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SP.236 / ESG.SP236 Exploring Pharmacology  
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# Atypical (2<sup>nd</sup> Generation) Antipsychotics



# What do antipsychotics treat?

- Psychotic Disorders (Psychosis)
  - Abnormal Thinking and Perceptions
  - Loss of Contact with Reality
  - Delusions (false beliefs)
  - Hallucinations
    - Schizophreniform
    - Brief Psychotic Disorder
    - Schizophrenia
    - Schizoaffective Disorder
    - Delusional Disorder
    - Shared Psychotic Disorder (rare)
    - Korsakoff Psychosis (rare)

# 1<sup>st</sup> Generation vs. 2<sup>nd</sup> Generation

- 1<sup>st</sup> Generation - Typical
- Dopamine Antagonists
- Unpleasant Side Effects
  - Muscle stiffness
  - Tremor
  - Abnormal movements
  - Tardive Dyskinesia
  - Decreased sexual interest
  - Amenorrhea
  - Anorgasmia
  - Oligomenorrhea
  - Galactorrhea
  - Impaired Cognition
- 2<sup>nd</sup> Generation - Atypical
- Dopamine and other Neurotransmitter Antagonists
- Mild, Temporary, Unpleasant Side Effects
  - Drowsiness
  - Rapid heartbeat
  - Dizziness when changing position
  - Weight gain
  - Decreased sexual interest
  - Possible amenorrhea
  - Agranulocytosis (Clozapine - ~1% of patients)

# Atypical Antipsychotic Medications

- Clozapine (Clozaril)
- Risperidone (Risperdal)
- Olanzapine (Zyprexa)
- Quetiapine (Seroquel)
- Ziprasidone (Geodon)
- Sertindole
- Aripiprazole
  - All vary in specific side-effect profiles

