CHILD AND ADOLESCENT PSYCHOSES

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What is Psychosis?

- Impaired reality testing: the inability to distinguish between what is real and not real.
- Presence of characteristic symptoms:
  - Disorders of perception (hallucinations)
  - Disorders of thought (delusions)
  - Disorganized speech (disordered associations)
  - Disorganized or catatonic behavior (rituals)
- Note that severe episodes of mood disorders may have psychotic features as secondary symptoms and are not a primary psychotic disorder, I.e. Major Depressive Episode with psychosis or acute mania
- Patients with personality disorders (schizotypal, schizoid, borderline and paranoid) can present with psychotic symptoms

Important Vocabulary

- **Disorders of Perception**
  - Hallucination
  - Illusion
- **Disorders of Thought Content**
  - Delusions
  - Ideas of Reference
- **Disorders of Though Process**
  - Loss of Ego Boundaries
  - Impaired Abstraction
  - Magical thinking
  - Avolition
- **Affect**
- **Disorders of Form of Thought**
  - Impaired Associations
  - Perseveration
  - Neologisms
  - Echolalia
  - Tangentiality
  - Thought Blocking
  - Alogia
  - Word Salad
- **Prodromal Symptoms**
- **Premorbid Symptoms**

Psychotic Disorders

Primary Psychiatric Disorders

- Schizophrenia
- Schizophreniform disorder
- Schizoaffective disorder
- Brief psychotic disorder
- Shared psychotic disorder
- Delusional disorder

Psychotic Disorders

Medical Conditions With Psychotic Symptoms

- **Due to General Medical Condition**
  - –Dementia
  - –Delirium
- **Substance-induced**
  - –Substance-intoxication
  - –Substance-withdrawal
- **Psychotic disorder NOS**

Psychotic Disorders

Diagnoses Which Must Be Differentiated

Dementia	vs.	Psychosis due to Medical Condition
Delirium	vs.	Substance-Induced Psychosis
Schizophrenia	vs.	Schizophreniform Disorder
Schizoaffective Disorder	vs.	Post-partum Psychosis
Delusional Disorder	vs.	Brief Psychiatric Disorder
Shared Psychosis	vs.	Psychotic Disorder NOS
Psychotic Depression	vs.	Bipolar Affective Disorder I

Psychotic Disorders

Differentials from Schizophrenia

Brief Psychotic disorder

Schizophreniform disorder

Schizoaffective disorder

Delusional disorder (shared psychosis)

Manic phase of bipolar disorder

Schizoid, schizotypal or borderline personality disorder

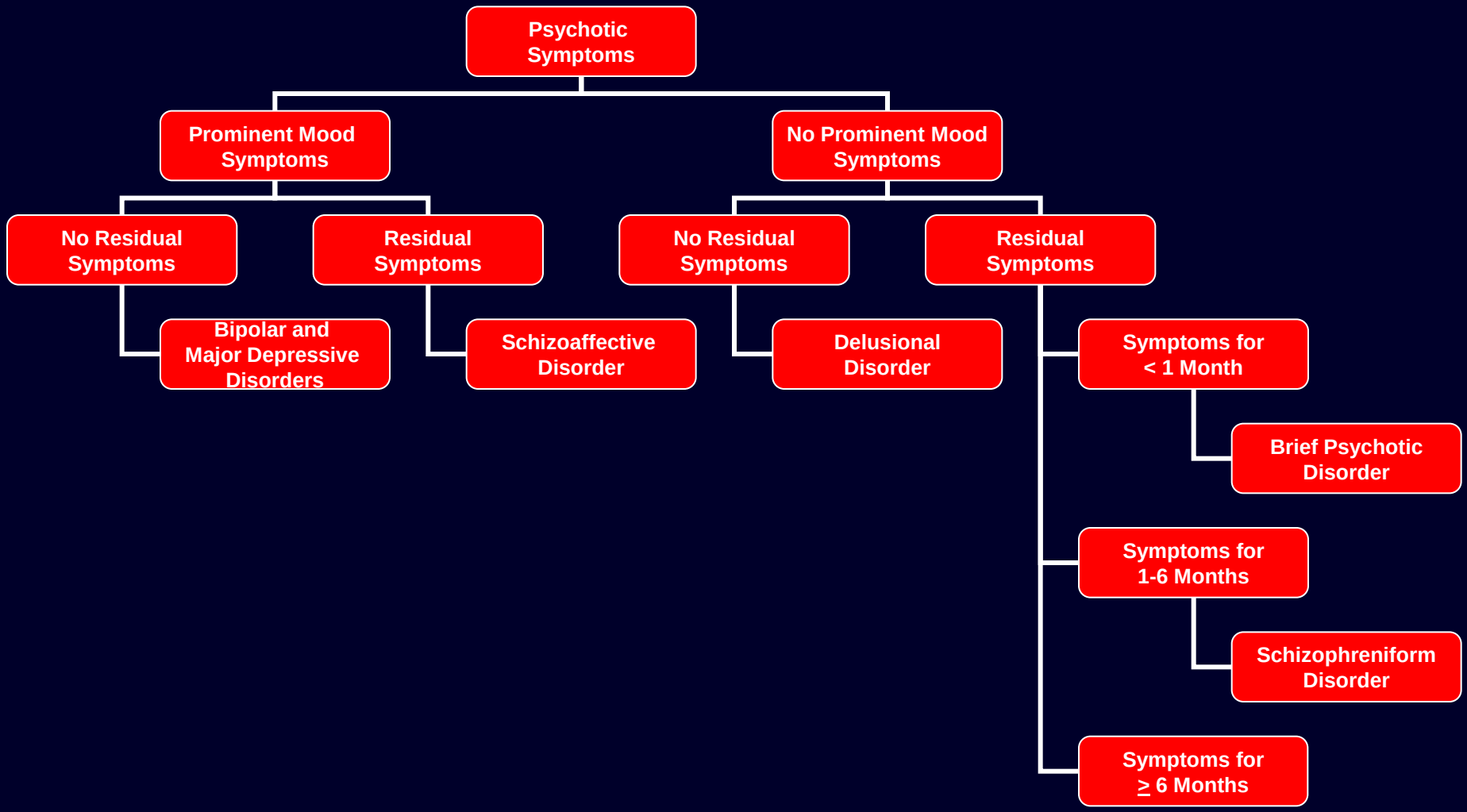
Syndromes That May Look Like Psychosis

- Schizotypal PD – includes cognitive or perceptual disturbances (ideas of reference, magical thinking, paranoid delusions) but without persistent hallucinations or delusions
- Paranoid PD – pervasive suspicion of others without persistent delusions
- Malingering – intentional production of false or grossly exaggerated symptoms motivated by external incentives.
- Factitious Disorder – intentional production of symptoms to assume the sick role
- Confabulation – invention of false information to cover a gap in memory
- Over-valued Ideas – unreasonable belief or idea that is not as firmly held as a delusion
- Dissociation – disruption in the usually integrated functions of conciousness, memory, identity, or perception of the environment

Approach to the Patient

- Mental Status Exam
  - Assess for presence and nature of psychotic symptoms
  - Note character of mood, affect, thought process and thought content
- Psychiatric History
  - Prodromal vs. premorbid signs and symptoms
  - Morbid or clinical presentation
  - Physical Examination and clinical labs

