*** can be considered as rescue therapy for **status migrainous** (a severe, continuous migraine that can last up to 1 week)
- ***Intranasal lidocaine***, 1 to 4 drops of a 4% solution, provides rapid pain relief within 15 minutes of administration

Ergot Alkaloids and Derivatives

- For the treatment of **moderate to severe** migraine attacks
- These drugs are nonselective 5-HT1 receptor agonists that constrict intracranial blood vessels and inhibit the development of neurogenic inflammation in the trigeminovascular system
- ***Nausea*** **and** ***vomiting*** (resulting from stimulation of the chemoreceptor trigger zone) are among the most common adverse effects of the ergotamine derivatives.
- Pretreatment with an ***antiemetic*** agent should be considered with ergotamine or intravenous dihydroergotamine therapy.

Ergot Alkaloids and Derivatives

- Ergotamine tartrate:
  - Oral tablet (1 mg) with caffeine 100 mg: 2 mg at onset; then 1–2 mg every 30 minutes as needed
  - Sublingual tablet (2 mg)
  - Rectal suppository (2 mg) with caffeine 100 mg: Insert 1/2to 1 suppository at onset; repeat after 1 hour as needed
- Dihydroergotamine
  - Injection 1 mg/mL: 0.25–1 mg at onset IM or SC; repeat Qhr PRN

Serotonin Receptor Agonists (Triptans)

- Relief of migraine headache is the result of three key actions:
  - Normalization of dilated intracranial arteries through enhanced vasoconstriction,
  - Peripheral neuronal inhibition, and
  - Inhibition of transmission through second-order neurons of the trigeminocervical complex
- First-line therapy for patients with **moderate to severe migraine** and are used for rescue therapy when nonspecific medications are ineffective

Serotonin Receptor Agonists (Triptans)

- Are selective agonists of the 5-HT1B and 5-HT1D receptors
- **First generation**:
  - ✍Sumatriptan,
- **Second-generation**:
  - ✍Zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan

Prophylactic Pharmacologic Therapy

- **β-Adrenergic Antagonists:**
  - Propranolol (40 – 160 mg daily), BID
  - Atenolol (100 mg daily), QD
  - Metoprolol (100 – 200 mg daily), QD
  - Useful in patients with comorbid anxiety, hypertension, or angina.
- **Antidepressants**:
  - Down regulation of central 5-HT2 and adrenergic receptors
  - Amitriptyline (20 – 50 mg at bed time)
  - Doxepin, imipramine, nortriptyline, fluoxetine, phenelzine

Prophylactic Pharmacologic Therapy

- **Anticonvulsants**:
  - Enhancement of γ-aminobutyric acid (GABA)-mediated inhibition, modulation of the excitatory neurotransmitter glutamate, and inhibition of sodium and calcium ion channel activity
  - Usefull for migraineurs with comorbid **seizures, anxiety disorder, or bipolar disorder**
  - Gapapentin, Topiramate, Valproic acid
- **Calcium Channel Blockers: Verapamil**
  - Second or third line options

Prophylactic Pharmacologic Therapy

- **NSAIDs:**
  - To prevent headaches that recur in a predictable pattern, such as menstrual migraine
  - Initiated 1 to 2 days prior to the expected onset of headache and continued during the period of vulnerability

Tension-Type Headache

- **Epidemiology**
  - ✓ The most common type of primary headache
  - ✓ First onset of tension-type headache typically is early in life (younger than age 20 in 40% of patients), and prevalence peaks between the ages of 20 and 50 years.
  - ✓ It is more common among women in adulthood, with a female-to-male ratio of 5:4

Tension-Type Headache

- **Clinical Presentation:**
  - Premonitory symptoms and aura are absent
  - Pain is mild to moderate in intensity and often is described as a dull, nonpulsatile tightness or pressure
  - Bilateral pain is most common, but the location can vary (frontal and temporal pain are most common; occipital and parietal regions also may be affected)
  - “Hatband” pattern
  - Associated symptoms generally are absent, but mild photophobia or phonophobia may be reported.

Tension-Type Headache

- **Treatment**
  - ✓ Self-medicate with over-the-counter medications
  - ✓ Simple analgesics and NSAIDs are the mainstay of acute therapy
  - ✓ Acetaminophen, aspirin, ibuprofen, naproxen, ketoprofen, indomethacin, and ketorolac

Cluster Headache

- **Definition**:
  - ✍Cluster headache, the most severe of the primary headache disorders, is characterized by attacks of severe, unilateral head pain that occur in series lasting for weeks or months (i.e., cluster periods) separated by **remission** periods usually lasting months or years

Cluster Headache

- **CLINICAL PRESENTATION:**
  - Attacks occur in cluster periods lasting 2 weeks to 3 months in most patients, followed by long pain-free intervals.
  - Periods of remission average 2 years (range:2 months to 20 years).
  - In 10%, **chronic symptoms** with attacks recurring for over 1 year without remission or with remission periods of less than 1 month
  - Attacks occur suddenly, with pain peaking quickly after onset and generally lasting 15 to 180 minutes.

Cluster Headache

- Auras are **not** present with cluster headaches.
- The pain is excruciating, penetrating, and of a boring intensity in orbital, supraorbital, and temporal unilateral locations
- The headache can be accompanied by conjunctival injection, lacrimation, nasal stuffiness, rhinorrhea, eyelid edema, facial sweating, miosis/ptosis, and restlessness or agitation
- During the cluster period, attacks occur from **once every other day to eight times per day**.
- Whereas migraine patients retreat to a quiet dark room, cluster headache patients generally sit and rock or pace about the room clutching their head.

Treatment

- Involves both
  - Abortive
  - Prophylactic therapy

Abortive Therapy

- **Oxygen**
  - Inhalation of 100% oxygen by non breather facial mask at a rate of 7 to 10 L/min
- **Ergotamine Derivatives**
  - Intravenous dihydroergotamine: quickest response
  - Ergotamine tartrate
- **Triptans**
  - Quick onset of subcutaneous and intranasal triptans make them safe and effective abortive agents for cluster headaches.

Prophylactic Therapy

- **Verapamil**
  - Effects of verapamil appear after 1 week of therapy.
  - Dosage range is from 360 mg/day to 720 mg/day
- **Lithium**
  - Can be used in combination with verapamil.
  - 600 to 1,200 mg/day
- **Ergotamine**
  - A 2-mg bedtime dose
  - In combination with verapamil or lithium

Prophylactic Therapy

- **Corticosteroids**
  - for inducing remission
  - initiated with 40 to 60 mg/day prednisone and tapered over approximately 3 weeks
  - Relief appears within 1 to 2 days of initiating therapy.
  - To avoid steroid-induced complications, long-term use is not recommended

PAIN MANAGEMENT

Learning Objectives

- Upon completion of the chapter, the reader will be able to:

1. Explain the mechanisms involved in pain transmission.
2. Select an appropriate method of pain assessment.
3. Recommend an appropriate choice of analgesic, dose, and monitoring plan .
4. Educate patients and caregivers about effective pain management

THE PAIN SENSORY SYSTEM

- Once thought to be a punishment from the gods, the word is derived from the Latin *peone* and the Greek *poine*, meaning “penalty” or “punishment.
- Pain is an unpleasant sensation localized to a part of the body
- It is often described in terms of a penetrating or tissue-destructive process (e.g., stabbing, burning, twisting, tearing, squeezing) and/or of a bodily or emotional reaction (e.g., terrifying, nauseating, sickening)
- Any pain of moderate or higher intensity is accompanied by **anxiety** and **the urge to escape** or **terminate** the feeling.
  - These properties illustrate the duality of pain: it is both **sensation** and **emotion**.

Nociceptive Pain

- Nociceptive pain typically is classified as:

1. Somatic (arising from skin, bone, joint, muscle, or connective tissue)
   - Presents as throbbing and well localized,
2. Visceral (arising from internal organs such as the large intestine or pancreas)
   - Manifest as pain feeling as if it is coming from other structures (**referred**) or as a **well-localized** phenomenon.

Chemical Mediators of Pain

Neurotransmitter	Receptor	Effect on nociception
Substance P	NK-1	Excitatory
Glutamate	NMDA	Excitatory
Aspartate	NMDA	Excitatory
ATP	P_1, P_2	Excitatory
Acetylcholine	Muscarinic	Inhibitory
Encephalins	μ, δ, κ	Inhibitory
β-Endorphin	μ, δ, κ	Inhibitory
Norepinephrine	α_2	Inhibitory
Adenosine	A_1	Inhibitory
Serotonin	5-HT_1 (5-HT_3)	Inhibitory
GABA	A, B	Inhibitory

Neuropathic Pain/Functional Pain

- **Neuropathic** and **functional** pain is distinctly different from **nociceptive pain** in that it becomes disengaged from **noxious stimuli** or **healing** and often is described in terms of **chronic pain**.
- **Neuropathic pain** is a result of **nerve damage**, whereas **functional pain** can be thought of as **abnormal operation** of the nervous system
- **Neuropathic pain syndromes**: post-herpetic neuralgia, diabetic neuropathy, trigeminal neuralgia
- **Functional pain syndromes:** fibromyalgia, irritable bowel syndrome, sympathetic induced pain, tension-type headaches, and some noncardiac chest pain

Neuropathic Pain/Functional Pain

- The mechanism responsible for neuropathic and functional pain may be the nervous system's endogenous dynamic nature.
  - Nerve damage or certain disease states may evoke changes seen in inflammatory pain,
  - Ectopic excitability,
  - Enhanced sensory transmission,
  - Nerve structure reorganization, and
  - Loss of modulatory pain inhibition

Neuropathic Pain/Functional Pain

- Clinically, patients present with:
  - **Spontaneous** pain transmission (often described as burning, tingling, shock-like, or shooting),
  - Exaggerated painful response to normally noxious stimuli (**hyperalgesia**), and/or
  - Painful response to normally nonnoxious stimuli (**allodynia**).
- This change over time may help to explain why this type of pain often manifests long after the actual nerve-related injury or when no actual injury is identified

Classification Of Pain

Acute Pain

- Acute pain can be a useful physiologic process warning individuals of disease states and potentially harmful situations.
- Unfortunately, severe, unremitting, undertreated, acute pain, when it outlives its biologic usefulness, can produce many deleterious effects (e.g., psychological problems).
- Acute pain usually is **nociceptive**.
- Common causes of acute pain include surgery, acute illness, trauma, labor, and medical procedures

Classification Of Pain

Chronic Pain

- Acute pain persists for months to years, leading to a chronic pain state with features quite different from those of acute pain
- Can be nociceptive, neuropathic/functional, or both
- Subtypes include:
  - Pain that persists beyond the normal healing time for an **acute injury**,
  - Pain related to a **chronic disease** (e.g., pain secondary to osteoarthritis),
  - Pain without an identifiable organic cause, and
  - Pain associated with **cancer**

Characteristics of Acute and Chronic Pain

Characteristic	Acute Pain	Chronic Pain
Relief of pain	Highly desirable	Highly desirable
Dependence and tolerance to medication	Unusual	Common
Psychological component	Usually not present	Often a major problem
Organic cause	Common	May not be present
Environmental/family Issues	Small	Significant
Insomnia	Unusual	Common component
Treatment goal	Pain reduction	Functionality
Depression	Uncommon	Common

Cancer Pain

- This type of pain includes both chronic and acute components and often has multiple etiologies.
- It is pain caused by:
  - The disease itself (e.g., tumor invasion, organ obstruction),
  - Treatment (e.g., chemotherapy, radiation, surgical incisions), or
  - Diagnostic procedures (e.g., biopsy)

Management of Pain

- Pharmacologic interventions
  - Cyclooxygenase inhibitors,
  - Opiods,
  - Antidepressants,
  - Neuroleptc agents,
  - Anticonvulsants,
  - Corticosteroids.

1. Antidepressants

- At lower dose antidepressant action, cause analgesia
- Analgesic effect is due to blockade of presynaptic reuptake of **serotonin**, **norepinephrine**
- Most useful in patients with neuropathic (postherpetic neuralgia and diabetic neuropathy)
  - **Desipramine**, **imipramine**, **amitriptyline**
  - Side effects :
    - ✓ Antimuscarinic effect (dry mouth)
    - ✓ Antihistaminic effect
    - ✓ α-adrenergic blockade (orthostatic hypotension)

2. Neuroleptics

- Useful in patients with refractory neuropathic pain
- Most useful in patients with marked ***agitation*** or ***psychotic*** symptoms
- Therapeutic action due to blockade of dopaminergic receptors in mesolimbic sites
- **Haloperidol**, **chlorpromazine**, **fluphenazine**
- Undesirable extrapyramidal side effects: rigidity, bradykinesia

3. Anticonvulsants

- Useful in patients with neuropathic pain, especially trigeminal neuralgia
- Suppress the spontaneous neural discharge
- Commonly used drugs:
  - ✓ **Phenytoin**, **carbamazepine**, **valproic acid** and **clonazepam**

4. Corticosteroids

- Glucocorticoids used for their anti-inflammatory and possibly for their analgesic effect
- Can be used topically, orally, parenterally (IV, SC, intrabursally, intra-articularly, epidurally)

✍ **Hydrocortisone, prednisolone, triamicinolone, dexamithasone**

5. Non-opioid Agents

- Acetaminophen, acetylsalicylic acid (aspirin), and NSAIDs often are preferred over opiates in the treatment of mild-to-moderate pain
- These drugs (with the exception of acetaminophen) prevent formation of prostaglandins produced in response to noxious stimuli, thereby decreasing the number of pain impulses received by the CNS.

Monitoring Parameters

NSAIDs	Upper GI bleeding	Complete blood count, stool guaiac (if symptoms such as black tarry stools, warrant)
	Acute renal failure	Serum creatinine
Acetaminophen	Hepatotoxicity	Serum transaminases (ALT/AST)
		Liver synthesis tests (PT/INR, albumin)
		Acetaminophen serum concentration

5. Opioids

- For acute pain and cancer-related chronic pain
- SEs: Mood changes, sedation, nausea, vomiting, decreased gastrointestinal motility, constipation, respiratory depression, dependence, and tolerance
- Severe pain: **morphine, hydromorphone, oxymorphone, meperidine, fentanyl, methadone**
- Moderate-to-severe pain: **Pentazocine**
- Moderate pain: **Propoxyphene, oxycodone, codeine, tramadol**

Opioids

Morphine	PO 5–30 mg every 4 hours[a] IM 5–10 mg every 4 hours[a]
	IV 2–5 mg every 3–4 hours[a]
	SR 15–30 mg every 12 hours (may need to be every 8 hours in some patients)
	Rectal 10–20 mg every 4 hours[a]
Hydromorphone	PO 2–4 mg every 4–6 hours[a]
	IM 0.8–1 mg every 4–6 hours[a]
	IV 0.2–0.6 mg every 2–3 hours[a] Rectal 3 mg every 6–8 hours[a]
Oxymorphone	IM/SQ 1–1.5 mg every 4–6 hours[a] IV 0.5 mg initial dose
	PO immediate-release 5–10 mg every 4–6 hours[a] PO extended-release 5–10 mg every 12 hours

Opioids

Levorphanol	PO 2 mg every 6–8 hours
Codeine	PO 15–30 mg every 4–6 hours[a] Maximum 360 mg day IM 15–30 mg every 4 hours[a]
Hydrocodone	PO 5–10 mg every 4–6 hours[a]
Oxycodone	PO 5–15 mg every 4–6 hours[a] Controlled release 10 mg every 12 hours
Meperidine	IM 50–100 mg every 3–4 hours[a] IV 5–10 mg every 5 minutes as needed[a]

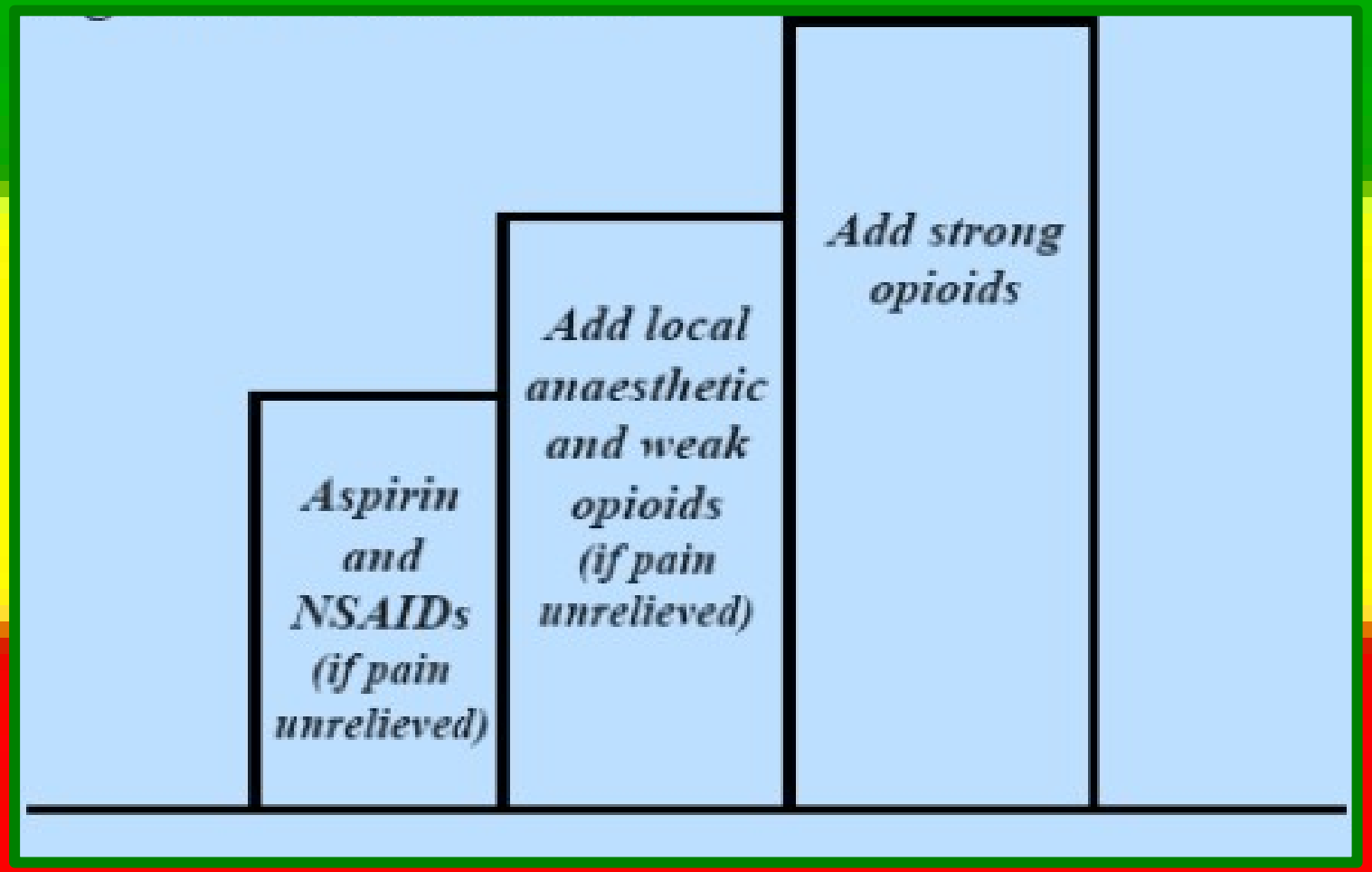
Opioids

Drug (class)	Adverse Reaction	Monitoring Parameter
Opioids	Respiratory depression	Respiratory rate OR end-tidal capnography
	Constipation	Bowel movement frequency and consistency
	Sedation	Sedation scale
	Nausea, vomiting	Nausea, vomiting
	Tolerance	Regular efficacy Monitoring
	Dependence	Regular efficacy Monitoring
	Addiction/abuse	Regular efficacy Monitoring

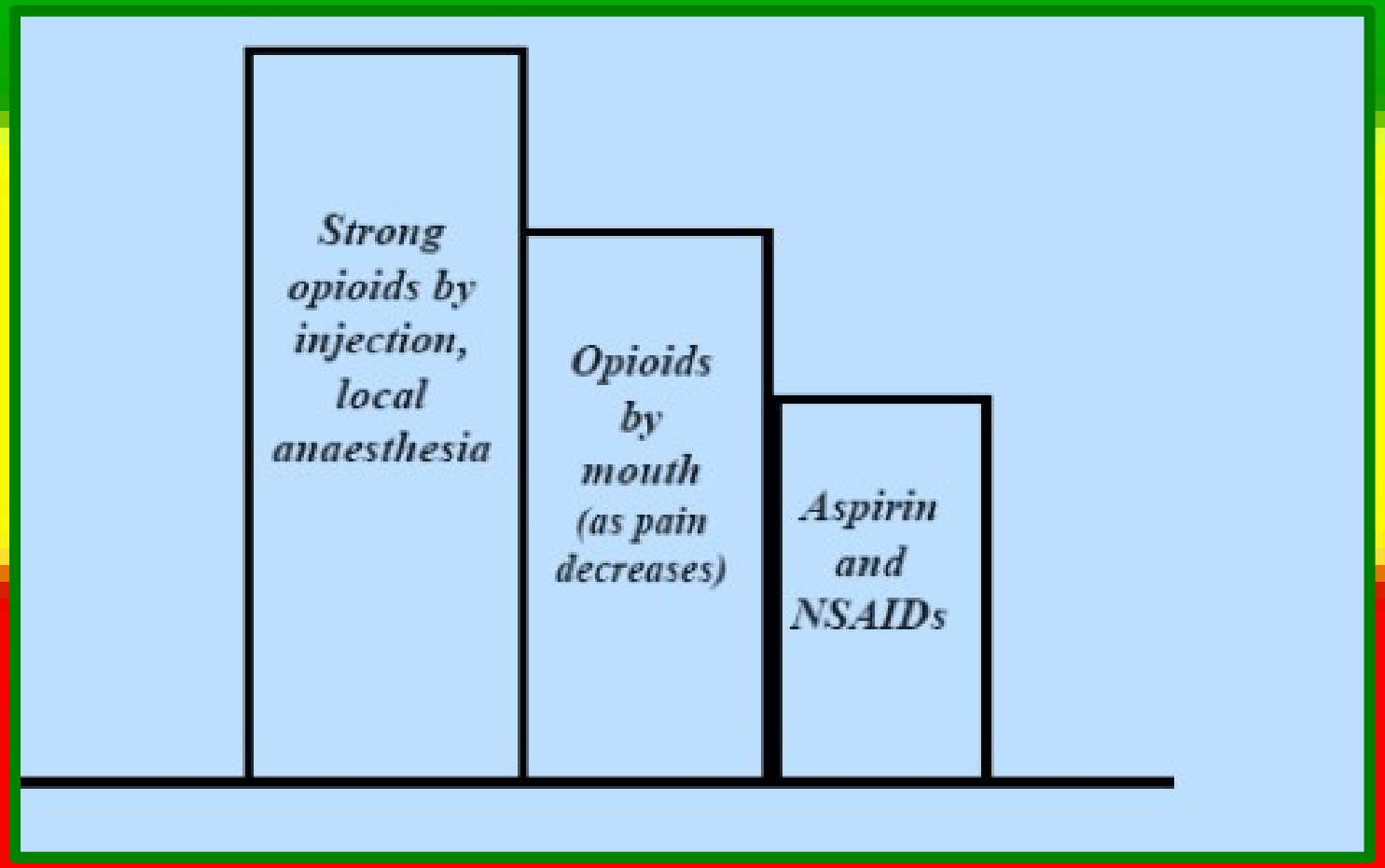
Therapeutic adjuncts

- Psychological interventions
- Physical therapy
  - Heat and cold can provide pain relief by alleviating muscle spasm
  - Heat decrease joint stiffness and increases blood flow
  - Cold vasoconstricts and can reduce tissue edema
- Acupuncture (release of endogenous

Analgesic ladder



Analgesic ladder



THANK YOU!

ENDOCRINOLOGIC DISORDERS

Chapter Four

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ENDOCRINOLOGIC DISORDERS

- Diabetes mellitus
- Thyroid disorders
- Adrenal Gland Disorders
- Pituitary Gland Disorders

Diabetes Mellitus

Antidiabetic Agents Available in Ethiopia

Class	Examples
• Biguanide	• **Glyburide**
• Meglinitides	• **Saxagliptin**
• Sulfonyl Ureas	• **Canagliflozin**
• DPP4-Inhibitors	• **Glimepride**
• GLP-1 Analogs	• **Metformin**
• SGLT2-Inhibitors	• Nateglinide
• Glitazones	• Pioglitazone
• Alpha glucosidase inhibitors	• **Vildagliptin**
	• Exenitide
	• Dapagliflozin
	• Meglitol
	• Liraglutide
	• Rosiglitazone

Match: Insulin Preparations

Type	Insulin Preparation
• Rapid Acting Insulin	• Lispro
• Short Acting Insulin	• Detemir
• Intermediate Acting Insulin	• Glulisine
• Long Acting Insulin	• Regular
	• NPH
	• Aspart
	• Glargine



Objectives

Upon completion of the session, you will be able to:

1. Distinguish type 1, type 2, and gestational diabetes.
2. List screening and diagnostic criteria for diabetes.
3. Set therapeutic goals for blood glucose for DM patient.
4. Recommend pharmacologic therapies for patients with T1 and T2 DM
5. Recommend pharmacologic management of acute complications of DM
6. Develop therapeutic monitoring plan for a patient with diabetes

Definition

- Diabetes mellitus (DM) is a heterogeneous group of metabolic disorders characterized by hyperglycemia.
- It is associated with abnormalities in carbohydrate, fat, and protein metabolism and may result in chronic complications including
  - **Microvascular**: neuropathy, retinopathy, nephropathy
  - **Macrovascular**: CVA (stroke), PAD
- DM is characterized by a complete lack of insulin, a relative
  lack of insulin, or insulin resistance as well as disorders of other hormones.
- These defects result in an inability to use glucose for energy

Epidemiology

- The global prevalence of DM among adults over 18 years was 8.5% in 2014
- Globally 425 million people with DM in 2017
- The total impact of DM in 2012 was approximately $245 billion in US,
  - Direct medical costs: $176 billion
  - Indirect costs: $69 billion (secondary to disability, work loss, and premature mortality)
- Ethiopia: 5.2% of the adult population (2015)
  - 2,567,900 adult DM cases

