Therapeutic Mechanisms for Psychosis

Typical, 1st generation, antipsychotics *haloperidol, chlorpromazine, fluphenazine, thioridazine*

- Use is decreasing due to incidence of adverse effects
- Due to blockade of dopamine receptors in nigrostriatal pathway
- Side effect onset seen in 1-2 weeks
    - Extrapyramidal symptoms (EPS)Akathisia, dystonia, and pseudo parkinsonism
    - Tardive dyskinesia (TD) Choreiform movements -rapid, objectively purposeless, irregular, and spontaneous
    - Athetoid movements –slow and irregular
        - Late in onset developing over several months after treatment initiation
    - Can be very severe and occurs in ~20% of patients
    - Condition typically worsens when treatment is initially tapered off
- Neuroleptic malignant syndrome (NMS)Life-threatening emergency
    - Muscular rigidity, autonomic instability, and altered consciousness
- Chlorpromazine is prototype
- All are potent D2receptor antagonists
    - Also have varying degree of antagonism at other receptorsα, muscarinic cholinergic, H1histamine, 5-HT2

Atypical (second-generation) antipsychotics

- all are potent D2receptor antagonists with rapid dissociation, SDA: serotonin dopamine agonists, D2 partial agonist, serotonin partial agonists at 5HT1A
- All have greater potency as 5-HT2A receptor antagonists than as D2receptor antagonists
- Differentiation in pharmacology from the typical

Lower propensity to cause extrapyramidal symptoms (EPS), less negative symptoms, and tardive dyskinesia (TD*)*

- *Clozapine* is prototype, *Aripiprazole, asenapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone*
- *Aripiprazole(Abilify*) theoretically should produce fewer movement-related adverse effects due, in part, to its pharmacology as a D2partial agonist

Receptors

Muscarinic Cholinergic Blocking

- SE: dry mouth, blurred vision etc.
- MCB decreases EPS in nigrostriatal pathway.
- DA can no longer suppress acetylcholine
- When DA blocked acetylcholine becomes overactive.
- So we block with an anticholinergic.

Blockade of Histamine 1-receptors

- weight gain and drowsiness

Blockade of alpha 1 adrenergic receptor

- cardiovascular: hypotension and drowsiness

Dopamine 2 Antagonism

Medications:

- D2 antagonist
- 5HTN2A/D2
- D2/5HT1A partial agonist
- 5HT2A antagonist

Mesolimbic/Mesostriatal Pathway

- Dopamine too high
- D2 antagonist/partial agonist will go in and block Dopamine receptors.
    - Therapeutic: reduced positive symptoms
    - Side effects: Apathy Anhedonia

Mesocortical Pathway

- Dopamine loo tow
- D2 Antagonist/partial agonist will make the bad symptoms worst (cognitive symptoms, affective symptoms, negative symptoms)

Tuberoinfundibular Pathway (hypothalamus & Pituitary)

- Regulates D2 receptors with prolactin
- If you block D2 receptor in this part of the brain prolactin can go up
    - Side effects:
        - Can cause breast secretions
        - Breast increase in size in men

Nigrostriatal Pathway

- Chronic blockade of D2 receptors in the nigrostriatal dopamine pathway can cause upregulation of those receptors, which can lead to a hyperkinetic motor condition known as tardive dyskinesia, characterized by facial and tongue movements (e.g., tongue protrusions, facial grimaces, chewing) as well as quick, jerky limb movements.
- Side effects: motor side effects
    - Akathisia
    - Dystonia
    - DIP drug induced parkinsonism

Side effects: When the dopamine receptors are blocked chronically then more dopamine receptors get made which leads to tardive dyskinesia, or fast moving of limbs of the body. Old drugs caused this ½ the time.

Dopamine inhibits Ach release because it inhibits the striatum neuron. If you block the receptor with a D2 antagonist then it is going to disinhibit the ach neuron which will cause an increase of Ach which will lead to drug induced parkinsonism. Then we use an anticholinergic

M1 Inserted (muscanric cholinergic neurons)

- When blocked cause cognitive dysfunction and drowsiness
- Dry mouth, Blurred vision, and Constipation

VMAT2 storage of dopamine

- VMAT2 is the pump on the vesicle that transports dopamine into the vesicle.

