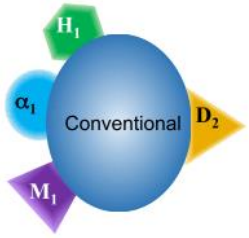
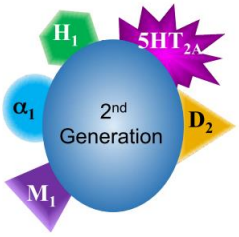
FIRST GENERATION ANTIPSYCHOTICS:



Chlorpromazine
Flupenthixol*
Fluphenazine*
Haloperidol*
Loxapine
Perphenazine
Pimozide
Thiothixene
Trifluoperazine
Zuclopenthixol*
* = available as long-acting IM injectables

SECOND GENERATION ANTIPSYCHOTICS:



Aripiprazole*
Asenapine
Brexpiprazole
Clozapine
Olanzapine
Paliperidone ER*
Quetiapine
Quetiapine SR
Risperidone*
Ziprasidone
* = available as long-acting IM injectables

RECEPTOR BINDING: All SGAs bind 5HT2A before D2 except aripiprazole

D1	? postulated to improve cognitive impairment
D2	Antipsychotic, causes EPS, secondary negative symptoms, endocrine effects
D3	Antidepressant (?)
D4	?
5HT1A	DO NOT BLOCK; as an agonist: antidepressant, anxiolytic, reduced EPS and negative symptoms
5HT2A*	Reduces EPS, potentially reduces negative symptoms
5HT2C*	Potentially treats negative sx and cognition, antidepressant
α1	Orthostatic hypotension, sedation, dizziness, reflex tachycardia
H1	Sedation, increased appetite, weight change, hypotension
M1	Blurred vision, dry mouth, constipation, urinary retention, impaired memory

*5HT2A/2C AGONISM (somatodendritic) = decrease of NE and DA in PFC
ANTAGONISM = increase of NE and DA in PFC

COMPARING ANTIPSYCHOTICS:

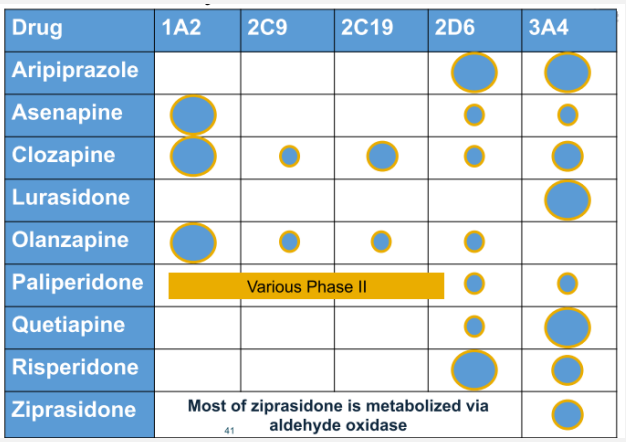
- No clear and consistent difference between the FGA and SGA agents with regards to treatment response to positive symptoms
  - EXCEPTION: clozapine for treatment-resistant patients
- SGA agents may be better than FGA agents with regards to treatment response to negative sx (small but positive size)
- SGA agents have greater propensity to cause metabolic SE (weight gain, diabetes mellitus, dyslipidemia, metabolic syndrome)
  - Clozapine, quetiapine, risperidone

PHARMACODYNAMICS OF ANTIPSYCHOTICS:

		FGA	SGA (+ 5HT2A antagonism)
D2	**Mesolimbic**	Psychosis treated by D2 receptor antagonism	Psychosis treated by D2 and 5HT2A receptor antagonism*
	Mesocortical	Neuroleptic induced deficit syndrome (worsening of negative symptoms)	Reduced neuroleptic induced deficit syndrome
	Nigrostriatal	Extrapyramidal sx (EPS)	Reduced EPS liability
	Tubero-infundibular	Increase in prolactin release	Reduced prolactin release **
H1	• Sedation; weight gain		
α1	• Decreased BP; dizziness; drowsiness		
M1	• Dry mouth; urinary retention; blurred vision; constipation		

* 5HT2A antagonism increases dopamine in other pathways = offsets negative D2 antagonistic effects
** dopamine = prolactin decreases; antagonize = prolactin increases
serotonin = prolactin increases; antagonize = prolactin decreases

CYTOCHROME P450:



Palperidone and ziprasidone = least likely to cause drug interactions
Aromatic hydrocarbons induce CYP1A2 (smoke from cigarettes, marijuana)

ANTIPSYCHOTIC PROPERTIES AND THEIR SIDE EFFECTS:

	Clozapine	Quetiapine	Olanzapine	Risperidone	Haloperidol
Off rate	15 secs	16 secs	17 mins	27 mins	38 mins

Low D2 receptor affinity	**High D2 receptor affinity**
Chlorpromazine	Haloperidol, pimozide, perphenazine
↓	↓
SEs due to: H1, α1, M1 receptor antagonism	D2 receptor antagonism
SEs Sedation, weight gain, orthostatic hypotension, urinary retention	EPS (dose-related)

EXTRAPYRAMIDAL SYMPTOMS (EPS):

- Extrapyramidal sx is directly related to D2 receptor antagonism
  - Decrease dopaminergic neurotransmission
  - Increased cholinergic transmission
- Treatment: anticholinergic agents (M1 antagonists)
  - Benztropine 2-6 mg/day
  - Trihexphenidyl 4-12 mg/day
- Some antipsychotics have potent anticholinergic action which inherently provides an anti-EPS mechanism

WEIGHT GAIN AND DIABETES:

Clozapine > olanzapine > chlorpromazine > quetiapine > risperidone > haloperidol > aripiprazole > **ziprasidone**