DIABETES IS ON THE RISE

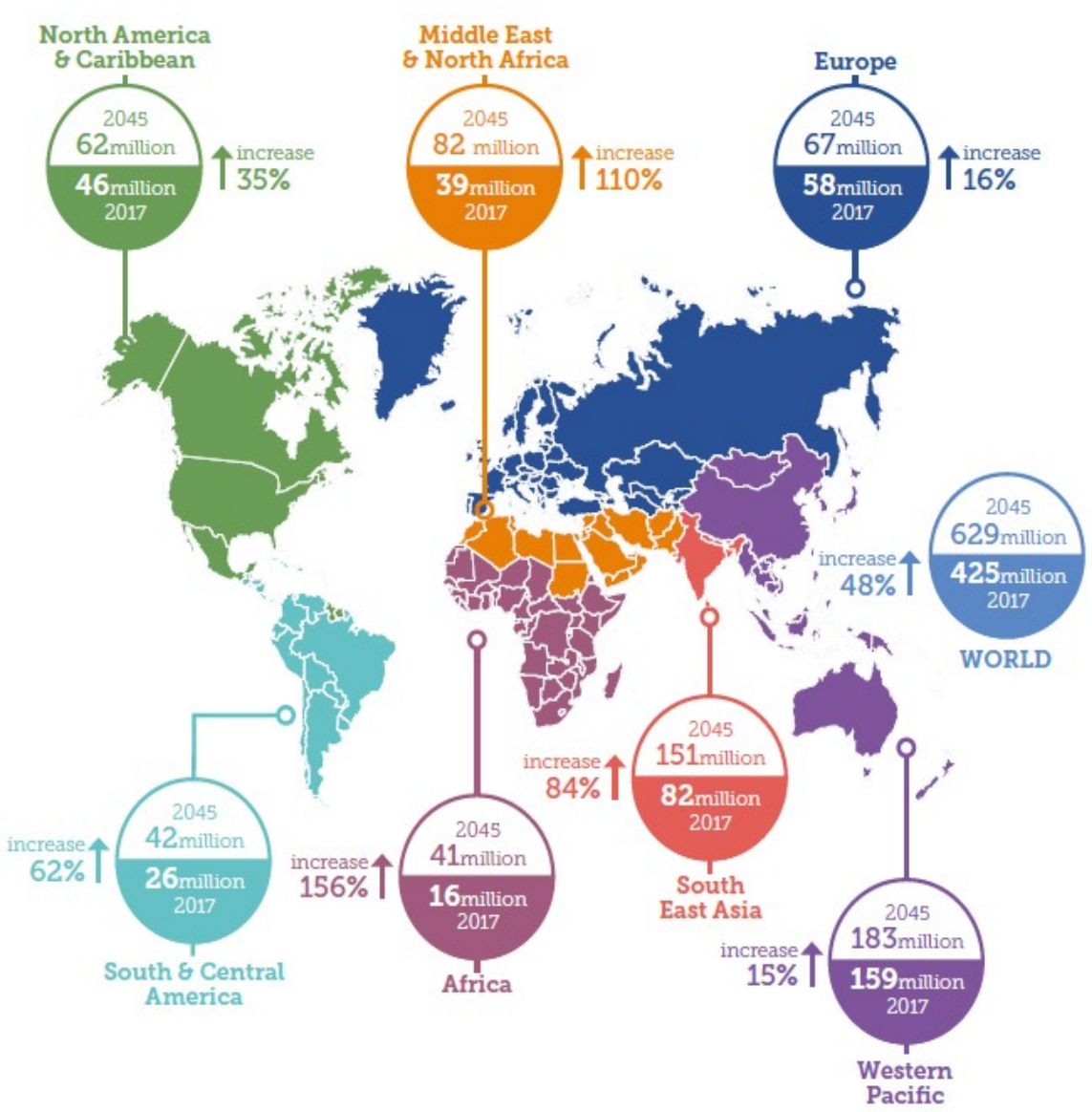


425 MILLION
adults have diabetes

THAT'S 1 PERSON IN 11



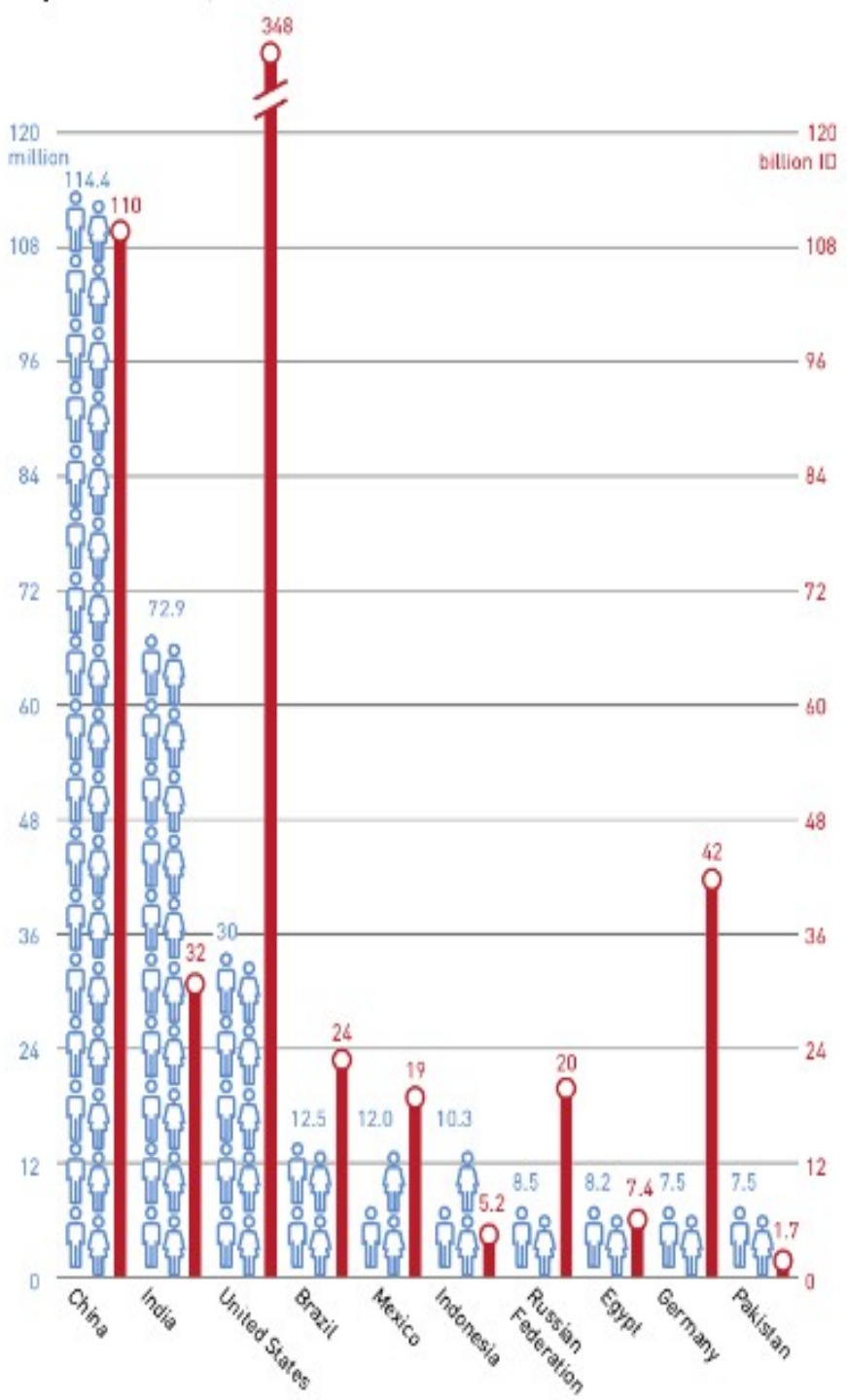
EPIDEMIOLOGY



Number of people with diabetes worldwide and per region in 2017 and 2045 (20-79 years)

EPIDEMIOLOGY

Top 10 countries for number of adults with diabetes (20-79 years) and their healthcare expenditure, 2017



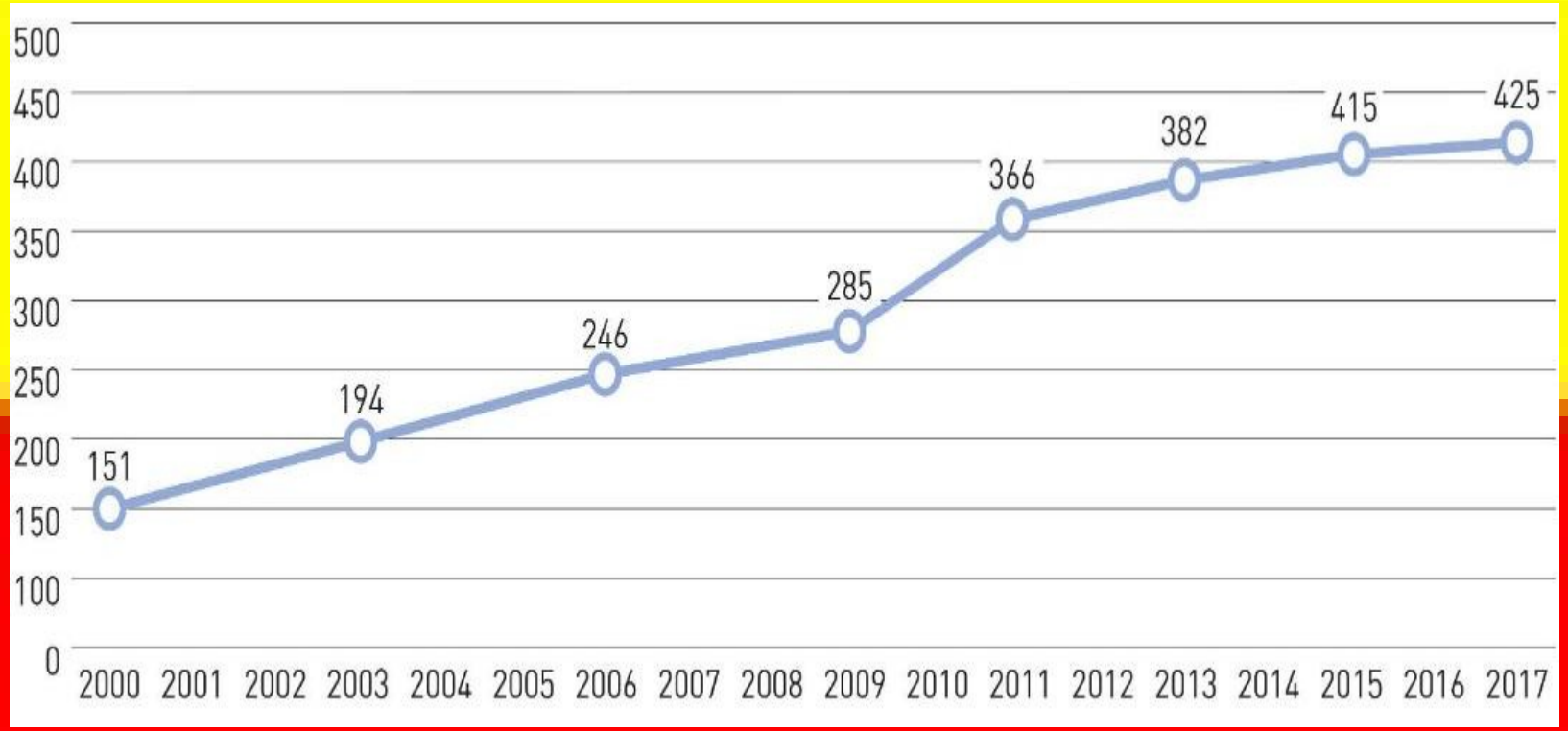
Epidemiology

- The increasing prevalence of DM is partly caused by three influences:
  - **Lifestyle**: A sedentary lifestyle coupled with greater consumption of high-fat, high-carbohydrate foods, and larger portion sizes
  - **Ethnicity**: Native Americans, Hispanic Americans, Asian Americans, African Americans, and Pacific Islanders.
  - **Age**: As the population ages, the incidence of T2DM is expected to increase

Epidemiology

Diabetes around the world

Total number of adults with diabetes (20-79 years)



Classification of Diabetes

- The vast majority of diabetic patients are classified into one of two broad categories:
  - **Type 1 diabetes** caused by an absolute deficiency of insulin or
    - ~65% of pediatric patients with DM; 5 – 10% of adults with DM.
  - **Type 2 diabetes** defined by the presence of insulin resistance with an inadequate compensatory increase in insulin secretion.
    - ~35% of pediatric patients with DM; 90% to 95% of adults with DM.

Etiologic Classification of DM

1. **Type 1 diabetes** (β-cell destruction, usually leading to absolute insulin deficiency)
   - Immune mediated
   - Idiopathic
2. **Type 2 diabetes**
   - Insulin resistance with relative insulin deficiency
   - Insulin secretory defect with insulin resistance
3. **Other specific types**
   - Genetic defects of β-cell function
   - Diseases of the exocrine pancreas (pancreatitis, trauma, pancreatectomy, neoplasia, cystic fibrosis)
   - Endocrinopathies (Acromegaly, cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma)

Etiologic Classification of DM

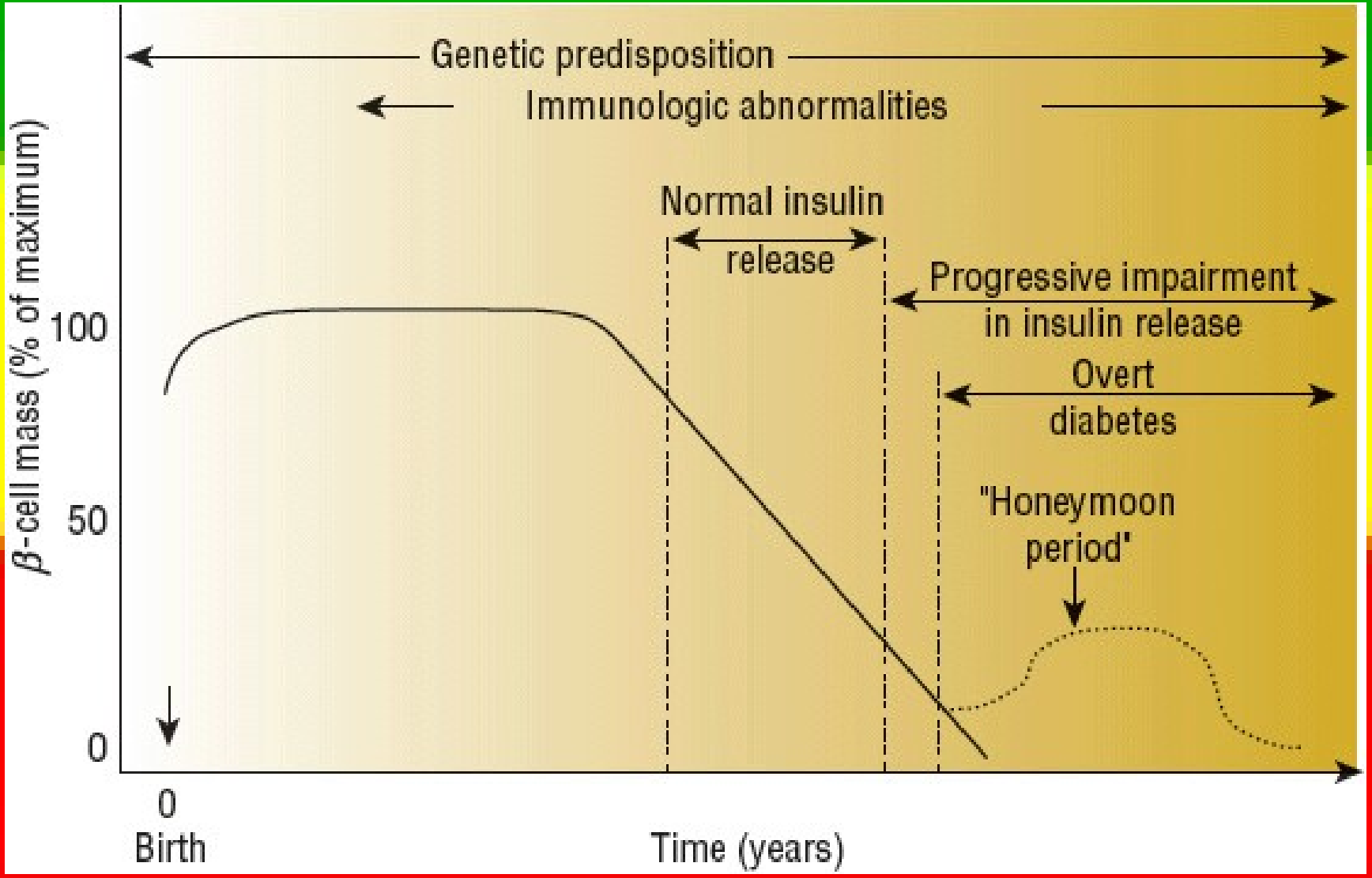
3. **Other specific types, Continued**
   - Drug- or chemical-induced: pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, interferon alpha
4. **Gestational diabetes mellitus (GDM)**

Pathogenesis

Type 1 DM

- Type 1 DM results from pancreatic *β*-cell failure with “**absolute**” deficiency of insulin secretion.
  - Immune-mediated destruction of pancreatic *β* cells,
  - Unknown or idiopathic processes (rare).
- There often is a long preclinical period of immune-mediated *β*-cell destruction later followed by onset of hyperglycemia when 80% to 90% of the *β* cells have been destroyed.
- Occasionally there is a period of transient remission called the “honeymoon” phase

The natural history of the β-cell defect in type 1DM



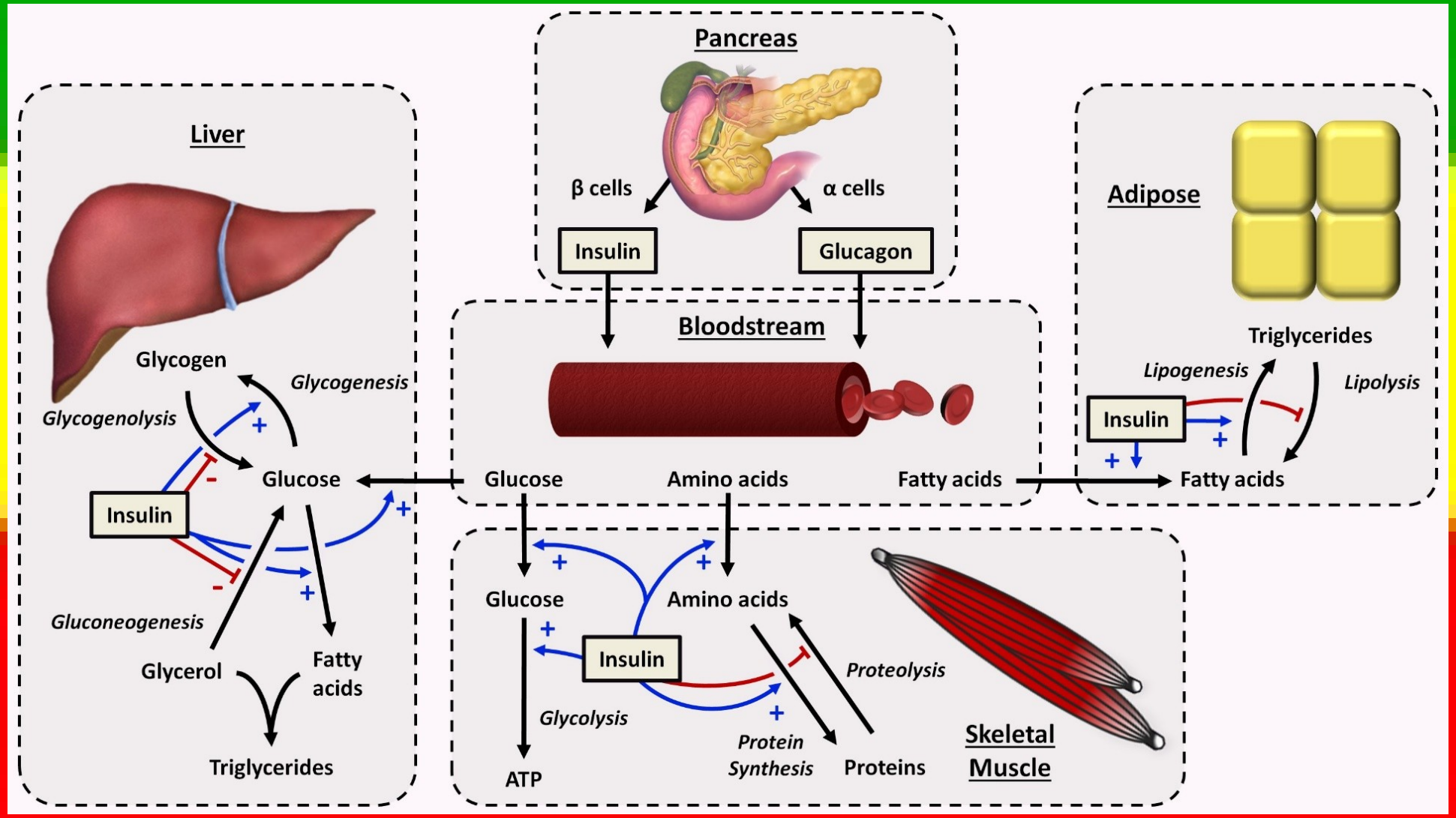
Pathogenesis

- The autoimmune process is mediated by macrophages and T lymphocytes with circulating autoantibodies to various β-cell antigens.
- The most commonly detected antibody associated with type 1 DM is the islet cell antibodies (ICA)
- β-Cell autoimmunity may precede the diagnosis of type 1 DM by up to 9 to 13 years.
- Autoimmunity may remit in some individuals, or can progress to absolute β-cell failure in others.
- Other autoimmune disorders frequently associated with type 1 DM include Hashimoto's thyroiditis, Graves' disease, Addison's disease, vitiligo, and celiac sprue.

Pathogenesis

- The autoimmune destruction of pancreatic β-cell function results in **hyperglycemia** due to an absolute deficiency of insulin.
- Insulin lowers blood glucose (BG) by a variety of mechanisms, including stimulation of tissue glucose uptake, suppression of glucose production by the liver, and suppression of free fatty acid (FFA) release from fat cells.
- The suppression of FFAs plays an important role in glucose homeostasis.
- Increased levels of FFAs inhibit the uptake of glucose by muscle and stimulate hepatic gluconeogenesis

Pathogenesis



Pathogenesis

Normal Metabolism

- In the fasting state:
  - Glucagon is produced by pancreatic α cells to:
    - Oppose the action of insulin and
    - Stimulate hepatic glucose production and glycogenolysis.
  - 85% of glucose production is derived from the liver, and the remaining is by the kidney.
  - 75% of total body glucose disposal takes place in brain, neurons, and others.
    - Non–insulin-dependent tissues
  - The remaining 25% of glucose metabolism takes place in the liver and muscle
    - Insulin dependent tissues.

Pathogenesis

- In the fed state,
  - Carbohydrate ingestion increases the plasma glucose concentration and
  - Stimulates insulin release from the pancreatic β cells.
    - The resultant hyperinsulinemia
      (a) Suppresses hepatic glucose production,
      (b) Stimulates glucose uptake by peripheral tissues,
      (c) Suppresses glucagon release (in conjunction with incretin hormones).
  - The majority (80 to 85%) of glucose is taken up by muscle, with only a small amount (4 to 5%) being metabolized by adipocytes

Pathogenesis

Type 2 Diabetes

- Individuals are characterized by multiple defects including
  - (a) Defects in insulin secretion;
  - (b) Insulin resistance involving muscle, liver, and adipocyte;
  - (c) Excess glucagon secretion;
  - (d) Glucagon-like peptide-1 (GLP-1) deficiency and possibly resistance

Pathogenesis

Impaired Insulin Secretion

- The pancreas in people with a normal-functioning β cell is able to adjust its secretion of insulin to maintain normal plasma glucose levels.
- In nondiabetic individuals, insulin increases in proportion to the severity of the insulin resistance and plasma glucose remains normal.
- Impaired insulin secretion is a hallmark finding in T2DM.
- People with T2DM lose 5% to 7% of β-cell function per year of diabetes.
- The reasons for this loss are likely multifactorial including (a) glucose toxicity; (b) lipotoxicity; (c) insulin resistance; (d) age; (e) genetics; and (f) incretin deficiency.

Pathogenesis

Incretins

- In the type 2 diabetic patient, decreased postprandial insulin secretion is due to both
  - Impaired pancreatic β-cell function and
  - Reduced stimulus for insulin secretion from gut hormones.
- Increased insulin secretion in response to an oral glucose stimulus: “the incretin effect”
- **GLP-1** and **glucose-dependent insulinotropic polypeptide** (GIP), are responsible for over 90% of the increased insulin secretion seen in response to an oral glucose load.
- Both hormones are rapidly inactivated by the enzyme **dipeptidyl peptidase-4 (DPP-4)**
- In type 2 diabetic patients, this “incretin effect” is blunted

Pathogenesis

Insulin Resistance

- **Liver:**
  - Fasting hyperglycemia
    - Increase in fasting hepatic glucose production
  - Postprandial hyperglycemia
    - From the diet and
    - From continued glucose production from the liver.
- **Peripheral (Muscle)**
  - Impaired intracellular insulin signaling: insulin resistance

Pathogenesis

- **Peripheral (Adipocyte)**
  - ↳Insulin resistance
    - Lipolysis: release of FFAs from the adipocyte
    - Gluconeogenesis indirectly through glycerol and FFAs

CLINICAL PRESENTATION

Characteristic	Type 1 DM	Type 2 DM
Age	<30 years	>30 years
Onset	Abrupt	Gradual
Body habitus	Lean	Obese or history of obesity
Insulin resistance	Absent	Present
Autoantibodies	Often present	Rarely present
Symptoms	Symptomatic	Often asymptomatic
Ketones at diagnosis	Present	Absent
Need for insulin therapy	Immediate	Years after diagnosis
Acute complications	DKA	HHS
Microvascular complications at diagnosis	No	Common
Macrovascular	No	Common

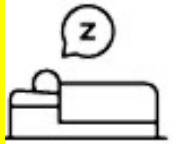
Symptoms of type 1 diabetes



Abnormal thirst and dry mouth



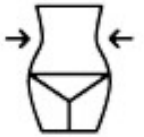
Frequent urination



Lack of energy, fatigue



Constant hunger



Sudden weight loss



Bedwetting



Blurred vision

Symptoms of type 2 diabetes



Excessive thirst and dry mouth



Frequent and abundant urination



Lack of energy, extreme tiredness



Tingling or numbness
in hands and feet



Recurrent fungal infections
in the skin



Slow healing wounds



Blurred vision

Screening

Type 1 Diabetes Mellitus

- Screening for type 1 DM not recommended
  - The prevalence of type 1 DM is low in the general population.
  - The acute onset of symptoms in most individuals at time of diagnosis.
- Screening for β-cell autoantibody status in high-risk family members may be appropriate

Screening

Type 2 Diabetes Mellitus

- ADA recommends screening
  - Adults without risk factors starting at age 45 years
    - Repeat every 3 years if normal
  - Any age in individuals who are overweight (BMI ≥25 kg/m^2) and have at least one other risk factor
    - Physical inactivity,
    - First-degree relative with diabetes or high-risk ethnicity/race,
    - Women who have delivered a baby >4 kg or a history of GDM,
    - Hypertension,
    - High triglycerides,
    - Low HDL,
    - Women with polycystic ovary syndrome,
    - A1C is 5.7% or greater, IGT, or IFG in previous testing
    - Acanthosis nigricans, or
    - History of cardiovascular disease

Screening

Gestational DM

- Screen at first prenatal visit for undiagnosed type 2 DM
- Screen at 24–28 weeks' gestation using a 75-g OGTT.
- If a diagnosis of gestational DM is made, screen for diabetes 6 – 12 weeks after delivery.
- Continue to screen patients who have had gestational DM every 3 years for type 2 DM for life

DM Diagnosis

1. Type 1 and type 2 DM diagnosis

a) Glycemic values in nonpregnant patients

i. FPG: ≥126 mg/dL

- ✓ Easy and preferred method

ii. Random plasma glucose: ≥200 mg/dL

- ✓ With symptoms of hyperglycemia: polyuria, polydipsia, and unexplained weight loss

iii. OGTT: ≥200 mg/dL

- ✓ Plasma glucose concentration obtained 2 hours after a 75-g oral glucose ingestion

iv. A1C (glycated hemoglobin): ≥6.5%

DM Diagnosis

b) Gestational diabetes diagnosis:
Glycemic values in pregnancy

- 75-g OGTT at 24 – 28 weeks' gestation
  - ✍1 hour after OGTT: 180 mg/dL or greater
  - ✍2 hours after OGTT: 153 mg/dL or greater

DM Diagnosis

c) **Prediabetes diagnosis** (high-risk population)

- **IFG**: FPG between 100 and 125 mg/dL
- **IGT**: 2-hour plasma glucose after OGTT (75 g) between 140 and 199 mg/dL
- **A1C**: between 5.7% and 6.4%

Management of DM

Goals of Diabetes Management

1. Prevent the onset of acute or chronic complications.
2. Glycemic therapy goals
   - A1C less than 6.5%
     - Obtain every 6 months in patients at goal A1C and every 3 months in those over goal.
   - FPG: 80–125 mg/dL.
   - Postprandial glucose (1–2 hours after a meal): <200 mg/dL
3. Nonglycemic therapy goals
   - Blood pressure <140/90 mm Hg

Management of Type 1 DM

Insulin agents

- Categorized on the basis of duration after injection
  i. Rapid acting: Insulin aspart, lispro and glulisine
  ii. Short acting: Regular human insulin
  iii. Intermediate acting: Neutral protamine Hagedorn (NPH)
  iv. Long acting: Insulin glargine and detemir; cannot be mixed with other insulins
- Combination insulins (intermediate or long-acting, regular or rapid acting): 70/30, 75/25

Characteristics of U-100 (100 units/mL) Insulins

Category	Drug Name	Clarity	Onset	Inj. Time Before Meal	Peak (hours)	Duration (hours
Rapid acting	Aspart Lispro Glulisine	Clear	15–30 minutes	15 minutes	1–3	2–5
Short acting	Regular	Clear	30–60 minutes	30	2–3	4–6
Intermediate acting	NPH	Cloudy	1–2 hours	N/A	4–8	10–20
Long acting	Detemir Glargine	Clear	2–4 hours 1–2 hours	N/A	6–8 “Peakless” “Peakle	6–24 ~24 24–42

Management of Type 1 DM

- **Glycemic target**
  i. Regular and short-acting insulins: target postprandial glucose concentrations.
  ii. Intermediate and long-acting insulins: target fasting glucose concentrations.