- VMAT2 inhibitor the pumps on the vesicles can no longer be kept away from the enzymes that destroys the dopamine.
- VMAT2 inhibits the indirect pathway (D2) and direct pathway (D1)
- Drugs:
  - *tetrabenazine* is used for Huntington's disease
    - Destroyed by CYP450 2D6 fast half life or given 3 times a day.
  - *Deu-tetrabenazine*
    - So you do not have to give as frequently
    - Treatment for tardive dyskinesia
  - *Valine-alpha tetrabenazine*
    - Prodrug: in the stomach and blood treat valine is taken off and then alpha tetrabenazine is the VMAT2 inhibitor

Earliest D2 Antagonists used to treat psychosis.

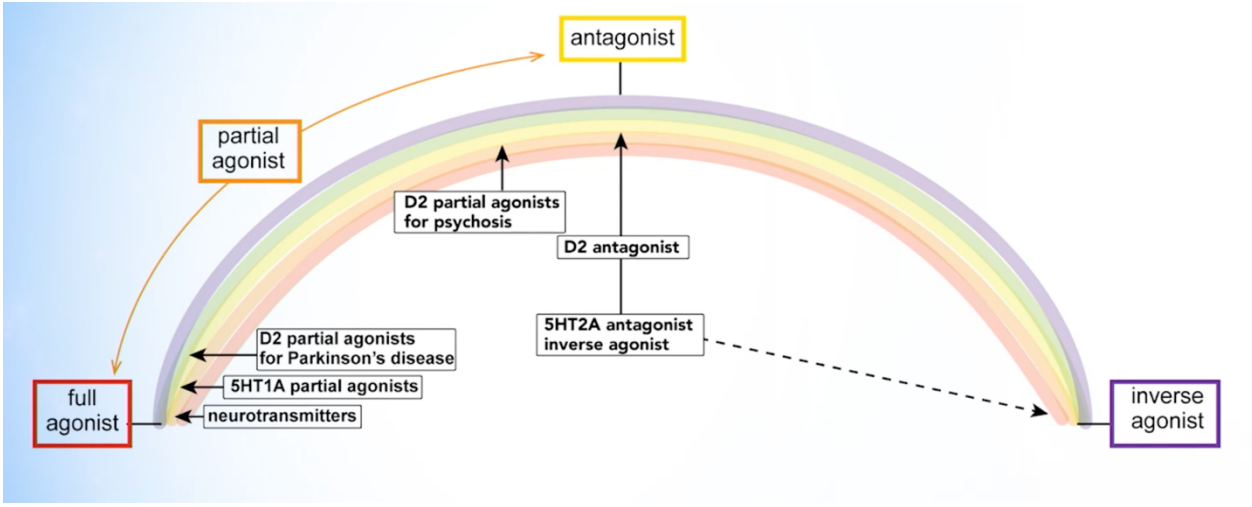
Generic name	Trade name	Comment
Chlorpromazine	Thorazine	Low potency
Cyamemazine	Tercian	Popular in France; not available in the US
Flupenthixol	Depixol	Depot; not available in the US
Fluphenazine	Prolixin	High potency; depot
Haloperidol	Haldol	High potency; depot
Loxapine	Loxitane	
Mesoridazine	Serentil	Low potency; QTc issues; discontinued
Perphenazine	Trilafon	High potency
Pimozide	Orap	High potency; Tourette syndrome; QTc issues; second line
Pipothiazine	Piportil	Depot; not available in the US
Sulpiride	Dolmatil	Not available in the US
Thioridazine	Mellaril	Low potency; QTc issues; second line
Thiothixene	Navane	High potency
Trifluoperazine	Stelazine	High potency
Zuclopenthixol	Clopixol	Depot; not available in the US

- H1(histamine) Inserted:
  - Side effects: weight gain, drowsiness
- Alpha 1 Inserted
  - Side effects: dizziness, decrease blood pressure, drowsiness
- Both help calm people down