Diagnostic Flow Chart for Psychosis



Schizophrenia

- Course of Illness
  - Risk factors
  - Onset
  - Progression
  - Prognostic variables
- Diagnosis
  - DSM-TR criteria
  - Postive vs Negative Symptoms debate
  - Subtypes

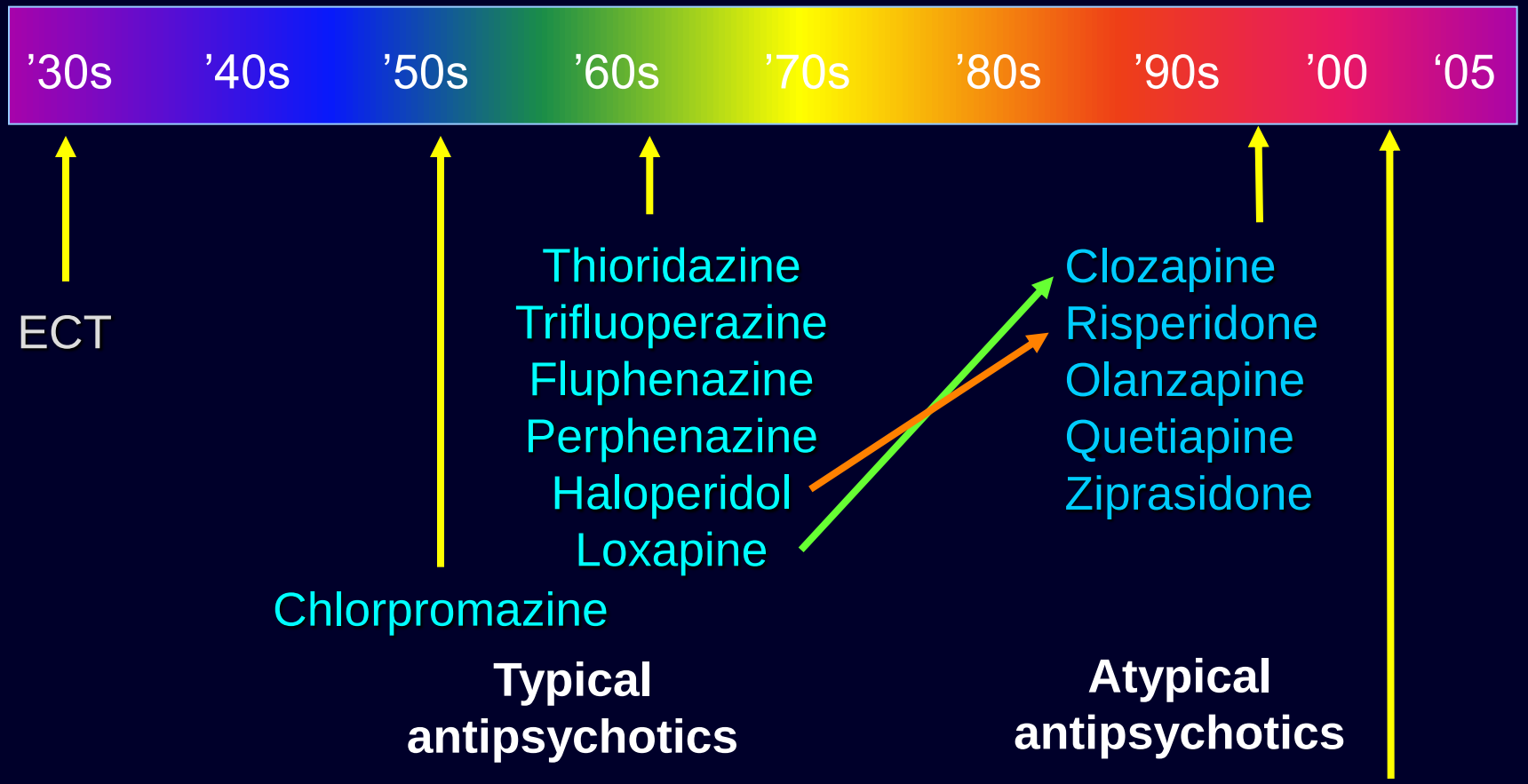
Schizophrenia: Subtypes

- Undifferentiated — Characteristics of > one subtype
- Paranoid — Systematized persecutory delusions, older age of onset better functioning
- Residual — One previous psychotic episode, subsequent negative symptoms, mild positive symptoms but no current psychosis
- Disorganized — Incoherent speech, mirror gazing, facial grimacing poor grooming, inappropriate emotional responses (silliness), onset before age 25
- Catatonic — Stupor or extreme agitation, incoherent speech or muteness blank facial expression, bizarre posturing (waxy flexibility), rare since introduction of antipsychotic agents.

Schizophrenia: Etiology

- Genetics
  - Concordance for monozygotic twins about 50% v. dizygotes 10%
  - De novo mutations arising in paternal germ cells
- Environmental factors
  - First and Second trimester pregnancy: Viral infections, Drug Exposure
  - Third trimester pregnancy: Hypertension, Diuretics
- Neurological Abnormalities
  - Decreased size/activity of pre-frontal cortex; lateral and third ventricular enlargement; abnormal cerebral symmetry; decreased brain density; decreased volume of hippocampus, amygdala and parahippocampal gyrus
  - EEG shows decreased alpha waves, increased theta and delta waves, epileptiform activity. Also, saccadic eye movements (poor smooth visual persuit
- Neurotransmitter Abnormalities: DA, 5-HT, NE, Glutamate

Developments in Medical Treatments for Psychotic Disorders



Antipsychotic Drug Classification
"Typical Antipsychotic Drugs"

Classification	Prototype
Phenothiazines	
Aliphatics	Chlorpromazine (Thorazine)
Piperazine	Fluphenazine (Prolixin)
	Perphenazine (Trilafon)
Piperidine	Thioridazine (Mellaril)
	Mesoridazine (Serentil)
Butyrophenone	Haloperidol (Haldol)
	Pimozide (Orap)
Thioxanthine	Thiothixene (Navane)
Dibenzoxazepines	Loxapine (Loxitane)
Dihydroindolones	Molindone (Moban)

Limitations of Conventional Antipsychotics*

- Gaps in efficacy
  - Cognitive function
  - Negative symptoms
  - Depressive symptoms
- Profound number of side-effects with long-term health consequences
  - Anticholinergic (dry mouth, ocular changes, constipation, tachycardia, etc)
  - Extrapyramidal (dystonia, akathisia, parkinsonian, dyskinesia, TD)
  - Sedation
  - Cardiovascular (arrhythmias, blood pressure changes)
  - Metabolic (weight gain, altered glucose, hyperlipidemia)
  - Altered hormones (hyperprolactinemia, FSH, LH)
  - Lowered seizure threshold