Insulin therapy

- Estimate total daily insulin (TDI) requirements
  - ✍Weight-based estimate if insulin naïve
    - 0.3 – 0.6 unit/kg/day

1. NPH (2/3) and regular (1/3) insulin

- ✍Two-thirds of TDI given before morning meal.
  - Two-thirds of this is given as NPH and one third as regular insulin.
- ✍One-third of TDI given before the evening meal
  - Two-thirds of this is given as NPH and one-third as regular insulin
- ✍**Advantages**: Daily insulin injection frequency two or three times daily and inexpensive
- ✍**Disadvantages**: Does not mimic natural insulin secretion pattern; prone to hypoglycemic events

Insulin therapy

2. **Basal/bolus insulin therapy** (physiologic insulin therapy)

- Use of newer insulin analogs to better mimic natural insulin secretion patterns
- Provides day-long basal insulin to prevent ketosis and control FPG
  - **NPH insulin** twice daily, **insulin glargine** once daily or **insulin detemir** once or twice daily
  - Basal requirements are 50% of estimated TDI.
- Provides bolus insulin to control postprandial hyperglycemia
  - Rapid-acting insulin (lispro, aspart, glulisine),

Insulin therapy

2. Basal/bolus insulin therapy

- Advantage:
  - More physiologic,
  - Less hypoglycemia,
  - More flexible to patient meal times
- Disadvantage:
  - Cost
  - Increased frequency and number of daily injections (rapid-acting and basal insulin must be injected separately)

Insulin therapy

2. Basal/bolus insulin therapy

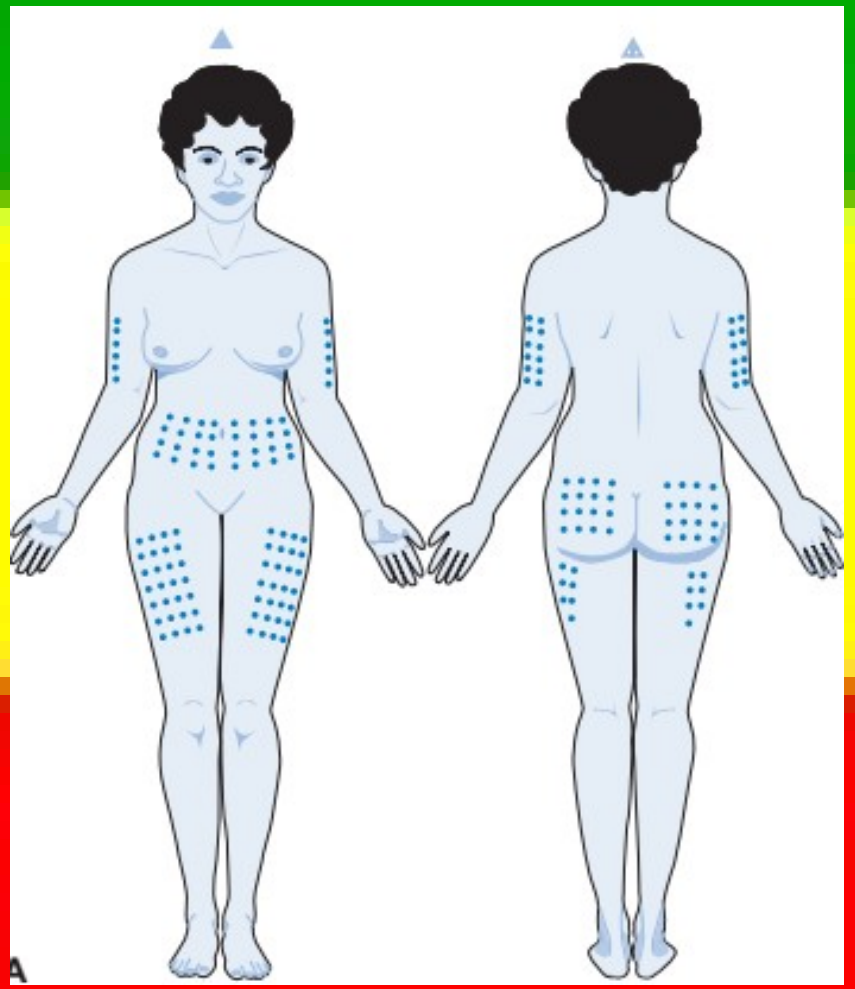
- **Correctional insulin needs**
  - Always a need to correct for hyperglycemic excursions, despite optimal basal/bolus therapy
  - "1800 rule": 1800/TDI = # mg/dL of glucose lowering per 1 unit of rapid-acting insulin.
    - For example, if TDI is 60 units, 1800/60 = 30, suggesting 1 unit of rapid-acting insulin will reduce BG concentrations by 30 mg/dL.
  - Also referred to as **insulin sensitivity**

Insulin therapy

3. Continuous subcutaneous insulin infusion (CSII)

- **Insulin pump**
- Device allows every patient-specific hourly basal dosing and bolus insulin dosing.
- Uses rapid-acting insulins
- Requires patient education and carbohydrate counting

Insulin Injection Sites



- Insulin absorption is affected by

1) Site: abdomen > arm, buttock
2) Exercise: increases absorption

Case Study, Type 1 DM

- A.H., a slender, 18-year-old woman who was recently discharged from the hospital for severe dehydration and mild ketoacidosis, is referred to the Diabetes Clinic. A fasting and a random plasma glucose ordered subsequently were 190 mg/dL and 250 mg/dL. Approximately 4 weeks before she was hospitalized, A.H. had moved from her hometown to Addis Ababa to attend college. This is her first time to move away from home.

Case Study, Type 1 DM

- In retrospect, she remembers that she had symptoms
of polydipsia, nocturia (six times a night), fatigue, and a 5-KG weight loss during this period, which she attributed to the anxiety associated with her move away from home and adjustment to her new environment. Her medical history is remarkable for recurrent upper respiratory infections and three cases of vaginal candidiasis in the past 6 months. Her family history is negative for diabetes, and she takes no medications.

Case Study, Type 1 DM

- Physical examination is within normal limits. She weighs 50 kg and is 165cm tall. Laboratory results are as follows: FPG, 280 mg/dL; A1C, 14%; and trace urine ketones. On the basis of her history and laboratory findings, the presumptive diagnosis is type 1 diabetes.

Case Study, Type 1 DM

1. Which findings are consistent with this diagnosis in A.H.?
2. How do you consider insulin therapy for this patient?

Management of Type 2 DM

- Metformin
- Sulfonylureas
- Meglitinides
- Thiazolidinediones (TZDs)
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Sodium glucose cotransporter-2 (SGLT-2) inhibitors
- GLP-1 agonists
- Basal insulin

Metformin (Biguanide)

- **Mechanism**
  - Reduces hepatic gluconeogenesis.
  - Also favorably affects insulin sensitivity and, to a lesser extent, intestinal absorption of glucose
- **Dosing**
  - Initial: 500 mg once or twice daily (once daily with extended-release formulation)
  - Maximal daily dose: 2550 mg (more commonly, 2000 mg/day)
  - Can increase at weekly intervals as necessary

Metformin

- Adverse effects
  - Common: Nausea, vomiting, diarrhea, epigastric pain
  - Less common: Decrease in vitamin B levels, lactic acidosis (rare)
    - Signs or symptoms of lactic acidosis: acidosis, nausea, vomiting, increased RR, abdominal pain, shock, and tachycardia.
- Contraindications and precautions (because of risk of lactic acidosis)
  - Renal impairment
  - Age 80 years or older
  - High risk of cardiovascular event or hypoxic state
  - Hepatic impairment
  - Congestive heart failure

Metformin

- **Efficacy**
  - 1%–2% A1C reduction
  - Some benefit in TG reduction and weight loss
  - Considered first-line therapy

Sulfonylureas

- Bind to receptors on pancreatic ß cells, leading to membrane depolarization, with subsequent stimulation of insulin secretion (insulin secretagogue)
- **1st – generation agents** seldom used today (chlorpropamide, tolbutamide)
- **2nd – generation agents** (e.g., glyburide, glipizide, glimepiride).
- Dosage titration: Can increase at weekly intervals as necessary

Sulfonylureas

- **Adverse effects**
  - Common: Hypoglycemia, weight gain
  - Less common: Rash, headache, nausea, vomiting, photosensitivity
- **Contraindications and precautions**
  - Hypersensitivity to sulfonamides
  - Patients with hypoglycemic unawareness
  - Poor renal function (glipizide may be a better option than glyburide or glimepiride)
- **Efficacy**
  - 1 – 2% A1C reduction

Second-Generation Sulfonylurea Dosing

Drug	Initial Dosage	Maximal Daily Dosage (mg)
Glyburide (nonmicronized)	2.5 – 5.0 mg once or twice daily	20
Glyburide (micronized)	1.5 – 3 mg once or twice daily	12
Glipizide	5 mg once or twice daily (once daily with extended release)	40
Glimepiride	1–2 mg once daily	8

Meglitinides

- Very similar mechanism to that of sulfonylureas in increasing insulin secretion from the pancreas
- Dosing
  - **Repaglinide**
    - Initial: 0.5 – 1 mg 15 minutes before meals
    - Maximal daily dosage: 16 mg
  - **Nateglinide**
    - 120 mg before meals
    - 60 mg if A1C near goal
- Adverse effects: Hypoglycemia

TZDs (Glitazones)

- Increases expression of genes responsible for glucose metabolism, resulting in **improved insulin sensitivity**
- Dosing
  - Pioglitazone
    - Initial: 15 mg once daily
    - Maximal daily dosage: 45 mg
  - Rosiglitazone
    - Initial: 4 mg daily as a single daily dose or in divided doses twice daily, increase to 8 mg

TZDs (Glitazones)

- Adverse effects
  - Weight gain
  - Fluid retention
  - Risk of proximal bone fractures;
  - Possible risk of bladder cancer (pioglitazone)
  - Increased risk of heart failure
- Contraindications and precautions
  - Hepatic impairment
  - Class III/IV heart failure (symptomatic heart failure)
  - Existing fluid retention

DPP-4 inhibitors

- Inhibit the breakdown of **GLP-1** secreted during meals,
  - Increase pancreatic insulin secretion,
  - Limits glucagon secretion,
  - Slows gastric emptying, and
  - Promotes satiety

DPP-4 inhibitors

- Dosing
  - **Sitagliptin**: 100 mg once daily
    - CrCl 30 – 50 mL/min: 50 mg once daily.
    - CrCl < 30 mL/min: 25 mg once daily.
  - **Saxagliptin**: 5 mg once daily.
    - CrCl ≤ 50 mL/min: 2.5 mg once daily.
    - When coadministered with strong CYP3A4/5 inhibitor (e.g., ketoconazole): 2.5 mg once daily.
  - **Linagliptin**: 5 mg once daily (no dosage adjustment for renal impairment)
  - **Alogliptin**: 25 mg once daily
    - CrCl 30 – 60 mL/min: 12.5 mg once daily.
    - CrCl <30 mL/min: 6.25 mg once daily.

DPP-4 inhibitors

- **Vildagliptin : 50 mg twice daily**
  - CrCl <15mL/min: 50 mg once daily.
- **Adverse effects**
  - Upper respiratory and urinary tract infections, headache, severe joint pain
- Efficacy: 0.5%–0.8% reduction in A1C,
  - Considered weight neutral

SGLT-2 Inhibitor (Gliflozins)

- Increases urinary glucose excretion by blocking normal reabsorption in the proximal convoluted tubule.
- Has some effect on delaying GI glucose absorption

✍**Canagliflozin**

- 100 mg once daily before the first meal of the day
- Maximal daily dosage: 300 mg
- CrCl 45 - 59 mL/min: 100 mg daily.
- Discontinue or do not initiate if eGFR is <45mL/min/1.73m^2

SGLT-2 Inhibitor (Gliflozins)

Dapagliflozin

- 5 mg once daily in the morning (with or without food)
- Maximal daily dosage: 10 mg
- Discontinue or do not initiate if eGFR is <60mL/min/1.73m^2

Empagliflozin

- 10 mg once daily in the morning (with or without food)
- Maximal daily dosage: 25 mg
- Discontinue or do not initiate if eGFR is <60mL/min/1.73m^2

SGLT-2 Inhibitor (Gliflozins)

- **Adverse effects**
  - Increased urination
  - Urinary tract infections
  - Genital mycotic infections
  - Hypotension
  - Increased hypoglycemia risk with concomitant insulin or insulin secretagogue
- **Contraindications and precautions**
  - Significant renal impairment
  - Suggested to ensure euvolemia before initiating agent

GLP-1 analogs

- Synthetic analog of human GLP-1 that binds to GLP-1 receptors, resulting in:
  - Glucose-dependent insulin secretion,
  - Reduction in glucagon secretion, and
  - Reduced gastric emptying;
  - Promotes satiety

GLP-1 analogs

- **Exenatide:**
  - Twice-daily formulation (5 mcg SC twice daily)
  - Once-weekly formulation (2 mg SC once weekly)
- **Liraglutide:**
  - 0.6 to 1.2 mg SC once daily
- **Albiglutide:**
  - 30 mg SC once weekly
- **Dulaglutide**
  - 0.75 mg SC once weekly

α-Glucosidase inhibitors

- Slow the absorption of glucose from the intestine to the bloodstream by slowing the breakdown of large carbohydrates into smaller absorbable sugars
- Two agents available: Acarbose and miglitol
- Dosing (both agents dosed similarly)
  - Initial: 25 mg three times daily at each meal
  - Maximal daily dosage: 300 mg
- Adverse effects
  - Flatulence, diarrhea, abdominal pain
  - Increased liver enzymes observed with high dosages of acarbose

Insulin

- Initial insulin therapy:
  - ✓ Use insulin early with any of the following baseline characteristics:
    - ✍ A1C greater than 10%
    - ✍ Glucose greater than 300 – 350 mg/dL
    - ✍ Hyperglycemic symptoms
    - ✍ Presence of urine ketones

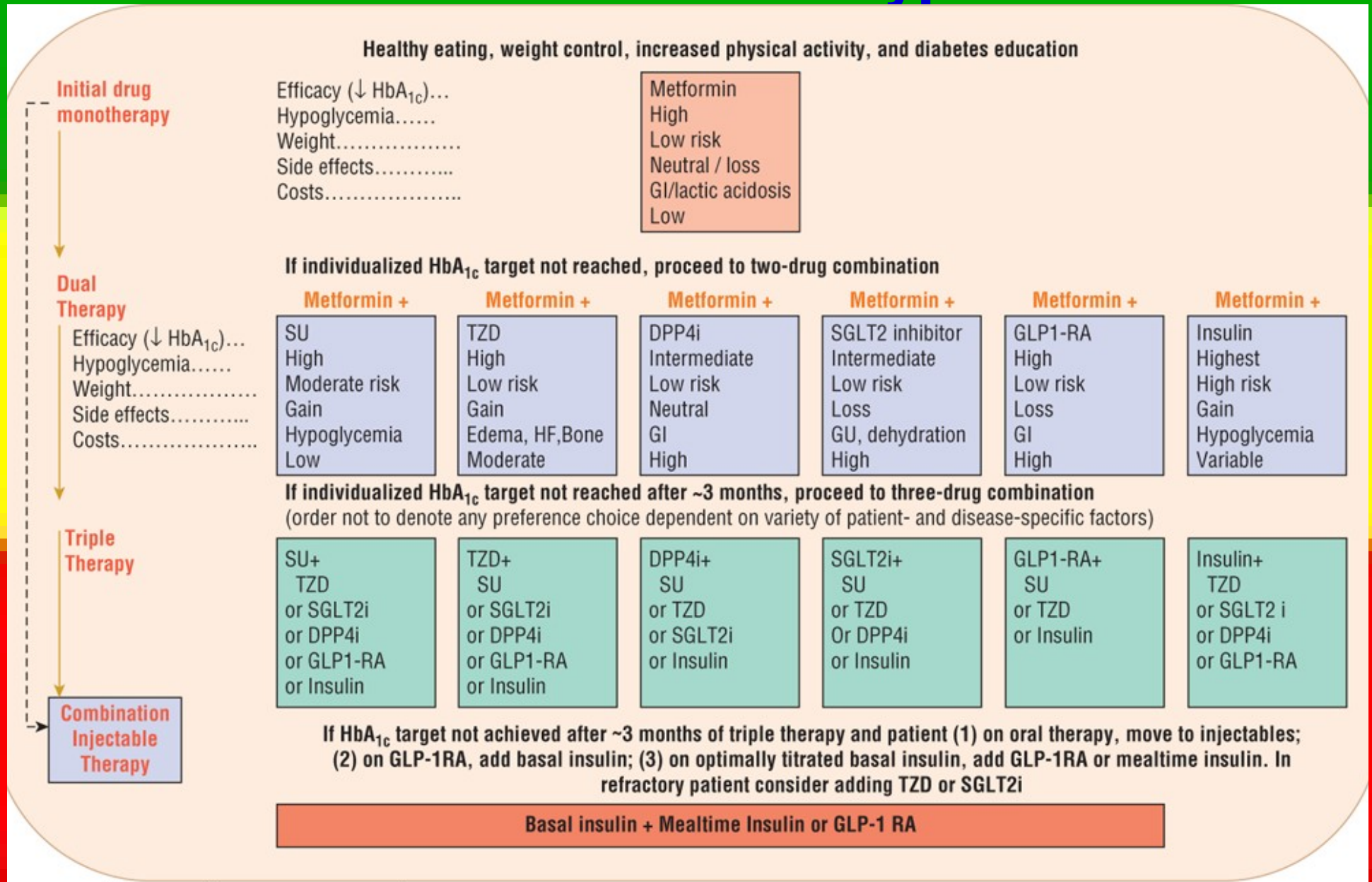
Insulin

- Adding insulin to existing oral DM agents
  - Common to add a basal insulin regimen to existing oral agents when hyperglycemia still not controlled
    - Weight-based dosing: For example, 0.1–0.2 unit/kg/day (higher dosages if significant hyperglycemia exists)
  - Can add bolus insulin to one or more meals if postprandial glucose is of concern
  - **Insulin secretagogues** should be lowered in dosage or d/c altogether when bolus insulin added to reduce risk of hypoglycemia.
  - **TZDs** should be lowered or discontinued when basal or bolus insulin is added to regimen because of increased risk of **edema**

Insulin

- Changing from oral DM medications to insulin-only management
  - Because of adverse effects, contraindications, lack of efficacy of oral medications
  - Can follow NPH/regular insulin or basal/bolus approach similar to that in type 1 DM
  - The TDI requirements in type 2 DM are usually much higher than in type 1 DM because of insulin resistance.

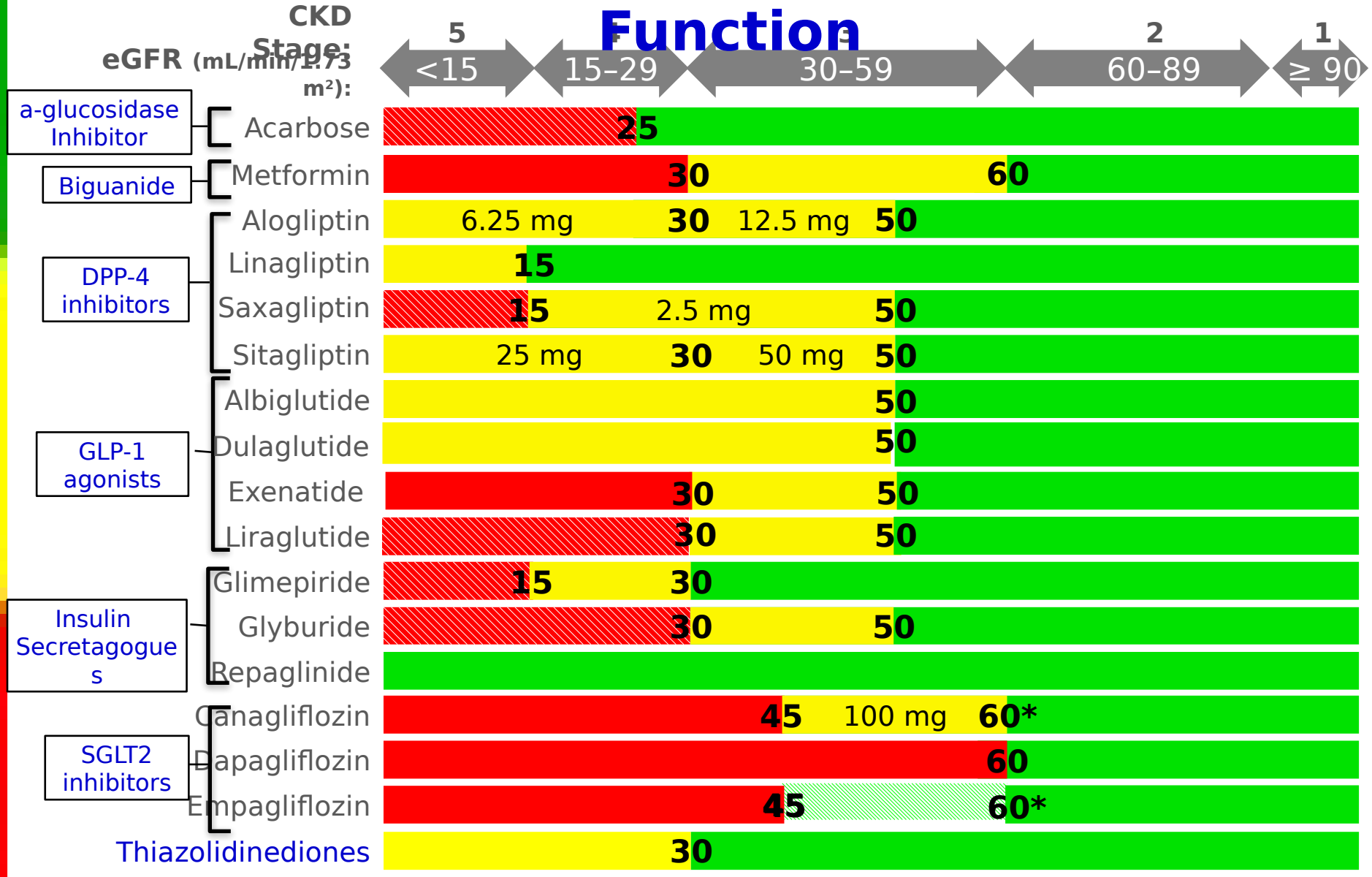
Antihyperglycemic Therapy Recommendations in Type 2 DM



COMPARISON OF ANTIDIABETIC AGENTS

Class	Relative A1C Lowering	Hypoglycemia	Weight	Effect in Cardiovascular Outcome Trial
α-glucosidase inhibitor (acarbose)	↓	Rare	Neutral to ↓	
DPP-4 Inhibitors	↓↓	Rare	Neutral to ↓	alo, saxa, sita: Neutral
GLP-1R agonists	↓↓ to ↓↓↓	Rare	↓↓	**lira**: Superiority in T2DM patients with clinical CVD lixi: Neutral
Insulin	↓↓↓	**Yes**	↑↑	Neutral (glar)
Insulin secretagogue: Meglitinide Sulfonylurea	↓↓ ↓↓	**Yes** **Yes**	↑ ↑	
SGLT2 inhibitors	↓↓ to ↓↓↓	Rare	↓↓	**empa**: Superiority in T2DM patients with clinical CVD
Thiazolidinediones	↓↓	Rare	↑↑	Neutral

Antihyperglycemic agents and Renal Function



* = do not initiate if eGFR <60 ml/min

Case Study, Type 2 DM

- L.H. is a 45-year-old, overweight woman with central obesity (height, 163cm; weight, 75 KG; BMI, 28.2 kg/m^2).
- She was referred to the diabetes clinic when her gynecologist, who had been treating her for recurrent candiadial infections, noted glucosuria on routine urinalysis.
- Subsequently, on two separate occasions she was found to have an FPG of 150 mg/dL and 167 mg/dL; an A1C was also checked and it was 8.2%.
- L.H. denies any symptoms of polyphagia or polyuria, although lately she has been more thirsty than usual.
- She does complain of lethargy and takes afternoon naps when she can.

Case Study, Type 2 DM

- L.H.’s other medical problems include **hypertension**, which is well controlled on lisinopril 20 mg/day, and recurrent candidial infections, which are treated with fluconazole.
- She has given birth to four children (birth weights, 3.2, 3.9, 4.5, and 5 Kg) and was told during her last pregnancy that she had “borderline diabetes.”
- She currently works as a loan officer in a local bank and spends her weekends “catching up on her sleep” and reading.
- L.H. has been smoking one pack of cigarettes per day for 20 years and drinks an occasional glass of wine. She drinks at least two regular sodas daily and has a “large” glass of orange juice every morning.

Case Study, Type 2 DM

- Her physical activity consists of routine walking during the
day (e.g., to her car).
- Her family history is significant for a sister, aunt, and grandmother with type 2 diabetes; all have “weight problems.” L.H.’s mother is alive and well at age 77; her father died of a heart attack at age 47.
- Fasting laboratory assessment reveals glucose of 147 mg/dL, triglycerides of 400 mg/dL, and an A1C of 8.3% (normal, 4%–6%). All other values (including the complete blood count, electrolytes, LFTs, and renal function tests) are within normal limits.
- L.H. is given the diagnosis of type 2 diabetes.

Case Study, Type 2 DM

1. What features in L.H.’s history and physical examination are consistent with this diagnosis?
2. What should the goals of therapy be for L.H. and other patients with type 2 diabetes? Which biochemical indices should be monitored?
3. How should L.H. be managed initially?

GDM and Pregnancy with Preexisting DM

- The adverse outcomes associated with GDM include
  - Birth defects,
  - Miscarriage,
  - Cesarean section delivery,
  - Maternal preeclampsia/eclampsia,
  - Preterm delivery,
  - Neonatal hypoglycemia,
  - Shoulder dystocia,
  - Birth injury, and
  - Hyperbilirubinemia

GDM

- **Goals during therapy are**
  - Preprandial ≤95 mg/dL
  - 1-hour postprandial ≤140 mg/dL
  - 2-hour postprandial ≤120 mg/dL

GDM

- Insulin is the preferred agent for management of pregestational type 1 DM and type 2 DM that are not adequately controlled with diet, exercise, and metformin.
- Insulin therapy in the form of **multiple injections** should be used
- For women who are non-adherent to or who refuse insulin, **glyburide or metformin** may be used as alternative agents for glycemic control

MANAGEMENT OF DM COMPLICATIONS

- Acute complications
  - Hypoglycemia
  - Diabetic ketoacidosis
  - HHS
- Chronic complications
  - Microvascular complications
  - Macrovascular complications

Hypoglycemia

- Symptoms: anxiousness, sweating, nausea, tachycardia, hunger, clammy skin,
- Blood glucose concentration <60 mg/dL: Patient may or may not be symptomatic.
- Blood glucose <40 mg/dL: Patient is generally symptomatic.
- Blood glucose <20 mg/dL: Can be associated with seizures and coma.