Chlorpromazine
- Alpha 1 antagonist
- Histamine 1 antagonist
- D2 antagonist

Fluphenazine
- D2, D3

Haloperidol
- D2, D3
- Alpha 1



Full agonist: stimulates the receptor as much as it can be stimulated

5HT2A antagonist (remember 5HT2A is always excitatory)

- regulates serotonin in at least three pathways.
    - Pathways
        - PFC to SN/VTA to Emotional striatum. Seen in Hallucinogens. Causes hallucinations
            - Block with 5HT2A antagonist
        - PFC SN/VTA to motor striatum. Causes drug induced parkinsonism
            - Block with 5HT2A antagonist
        - PFC to VTA to PFC. Side effects: flat emotional blunting, flattening of affect, lack of mental sharpness
            - Block with 5HT2A antagonist

Pituitary

- Serotonin increase prolactin
- Dopamine decreases prolactin
- If you have a drug that is a 5HT2a antagonist evens out

Full D2 antagonist

- Increase prolactin
- Drug induced parkinsonism
- No antipsychosis

Dopamine stimulant

- Leads to psychosis

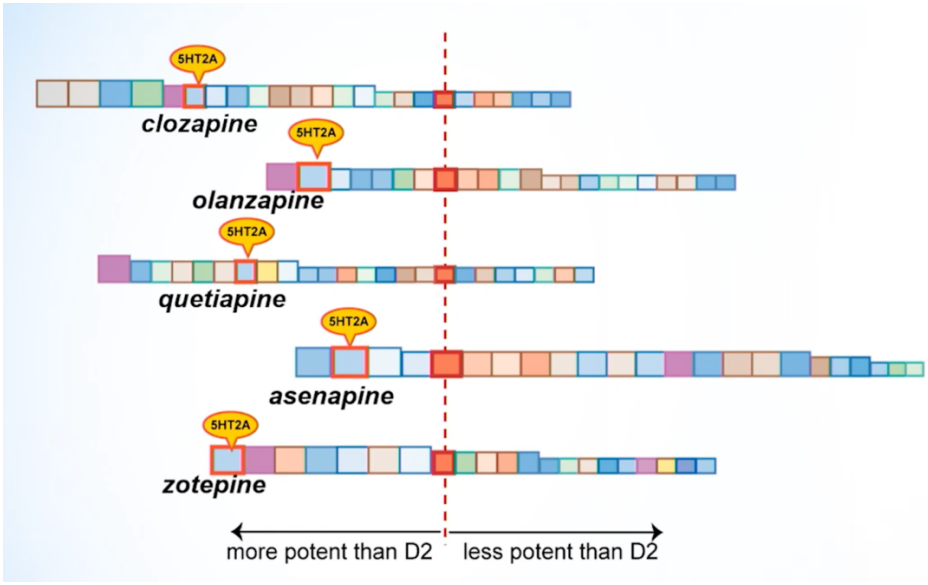
Dopamine partial agonist dopamine stabilizer: balance between agonist and antagonist action
Would lead not no psychosis, no prolactin changes, no drug induced parkinsonism.

5HT1A partial agonist (remember brake, inhibitory)

- Dopamine goes up lessen drug induced parkinsonism
- Decreases negative, cognitive, and affective symptoms