*Considerable differences exist among drugs conventional antipsychotics

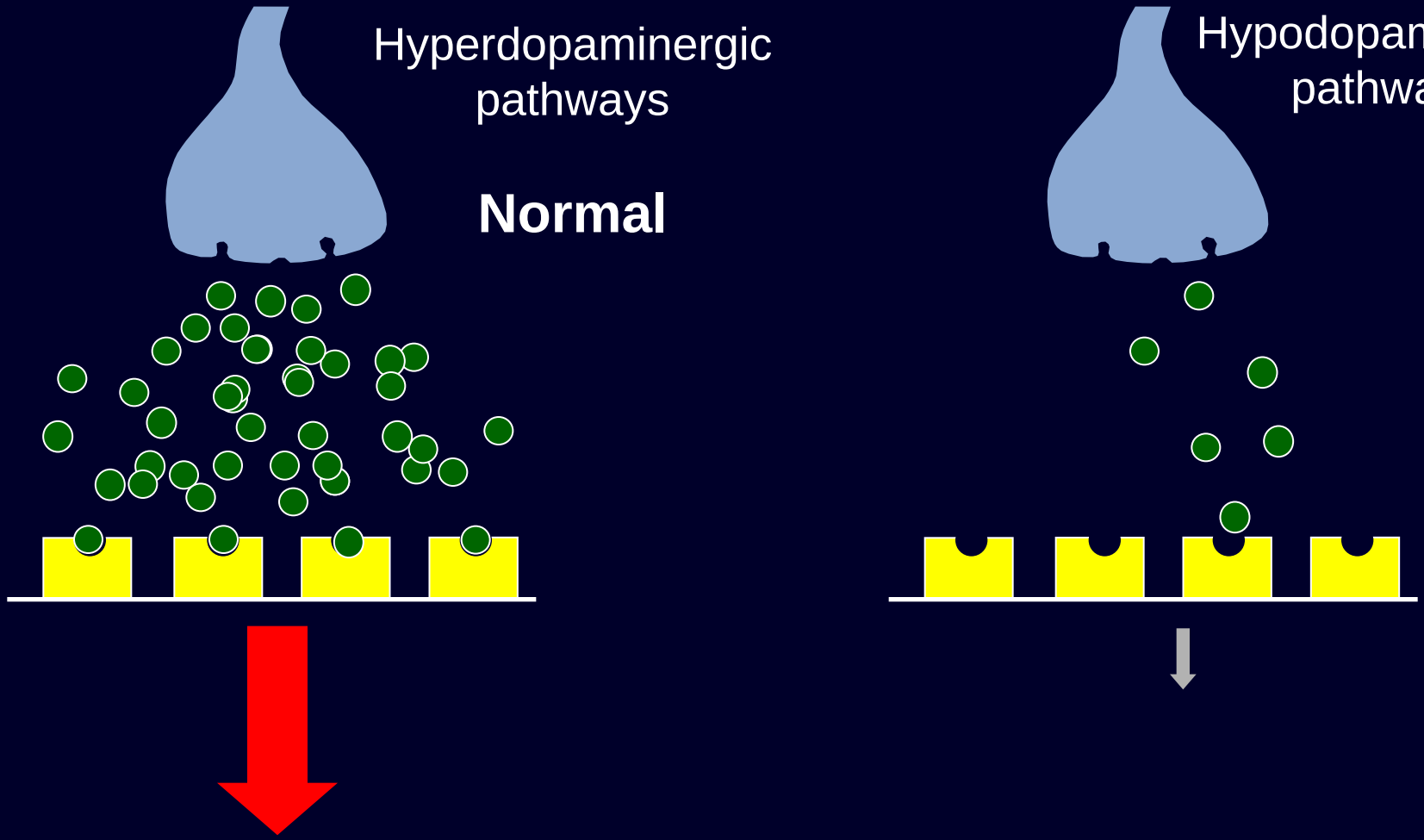
Antipsychotic Drug Classification
"Atypical Antipsychotic Drugs"

Classification	Prototype
Dibenzodiazepines	Clozapine (Clozaril)
Benzisoazoles	Risperidone (Risperdal)
Thienbenzodiazepines	Olanzapine (Zyprexa)
Dibenzthiazepines	Quetiapine (Seroquel)
Benzisothiazolyls	Ziprasidone (Geodon)
Piperazinyl quinolinone	Aripiprazole (Abilify)

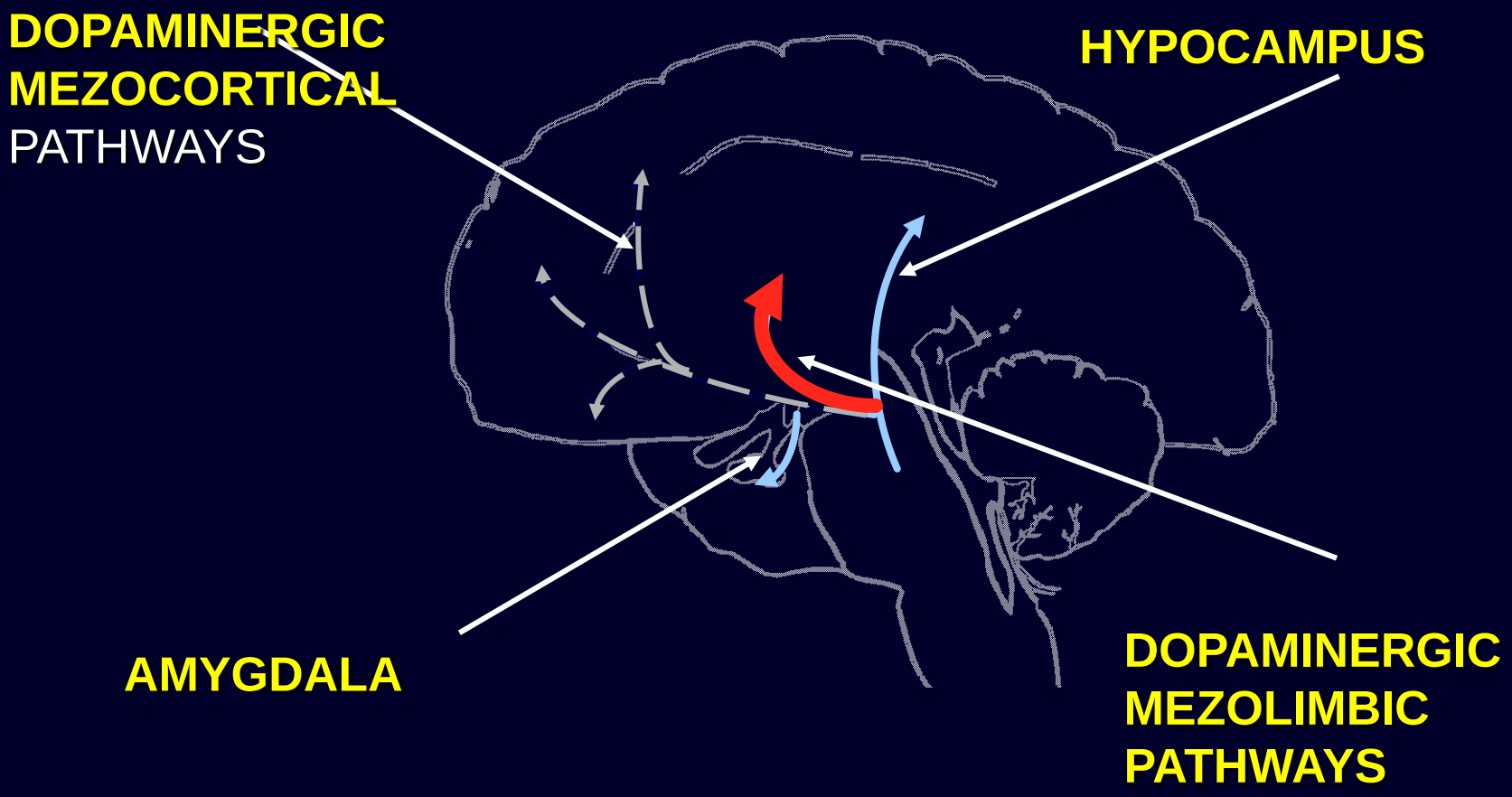
Limitations of Current Atypical Antipsychotics*