Hypoglycemia

SYMPTOMS	
Trembling	Difficulty concentrating
Palpitations	Confusion
Sweating	Weakness
Anxiety	Drowsiness
Hunger	Vision changes
Nausea	Difficulty speaking
	Dizziness

Hypoglycemia

- **Causes**
  - Irregular eating patterns
  - ↑ Physical exercise
  - Gastroparesis (delayed gastric emptying)
  - Defective counter-regulatory responses
  - Excessive dose of insulin or insulin secretagogues (sulfonylureas, glinides)
  - Alcohol ingestion
  - Drugs

Hypoglycemia

Management

- **Mild to moderate hypoglycemia**
  - Oral ingestion of 15 g glucose
- **Severe hypoglycemia** in a **conscious person**
  - Oral ingestion of 20 g of glucose
- **Severe hypoglycemia** in an **unconscious individual:**
  - No IV access:
    - **1 mg of glucagon SC/IM**
  - **IV access**
    - **10-25 g glucose** (20-50 cc of D50W) over 1-3 minutes

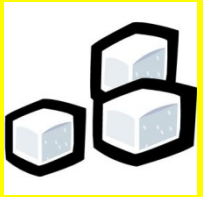
Hypoglycemia

Simple Carbohydrate to treat hypoglycemia

- 15 g of glucose in the form of **glucose tablets**



- 15 mL (3 teaspoons) or 3 **packets** of sugar dissolved in water



- 175 mL (3/4 cup) of **juice** or regular **soft drink**



- 15 mL (1 tablespoon) of **honey**



Diabetic ketoacidosis

- Diabetic ketoacidosis is a reversible but potentially life-threatening medical emergency that results from a relative or absolute deficiency in insulin
- Without insulin, the body cannot use glucose as an energy source and must obtain energy via **lipolysis**.
- This process produces **ketones** and leads to **acidosis**.
- DKA occurs frequently in young patients with T1DM on initial presentation

Diabetic Ketoacidosis

Clinical Presentation

- Polyuria, polydipsia, polyphagia
- Weight loss
- Fatigue
- Dyspnea
- Vomiting
- Preceding febrile illness
- Abdominal pain
- Dehydration (tachycardia, poor skin turgor, dry mucous membranes, and orthostatic hypotension)
- Metabolic acidosis (compensatory deep (Kussmaul) respirations),
- Fruity smell on the patient's breath.
- Mental status change (somnolence, lethargy and coma)

Precipitating Factors for DKA

- Insulin omission – most common cause of DKA
- New diagnosis of diabetes
- Infection/sepsis
- Myocardial infarction
- Thyrotoxicosis
- Drugs

Diagnostic Criteria for DKA:

- pH ≤7.3
- Bicarbonate ≤15 mmol/L
- Anion gap >12 mEq/L

  = (sodium + potassium) – (chloride + bicarbonate)
- Positive serum or urine ketones
- Plasma glucose ≥250 mg/dL (but may be lower)
- Precipitating factor

Treatment of DKA

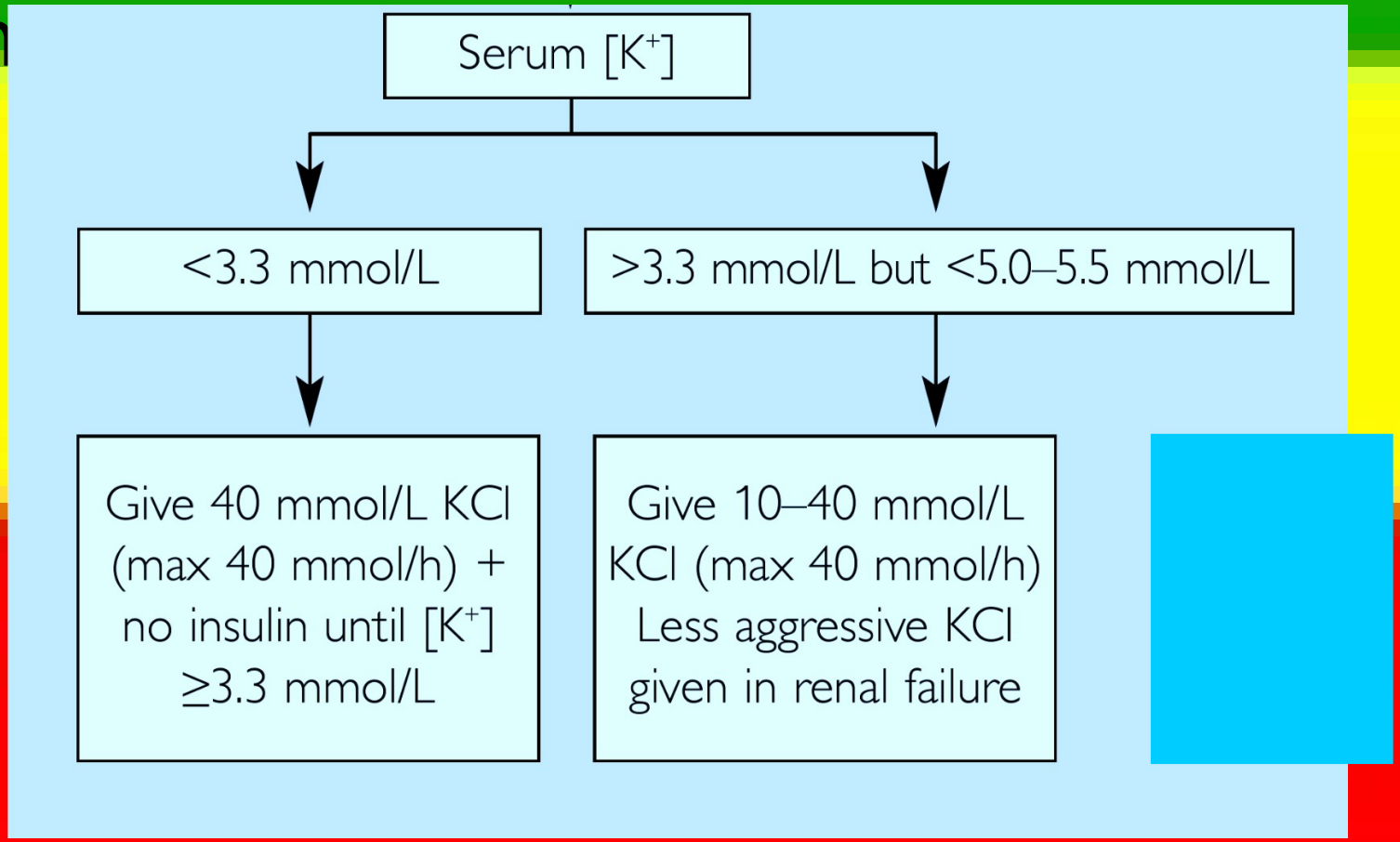
- Treatment
  a) Fluid resuscitation
  b) Avoidance of hypokalemia
  c) Insulin administration
  d) Avoidance of rapidly falling serum osmolality
  e) Identify and treat precipitating cause

Treatment of DKA

- **Fluid replacement**
  - The fluid deficit is typically about 100 ml/kg body weight, which amounts to 5 – 7 L in adult patient
  - **IV 0.9% sodium chloride** 1 to 1.5 L of fluid within the first hour and thereafter 250 to 500 ml/hour.
  - Change to 5% dextrose with NS when serum glucose is less than 200 mg/dL

Treatment of DKA

- **Potassium**: Correct K^+ first THEN start in



Treatment of DKA

- **Insulin**
  - First line:
    - Intravenous bolus: 0.1 unit/kg
    - Intravenous infusion: 0.1unit/kg/hour
  - Alternatively,
    - IV infusion of 0.14 unit/kg/hour if no insulin bolus is given
  - Reduce infusion rate to 0.02–0.05 unit/kg/hour when serum glucose reaches 200 mg/dL
  - Keep glucose between 150 and 200 mg/dL until DKA resolves

Hyperosmolar Hyperglycemic State

- HHS occurs primarily in older patients with T2DM.
- Dx criteria: plasma glucose value of > 600 mg/dL and serum osmolality of > 320 mOsm/kg
- Treatment:
  - Aggressive rehydration,
  - Correction of electrolyte imbalances, and
  - Continuous insulin infusion to normalize

DKA vs HHS

DKA

- Ketoacidosis
- ECFV contraction
- Milder hyperosmolarity
- Normal to high glucose
- May have LOC
- Beware hypokalemia
- Must use insulin
- Absolute insulin deficiency + glucagon

HHS

- Minimal acid-base problem
- ECFV contraction
- Hyperosmolarity
- Marked hyperglycemia
- Marked LOC
- Beware hypokalemia
- May need insulin
- Relative insulin deficiency

ECFV = extracellular fluid volume; LOC = level of consciousness

Treatment of Long-Term Complications

- **Retinopathy**
  - Diabetic retinopathy occurs when the microvasculature that supplies blood to the retina becomes damaged.
  - Leading cause of blindness in adults
  - Routine ophthalmic examination
  - Glucose and blood pressure control

Chronic Complications

Neuropathy

- The most common types of peripheral neuropathy are
  1. Chronic sensorimotor distal peripheral neuropathy
     - Pain, tingling, and numbness in the feet and hands,
  2. Autonomic neuropathy
     - Hypotension, gastroparesis, sexual dysfunction, and autonomic failure in response to hypoglycemia
- Treatment:
  - TCAs: amitriptyline, desipramine
  - Anticonvulsants: gabapentin, lamotrigine, pregabalin
  - SSRI: paroxetine, citalopram
  - Opioids: tramadol

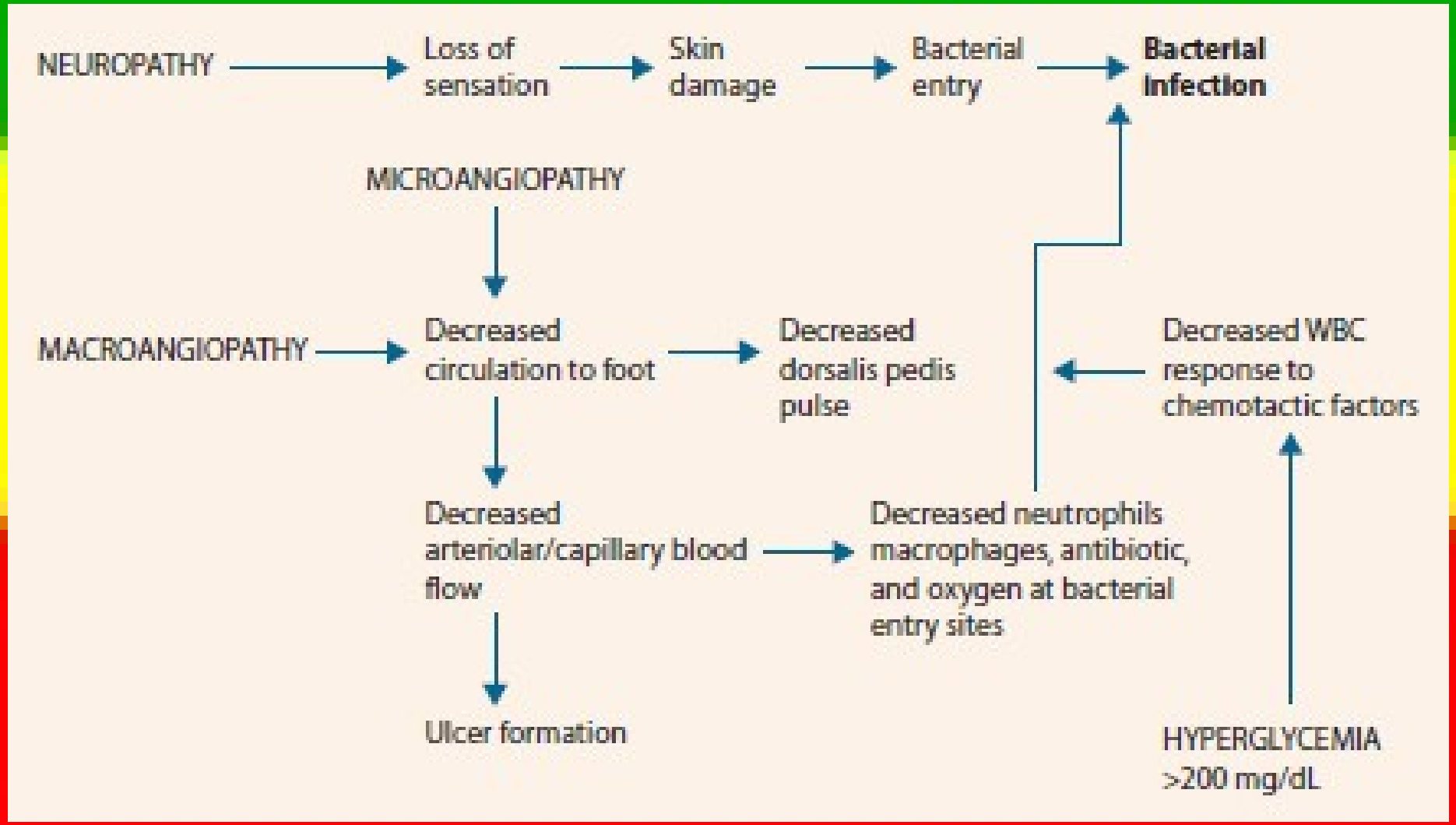
Chronic Complications

- **Nephropathy**
  - DM is a leading contributor to end-stage renal disease.
  - Urine protein tests annually in T2DM patients.
  - Glycemic control and blood pressure control are primary measures
  - ACE inhibitors and angiotensin II receptor blockers

Chronic Complications

- **Foot Ulcers**
  - Peripheral arterial disease causes ischemia to the lower limbs.
  - This decreased blood flow deprives the tissues of oxygen and nutrients and impairs the ability of the immune system to function adequately
  - Loss of sensation in the feet due to neuropathies allows trauma to go unnoticed.
  - Daily visual examination of the feet

Pathogenesis



Diabetic Foot Ulcer

Patient Counselling:

1. Avoid activities that can injure the feet
2. Use care when trimming the nails
3. Wash and check the feet daily
4. Choose socks and shoes carefully
5. Routine foot exams

THYROID DISORDERS

Hyperthyroid Disorders (Thyrotoxicosis)

- **Classifications**

a) Toxic diffuse goiter (Graves' disease):

- Most common hyperthyroid disorder
- Autoimmune disorder:
  - Thyroid-stimulating antibodies directed at thyrotropin receptors mimic thyroid-stimulating hormone (TSH) and stimulate triiodothyronine (T3), thyroxine (T4) production

b) Pituitary adenomas:

- Produce excessive TSH secretion that does not respond to normal T3 negative feedback

c) Toxic adenoma:

- Nodule in thyroid, autonomous of pituitary and TSH

Hyperthyroid Disorders (Thyrotoxicosis)

e) Toxic multinodular goiter (Plummer disease)

f) Painful subacute thyroiditis:

- Self-limiting inflammation of the thyroid gland caused by viral invasion of the parenchyma,
- Result in the release of stored hormone

g) Drug induced

- Excessive exogenous thyroid hormone dosages,
- Amiodarone therapy

Diagnosis

- Elevated free T4 serum concentrations
- Suppressed TSH concentrations (except in TSH-secreting adenomas)
- Radioactive iodine uptake
  - Elevated
    - Thyroid gland is actively and excessively secreting T4 and/or T3:
      - Graves' disease, TSH-secreting adenoma, toxic adenoma, multinodular goiter
  - Suppressed
    - Caused by thyroiditis or hormone ingestion

Clinical presentation

- Weight loss or increased appetite
- Lid lag
- Heat intolerance
- Goiter
- Fine hair
- Heart palpitations or tachycardia
- Nervousness, anxiety, insomnia
- Menstrual disturbances (lighter or more infrequent menstruation, amenorrhea) caused by hypermetabolism of estrogen
- Sweating or warm, moist skin
- Exophthalmos, pretibial myxedema in Graves' disease

Management of Hyperthyroidism

- **Therapy goals**
  - Minimize or eliminate symptoms, improve quality of life.
  - Minimize long-term damage to organs
    - Heart disease
    - Arrhythmias
    - Sudden cardiac death
    - Bone demineralization
    - Fractures
  - Normalize free T4 and TSH concentrations

Management of Hyperthyroidism

1. Ablative therapy:

- Treatment of choice for Graves' disease, toxic nodule, multinodular goiter
- According to patient preferences or comorbidities
  - Radioactive iodine ablative therapy
  - Surgical resection for adenomas.
- Ablative therapy often results in hypothyroidism

Management of Hyperthyroidism

2. Antithyroid pharmacotherapy usually reserved for

i. Those awaiting ablative therapy or surgical resection

   (a) Depletes stored hormone

   (b) Minimizes risk of post-treatment hyperthyroidism caused by thyroiditis

ii. Those who are not an ablative or surgical candidates

   a) Serious cardiovascular disease,

   b) Candidate unlikely to be adherent to radiation safety

iii. When ablative therapy or surgical resection fails to normalize thyroid function

Management of Hyperthyroidism

iv. Those with a high probability of remission with oral therapy for Graves' disease:
    a) Mild disease
    b) Small goiter
    c) Low or negative antibody titers
v. Those with limited life expectancy
vi. Those with moderate to severe active Graves' ophthalmopathy

Thioureas

- Inhibit iodination and synthesis of thyroid hormones; PTU may block T4/T3 conversion in the periphery as well

(a) PTU

(1) Preferred agent in pregnant women in the 1st trimester

(2) Dose:

- Initial: 100 mg by mouth three times daily
- Maximal: 400 mg three times daily
- Once euthyroid, may reduce to 50 mg 2-3 times daily

(b) Methimazole

(1) Preferred agent, except in pregnant women (1st trimester)

(2) Dose:

Thioureas

- Therapy duration: usually 12 – 18 months
- Adverse effects
  - Hepatotoxicity risk with PTU: Baseline LFT
  - Rash
  - Arthralgias, lupus-like symptoms
  - Fever
  - Agranulocytosis: Baseline CBC

Nonselective β-blockers (propranolol)

- Blocks many hyperthyroidism manifestations mediated by β-adrenergic receptors
  - Used primarily for symptomatic relief (palpitations, tachycardia, tremor, anxiety)
- Also block T4 (less active) conversion to T3 (more active)
- Dosing
  - Initial: 20–40 mg by mouth three or four times daily
  - Maximal: 240–480 mg/day
- Alternatives to β-blockers: Clonidine, nondihydropyridine calcium channel blocker

Iodine and iodides

- Inhibits the release of stored thyroid hormone.
- Minimal effect on hormone synthesis.
- Helps decrease vascularity and size of gland before surgery.
- Dosing: 120–400 mg split three times daily
  (a) Lugol’s solution (6.3–8 mg iodide per drop)
  (b) Saturated solution of potassium iodide (38–50 mg iodide per drop)
  (c) Potassium iodide tablets: (130-mg tablets contain 100 mg of iodide)

Iodine and iodides

- Adverse effects
  - (a) Hypersensitivity
  - (b) Metallic taste
  - (c) Soreness or burning in mouth or tongue
  - (d) Do not use in the days before ablative iodine therapy (may reduce uptake of radioactive iodine).

Thyroid Storm

- Severe and life-threatening decompensated thyrotoxicosis.
- Mortality rate may be as high as 20%.
- Precipitating causes:
  - Trauma
  - Infection
  - Antithyroid agent withdrawal
  - Severe thyroiditis
  - Postablative therapy (especially if inadequate pretreatment)
- Presentation:
  - Fever, tachycardia, vomiting, dehydration, coma, tachypnea, delirium

Management of Thyroid Storm

1) PTU: 500-1000-mg loading dose, then 250 mg Q4 hours
   - Blocks new hormone synthesis
2) Alternative: methimazole 60–80 mg daily
3) Iodide therapy 1 hour after PTU initiation
4) β-Blocker therapy: Propranolol to control symptoms and block conversion of T4 to T3
5) Paracetamol as antipyretic therapy, if needed (avoid NSAIDs)
6) Corticosteroid therapy: Prednisone 300 mg IV loading dose then 100 mg every 8 hours (Dexamethasone, hydrocortisone).
   - Prophylaxis against relative adrenal insufficiency and may block conversion of T4 to T3.

Case Study

A 43-year-old woman has received a diagnosis of Graves' disease. She is reluctant to try ablative therapy and wants to attempt oral pharmacotherapy first. Her thyroid laboratory values today include TSH 0.22 mIU/L (normal 0.5–4.5 mIU/L) and a free T4 concentration of 3.2 ng/dL (normal 0.8–1.9 ng/dL). She is anxious and always feels warm when others say it is too cold. Which would be considered the best drug for initial treatment of her condition?

A. Lugols solution
B. PTU
C. Atenolol

Hypothyroid Disorders

Classification

a) **Hashimoto's disease**: Most common hypothyroid disorder in areas with iodine sufficiency
   - Autoimmune-induced thyroid injury resulting in decreased thyroid secretion
   - Disproportionately affects women

b) **Iatrogenic:** Thyroid resection or radioiodine ablative therapy for treatment of hyperthyroidism

c) **Iodine deficiency:** most common cause worldwide

d) **Secondary causes**

   (i) **Pituitary insufficiency** (failure to produce adequate TSH secretion, **central** or **secondary hypothyroidism**)

   (ii) **Drug induced** (amiodarone, lithium)

Diagnosis of Hypothyroidism

a) Low free T4 serum concentrations

b) Elevated TSH concentrations, usually above 10 mIU/L (normal or low if **central hypothyroidism** is the etiology)

c) Thyroid antibodies such as **antithyroid peroxidase** and ***antithyroglobulin*** autoantibodies

d) Screen patients older than 60, especially women

Clinical Presentation

- Cold intolerance
- Dry skin
- Fatigue, lethargy, weakness
- Weight gain
- Bradycardia
- Slow reflexes
- Coarse skin and hair
- Periorbital swelling
- Menstrual disturbances (more frequent or longer menstruation, painful menstruation, menorrhagia) caused by hypometabolism of estrogen
- Goiter (primary hypothyroidism)

Management of Hypothyroidism

- Therapy goals
  - Minimize or eliminate symptoms; improve quality of life.
  - Minimize long-term damage to organs (myxedema coma, heart disease).
  - Normalize free T4 and TSH concentrations

Management of Hypothyroidism

Therapeutics

(a)Levothyroxine (drug of choice)

- Mechanism of action: Synthetic T4
- Dosing
  - ✓ Initial
    - In healthy adults, 1.6 mcg/kg per day.
    - In patients 50–60 years of age, consider 50 mcg/day.
    - In those with existing cardiovascular disease, consider 12.5–25 mcg/day
  - ✓ Dosage titration based on response
    - Can increase or decrease in 12.5- to 25-mcg/day increments

Management of Hypothyroidism

- **Adverse effects**
  - (a) Hyperthyroidism
  - (b) Cardiac abnormalities (tachyarrhythmias, angina, myocardial infarction)
  - (c) Linked to risk of fractures (usually at higher dosages or over supplementation)
- **Efficacy**
  - ✍ Considered drug of choice because of its adverse effect profile, cost, lack of antigenicity, and uniform potency

Myxedema Coma

- Severe and life-threatening decompensated hypothyroidism.
- Mortality rate 30%–60%
- Precipitating causes: Trauma, infections, heart failure, medications (e.g., sedatives, narcotics, anesthesia, lithium, amiodarone)
- Presentation: Coma is not required and is uncommon, despite terminology; altered mental state (very common); diastolic hypertension; hypothermia; hypoventilation

Myxedema Coma

Pharmacotherapy

(a)Intravenous thyroid hormone replacement

- T4: 100- to 500-mcg loading dose, followed by 75–100 mcg/day,
- T3 may be preferred over T4,
  - T3 is more biologically active
  - T4/T3 conversion may be suppressed in myxedema coma
    - Cost and availability limit intravenous T3

(b)Antibiotic therapy: empiric therapy with broad spectrum antibiotics

(c)Corticosteroid therapy

- Hydrocortisone 100 mg every 8 hours (or equivalent steroid)

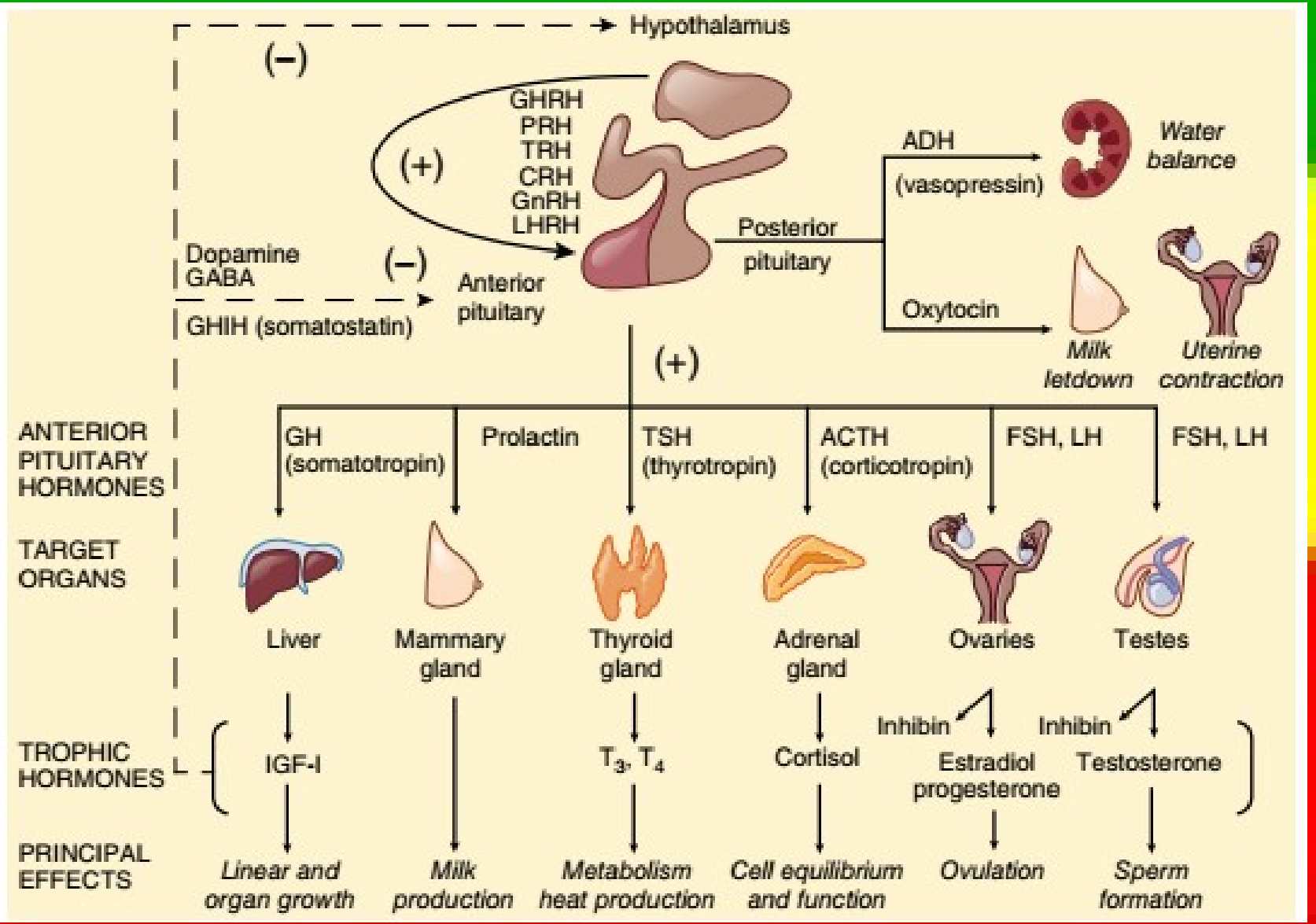
Case Study

A 63-year-old woman has Hashimoto's disease. Her thyroid laboratory values today include the following: TSH 10.6 mIU/L (normal 0.5–4.5 mIU/L) and a free T4 concentration of 0.5 ng/dL (normal 0.8–1.9 ng/dL). She feels consistently run down and has dry skin that does not respond to the use of hand creams. Which would be considered the best drug for initial treatment of her condition?