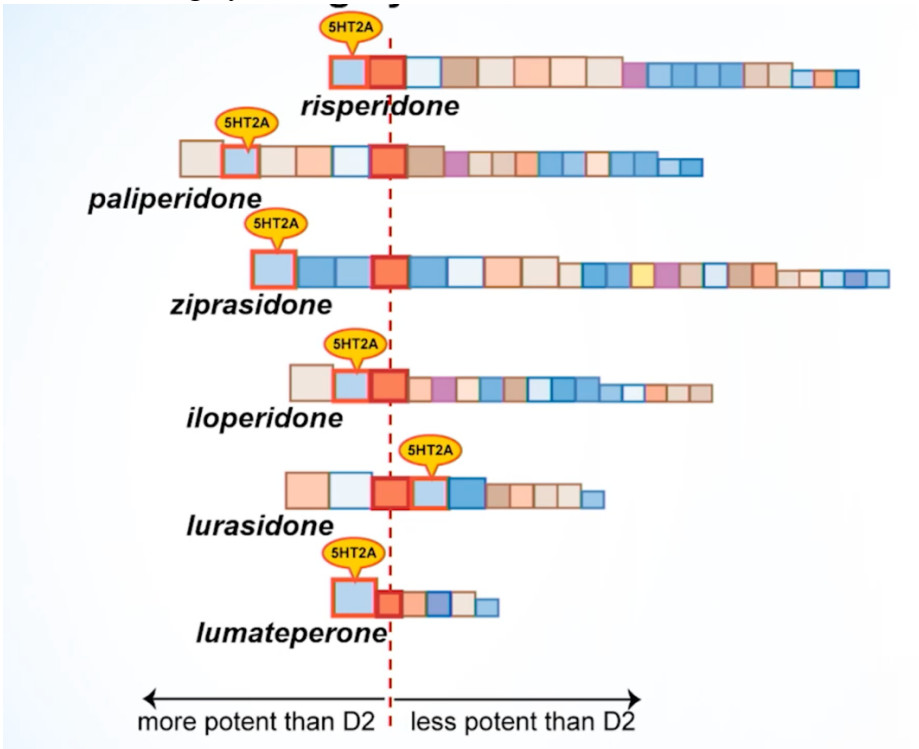
5HT2A binding by the “pines”

- Clozapine
- Olanzapine
- Quetiapine
- Asenapine
- zotepine



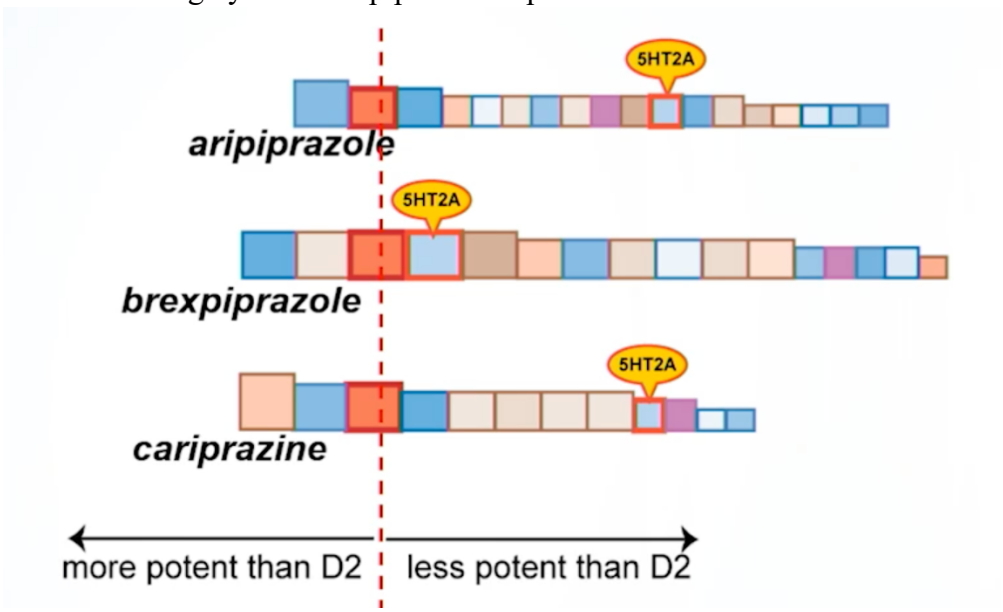
Monoamine reuptake inhibition (used for depression) is only clinical relevant is quetiapine
Alpha 2 (if blocked may have antidepressant effect) quetiapine and clozapine
D3 receptor is blocked by most antipsychotic drugs. Often times if it is blocked it is so weak that dopamine will pop it off.
5HT2C most pines have strong binding

5HT2A binding by the “dones and a rone”