- Gaps in efficacy remain
  - Cognitive function
  - Negative symptoms (improved vs conventional)
  - Depressive symptoms
  - Slower onset of therapeutic response
- Improved motor side effects but now different adverse effects for some, but not all atypicals, with long-term health consequences
  - Significant weight gain
  - Increased risk of hyperglycemia and type 2 diabetes
  - Altered lipid profiles (non-specific and increases in CHO and TGL)
  - Cardiac effects (orthostatic hypotension, tachycardia and QTc prolongation)
  - Hyperprolactinemia

Dopamine Theory of Schizophrenia



Dopamine Hypothesis of Schizophrenia



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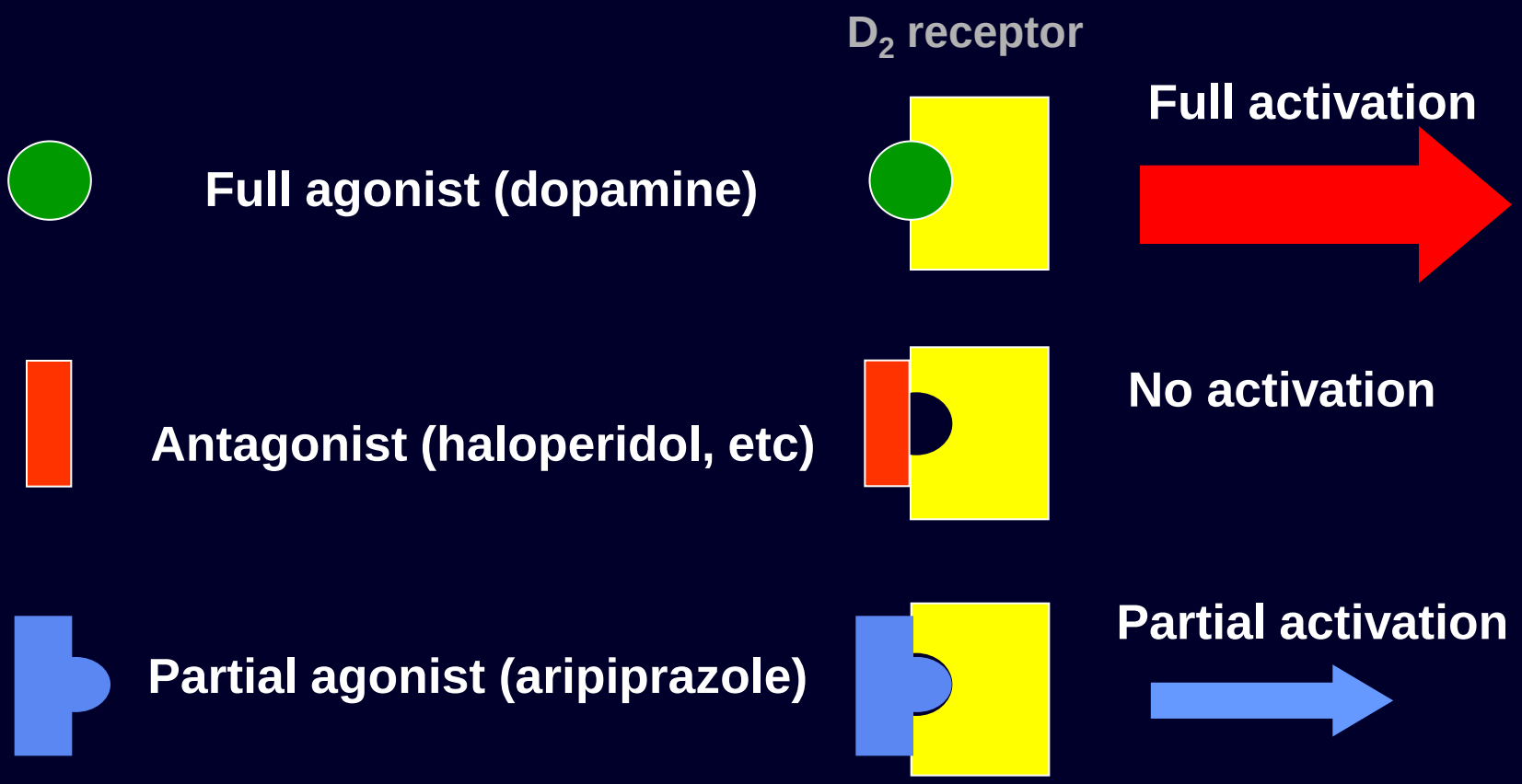
Intrinsic Activity at D_2 Receptors