A. Levothyroxine.
B. Liothyronine.
C. Desiccated thyroid.
D. Methimazole.

PITUITARY GLAND DISORDERS

Hypothalamic–Pituitary–Target-organ Axis



Anterior Pituitary Gland Hormones

Anterior Pituitary Hormone	Primary Functions	Hypothalamic Stimulator	Primary Secretion Inhibitor
GH	Promote tissue growth	GHRH	Somatostatin Elevated insulin-like growth factor-1
ACTH	Stimulate adrenal cortisol and androgen release	CTRH	Cortisol
TSH	Metabolic stability	TRH	Triiodothyronine
Prolactin	Regulate lactation	TRH	Dopamine
FSH	Maturation of ovarian follicles Sperm production	GTRH	Inhibin Estrogens

Pituitary Gland Disorders

- **Classification**

1. Hypersecretory diseases

a) Acromegaly and gigantism

b) Hyperprolactinemia

2. Hyposecretory disease

a) GH deficiency

b) Panhypopituitarism

Acromegaly

- Usually caused by growth hormone (GH)-secreting pituitary adenoma
- Clinical presentation
  i. Excessive sweating
  ii. Osteoarthritis, joint pain, paresthesias, or neuropathies
  iii. Coarsening of facial features
  iv. Increased hand volume or ring size, increased shoe size
  v. Hypertension, heart disease, cardiomyopathy
  vi. Sleep apnea
  vii. Type 2 diabetes mellitus (DM)

Acromegaly

- Therapeutics
  - Treatment of choice is **surgical resection** of tumor, if causative.
  - Pharmacotherapy
    - Dopamine agonists (e.g., bromocriptine, cabergoline
    - Somatostatin analog (e.g., octreotide)
    - GH receptor antagonist (e.g., pegvisomant)

Hyperprolactinemia

- Causes
  - ✍Direct: Pituitary tumor (lactotroph adenoma)
  - ✍Indirect: Drug induced (most frequent nontumor cause), renal failure, hypothyroidism, breastfeeding
    - Potential causative drugs: Typical antipsychotics, opiates, nondihydropyridine CCBs, antidepressant

Hyperprolactinemia

- Clinical presentation
  - Amenorrhea, anovulation, infertility, hirsutism, and acne in women
  - Erectile dysfunction, decreased libido, gynecomastia, and reduced muscle mass in men
  - Headache, visual disturbances, bone loss

Hyperprolactinemia

- Therapeutics
  - Treatment of choice is surgical resection of tumor, if causative
  - Pharmacotherapy
    - Dopamine agonists
      i. Cabergoline: preferred
      ii. Bromocriptine

GH deficiency

- Clinical presentation
  - Delayed growth velocity or short stature
  - Central obesity
  - Immaturity of the face or prominence of the forehead
- Therapeutics: Recombinant GH (somatropin)

Panhypopituitarism

- Result of partial or complete loss of anterior and posterior pituitary function.
- Can be caused by
  - Primary pituitary tumor,
  - Ischemic necrosis of the pituitary,
  - Trauma from surgery, or irradiation.
- Results in
  - Adrenocorticotropic hormone (ACTH) deficiency,
  - GH deficiency,
  - Hypothyroidism,
  - Gonadotropin deficiency

Panhypopituitarism

- **ACTH Deficiency**
  - hydrocortisone or other glucocorticoid
- **TSH Deficiency**
  - Levothyroxine
- **LH and FSH Deficiency**
  - Men: Testosterone replacement
  - Women: estrogen-progestin replacement
- **Growth Hormone Deficiency**
  - Recombinant human growth hormone preparations
- **Prolactin Deficiency**
  - Recombinant human prolactin

Thank You

Menstruation Related Disorders

Chapter Five

Menstrual Disorders

- Amenorrhea
- Menorrhagea
- Dysmenorrhea
- Premenstrual Syndrome (PMS) and
- Premenstrual Dysphoric Disorder (PMDD)
- Hormone Therapy and Menopause

Terms frequently used to describe abnormal uterine bleeding

- **Menorrhagia** - Prolonged (>7 days) or *excessive* (>80 mL daily) uterine bleeding occurring at *regular intervals*
- **Metrorrhagia** - Uterine bleeding occurring at *irregular* and *more frequent* than normal intervals
- **Menometrorrhagia** - *Prolonged* or *excessive* uterine bleeding occurring at *irregular* and *more frequent* than normal intervals
- **Intermenstrual bleeding** - Uterine bleeding of variable amounts occurring between regular menstrual periods
- **Midcycle spotting** - Spotting occurring just before ovulation, typically from declining estrogen levels
- **Postmenopausal bleeding** - Recurrence of bleeding in a menopausal woman at least 6 months to 1 year after cessation of cycles
- **Amenorrhea** - No uterine bleeding for 6 months or longer

1. AMENORRHEA

- Either primary or secondary
- **Primary amenorrhea** is
  - ✍The absence of menses by age 16 years in the presence of normal secondary sexual development or
  - ✍The absence of menses by age 14 in the absence of normal secondary sexual development.
- **Secondary amenorrhea** is
  - ✍The absence of menses for 6 months in a previously menstruating woman.

Pathophysiology

- **Uterus**:
  - Asherman’s syndrome
    - Postcurettage/postsurgical uterine adhesions
  - Congenital uterine abnormalities
    - Abnormal uterine development
- **Ovaries:**
  - Turner’s syndrome
    - Lack of ovarian follicles
  - Gonadal dysgenesis
    - Other genetic abnormalities
  - Premature ovarian failure
    - Early loss of follicles
  - Chemotherapy/radiation
    - Gonadal toxins

Pathophysiology

- **Anterior pituitary**
  - Pituitary prolactin-secreting adenoma
    - ✓ ↑ Prolactin suppresses HPO axis
  - Hypothyroidism
    - ✓ TRH causes ↑prolactin, other abnormalities
  - Medication (antipsychotics)
    - ✓ ↑Prolactin suppresses HPO axis
- **Hypothalamus**
  - "Functional" hypothalamic amenorrhea
    - ✓ ↓Pulsatile GnRH secretion in the absence of other abnormalities
  - Eating disorder
    - ✓ ↓Pulsatile GnRH secretion, ↓FSH and LH secondary to weight loss
  - Exercise
    - ✓ ↓Pulsatile GnRH secretion, ↓FSH and LH secondary to low body fat
  - Anovulation/PCOS
    - ✓ Asynchronous gonadotropin and estrogen production, abnormal endometrial growth

Clinical Presentation

- **Symptoms**
  - ✓ Cessation of menses
  - ✓ Possible complaints of infertility, vaginal dryness, decreased libido
- **Signs**
  - ✓ Cessation of menses for longer than 6 months in women with established menstruation, or
  - ✓ Absence of menses by age 16 in the presence of normal secondary sexual development, or
  - ✓ Absence of menses by age 14 in the absence of normal secondary sexual development
  - ✓ Recent significant weight loss or weight gain
  - ✓ Presence of acne, hirsutism, hair loss, or acanthosis nigricans may suggest androgen excess.

Laboratory Tests

- Pregnancy test
- TSH
- Prolactin
- If suspect PCOS, consider free or total testosterone, 17-hydroxyprogesterone, fasting glucose, and fasting lipid panel.
- If suspect premature ovarian failure, consider FSH and LH.
- Other Tests
  - ✓ Pelvic **ultrasound** to evaluate for polycystic ovaries

Treatment

Goals of therapy

- To restore the normal menstrual cycle
- Preservation of **bone density**, prevention of **bone loss**, and restoration of **ovulation**, thus improving **fertility** as desired
- Improve **QoL** related with;
  - ✓**Hot flashes** (premature ovarian failure),
  - ✓**Dyspareunia**, and,
  - ✓Lack of secondary sexual characteristics and absence of menarche (in prepubertal females)

Nonpharmacologic Therapy

- Amenorrhea secondary to **anorexia** may respond to **weight gain**.
- In young women for whom excessive exercise is an underlying cause, a **reduction in exercise** is recommended.

Pharmacologic Therapy

- **Estrogen/Progestin Replacement Therapy**
  - To reduce the risk of osteoporosis and
  - To improve quality of life.
  - Oral contraceptive (OC), conjugated equine estrogen, or estradiol patch
- **Hyperprolactinemia**
  - **Bromocriptine**, a dopamine agonist
- **PCOS** may respond to agents that reduce insulin resistance.
  - Metformin and the thiazolidinediones.

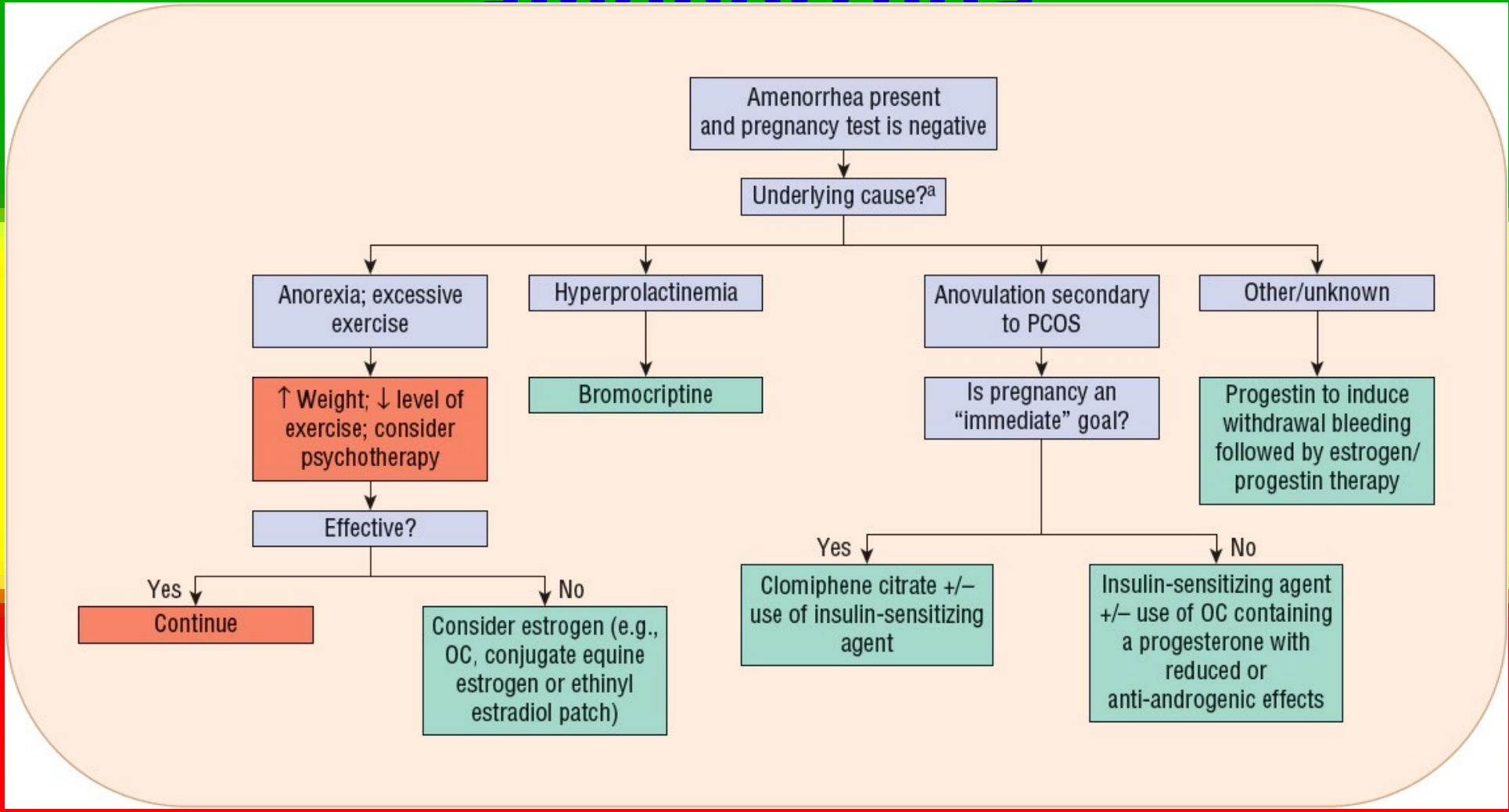
Pharmacologic Therapy

Causes	Drugs	Dose	Side effects
1^0, 2^0	Ethinyl estradiol patch	50 mcg/24 hours	tenderness, bloating, nausea
1^0, 2^0	Combination OC	30–40 mcg formulations	gastrointestinal (GI) upset, headache, peripheral edema
2^0	Oral medroxyprogesterone acetate	5–10 mg by mouth on days 14–25 of the cycle	Edema, anorexia, depression, insomnia, weight gain or loss, increase in serum total and LDL cholesterol, may reduce HDL cholesterol
Hyper-prolactine	Bromocriptine	2.5 mg by mouth 2–3	Hypotension, nausea, constipation,

Pharmacologic Therapy

Causes	Drugs	Dose	Side effects
PCOS	Clomiphene	50 mg by mouth daily × 5 days starting 3–5 days after the start of menses	Hot flashes, ovarian enlargement thromboembolism, blurred vision, breast enlargement
	Metformin	1500–2000 mg by mouth daily in 2–3 divided doses	Anorexia, nausea, vomiting, diarrhea, flatulence, lactic acidosis

Treatment algorithm for amenorrhea



[a] Regardless of cause, adequate calcium and vitamin D intake must be ensured. (OC, oral contraceptive; PCOS,

2. MENORRHAGIA

- Menstrual blood loss greater than 80 mL per cycle.

✓Difficulty quantifying menstrual loss in clinical practice.

⇒**“heavy menses”**

Pathophysiology

- **Hematologic:**
  - von Willebrand's disease
    - Factor VII defect causing impaired platelet adhesion and increased bleeding time
  - Idiopathic thrombocytopenic purpura
    - Decrease in circulating platelets
- **Hepatic**
  - Cirrhosis
    - Decreased estrogen metabolism, underlying coagulopathy
- **Endocrine**
  - Hypothyroidism
    - Alterations in HPO axis
- **Uterine**
  - Fibroids: Alteration of endometrium, changes in uterine contractility
  - Adenomyosis: Alteration of endometrium, changes in uterine contractility
  - Endometrial polyps: Alteration of endometrium
  - Gynecologic cancers: Various dysplastic alterations of endometrium, uterus, cervix

Clinical presentation

- Symptoms
  - Heavy/prolonged menstrual flow and fatigue and light-headedness in the case of severe blood loss.
- Signs
  - **Orthostasis**, **tachycardia**, and **pallor** may be noted, especially in cases of significant acute blood loss.

Laboratory Tests

- CBC and ferritin levels; Hgb and hematocrit results may be low.
- If the history dictates, testing may be done to identify coagulation disorder(s) as a cause.
- Other Diagnostic Tests
  - Pelvic ultrasound
  - Pelvic magnetic resonance imaging (MRI)
  - Pap smear
  - Endometrial biopsy
  - Hysteroscopy
  - Sonohysterogram

TREATMENT

- Desired Outcome
  - ✍Reduce menstrual blood flow,
  - ✍Improve the patient’s quality of life, and
  - ✍Defer the need for surgical intervention

TREATMENT

- Nonpharmacologic Therapy
  - ✍Surgical interventions
    - Conservative endometrial ablation
    - Hysterectomy

Pharmacologic Therapy

- NSAIDs
  - First-line treatments for menorrhagia associated with ovulatory cycles.
  - Advantage
    - Being taken only during menses, and their use is associated with a significant reduction in menstrual blood loss
    - A 20% to 50% reduction in blood loss
  - Mechanism
    - Inhibits prostaglandin release that occurs with menses, thus **reducing inflammatory response** contributing to dysmenorrhea
  - Significant Side Effects
    - Gastrointestinal upset, stomach ulcer, nausea, vomiting, heartburn, indigestion, rash, dizziness

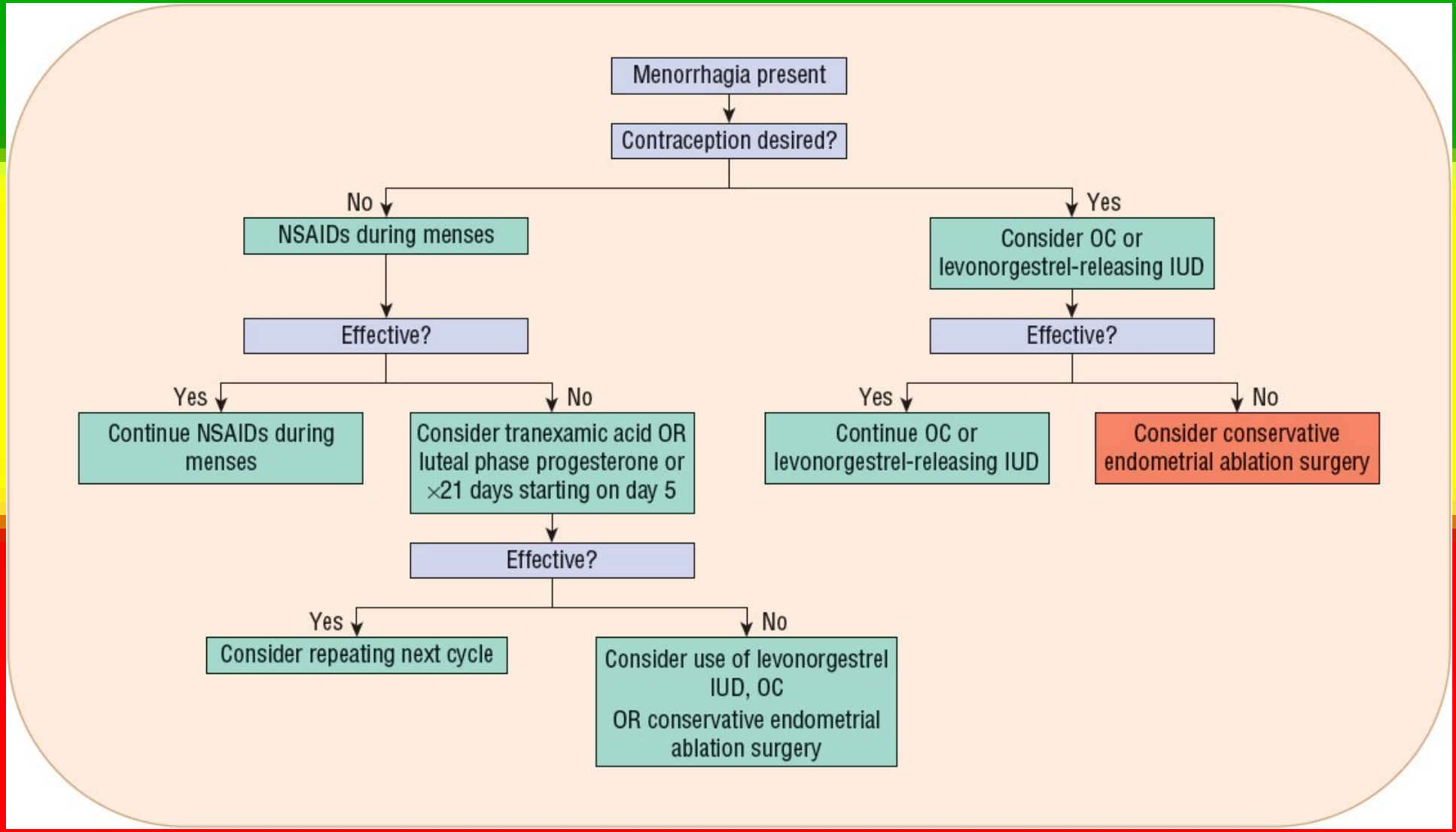
Pharmacologic Therapy

- OCs
  - Advantage
    - Beneficial in women with menorrhagia who do not desire pregnancy
    - A 43% to 53% reduction in menstrual blood loss
  - Mechanism
    - Exogenous estrogen and progesterone that suppresses FSH and LH production and thus inhibits ovulation
    - Can be used to reduce menstrual flow menorrhagia secondary to hypoestrogenism
  - Significant side effects
    - Thromboembolism,
    - Breast enlargement, breast tenderness,
    - Bloating, nausea, gastrointestinal upset,
    - Headache,
    - Peripheral edema

Pharmacologic Therapy

- Levonorgestrel releasing intrauterine device (IUD)
  - Advantage:
    - Very effective treatment that consistently reduces menstrual flow by 90% or greater
  - Mechanism:
    - Suppresses FSH and LH and ultimately estrogen and progesterone, inhibiting the usual growth of the endometrium
  - Significant side effects
    - Irregular menses, amenorrhea

Treatment algorithm for menorrhagia



3. Dysmenorrhea

Definition

- Crampy pelvic pain occurring with or just prior to menses,
- Pain usually radiating to the back and legs,
- Often accompanied by GI & neurological symptoms.

Epidemiology:

- Ranges from 20% to 90%.
- May be associated with significant interference in work and school attendance.

Etiology

✍Primary & Secondary dysmenorrhea

- **Primary dysmenorrhea** implies pain in the setting of normal pelvic anatomy and physiology.
- **Secondary dysmenorrhea** is associated with underlying pelvic pathology.

Pathophysiology

- **Primary dysmenorrhea**
  - Release of prostaglandins *and* leukotrienes into the menstrual fluid, initiating an inflammatory response and possibly vasopressin-mediated vasoconstriction.
- **Secondary dysmenorrhea**
  - Cervical stenosis, endometriosis, pelvic infections, pelvic congestion syndrome, uterine or cervical polyps, uterine fibroids, genital outflow tract obstructions, and pelvic adhesions.

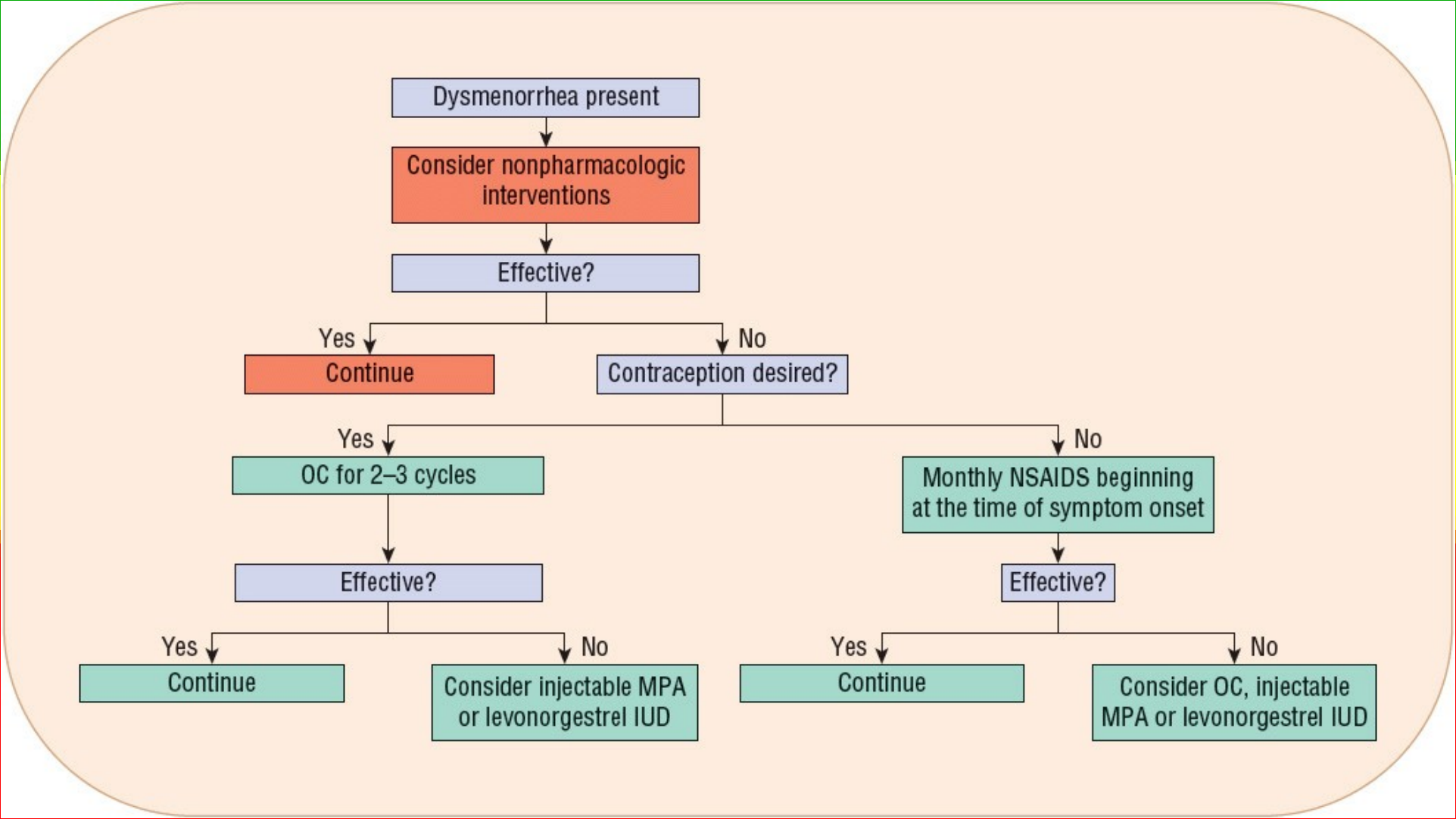
Clinical Presentation

- **Symptoms**
  - Patients complain of crampy pelvic pain beginning shortly before or at the onset of menses.
  - Symptoms typically last from 1 to 3 days.
  - Nausea, vomiting, diarrhea, and headache
- **Laboratory Tests**
  - Pelvic examination to screen for STD as a cause of the pain in sexually active females.
  - Gonorrhea, Chlamydia cultures or polymerase chain reaction, wet mount
- **Diagnostic Tests**
  - Pelvic US to identify potential anatomic abnormalities such as masses/lesions or to detect ovarian cysts and endometriomas

Management

- **Nonpharmacologic**
  - Topical heat therapy, exercise, and a low-fat vegetarian diet have been shown to reduce the intensity of dysmenorrhea
- **Pharmacologic**
  - NSAIDs
  - Oral contraceptives
  - Depot medroxyprogesterone acetate(MPA)
  - Levonorgestrel-releasing IUD

Treatment algorithm for dysmenorrhea



Agents	Dose recommendation	Common side effects
NSAIDs	***Diclofenac*** 50 mg by mouth 3 times daily; ***ibuprofen*** 800 mg by mouth 3 times daily; ***mefenamic acid*** 500 mg by mouth as a loading dose, then 250 mg by mouth up to 4 times daily as needed; ***Naproxen*** 550-mg loading dose by mouth started 1–2 days prior to menses followed by 275 mg by mouth every 6–12 hours as needed. Treatment should begin 1–2 days prior to the suspected onset of menses.	Gastrointestinal upset, stomach ulcer, nausea, vomiting, heartburn, indigestion, rash, dizziness
Combined OC	Less than 35 mcg formulations + ***norgestrel*** or ***levonorgestrel***; use of extended cycle formulations is beneficial.	Thromboembolism, breast enlargement, breast tenderness, bloating, nausea, gastrointestinal upset, headache, peripheral edema
Depo MPA	150 mg intramuscularly every 12 weeks	Edema, anorexia, depression, insomnia, weight gain or loss, increase in serum total and LDL cholesterol, may reduce HDL cholesterol.
Levonorges	20 mcg released daily	Irregular menses,

and
Premenstrual Dysphoric Disorder (PMDD)

- **Definition**
  - **PMS** is a combination of symptoms including mild mood disturbance *and* physical symptoms that occur prior to menses and resolve with initiation of menses.
  - **PMDD** is more sever premenstrual condition with markedly depressed mood, anxiety, irritability associated with functional impairment.

Epidemiology

Epidemiology

- Up to 75% of menstruating women experience symptoms of PMS.
- Approximately 3% to 8% of women have PMDD.

Etiology & Pathophysiology

- Theories to explain the etiology & pathophysiology of PMS & PMDD include:
  - Ovarian hormone hypothesis
  - Serotonin hypothesis
  - Psychosocial hypothesis
  - Cognitive and social learning theory
  - Sociocultural theory

Etiology & Pathophysiology

- The serotonin theory was postulated because patients who are:
  - PMDD shares many of the *features of depression and anxiety states* that have been linked to serotonergic dysregulation.
  - Most affected PMS patients have *decreased serotonin levels.*
  - Symptoms of PMS/PMDD *respond to selective serotonin reuptake inhibitors* (SSRIs), which increase the amount of circulating serotonin.