# Receptor Profiles

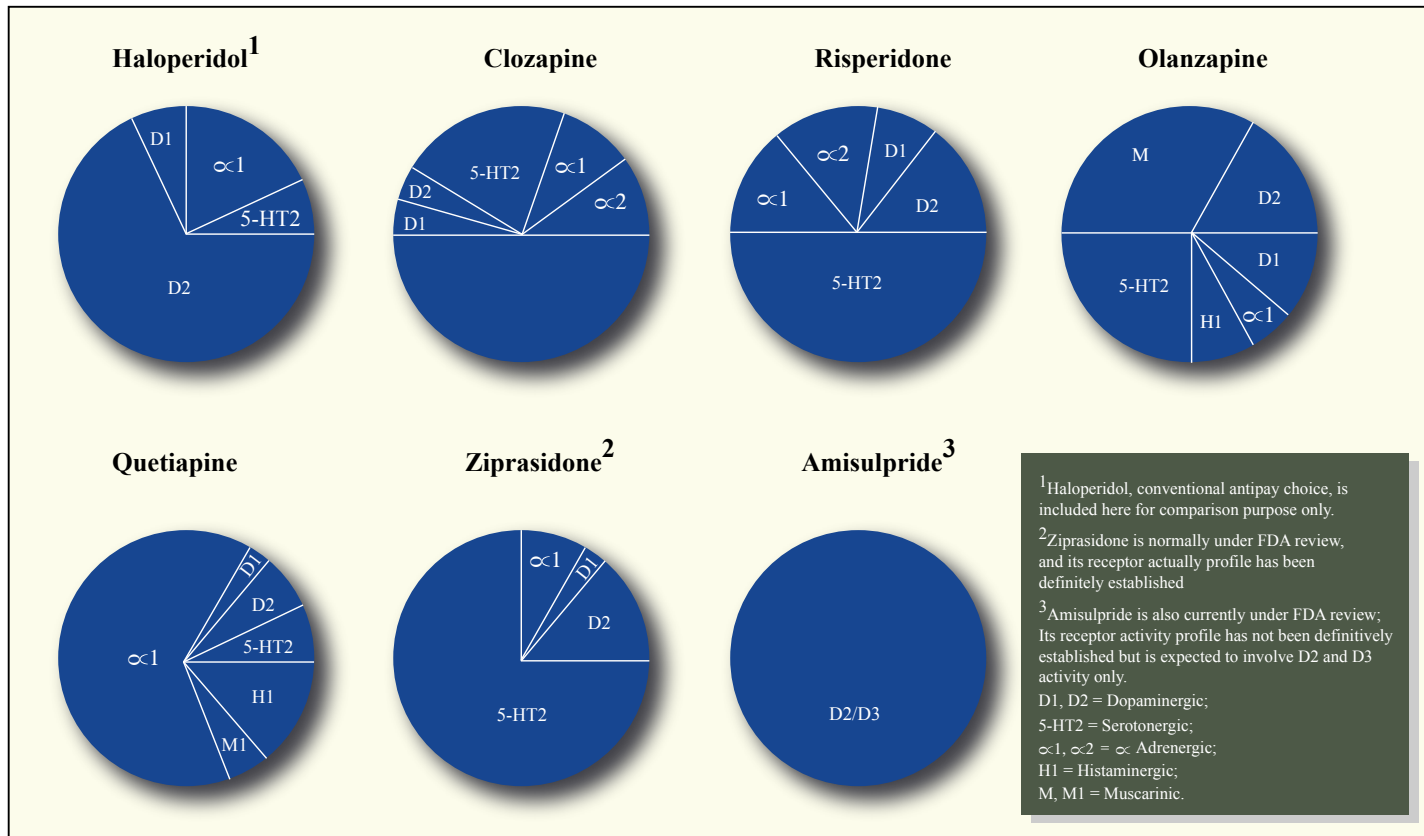


Figure by MIT OpenCourseWare.

# “Fast-Off-D2” Theory

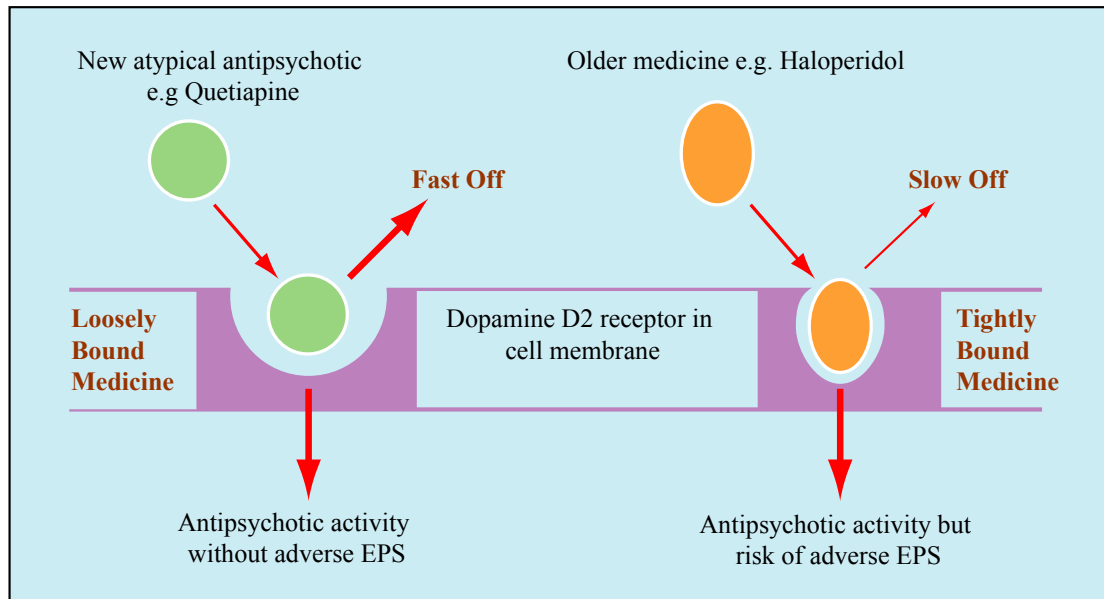


Figure by MIT OpenCourseWare.