Intrinsic Activity Describes the Ability of a Compound to Activate Receptors



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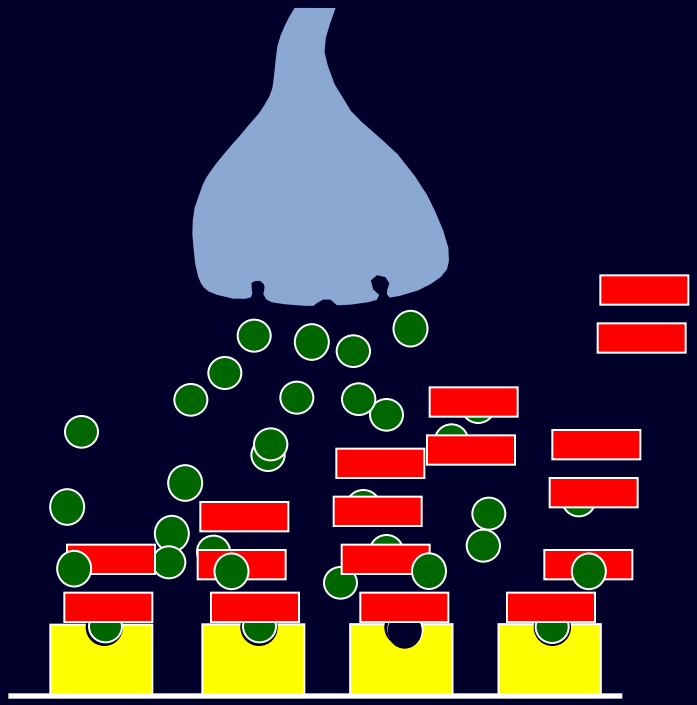
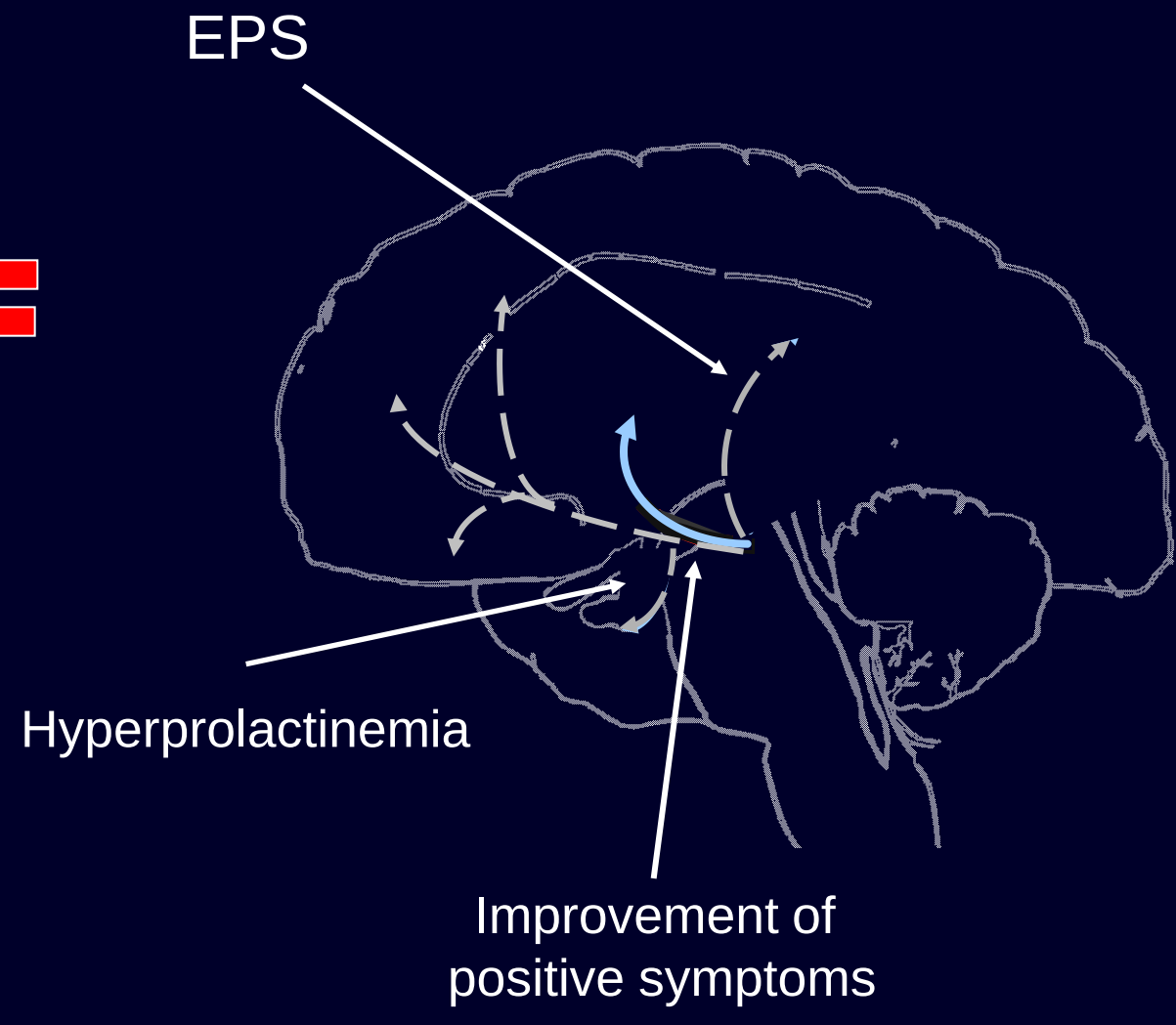
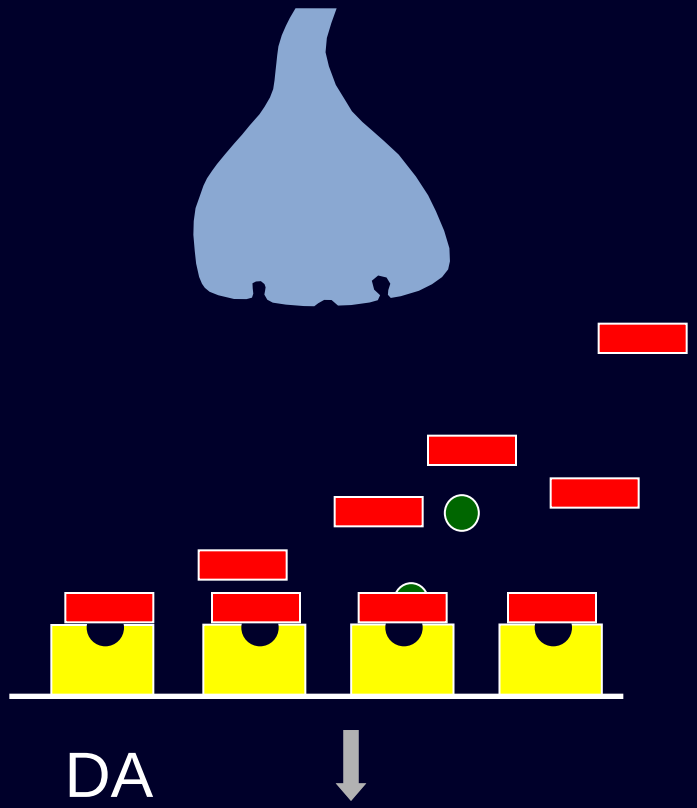
Dopamine Antagonism: Positive Symptoms and EPS