Clinical Presentation

- PMS
  - Mild to moderate physical symptoms, such as breast tenderness, abdominal pain or bloating and mild mood changes during the luteal phase of ovulation, with resolves when menses begins.
- PMDD
  - Symptoms are temporally associated with the last week of the luteal phase and remit with onset of menses.
  - At least five of the following symptoms are present

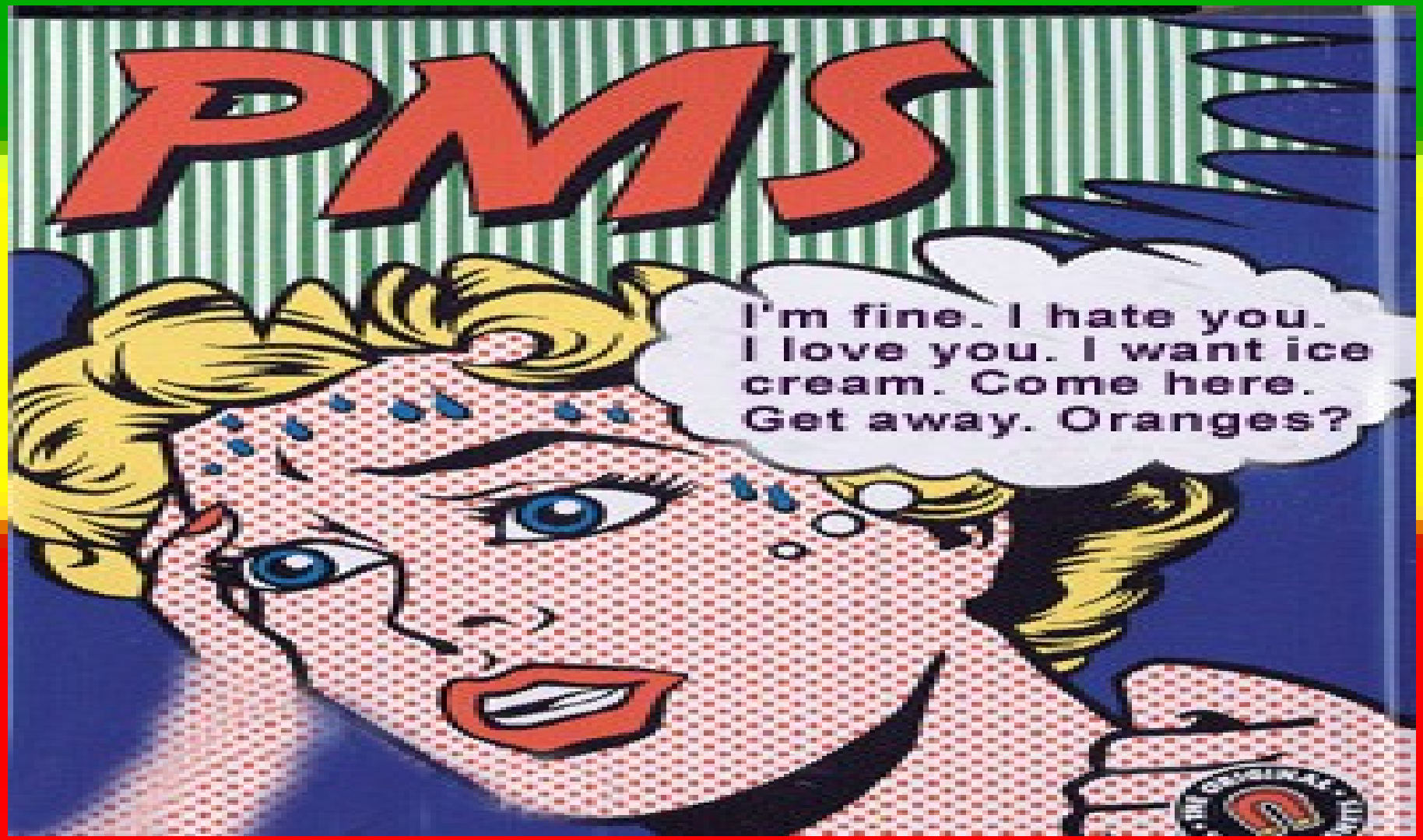
Clinical Presentation

- Markedly depressed mood
- Marked anxiety
- Marked affective lability
- Marked anger or irritability
- Feelings of being overwhelmed
- Physical symptoms, such as breast tenderness or bloating
- Difficulty concentrating
- Changes in appetite
- Sleep disturbance
- Fatigue
- Decreased interest in activities

Clinical Presentation

- One of the symptoms must be markedly depressed mood, anxiety, irritability, *or* affective lability.
- Symptoms interfere significantly with work and/or social relationships.
- Symptoms are not an exacerbation of another underlying psychiatric disorder.
- The criteria are confirmed prospectively by daily ratings over two menstrual cycles.

Clinical Presentation



Treatment

- **Nonpharmacologic**
  - Diet, exercise, relaxation training, light therapy, sleep deprivation, and cognitive-behavioral approaches.
- **Pharmacologic**
  - *Gonadotropin-releasing hormone* (GnRH) agonists (Leuprolide, nafarelin)
  - Combination oral contraceptives

Treatment

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Anxiolytics, antidepressants, and mood stabilizers (SSRIs)
  - First line pharmacologic treatment options for PMDD.
  - Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline
  - TCA (Clomipramine, Nortriptyline), alternative to SSRI.

Drugs	Dose recommendation	Common side effects
SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	Citalopram 10–30 mg; escitalopram 10–20 mg; fluoxetine 10–20 mg; fluvoxamine 50 mg; paroxetine 10–30 mg; sertraline 25–150 mg; all agents are given by mouth daily and can be dosed either continuously or during the luteal phase only.	Sexual dysfunction (reduced libido, anorgasmia), insomnia, sedation, weight gain, hypersomnia, nausea, diarrhea
TCA, Clomipramine	25–75 mg by mouth daily taken either continuously or only during the luteal phase.	Dry mouth, fatigue, vertigo, sweating
Drospirenone containing OC	Drospirenone 3 mg (+ 30 mcg ethinyl estradiol) by mouth on days 1–21 of the menstrual cycle	Thromboembolism, breast enlargement, breast tenderness, bloating, nausea, gastrointestinal upset, headache,

HORMONE THERAPY AND MENOPAUSE

- **Definition**: Cessation of menstrual periods for 1 year, also known as final menstrual period, loss of ovarian follicular function
- Average age of menopause is 52 years,
  - but age ranges from 40 to 58 years.
- Common symptoms
  - Vasomotor symptoms, also known as **hot flashes**
  - Genitourinary syndrome of menopause (GSM)

HORMONE THERAPY AND MENOPAUSE

- Vasomotor symptoms, also known as hot flashes
  - ✍Most common reason for treatment
  - ✍May interrupt sleep and cause insomnia
  - ✍May affect quality of life
  - ✍Occur in 75%–85% of women, usually within 12–24 months after the last menstrual period.
  - ✍May cause increased skin temperature, nausea, dizziness, headache, palpitations, diaphoresis, and night sweats.

HORMONE THERAPY & MENOPAUSE

- Genitourinary syndrome of menopause (GSM):
  - ✍Decrease in estrogen causes thinning of hair of the mons and shrinkage of the labia minora; **vulvovaginal atrophy** (VVA) leads to pruritus and pain.
  - ✍Loss of lubrication leads to **dyspareunia** (pain during sexual intercourse).
  - ✍Vaginal pH changes and becomes more basic (from 4.5-5 to 6-8), creating a favorable environment for **bacterial colonization.**
  - ✍Thinning of urethra and bladder lining and decreased muscle tone result in recurrent episodes of urinary frequency, urgency with dysuria and urinary tract infections

HORMONE THERAPY & MENOPAUSE

- **Treatments**

✍Hormone therapy (HT): estrogen and progestogen therapy (EPT), estrogen-only therapy (ET), and estrogen-receptor (ER) agonists or antagonists

✍Serotonin reuptake inhibitors

✍Natural products: Soy isoflavones, Evening primrose oil, Black cohosh:

✍Others: Clonidine, Gabapentin, Pregabalin

Hormone Therapy

- **Indications for HT:**
  - ✍Treatment of moderate to severe vasomotor symptoms (VMS),
  - ✍Treatment of moderate to severe VVA because of menopause,
  - ✍Prevention of postmenopausal osteoporosis,
  - ✍Hypoestrogenism caused by hypogonadism,
  - ✍Castration or premature ovarian failure.

Hormone Therapy

Benefits and risks of estrogen and progestogens

✍ **Benefits of estrogen**

- Relieves genitourinary atrophy
- Relieves vasomotor instability
- Reduction in hip fractures by 25%; reduction in vertebral fractures by 50%
- Improve sleep by decreasing hot flashes.
- Stabilizes mood changes
- Decrease vaginal atrophy, thus decreasing pain with sexual intercourse.

Hormone Therapy

- **Risks of estrogen**
  - Endometrial cancer: Risk increases with unopposed estrogen use in women with an intact uterus.
  - Breast cancer with unopposed estrogen: Not recommended for use in women with a history of breast cancer
  - CHD: Possible increased risk of cardiovascular outcomes
  - Gallbladder effects: oral estrogen may increase risk of gallbladder disease
  - Other adverse effects: Bloating, headache, breast tenderness (5%–10%)

Hormone Therapy

- **Benefits of progestogen**
  - Decreased risk of estrogen-induced irregular bleeding, endometrial hyperplasia, and carcinoma
- **Risks of progestogen**
  - Adverse effects: Bloating, weight gain, irritability, depression (dose related)
  - Unpredictable endometrial bleeding with continuous estrogen/progestin during first 8–12 months (30–50%)

Hormone Therapy

- **Risk assessment for HT**
  - For women with a high risk of VTE: **non-oral route** HT at lowest effective dose
  - For women with a high risk or history of breast cancer: **nonhormonal treatment**
  - For women with a high risk of CVD: **nonhormonal treatment**
  - For women with a moderate risk of CVD: **transdermal estradiol with progestogen**

Hormone Therapy

- **Preparations: estrogen**
  - ✍Oral Estrogen Products: estradiol
  - ✍Vaginal Estrogen Products: estradiol
    - Viginal creams
    - Vaginal rings
    - Vaginal tablets
  - ✍Transdermal Estrogen Products: estradiol
    - Patches,
    - Gels,
    - Spray

Hormone Therapy

- Combination Products
  - Estradiol/norethindrone acetate
  - Estradiol/drospirenone
  - Estradiol/levonorgestrel
- Progestogen Products
  - Norethindrone
  - Megestrol acetate
  - Levonorgestrel
  - Progesterone gel
  - Medroxyprogesterone acetate

THANK YOU

UROLOGIC DISORDERS

CHAPTER SIX

UROLOGICAL DISORDERS

- **Erectile Dysfunction (ED)**
- **Benign Prostatic Hyperplasia (BPH)**

ERECTILE DYSFUNCTION (ED)

“Man survives earthquakes, experiences the horrors of illness, and all of the tortures of the soul. But the most tormenting tragedy of all time is, and will be, the tragedy of the bedroom.”

TOLSTOY

Objectives

- Describe the physiology of a penile erection
- Identify drug classes contribute to ED
- Evaluate patient with ED
- Describe the nonpharmacologic and pharmacologic options for ED
- Understand the benefits and risks of phosphodiesterase inhibitors
- Cardiovascular risk and recommendations

Erectile Dysfunction (ED)

- **Erectile dysfunction:** the failure to achieve a penile erection to allow for satisfactory sexual intercourse.

- Patients may refer to it as **impotence**.

Type of Sexual Dysfunction

Type of Dysfunction	Definition
Decreased libido	Decreased sexual drive or desire
Increased libido	Inappropriate and excessive sexual drive or desire
Erectile dysfunction (impotence)	Failure to achieve a penile erection suitable for satisfactory sexual intercourse
Delayed ejaculation	Commonly referred to as “dry sex”; ejaculation is delayed or absent
Retrograde	Ejaculate passes retrograde into the bladder, instead of toward the

EPIDEMIOLOGY

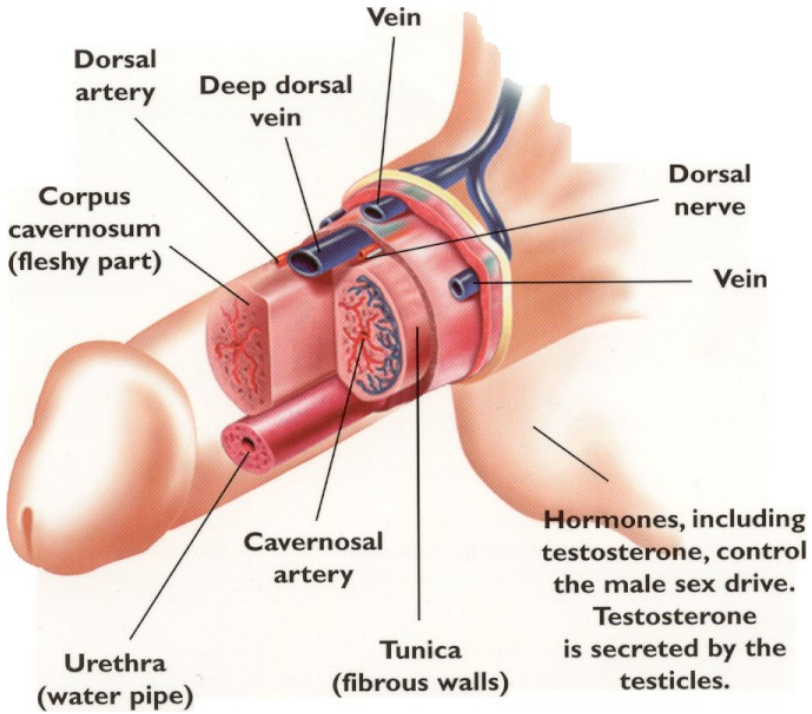
- Incidence is low in men younger than 40 years
- The Massachusetts Male Aging Study:
  - Prevalence of 52% for any degree of **DM** aged 40 to 70 yrs
  - Age-related
    - 12.4% in men aged 40 to 49 years
    - 46.4% in men aged 60 to 69 years.

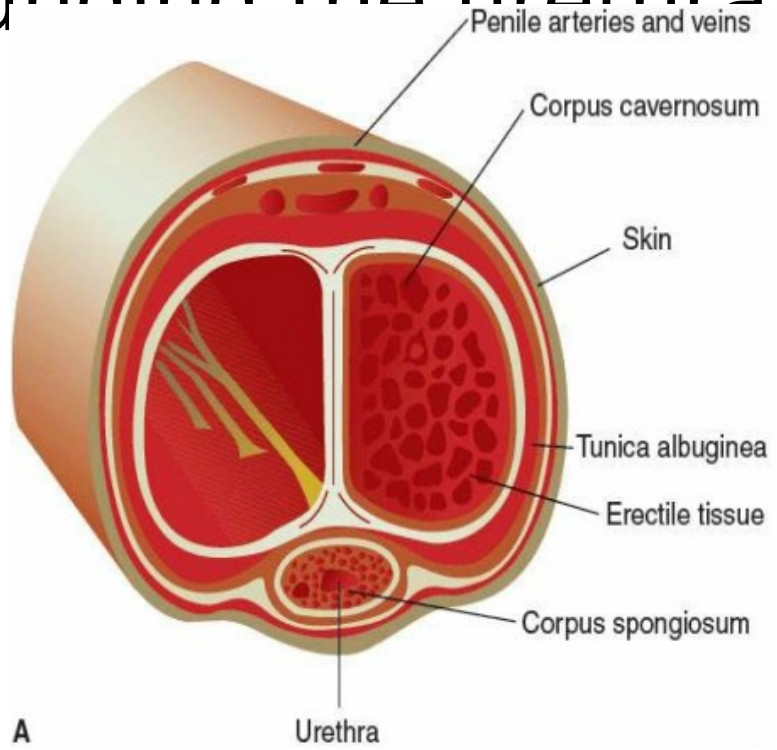
PHYSIOLOGY OF PENILE ERECTION

- A normal penile erection requires:
  - ↳**Vascular**, **nervous**, and **hormonal**.
- The patient also must be psychologically receptive to sexual stimuli.

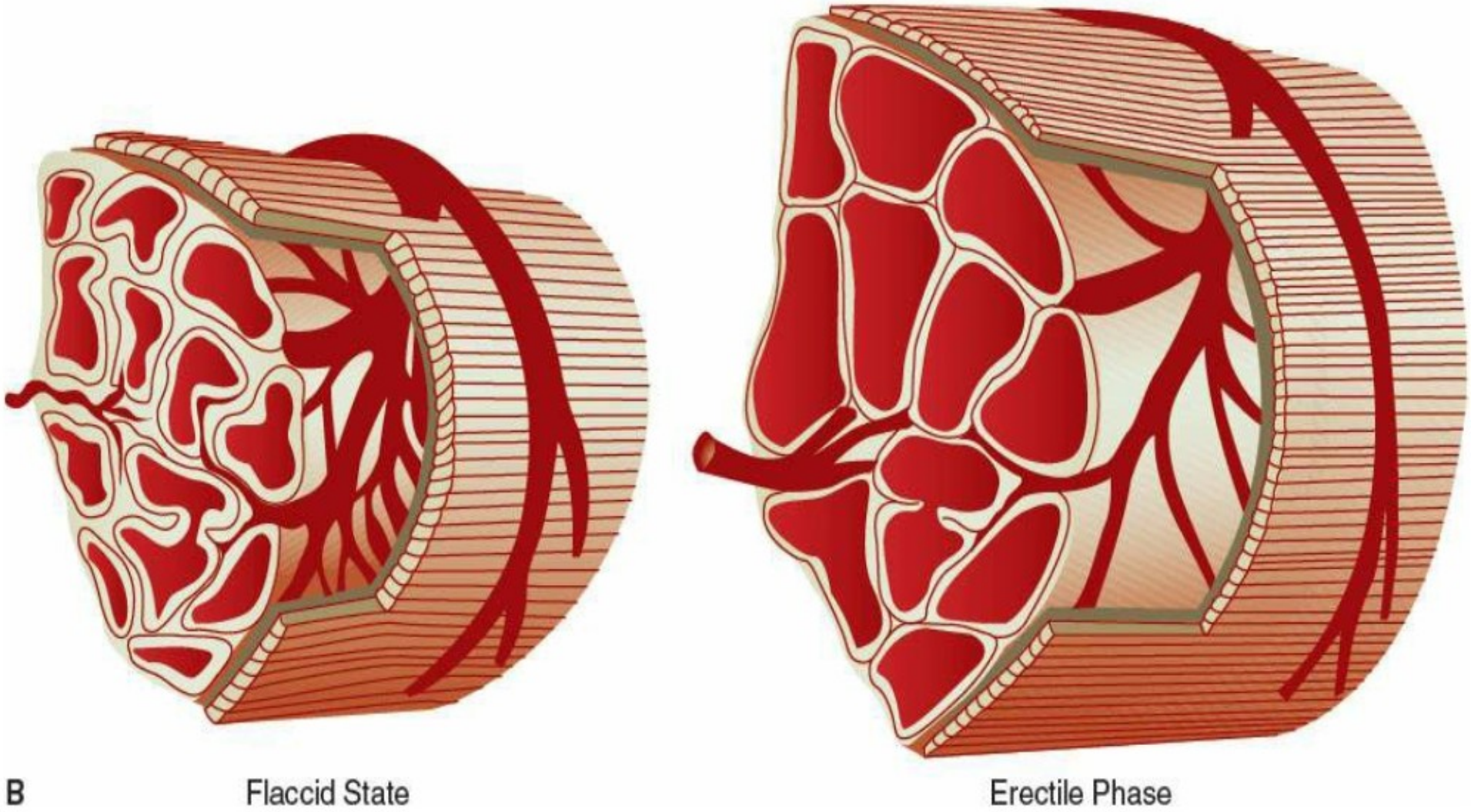
Vascular System

- 3 cylindrical erectile bodies: 2 paired corpora **cavernosa** and corpus **spongiosum** surrounding the urethra





Vascular changes in the penis in flaccid and erect states

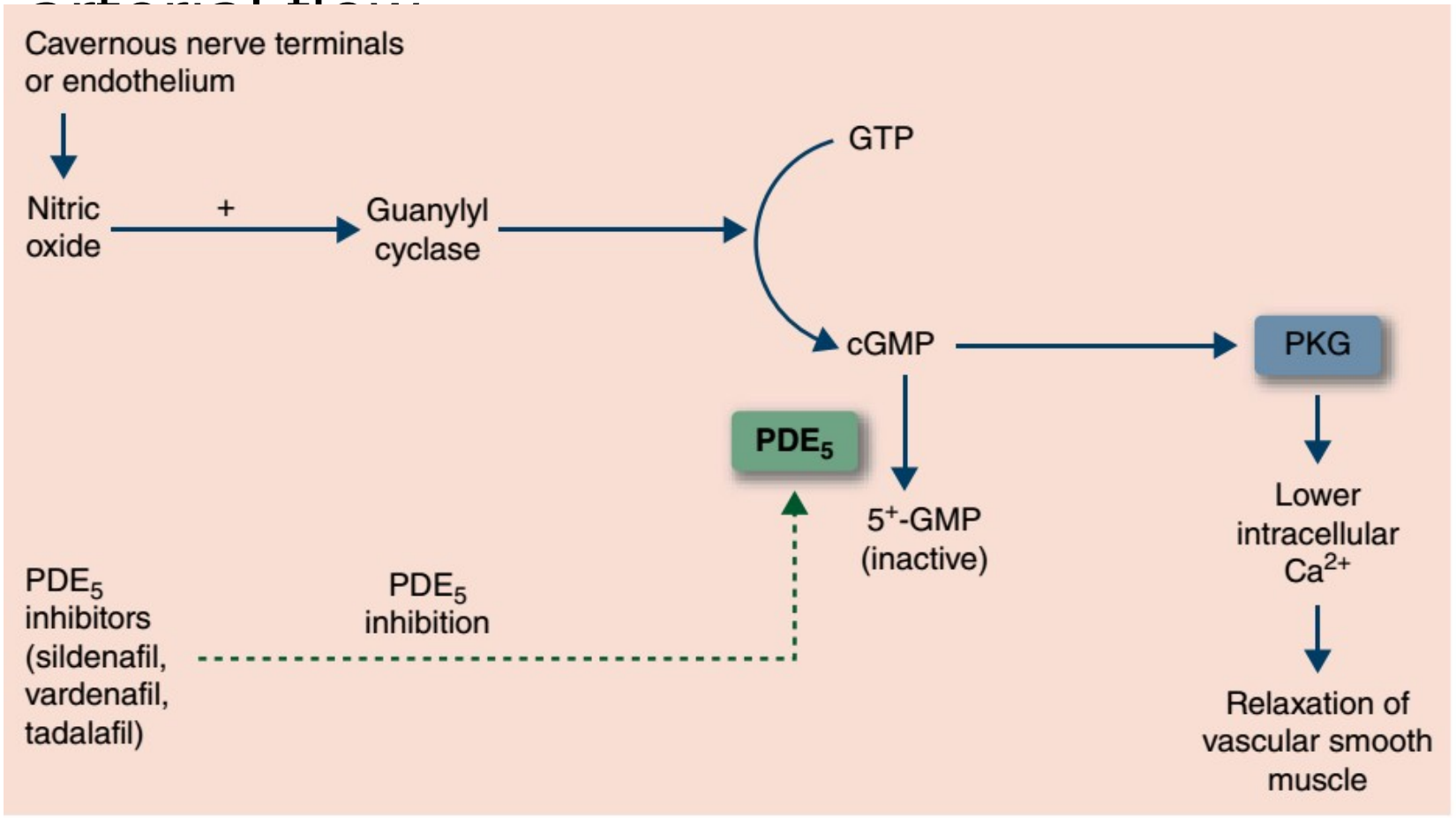


B Flaccid State

Erectile Phase

Vascular System

- Arterial flow is enhanced by acetylcholine
- Acetylcholine does not directly enhance arterial flow



Vascular system

- Release of neurotransmitters - Nitric oxide
- Conversion of GTP to cGMP – **Erection**
- Breakdown of cGMP by PDE type 5 – **Detumesence**

  ↳The reverse of erection, where by the erect penis or clitoris becomes flaccid after orgasm)

Hormonal System

- Testosterone stimulates libido or sexual drive in males.
- Within the normal physiologic serum concentration (normal 300 – 1,100 ng/dL), sexual drive is normal.
- Subphysiologic serum testosterone:
  - ↳Patients complain of loss of energy, loss of muscle strength, depressive mood, and decreased libido.
- **Relationship between erectile dysfunction and testosterone is**

PATHOPHYSIOLOGY

- **Organic erectile dysfunction**: Vascular, neurologic, or hormonal etiologies (80%)

- Patients who do not respond to psychogenic stimuli have **psychogenic erectile dysfunction**

PATHOPHYSIOLOGY

- Increased incidence of erectile dysfunction:
  - ↳Peripheral vascular disea
  - ↳Arteriosclerosis, and
  - ↳Essential hypertension

Compromise vascular flow to the corpora cavernosum

- Impaired nerve conduction to the brain (e.g., spinal cord injury or stroke)
- Impaired peripheral nerve conduction to the penile vasculature (e.g., diabetes mellitus)

PATHOPHYSIOLOGY

- Subphysiologic levels of testosterone due to hypogonadism, primary or secondary,
  - Result in decreased libido and secondary erectile dysfunction.
  - Primary hypogonadism can be associated with the aging process or surgical removal of the testes
  - Secondary hypogonadism may result from hypothalamic or pituitary disorders of LHRH or luteinizing hormone

PATHOPHYSIOLOGY

- Patients must be in the proper mental frame of mind to be receptive to sexual stimuli.
- Psychogenic erectile dysfunction generally exhibit a higher response rate to various interventions than do patients with organic.

PATHOPHYSIOLOGY

- **Cigarette smoking** may compromise blood flow to the corpora and decrease cavernosal filling.
- **Excessive alcohol** intake may lead to:
  - Androgen deficiency
  - Peripheral neuropathy
  - Chronic liver disease
  - All of which can contribute to erectile dysfunction.



PATHOPHYSIOLOGY

- **Medications**: 10% to 25% of cases

Drug Class	Proposed Mechanism by Which Drug Causes Erectile Dysfunction	Special Notes
Anticholinergic agents (antihistamines, antiparkinsonian agents, tricyclic antidepressants, phenothiazines)	Anticholinergic activity	• Second-generation nonsedating antihistamines (e.g., loratadine, fexofenadine, or cetirizine) are associated with less erectile dysfunction than first-generation agents • Selective serotonin reuptake inhibitor (SSRI) and multiple receptor reuptake inhibitor antidepressants cause less erectile dysfunction than tricyclic antidepressants. Of the SSRIs, paroxetine, sertraline, fluvoxamine, and fluoxetine cause erectile dysfunction more commonly than venlafaxine, nefazodone, trazodone, bupropion, duloxetine, or mirtazapine • Phenothiazines with less anticholinergic effect (e.g., chlorpromazine) can be substituted in some patients if erectile dysfunction is a problem
Dopamine antagonists (e.g., metoclopramide, phenothiazines)	Inhibit prolactin inhibitory factor, thereby increasing prolactin levels	• Increased prolactin levels inhibit testicular testosterone production; depressed libido results
Estrogens, antiandrogens (e.g., luteinizing hormone-releasing hormone superagonists, digoxin, spironolactone, ketoconazole, cimetidine)	Suppress testosterone-mediated stimulation of libido	• In the face of a decreased libido, a secondary erectile dysfunction develops because of diminished sexual drive
CNS depressants (e.g., barbiturates, narcotics, benzodiazepines, short-term use of large doses of alcohol, anticonvulsants)	Suppress perception of psychogenic stimuli	
Agents that decrease penile blood flow (e.g., diuretics, peripheral β-adrenergic antagonists, or central sympatholytics [methyldopa, clonidine, guanethidine])	Reduce arteriolar flow to corpora	• Any diuretic that produces a significant decrease in intravascular volume can decrease penile arteriolar flow • Safer antihypertensives include angiotensin-converting enzyme inhibitors, postsynaptic α_1-adrenergic antagonists (terazosin, doxazosin), calcium channel blockers, and angiotensin II receptor antagonists[9]
Miscellaneous • Finsteride, dutasteride • Lithium carbonate • Gemfibrozil • Interferon • Clofibrate • Monoamine oxidase inhibitors • Opiates	Unknown mechanism	

CLINICAL PRESENTATION

- **General**
  - Men are affected emotionally
  - Depression
  - Performance anxiety
  - Marital difficulties and avoidance of sexual intimacy
  - Nonadherence to medications patient believes are causing erectile dysfunction

CLINICAL PRESENTATION

- **Symptoms**
  - Impotence or inability to have sexual intercourse
- **Signs**
  - Low satisfaction with quality of erectile function
  - Medical history may identify concurrent medical illnesses, past surgical procedure
  - Medication history may reveal prescription or nonprescription medications
  - Physical examination may reveal signs of hypogonadism

CLINICAL PRESENTATION

- **Laboratory Tests**

  - Serum testosterone concentration

  - In enlarged prostate, a blood sample for prostate specific antigen should be obtained.