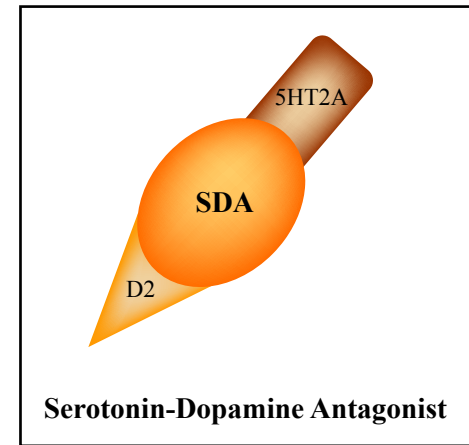
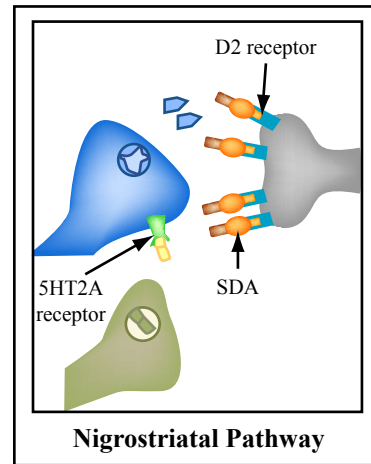
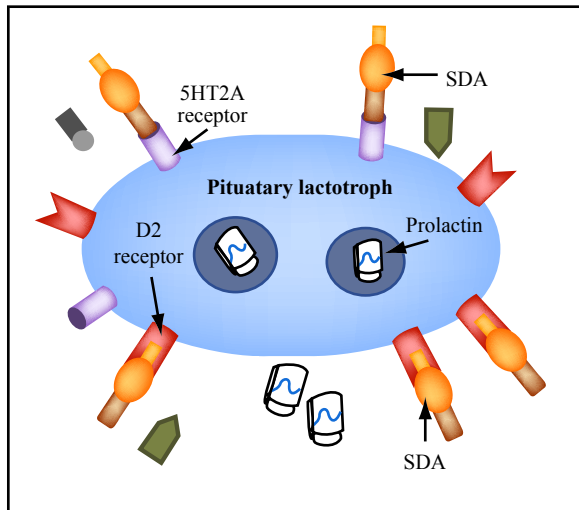
- D2 Antagonism
- EPS = Extrapyramidal Symptoms
- Seeman, 2004

# Partial Dopamine Agonism

- Aripiprazole (OPC-14597)
  - High Affinity for D2 and D3 receptors
    - Works on:
      - Postsynaptic D2 receptors
      - Presynaptic autoreceptors
  - 5-HT1A partial agonism
  - 5-HT2A antagonism
  - Modest affinity for alpha1-adrenergic, H1, 5-HT7 receptors



# Serotonin-Dopamine Antagonism



Figures by MIT OpenCourseWare.

- Higher ratio of drug affinity for serotonin receptor relative to dopamine receptor explains enhanced efficacy and reduce EPS (Meltzer *et al*)
- 5-HT2A AND D2 antagonist

# 5-HT<sub>1A</sub> Agonism

- Clozapine
- Increases effect of dopaminergic antagonists
- Counteracts induction of EPS
- Enhances prefrontal dopamine release
  - Useful against negative symptoms and cognitive dysfunction

# Glutamate Antagonism

- Phencyclidine (PCP)
- Ketamine
  - N-methyl-D-aspartate (NMDA) receptor antagonists
    - Induce Schizophrenia-like symptoms
- Clozapine and Olanzapine
  - Inhibit PCP in brain slices
  - Block ketamine-induced brain metabolic activation
- Metabotropic Receptors
  - Modify amounts of glutamate cells release, instead of turning them on or off