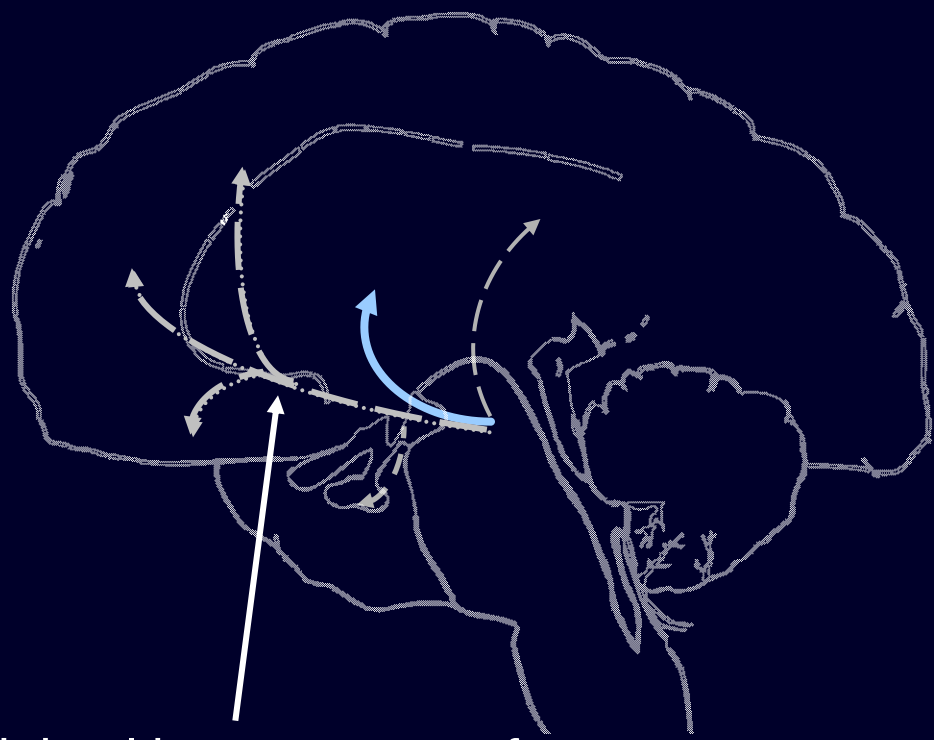
DA inhibition



Dopamine Antagonism: Negative Symptoms

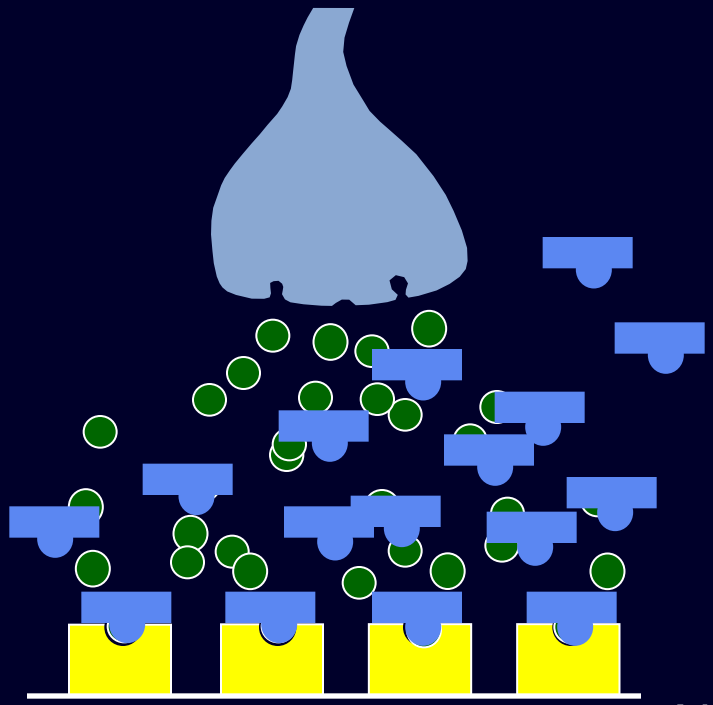


DA inhibition

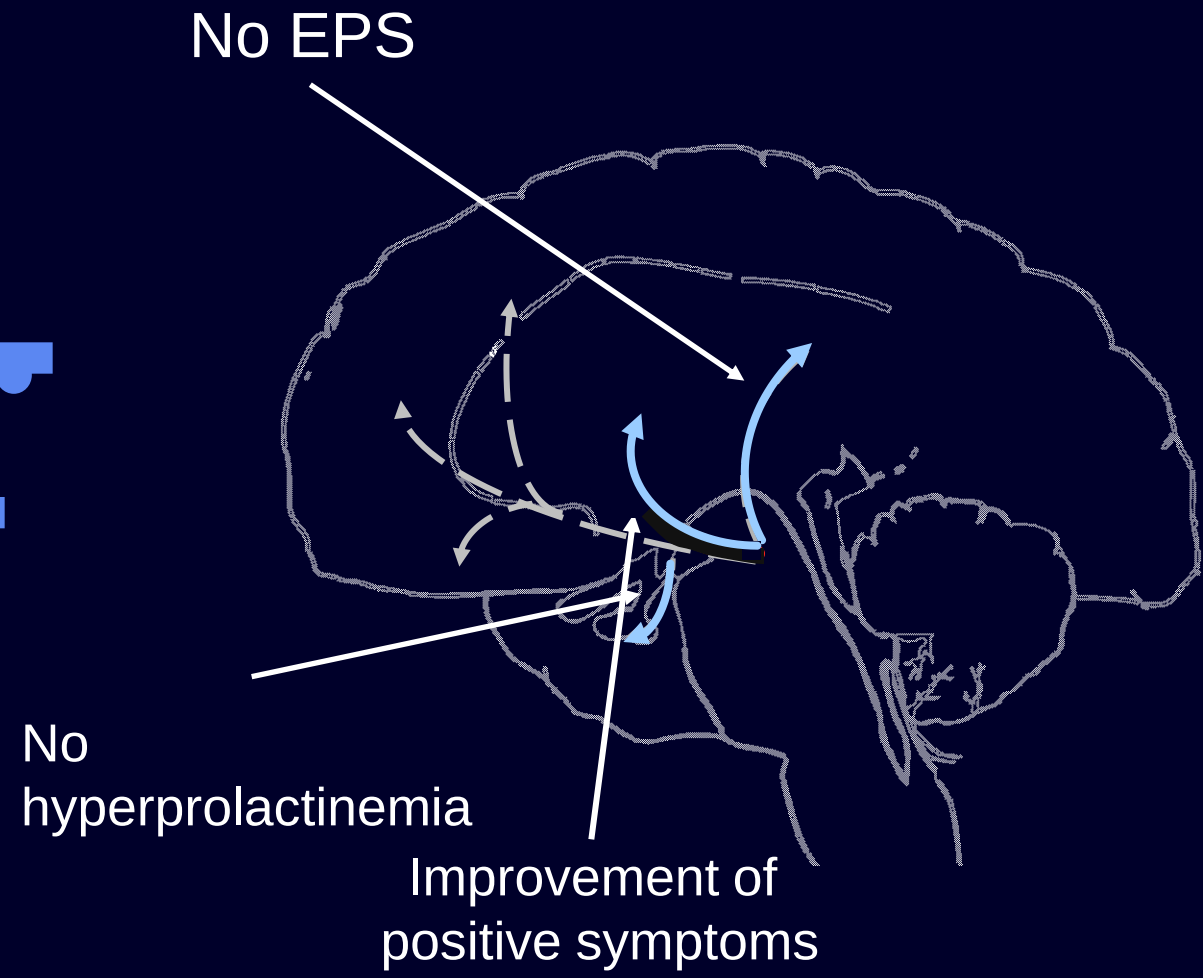


Minimal improvement of negative symptoms

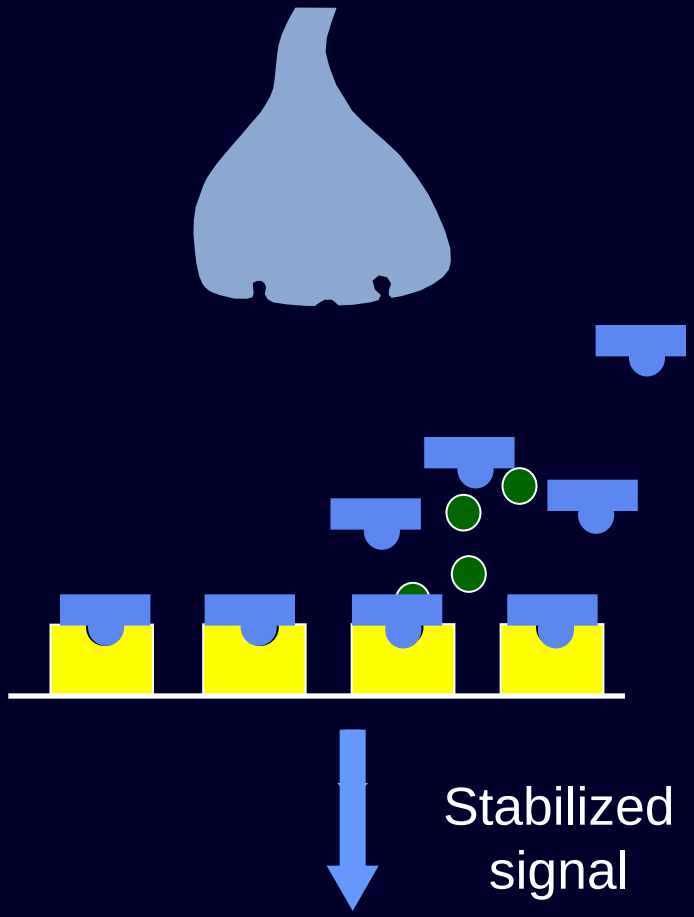
Dopamine Partial Agonism: Positive Symptoms and EPS