  - Fasting plasma glucose and lipid profile

TREATMENT

Desired Outcomes

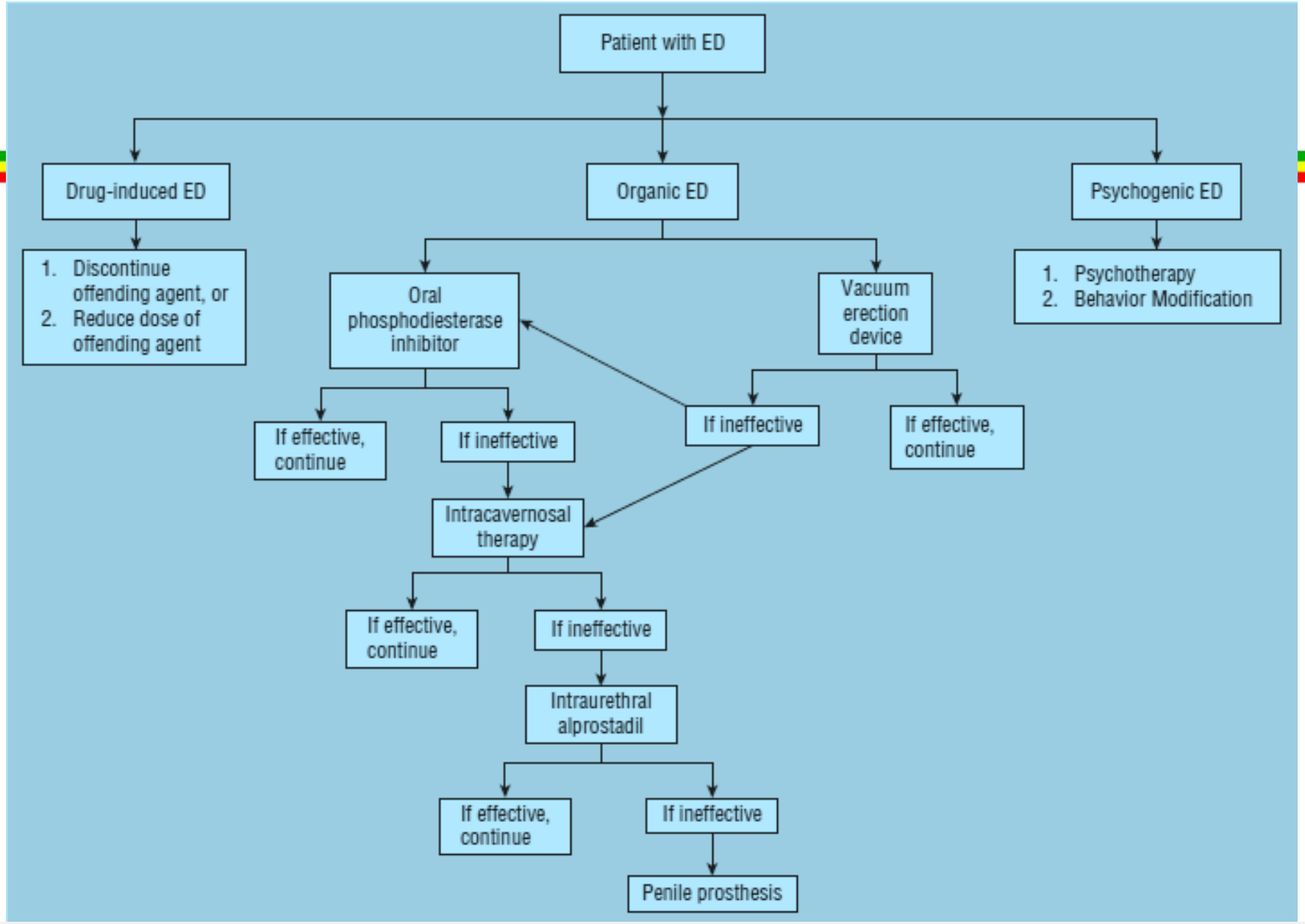
- Improvement in the quantity and quality of penile erections suitable for satisfactory intercourse.
- Patients and their partners have reasonable expectations for any therapies that are initiated.
- Patients who have normal sexual function should not seek – or be encouraged to seek – treatment in an effort to enhance sexual function or enable increased activity

GENERAL APPROACH TO TREATMENT

- Identify and, if possible, reverse underlying causes.
  - Hypertension,
  - Diabetes mellitus,
  - Smoking, or chronic ethanol abuse
- Physical fitness
- Specific treatment is indicated if these measures does not restore erectile function

GENERAL APPROACH TO TREATMENT

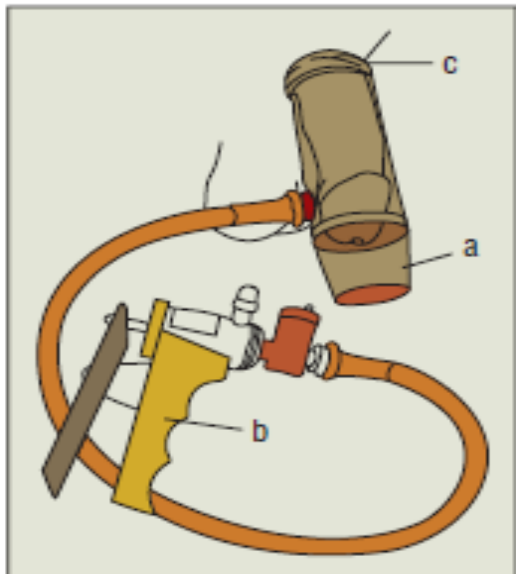
- Psychotherapy can be used as monotherapy or as an adjunct to specific treatments for psychogenic erectile dysfunction
- Specific treatments of erectile dysfunction
  - Vacuum erection devices (VEDs)
  - Pharmacologic treatments, and
  - Surgery



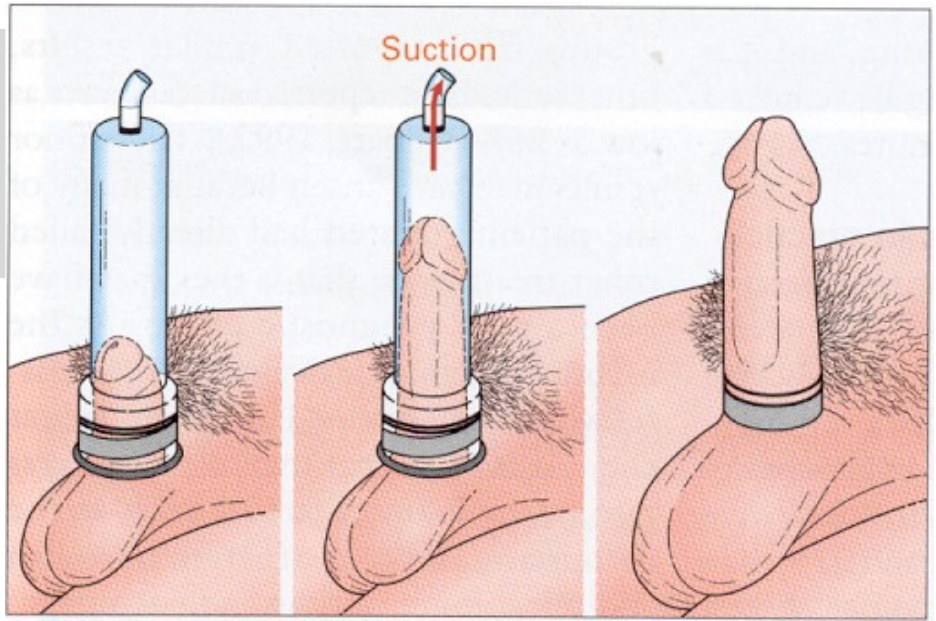
Oral agents are 1st-line therapy for younger patients, and vacuum erection devices are generally used first in older patients who are married or otherwise have a stable sexual relationship.

VACUUM ERECTION DEVICE

- Negative pressure on the penis, draws blood into the penis erection
- Constriction band at base of penis to maintain erection



a- cylinder
b- pump (manual or battery)
c- ring



VACUUM ERECTION DEVICE

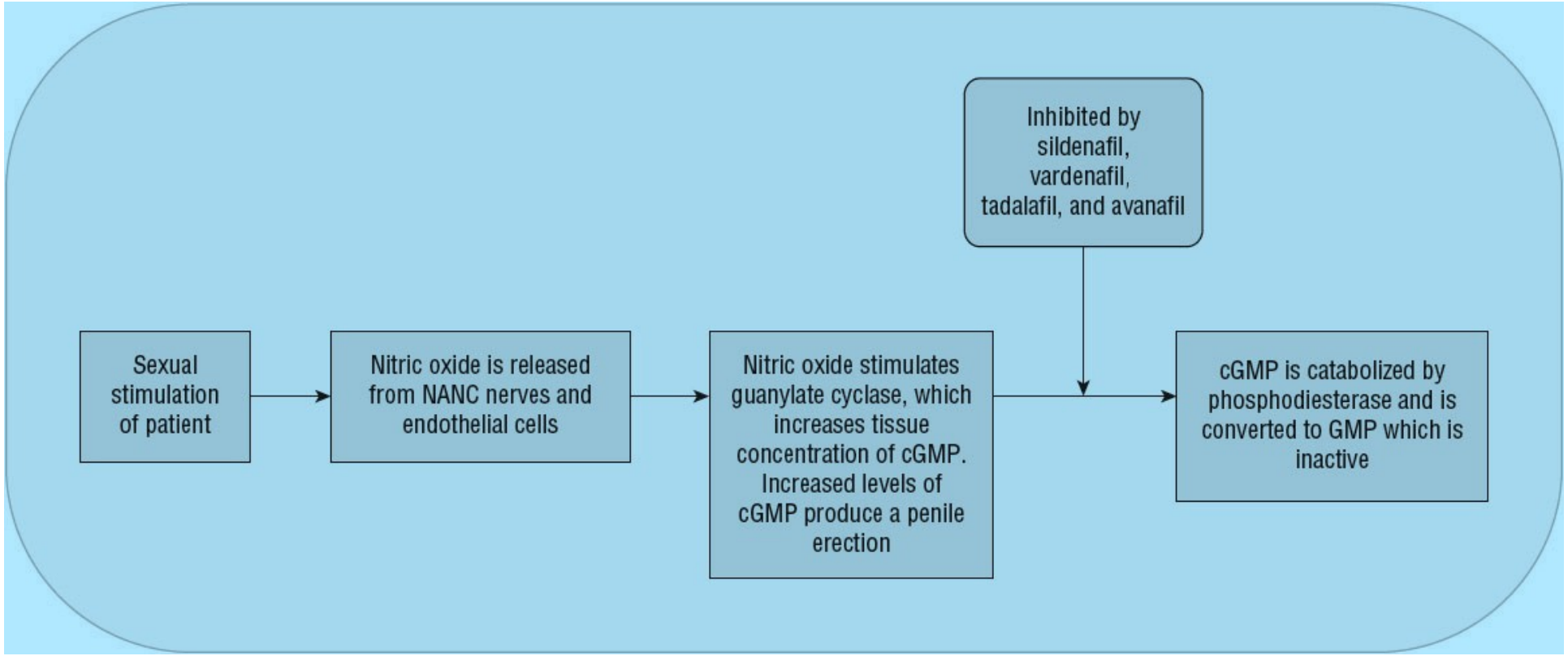
- The onset of action of the VED is comparatively **slow** (30 minutes): patience!
- VED is evident to the partner.
- Therefore, VEDs appear to work best in older patients
- Satisfaction rate is 60% to 80%.
- 6% to 11% of partners complain that the penis is **cool to the touch** or is **discolored** (bluish-for whites) in appearance

VACUUM ERECTION DEVICE

- Penile shaft may turn blue and hurt if the rubber applied >30 – 60min
- Patients sometimes fail to ejaculate
- VEDs are **contraindicated** in patients with **sickle cell disease**: (Priapism)
- VEDs should be **used cautiously** by patients taking oral anticoagulants because warfarin can cause priapism.

PHOSPHODIESTERASE INHIBITORS

- **Mechanism**



PHOSPHODIESTERASE INHIBITORS

- **Efficacy**
  - All the three PDEIs are equally effective.
  - Sildenafil produces satisfactory erections in 56% to 82%
  - 65%–80% for Vardenafil and 62%–77% for Tadalafil
  - Effectiveness of the drugs appears to be dose related.

PHOSPHODIESTERASE INHIBITORS

- Half of non-responders can benefit from education on proper use of the drugs
  - Patients must engage in sexual stimulation
  - Sildenafil should be taken on an empty stomach for the fastest response
  - Sildenafil or Vardenafil absorption rate decrease with a fatty meal
  - Patients who do not respond to 1st dose should continue with the PDEIs for at least 5-8 doses before failure is declared
  - Some patients require dosage titration up to 100 mg sildenafil, 20 mg vardenafil, or 20 mg tadalafil for a response

Pharmacodynamics and Pharmacokinetics of Phosphodiesterase Inhibitors

	Sildenafil (Viagra)	Vardenafil (Levitra/Staxyn)	Tadalafil (Cialis)	Avanafil (Stendra)
Inhibits PDE-5	Yes	Yes	Yes	Yes
Inhibits PDE-6	Yes	Minimally	No	Minimally
Inhibits PDE-11	No	No	Yes	Minimally
Time to peak plasma level (hours)	0.5–1	0.7–0.9/1.5	2	0.5–0.8
Oral bioavailability (%)	40	15/21–44	Not determined	15
Fatty meal decreases rate of oral absorption?	Yes	Yes/No[a]	No	No
Mean plasma half-life (hours)	3.7	4.4–4.8/4–6	18	4–5
Active metabolite	Yes	Yes/Yes	No	Yes
Percentage of dose excreted in feces	80	91–95/91–95	61	62
Percentage of dose excreted in urine	13	2–6/2–6	36	21
Onset (minutes)	30	30/60	45	30–45
Duration (hours)	4	4–5/4–6	24–36	4–5

PHOSPHODIESTERASE INHIBITORS

- Tadalafil – weekend drug – extended duration of action
  - ☆Has effect on PDE 11 □ myopathy

- Sildenafil
  - ☆Affects PDE 6 □ cause blurred vision

PHOSPHODIESTERASE INHIBITORS

- Concomitant ingestion of **ethanol** with PDEIs can result in orthostatic hypotension.

PDEI- Adverse Effect

- Drug discontinuation due to adverse effects: **2.1% to 2.5%**
  - Headache (11%)
  - Facial flushing (12%)
  - Dyspepsia (5%)
  - Nasal congestion (3.4%)
  - Dizziness (3%)

PDEI- Adverse Effect

- **Hypotension**:
  - ✍Sildenafil and vardenafil produce an 8-10mm Hg decrease in systolic and a 5-6mm Hg decrease in diastolic BP
  - ✍Tadalafil does not produce decreases in BP

PDEI- Adverse effect

- **Visual**
  - Sildenafil and Vardenafil cause increased sensitivity to light, blurred vision, or loss of blue–green color discrimination in 2% to 3% of patients.
  - Tadalafil has *no visual adverse effects*.
  - All PDEIs should be used cautiously in patients at risk for retinitis pigmentosa, phosphodiesterase deficiency
- **Priapism** is a rare adverse effect

PDEI- drug interaction

- Patients taking *organic nitrates* may develop severe hypotension
- Nitrates should be withheld for 24 hours after **sildenafil** or **vardenafil** administration and for 48 hours after **tadalafil**.

TESTOSTERONE REPLACEMENT REGIMENS

- **Mechanism**
  - ✍Correct symptoms of hypogonadism,
  - ✍Testosterone can directly stimulate androgen receptors in the CNS and is thought to be responsible for maintaining normal sexual drive.
  - ✍ Stimulate nitric oxide synthase, thereby increasing cavernosal concentrations of nitric oxide or enhance the effects of PDE type 5 in cavernosal tissue

TESTOSTERONE REPLACEMENT REGIMENS

- **Indications**

  ✍Testosterone replacement regimens are indicated in symptomatic patients with primary or secondary hypogonadism.

- Testosterone replacement regimens should never be administered to men with normal serum testosterone levels.

TESTOSTERONE REPLACEMENT REGIMENS

Efficacy

- Testosterone replacement regimens restore
  - Muscle strength
  - Sexual drive
  - Improve mood in patients
- Improvements are observed within days or weeks
- Testosterone do not directly correct erectile dysfunction; instead, they

TESTOSTERONE REPLACEMENT REGIMENS

- Testosterone replacement regimens can be administered orally, parenterally, or transdermally
- Injectable testosterone preferred
  - Effective
  - Inexpensive
  - Not associated with the bioavailability problems or hepatotoxic adverse effects of oral androgens.
- Patches and gels are much more expensive than other forms of androgen

TESTOSTERONE REPLACEMENT REGIMENS

- Ideal testosterone replacement regimen
  - The medication would mimic the normal circadian pattern of serum testosterone concentrations
    - Peak: early morning
    - Trough: late afternoon

TESTOSTERONE REPLACEMENT REGIMENS

Pharmacokinetics

- Natural testosterone: Extensive first-pass hepatic metabolism
- Oral bioavailability: alkylated derivatives
  - Methyltestosterone and fluoxymesterone
  - High incidence of hepatotoxicity

TESTOSTERONE REPLACEMENT REGIMENS

Pharmacokinetics

- **Testosterone buccal system** (Striant), which is applied to the gum above the upper incisor teeth twice per day.
- **Testosterone esters (im)**
  - Testosterone propionate, which requires dosing tiw
  - Testosterone cypionate or enanthate, which can be dosed every 2, 4, or 6 weeks
- **Subcutaneous implant** for dosing every 4 to 6 months
- **Topical testosterone replacement** regimens can be delivered as once-daily **patches** or **gel**.

TESTOSTERONE REPLACEMENT REGIMENS

Pharmacokinetics

- Testoderm brand patch was formulated for scrotal application.
- Androderm and Testoderm TTS patches: the arms, buttocks, or back.
- Testosterone gel 1% formulation (AndroGel): shoulders, upper arms, or abdomen.

TESTOSTERONE REPLACEMENT REGIMENS

Dosing

- Two to three months is considered an adequate treatment trial with a particular dose.
- Before initiating any testosterone replacement regimen in patients 40 years and older, patients should be *screened for BPH and prostate cancer*.

TESTOSTERONE REPLACEMENT REGIMENS

Adverse Effects

- Sodium rétention
  - Cause weight gain, or exacerbate hypertension, congestive heart failure, and edema.
- Gynecomastia
  - Due to conversion of testosterone to estrogen in peripheral tissues
- Topical testosterone patches may cause contact dermatitis

ALPROSTADIL

Mechanism

- Alprostadil, also known as prostaglandin E1, stimulates adenyl cyclase, resulting in increased production of cAMP that causes smooth muscle relaxation of the arterial blood vessels and sinusoidal tissues in the corpora.

- Alprostadil
  - Intracavernosal inj. (Caverject and Edex): more effective
  - Intraurethral insert (medicated urethral

ALPROSTADIL

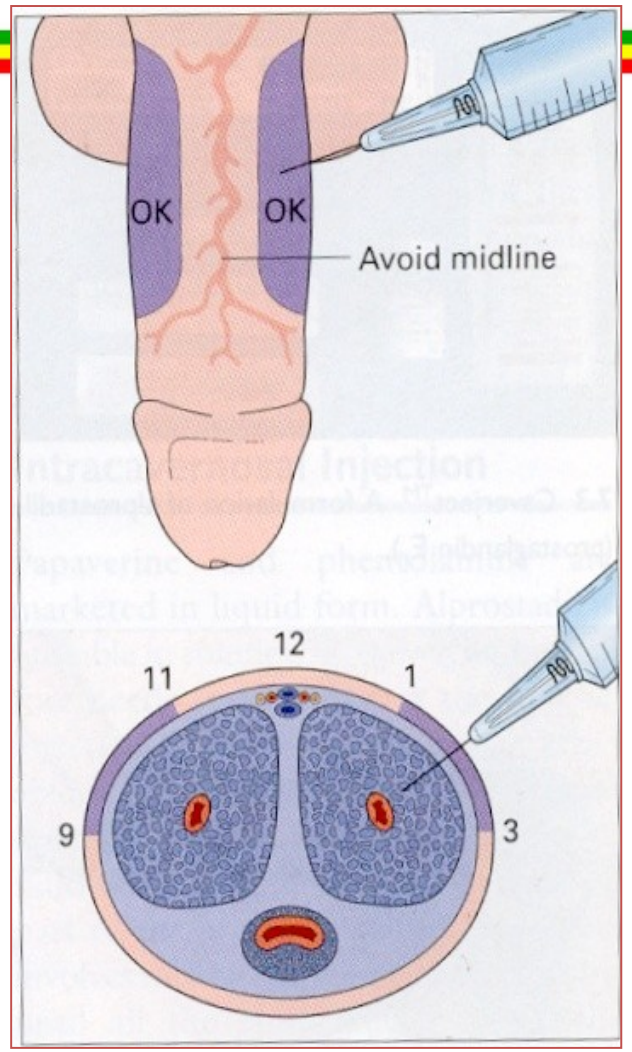
- Intracavernosal alprostadil: preferred in patients with diabetes mellitus

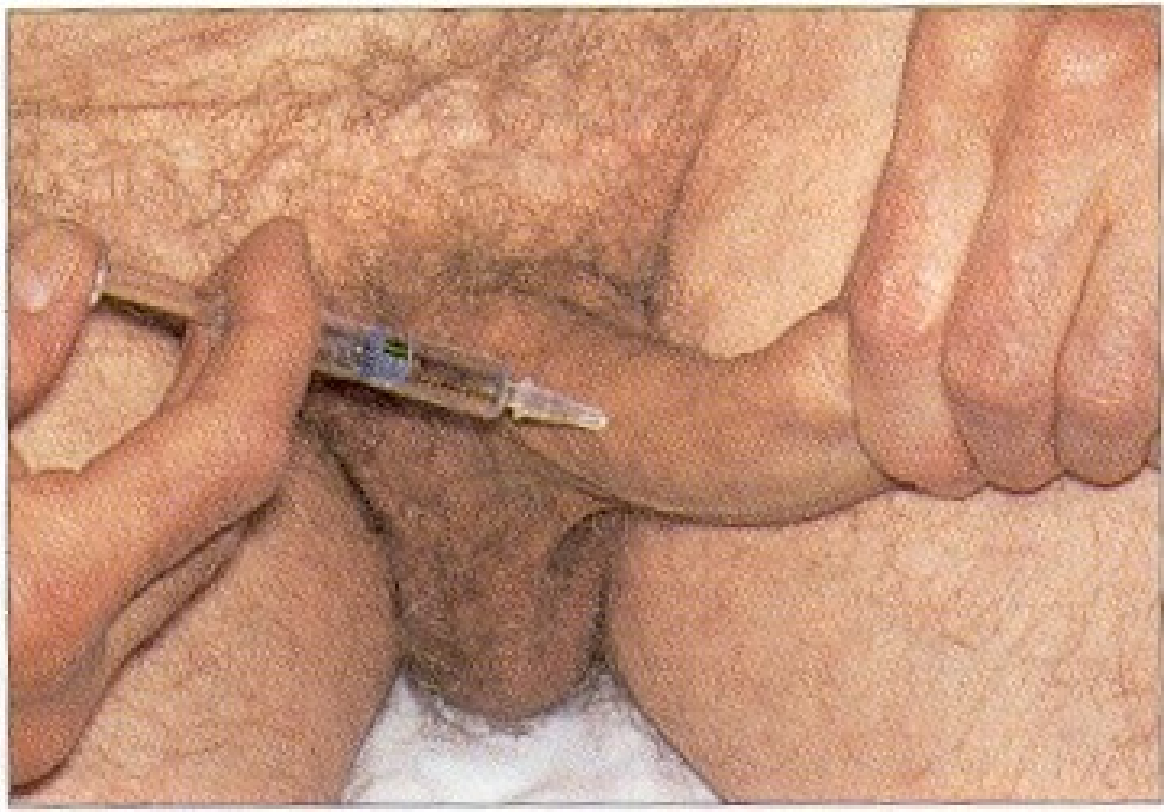
- Intraurethral alprostadil: reserved as a treatment of last resort for patients

ALPROSTADIL

Intracavernosal Alprostadil

- **Efficacy**
  - The overall efficacy of intracavernosal alprostadil is 70% to 90%.
  - Effectiveness of alprostadil is dose related over the range from 2.5 to 20 mcg.
  - Mean duration of erection ranges from 12 to 44 minutes.
  - Lower dose is enough for psychogenic and neurogenic ED
  - Higher dose: vasculogenic erectile


OK
OK
Avoid midline
12
11
1
9
3



ALPROSTADIL

- Adverse Effects: Intracavernosal alprostadil is most commonly associated with local adverse effects.
  - Cavernosal plaques or areas of fibrosis at injection sites [2% to 12% of patients]
  - Penile pain [10% to 44% of patients]
  - Priapism [1% to 15% of treated patient]

ALPROSTADIL

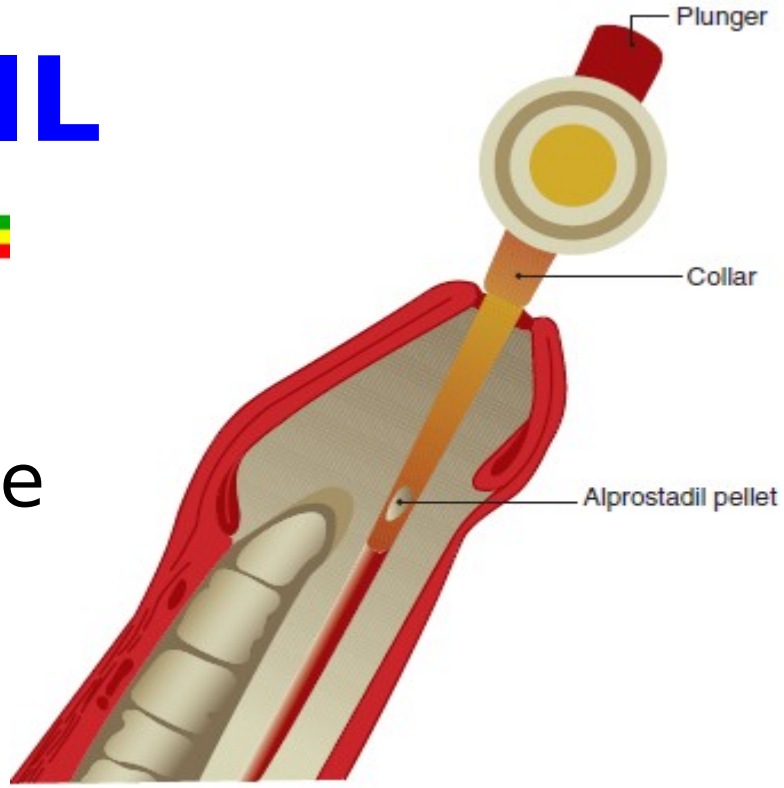
Intraurethral Alprostadil

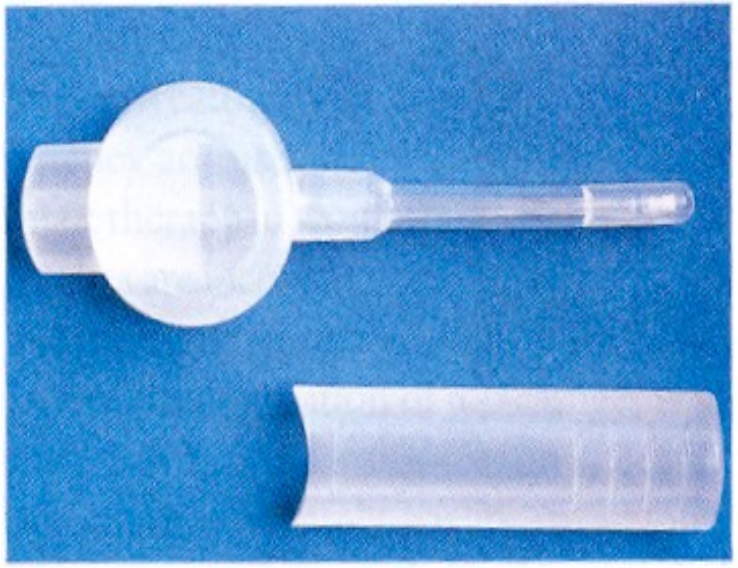
- Contains a medication pellet inside a prefilled urethral applicator.
- Response rate of 43% to 60%
- Estimated 20% of each dose is delivered to the corpora cavernosum.
- Onset of action is similar to intacavernosal route. [5-10min]
- **Dosing:** 125 to 1000mcg; max bid

ALPROSTADIL

MUSE:

- Massage to dissolve the pellet;
- Bladder void







ALPROSTADIL

Intraurethral Alprostadil

- **Adverse Effects**
  - **The urethra can be injured**
  - Patient require proper education about proper administration before starting treatment.
  - Urethral pain: 24% to 32% of patients
  - Female sexual partners may experience vaginal burning, itching, or pain.
  - Priapism have been rarely reported

Trazodone

- **Mechanism**
  - Is not clear. It likely acts peripherally to antagonize α-adrenergic receptors. Predominant cholinergic effect results, which causes peripheral arteriolar vasodilation
- Trials were generally poorly controlled
- Adverse effects
  - Dry mouth, sedation, and dizziness.