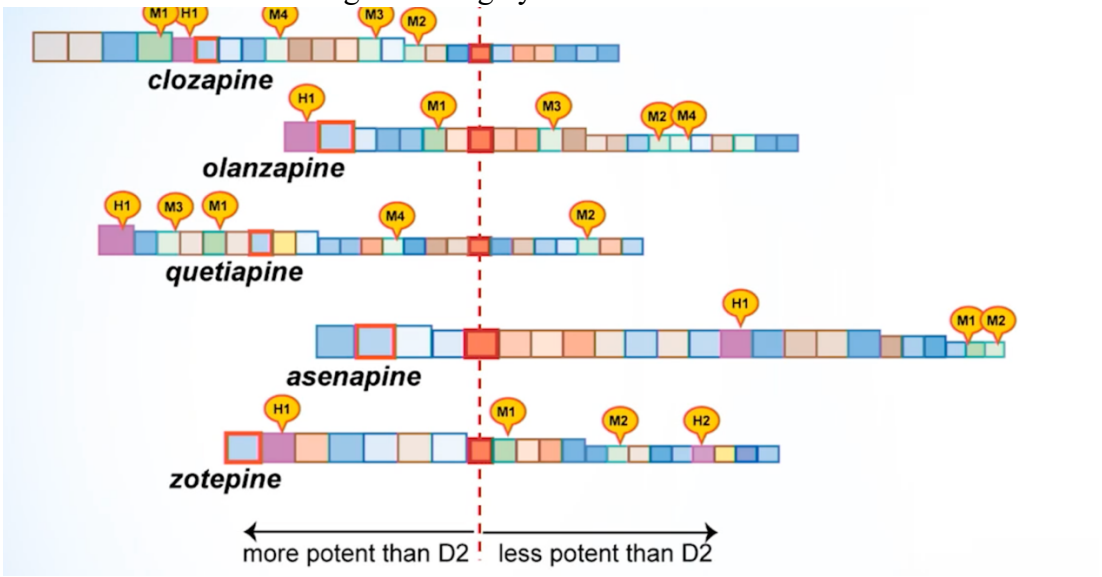
Monoamine reuptake inhibition is only clinically relevant in lumateprone

5HT2A binding by the “two pips and a rip”



Two pips and rip have Partial agonists for 5HT1A (dark blue box)
Used extensively for depression
D3: cariprazine has powerful D3 binding

Cortical Arousal
Alpha 1 receptors, M1 receptors, H1 receptors
Antihistamine/anticholinergic Binding by Pines



Antipsychotic Side effects

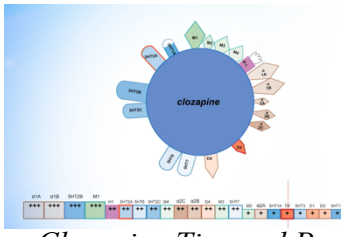
- increase triglycerides, Hyperinsulinism leads to prediabetes the diabetes. Can lead to premature death
- To prevent change the antipsychotic

Toolkit:

- Scale, BMI chart, fasting triglycerides, fasting glucose, chart on flow chart, or start on metformin, new drug samidorfan (when given with olanzapine reduces weight by 50%).

Medications Used to Treat Psychosis: Pharmacological and Clinical Profiles

Clozapine



- 5HT2C linked to weight gain
- M1, H1, alpha 1 causes sedation
- M1 sialorrhea (excess saliva), constipation (Paralytic ileus causes a bowel obstruction and is the number 1 cause of death with clozapine)
- Agranulocytosis

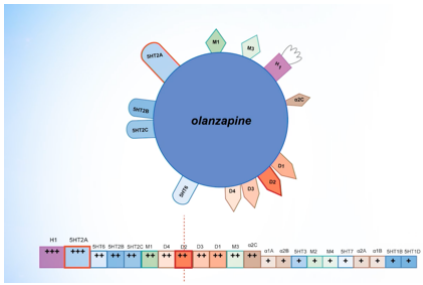
Clozapine Tips and Pearls

- Gold standard for efficacy in positive symptoms
- Approved specifically for treatment-resistant schizophrenia
- Only antipsychotic proven (and approved) to reduce risk for suicide in schizophrenia (and schizoaffective
- May reduce violence in forensic cases
- Does not seem to cause tardive dyskinesia or raise prolactin
- Stopping smoking can raise clozapine levels
- Unique side effect profile prevents its first-line use and requires careful monitoring and management