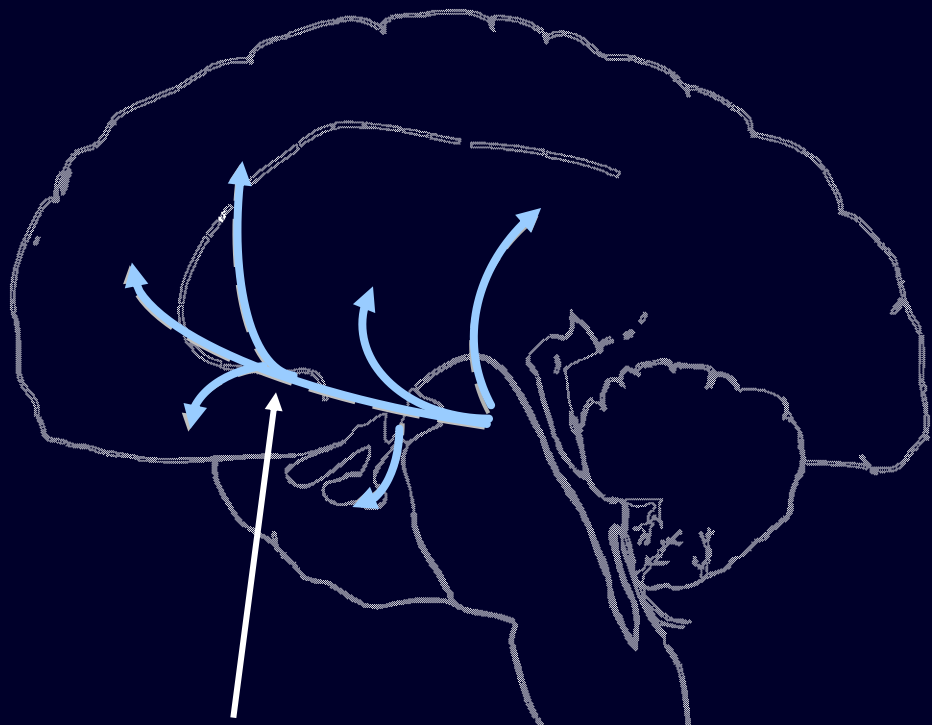
DA stabilization



Dopamine Partial Agonism: Negative Symptoms



Stabilized signal



Improvement of negative symptoms, cognition and amotivation

Antipsychotic Drugs

Mechanism of Action

- Blockade of dopamine (D2) receptors is associated with positive symptom therapeutic efficacy.
  - A threshold value of 65-70% of D2-receptor occupancy is needed for therapeutic response.
  - EPS incidence rises as D2-receptor occupancy increases above 80%.
- Blockade of Serotonin (5HT 2a) receptors is associated with negative (or mood) symptom therapeutic efficacy.

  Farde L, et al.: Arch Gen Psychiatry 1992; 49:538-544.

- Elevation of prolactin levels show a threshold relationship to D2-receptor occupancy.

  Schlegel S, et al.: Psychopharmacology (Berl) 1996; 124:285-287.

- Blockade of other receptors is generally responsible for side-effects.

Anticholinergic Side-Effects

Adverse Effect	Medical Complications
Decreased Secretions – Mouth – Lungs – Skin	Drying of membranes Dental caries, ulcers Mucous plugs Hyperthermia, dry skin
Increased Pupil Size	Acute narrow-angle glaucoma Photophobia
Inhibited Accomodation	Blurred vision, especially near vision
Tachycardia	Angina, Myocardial infarction
Urinary retention	Bladder distention, aggravates UTIs
Decreased GI Motility	Constipation, toxic adynamic ileus

Mostly Phenothiazines [PTZ's] (aliphatic and piperidine, lesser freqency and severity with piperazine), mild with atypicals

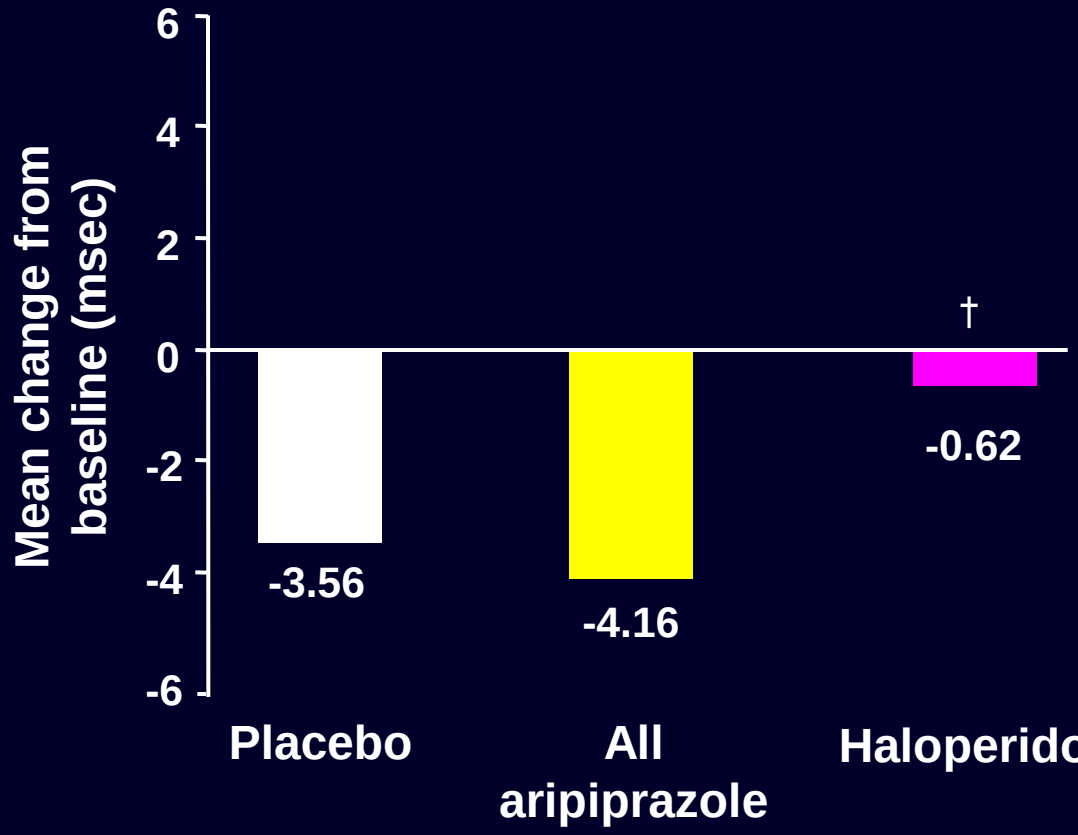
CNS Effects

- Cognitive Effects
  - Drowsiness
  - Weakness, lethargy, fatigue
  - Nightmares, agitation, restlessness, insomnia
  - Confusion, disturbed concentration, disorientation
- Neurological Effects (mostly traditional antipsychotics)
  - Fine tremor
  - Dystonia
  - Akathisia (rare)
  - Parkinsonian-like movements
  - Tardive Dyskinesia
- Seizures (abrupt withdrawal, rapid dose increases)
- Tinnitus
- Myoclonus

Cardiovascular Effects

- Typical Antipsychotic's
  - Orthostatic Hypotension (anti-adrenergic); avoid use of adrenergic blockers
    - Prazocin
  - Tachycardia and/or cardiac arrhythmias
  - Prolonged conduction time (QTc interval)
    - contraindicated in heart block or post- myocardial infarction
  - Congestive heart failure
  - ECG Abnormalities
    - Non-specific ST-T changes
    - Flattening of T-waves
  - Quinidine-like effect
  - Do not administer epinephrine in asthmatic attacks
- Atypical Antipsychotic's
  - Rare cardiodynamic effects other than mild Orthostatic Hypotension
  - Prolongation of the ECG QTc interval

Aripiprazole Short-Term Clinical Trials: Mean Change in QTc Interval*



- QTc interval (>450 msec) occurred in 1 patient treated with placebo, 2 patients treated with haloperidol, and in 2 patients treated with aripiprazole
- No patient had a QTc interval of >500 msec

*QTc interval determined by Fractional Exponent Correction Method (FDA).
†$P \leq 0.05$, significantly different from placebo.