Yohimbine

- Yohimbine *is widely* used as an aphrodisiac.
- Yohimbine is a central α_2-adrenergic antagonistic that increases catecholamines and improves mood.
- Some investigators believe that yohimbine has peripheral proerectogenic effects.
- The usual oral dose is 5.4 mg three times per day.
- Controlled clinical trial has shown that high-dose yohimbine (100mg daily) is no more effective than placebo.

Papaverine

- Nonspecific phosphodiesterase inhibitor that decreases metabolic catabolism of cAMP in cavernosal tissue.
- Papaverine is not FDA approved
- Papaverine is more often administered in lower doses combined with phentolamine and/or alprostadil.
- Adverse effects: priapism, corporal fibrosis, hypotension, and hepatotoxicity
  - Less if used with phentolamine and/or alprostadil

Phentolamine

- Phentolamine is a competitive nonselective α-adrenergic blocking agent.
- It reduces peripheral adrenergic tone and enhances cholinergic tone.
- Improves cavernosal filling
- Phentolamine has been used in combination with other vasoactive agents for intracavernosal administration.
  - Ratio of 30 mg papaverine to 0.5 to 1 mg phentolamine

Prostheses

- Semi-rigid malleable or inflatable rods
- Inserted surgically into the corpus cavernosa
- Malleable rods are rigid at all times, but may be bent into position by the patient when desired.
- The inflatable prostheses remain flaccid until the pump within the scrotum moves fluid from a reservoir to the cylinders within the penis.

Prostheses

- Prostheses are the most invasive treatment
- Considered in patients who do not respond to
  - medications or
  - external devices, or
  - those who have significant adverse effects
- Patient satisfaction rates 80% to 90% with partner satisfaction rates just slightly lower.
- Risk of prosthesis
  - Infection (2% to 3%) and device failure (2% to 14% of patient)

Patient Care and Monitoring

- Assess the patient’s specific symptoms
- Thorough medical history and physical exam should be performed to diagnose ED
- Perform a thorough medications history
- Treatment is started with the least invasive option
- Discontinue medications that may cause ED
- Counsel patient to ensure that they are using the therapy appropriately
- Provide patient education with regard to disease state, lifestyle modifications, drug therapy, and device technique

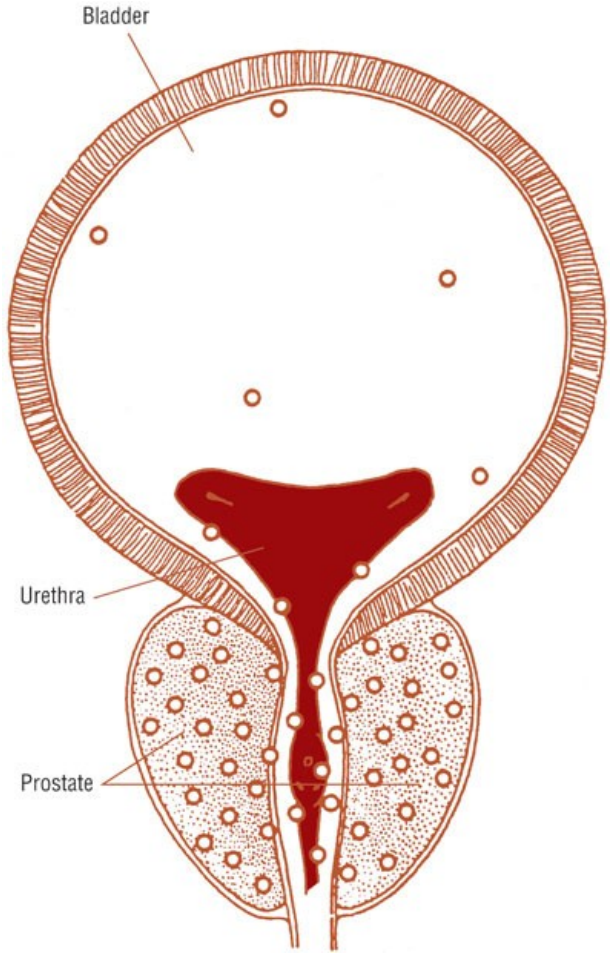
BENIGN PROSTATIC HYPERPLASIA (BPH)

Definition

- Is a nearly ubiquitous condition, and the most common benign (noncancerous) neoplasm of males who are at least 40 years of age
- BPH is of major societal concern,
  - Given the large number of men affected,
  - The progressive nature of the condition, and
  - The healthcare costs associated with it

Normal Physiology of Prostate

- Weighs 4 to 20 g.
- Located anterior to the rectum, below the urinary bladder surrounding the proximal urethra
- Has two major functions:
  - ✍ Secrete fluids that make up a portion (20 – 40%) of the **ejaculate volume**;
  - ✍ Provide secretions with possible **antibacterial** effect related to its high concentration of **zinc**.



Normal Physiology of Prostate

- Comprises three types of tissues:

1. Epithelial tissue (glandular),
   - Produces prostatic secretions
   - **Androgens** stimulate epithelial tissue growth
2. Stromal tissue (smooth muscle tissue)
   - Embedded with α_1-adrenergic receptors
   - Stimulation of these receptors by NE smooth muscle contraction an extrinsic compression of the urethra, reduction of the urethral lumen, and decreased urinary bladder emptying
3. The capsule (smooth m. + fibrous connective tissue)
   - Embedded with α_1-adrenergic receptors.
   - When stimulated with norepinephrine, the capsule contracts around the urethra

Normal Physiology of Prostate

- The normal prostate is composed of a higher amount of stromal tissue than epithelial tissue, as reflected by a stromal-to-epithelial tissue ratio of 2:1.
- This ratio is exaggerated to 5:1 in patients with BPH

Normal Physiology of Prostate

- **Testosterone** is the principal testicular androgen in males, whereas **androstenedione** is the principal adrenal androgen.
- These two hormones are responsible for penile and scrotal enlargement, increased muscle mass, and maintenance of the normal male libido.
- These androgens are converted by **5α-reductase** in target cells to **dihydrotestosterone** (DHT), an active metabolite.

Normal Physiology of Prostate

- Two types of 5α-reductase exist.
  - **Type I enzyme** is localized to hair follicles, sebaceous glands in the frontal scalp, liver, and skin.
    - DHT produced at these target tissues causes acne, increased body and facial hair, and male pattern baldness.
  - **Type II enzyme** is localized to the prostate, genital tissue, and scalp.
    - In the prostate, DHT induces growth and enlargement of the gland

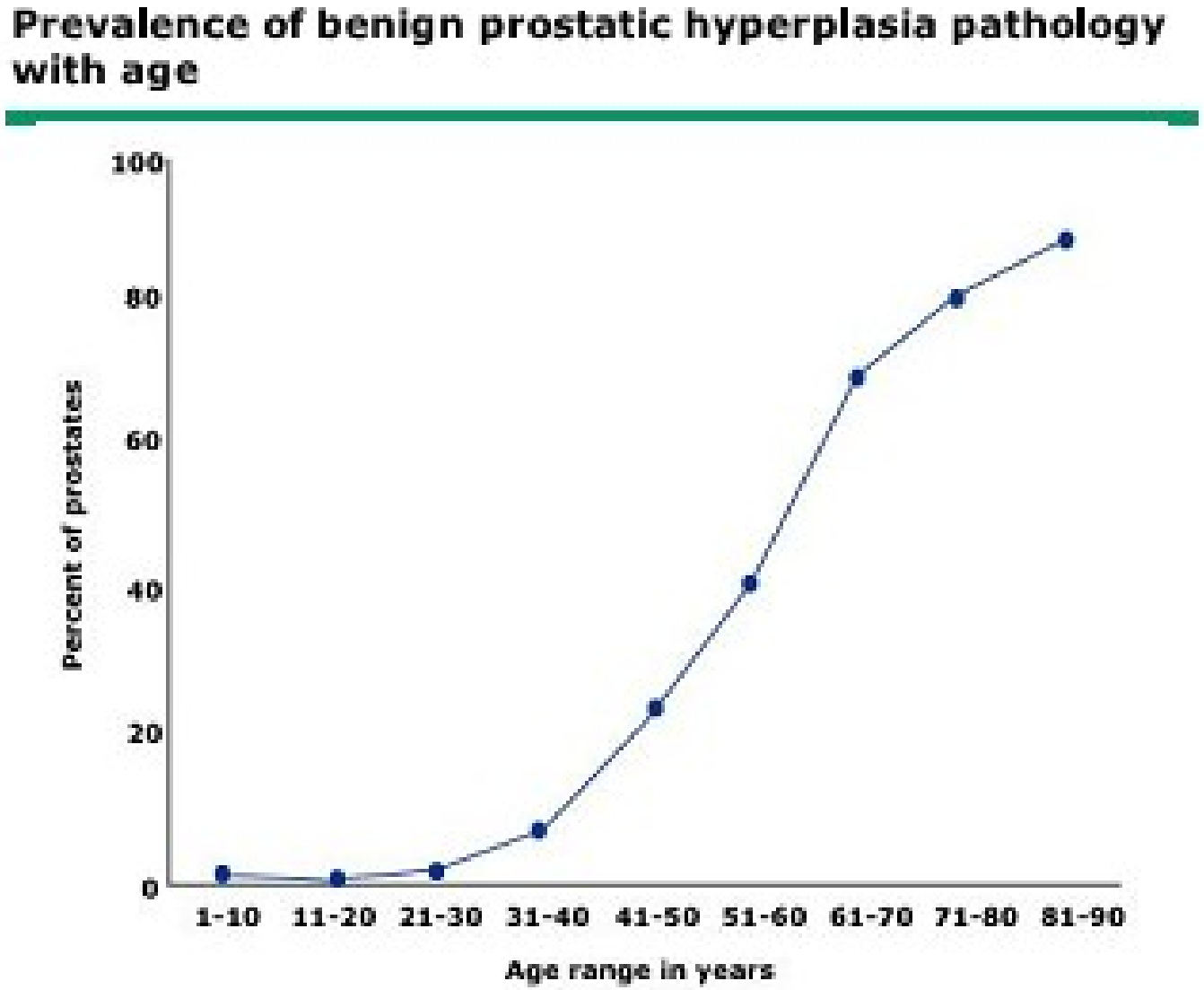
Normal Physiology of Prostate

- **Estrogen**, a product of peripheral metabolism of androgens
  - Stimulates the growth of the **stromal** portion of the prostate gland.
- Estrogens are produced when testosterone and androstenedione are converted by **aromatase enzymes** in adipose tissues.
- As men age, the ratio of serum levels of testosterone to estrogen decreases as a result of
  - A decline in testosterone production by the testes and
  - Increased adipose tissue conversion of androgen to

Epidemiology of BPH

- Prevalence
  - Approximately 80% of elderly men develop microscopic evidence of BPH.
  - 50% and 25% of patients with microscopic BPH disease develop an enlarged prostate on palpation and clinical voiding symptoms, respectively
- The peak incidence of clinical BPH occurs at 63 to 65 years of age.
- Symptomatic disease is uncommon in men younger than 50 years,

Cont’d


Prevalence of benign prostatic hyperplasia pathology with age
Percent of prostates
100
80
60
40
20
0
1-10
11-20
21-30
31-40
41-50
51-60
61-70
71-80
81-90
Age range in years

Pathophysiology

- The role of intraprostatic DHT and type II 5α-reductase in the development of BPH is evidenced by several observations:
  - ⇒BPH does not develop in men who are **castrated** before puberty.
  - ⇒**Castration** causes an enlarged prostate to shrink.
  - ⇒Patients with type II **5α-reductase enzyme deficiency** do not develop BPH.
  - ⇒Administration of **testosterone** to orchiectomized dogs of advanced age produces BPH.

Pathophysiology

- BPH is often described as resulting from both static and dynamic factors.
  - **Static factors** relate to anatomic enlargement of the prostate gland,
  - ⇒Produces a physical block at the bladder neck and thereby obstructs urinary outflow.
  - ⇒Enlargement of the gland depends on:
    - ✍Androgen stimulation of epithelial tissue and
    - ✍Estrogen stimulation of stromal tissue in the prostate.

Pathophysiology

- **Dynamic factors** relate to excessive α-adrenergic tone of the stromal component of the prostate gland, bladder neck, and posterior urethra,
  - ⇒Contraction of the prostate gland around the urethra
  - ⇒Narrowing of the urethral lumen.
- ❖Voiding symptoms with prostates of normal size

Pathophysiology

- **Static factors** may be accentuated by environmental factors.

  ✍Patients who are stressed or in pain may experience an exacerbation of voiding difficulty.

    ⇒Increased α-adrenergic tone may precipitate excessive contraction of prostatic stromal tissue.

    ⇒When the stressful event resolves, voiding symptoms often disappear

Clinical Presentation

- **General**
  - Patient may/may not be in acute distress
- **Symptoms**
  - Urinary frequency, urgency, intermittency, nocturia, decreased force of stream, hesitancy, straining, suprapubic pain
- **Signs**
  - Digital rectal examination reveals an enlarged prostate (>20 g)
- **Laboratory Tests**
  - Increased BUN and Scr, elevated prostate-specific antigen (PSA) level

Clinical Presentation

- **Obstructive**
  - Urinary hesitancy
  - Urine dribbles out of the penis
  - The bladder feels full even after voiding.
  - Straining
- **Irritative**
  - Frequency,
  - Urgency, and
  - Nocturia

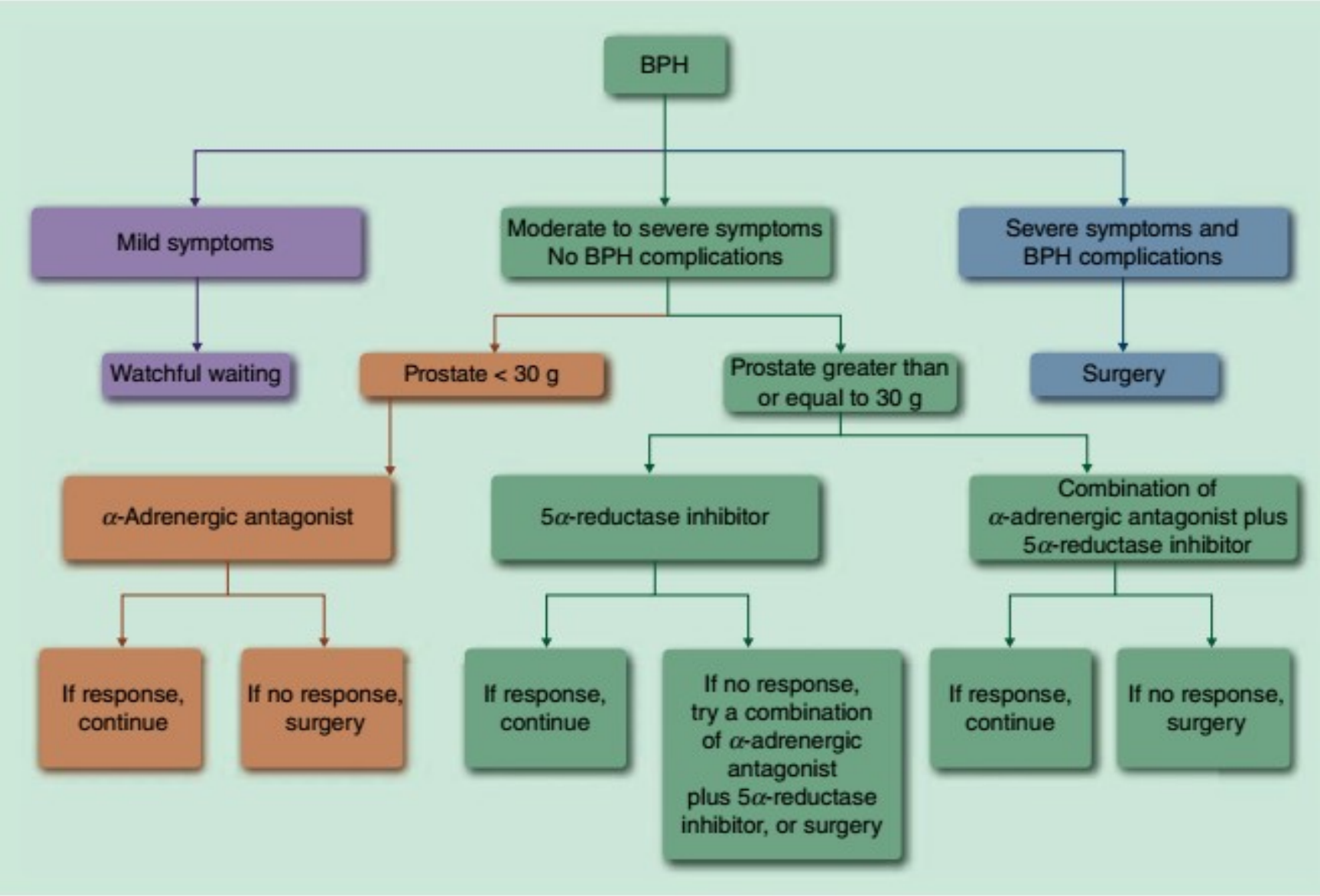
Complications: if untreated

- Upper and lower urinary tract infection,
- Urosepsis,
- Urinary incontinence
- Chronic kidney failure,
- Bladder diverticuli,
- Bladder stones,
- Recurrent gross hematuria

Treatment

- Desired outcome
  - Primarily at relieving manifestations of the disease that are bothersome for the patient
  - Slowing disease progression
  - Preventing serious complications
  - Providing economical therapy
  - Maintaining or improving quality of life.

General approach



Treatment

- Patients with mild disease
  - ✍Are asymptomatic or have mildly bothersome symptoms
  - ✍Have no complications of BPH disease.
  - No specific treatment is indicated.
  - Managed with **watchful waiting**,
  - The patient return for reassessment at yearly intervals.

Treatment

- Watchful waiting should be accompanied by patient education including
  - Fluid restriction close to bedtime,
  - Avoiding caffeine and alcohol intake,
  - Frequent emptying of the bladder during waking hours (to avoid overflow incontinence and urgency), and
  - Avoiding drugs that could exacerbate voiding symptoms

Treatment

- For moderate or severe symptoms
  - The patient should be offered specific treatment
  - Recommended treatment options include
    - Drug therapy with
      - α1-adrenergic antagonist or
      - 5α-reductase inhibitor,
      - Combination
    - Surgery
- Patients with serious complications of BPH

PHARMACOLOGIC THERAPY

- Three types:
  - Agents that relax prostatic smooth muscle (reducing the dynamic factor),
  - Agents that interfere with testosterone's stimulatory effect on prostate gland enlargement (reducing the static factor), and
  - Combination therapy of an α_1 – adrenergic antagonist and a 5α-reductase inhibitor

α-Adrenergic Antagonists

- Three generations of α-adrenergic antagonists
  - ✍ They all relax smooth muscle in the prostate and bladder neck.
- First-generation agents (phenoxybenzamine)
  - ✍ Because of their antagonism of presynaptic α_2-adrenergic receptors
    - Results in tachycardia and arrhythmias,
- Second-generation: postsynaptic α_1-adrenergic antagonists
- Third-generation **uroselective** postsynaptic α_1-adrenergic antagonists.

α-Adrenergic Antagonists

- The second- and third-generation α_1-adrenergic antagonists are considered **equally effective**
- They have no effect on decreasing prostate volume.
- α_1-adrenergic antagonists do not reduce PSA levels,
  - ✍Preserving the utility of this prostate cancer marker in this high-risk population.

α-Adrenergic Antagonists

- Second-generation agents include **prazosin**, **terazosin**, **doxazosin**, and **alfuzosin**.
- At the usual doses used to treat BPH, prazosin, terazosin, and doxazosin antagonize peripheral vascular α_1 – adrenergic receptors in addition to those in the prostate.
  - ⇒First-dose syncope, orthostatic hypotension, and dizziness
  - ⇒To improve tolerance to these adverse effects, therapy
    - ⇒Should start with a low dose of 1 mg daily and then should be slowly

α-Adrenergic Antagonists

- For second-generation α_1-adrenergic antagonists terazosin and doxazosin,
  - Slow titration up to a therapeutic maintenance dose is necessary
    - Minimize orthostatic hypotension and first-dose syncope.
  1. Conservatively, dosages should be increased in an orderly stepwise process, at 2- to 7-day intervals, depending on the patient's response to the medication.
  2. A faster titration schedule can be used if the patient does not develop orthostatic hypotension or dizziness.

α-Adrenergic Antagonists

- **Schedule 1: Slow titration**
  - Days 4 to 14: 2 mg at bedtime
  - Weeks 2 to 6: 5 mg at bedtime
  - Weeks 7 and on: 10 mg at bedtime
- **Schedule 2: Quicker titration**
  - Days 1 to 3: 1 mg at bedtime
  - Days 4 to 14: 2 mg at bedtime
  - Weeks 2 to 3: 5 mg at bedtime
  - Weeks 4 and on: 10 mg at bedtime

α-Adrenergic Antagonists

- **Alfuzosin** is uroselective at usual doses used to treat BPH

  ⇒Less likely to cause cardiovascular adverse effects

- 3rd generation α_1-adrenergic antagonist:

  Tamsulosin

  ✓It is selective for prostatic α_{1A}-adrenergic receptors, (70% of the adrenergic receptors in the prostate gland)

  ✓Has low affinity for vascular α_{1B}-adrenergic

Dosing Schedule of α1-Adrenergic Antagonists in Patients with BPH

Drug	Half-Life (h)	Usual Daily Dosage	Time to Peak Effect on BPH Symptom
Prazocin	2 – 3	2–10 mg in two to three divided doses	2–6 weeks
Terazocin	11–14	1–10 mg as a single dose; maximum 20 mg	2–6 weeks
Doxazocin	15 – 19	1–4 mg as a single dose; maximum 8 mg	2–6 weeks
Alfuzosin	15 – 19	10 mg as a single dose	Several days
Tamsulo	14 –15	0.4 or 0.8 mg as a	Several days

α-Adrenergic Antagonists

Duration

- Patients should continue taking the drug as long as they continue to respond to it.
- Durable responses for 6 and 10 years have been reported for tamsulosin and doxazosin, respectively.
- If BPH symptoms worsen despite maximum tolerable drug doses, surgery should be considered.

Adverse effects

- **Non selective:**
  - Cardiovascular system: syncope, dizziness, hypotension
  - Avoid for patients with
    - Poorly controlled angina, serious cardiac arrhythmias,
    - Patients with reduced circulating volume, and
    - Patients taking multiple antihypertensives
  - These patients are candidates for tamsulosin or finasteride
- **Tamsulosin:**

5-Alpha-Reductase Inhibitor

- Inhibit the production of intraprostatic DHT
- Reduce the static factor
  - ☝ Shrinkage of an enlarged prostate.
- Induce **apoptosis** of prostatic epithelial cells
- Include
  - Finasteride (type II selective)
  - Dutasteride (nonselective)
- Reduce serum PSA levels by 50% (6 month)

5α-Reductase Inhibitors

- **Finasteride** competitively inhibits type II 5α-reductase,
  - Suppresses intraprostatic DHT by 80% to 90%,
  - Decreases serum DHT levels by 70%.
- **Dutasteride** is a nonselective inhibitor of type I and II 5α-reductase.
  - It more quickly and completely suppresses intraprostatic DHT production
  - Decreases serum DHT levels by 90%.

5α-Reductase Inhibitors

- Indication
  - ✍For management of moderate to severe BPH disease in patients with enlarged prostate glands of at least 40 g
  - ✍Patients with BPH who
    - Have uncontrolled arrhythmias, angina,
    - Are taking multiple antihypertensive agents, or
    - Are unable to tolerate hypotensive adverse effects of second-generation α_1-adrenergic antagonists

5α-Reductase Inhibitors

- **Dosing**
  - Finasteride is given in doses of 5 mg by mouth daily.
  - The dose can be taken with meals or on an empty stomach
  - Dutasteride can be initiated and maintained at 0.5 mg once daily
  - Patients must continue to take 5α-reductase inhibitors as long as they respond

Adverse effects

- Sexual dysfunction: led to discontinuation of therapy in up to 12% of treated patients
- Ejaculation disorders (dry sex or delayed ejaculation)
  - Reversible with drug discontinuation
- Other minor adverse effects include
  - Nausea, abdominal pain, asthenia, dizziness, flatulence, headache, rash, muscle weakness, and gynecomastia.

Adverse effects

- 5α-Reductase inhibitors are in FDA pregnancy category X
- Exposure of the male fetus to finasteride may produce pseudohermaphroditic offspring with ambiguous genitalia.
- Because of this teratogenic effect, women who are pregnant or seeking to become pregnant
  - ✍Should not handle 5α-reductase inhibitor tablets and
  - ✍Should not have contact with semen from men being treated with 5α-reductase inhibitors

Comparison of α1-Adrenergic Antagonists and 5α-Reductase Inhibitors

Criteria	α_1-Adrenergic Antagonists	5α-Reductase Inhibitors
Decreases prostate size	No	Yes
Halts disease progression	No	Yes
Peak onset	1–6 weeks	3–6 months
Efficacy	++	++ (in patients with enlarged prostates)
Frequency of dosing	1–2 times per day, depending on the agent	Once per day
Decreases prostate-specific antigen	No	Yes
Sexual dysfunction adverse effects	+	++
Cardiovascular	Yes	No

Combination Therapy

- α-adrenergic antagonist and 5α-reductase inhibitor
  - For those with
    - An enlarged prostate of at least 40 g
    - PSA of at least 4 ng/mL (4 mcg/L)
  - Reduce the risk of developing BPH related complications and reduce the need for prostatectomy by 67%
  - Short-term therapy appears to be superior to either agent alone in men with BPH/LUTS and larger prostate glands, but not in men with only moderate BPH .

Miscellaneous

• Bicalutamide • Flutamide	Block dihydrotestosterone at its intracellular receptor
• Leuprolide • Nafarelin	Block pituitary release of luteinizing hormone
• Megestrol acetate	Blocks pituitary release of luteinizing hormone and blocks androgen receptor

Surgical Intervention

- The gold standard for treatment of patients with complications of BPH is **prostatectomy**
- Surgical intervention is also used in patients
  - with **moderate to severe** symptoms,
  - who are **not responsive** to drug therapy,
  - who are **noncompliant** with drug therapy, or
  - who **prefer** surgical intervention.
- Surgical removal of the prostate offers

THANK YOU