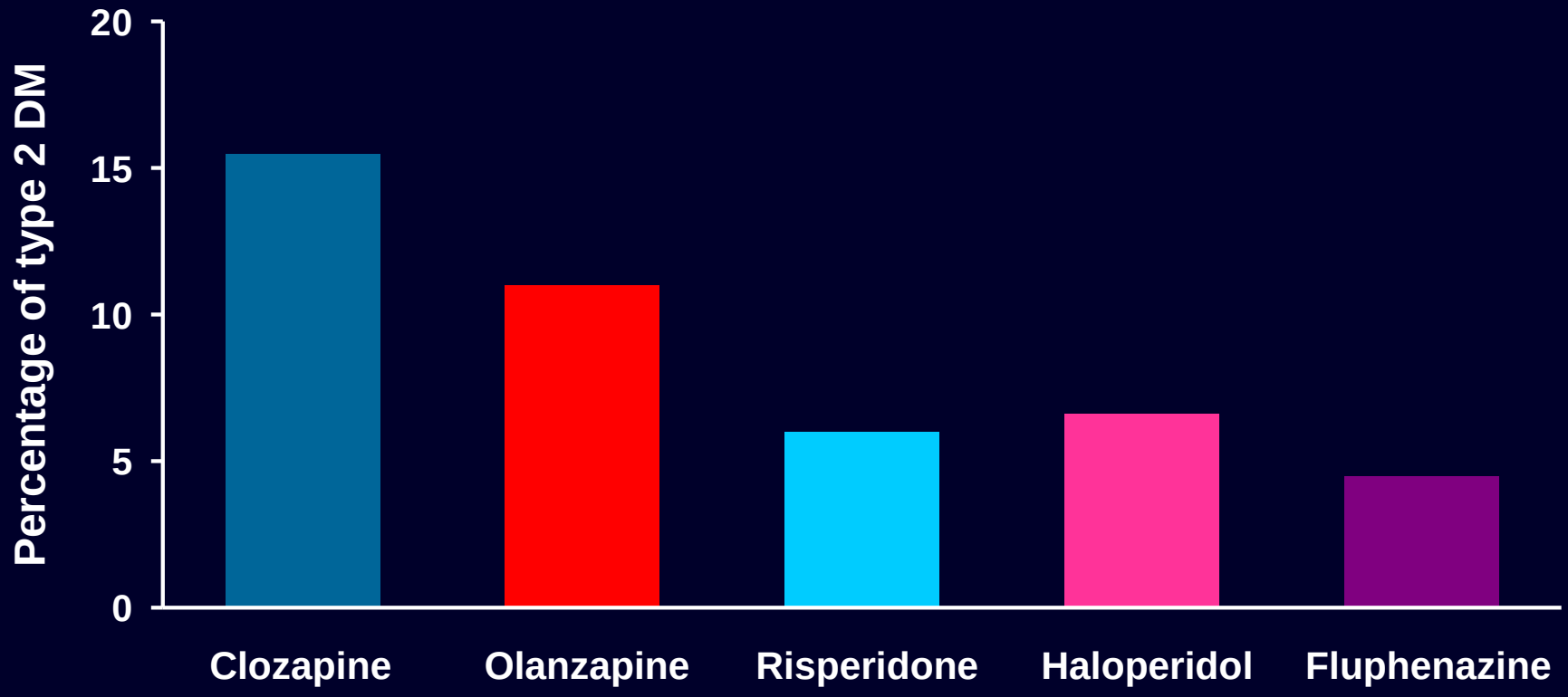
*

Endocrine and Sexual Side-Effects

- Gynecomastia, Galactorrhea, Breast tenderness - males and females
  - mostly Typical antipsychotic's, rare with Risperidone
- Testicular swelling, Decreased libido
- Anorgasmia
  - (helped by bethanecol, pseudoephedrine or cyproheptadine
- Weight gain
  - (mostly olanzapine, clozapine or quetiapine, also chlorpromazine)
- Increased blood sugar levels
  - (clozapine > olanzapine > chlorpromazine)
- Increased blood triglyceride, cholesterol (LDL)
  - (clozapine > olanzapine > chlorpromazine)

Differential Incidence of Type 2 Diabetes Mellitus

Retrospective Assessment of 396 Patients With Schizophrenia by Chart Review[1,2]



McIntyre et al. *Can J Psychiatry.* 2001;46:273.
Zoler. *Clin Psychiatr News.* 1999;27;20.

Allergic and Miscellaneous Reactions

- Allergic Reactions (more with PTZ's)
  - Pigment deposition in lens and cornea (may cause visual changes)
  - Pigment deposition in retina can lead to irreversible blindness
  - Allergic maculopapular skin rashes, urticaria, pruritis are common
  - Photosensitivity
  - Serum sickness (all)
- Miscellaneous Reactions
  - Effects on Hepatic Function
  - Increased AST/ALT levels: ? Problem
  - Increased GGTP and bilirubin levels: obstructive disease
  - Hematological Effects (mostly Clozapine)
  - Transient leukopenia or leukocytosis
  - Agranulocytosis
  - Poikilothermia

Use During Pregnancy

- Antipsychotics have not been clearly demonstrated to have teratogenic effects, but potential is present. Psychosis may also cause malformations.
- If possible, avoid during first trimester
- Lethergy and urinary retention in neonate has been associated with antipsychotic use in third trimester
- Avoid breast feeding: antipsychotics are excreted into breast milk (1-3% of mother's dose)
- Effectiveness of oral contraceptives may be reduced in first two months of taking antipsychotics (exceptions ziprasidone and aripiprazole).

General Treatment Guidelines

- A high potency conventional antipsychotic (e.g., haloperidol) or atypical antipsychotic is considered first line treatment.
- Second-line drug choices include another “atypical” or “typical” antipsychotic or decanoate formulation. Combinations (although without proven efficacy) are reserved for refractory patients.
- A drug trial should last 4-6 weeks
- The trial should be extended when there is a partial but continued response and shortened when no response occurs or side effects are intolerable or unmanageable
  - Ziprasidone or Aripiprazole may be the better choice in patients at risk for weight gain, altered lipid profile
  - Aripiprazole, Ziprasidone or Quetiapine may be favored when low EPS or low prolactin levels are desired
- Start dosing low with gradual increases according to response with conventional antipsychotics, stay within FDA guidelines for atypicals
- Clozapine is the only efficacious drug for treatment-resistant patients.