Side Effects

- Neutropenia
- Constipation/paralytic ileus
- Sedation, orthostatic, tachycardia
- Sialorrhea
- Seizures (dose-dependent)
- Weight gain, dyslipidemia, hyperglycemia
- Myocarditis, cardiomyopathy, interstitial nephritis
- DRESS (Drug reaction with eosinophilia and systemic symptoms), serositis

Olanzapine



- 5HT2C & H1 linked to weight gain/metabolic
- 5HT2C & Alpha 2C antidepressant
- M1, H1, alpha 1 causes sedation
- M1 sialorrhea (excess saliva), constipation (Paralytic ileus causes a bowel obstruction and is the number 1 cause of death with clozapine)
- Bipolar I manic or mixed, ages 13-17 acute, 12.5 mg children, 20 mg adolescents

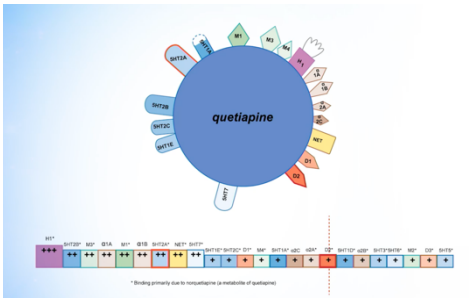
Olanzapine: Expert Tips and Pearls

- Some evidence of better efficacy than other first-line options, although this is controversial because efficacy varies greatly from one patient to another
- Also has a higher risk of metabolic side effects
- Tends to be used in higher doses than originally studied/approved for marketing
- Available as a long-acting injectable

	Schizophrenia, Acute	Schizophrenia, Maint.	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X	X	X (IM)	X	X	X*	X*	

*with fluoxetine

Quetiapine



- 5HT2C & H1 linked to weight gain/metabolic
- M1, H1, & alpha 1A linked to sedation
- 5HT2C, 5HT1A, NET, 5HT7 & Alpha 2C antidepressant

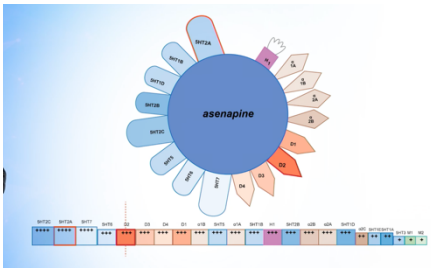
*Goldilocks and the three quetiapine's
800mg antipsychotic: to get D2 antagonism
300mg antidepressant:
50mg hypnotic

Quetiapine: Expert Tips and Pearls

- Lower risk of drug induced parkinsonism
- Major side effect is sedation, but it often wears off, especially with once-daily administration at night, also weight gain, insulin resistance and increased lipids. no EPS at any dose, No prolactin elevation
- Most often prescribed for conditions other than psychosis
    - Insomnia
    - Depression
    - Anxiety
    - Parkinson's disease psychosis

	Schizophrenia, Acute	Schizophrenia, Maint.	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X	X		X	X	X		

Asenapine



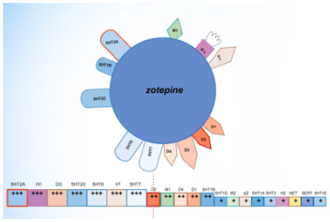
- taken sublingually
- 5HT2C & H1 linked to weight gain/metabolic
- H1 & Alpha 1A sedation
- 5HT2C, 5HT7, D3 & Alpha 2A antidepressant
- Pediatric bipolar: Bipolar I manic or mixed ages 10-17. 20 mg daily

Asenapine: Expert Tips and Pearls

- Chemical structure related to Mirtazapine
- Pharmacological properties suggest antidepressant actions but this has no been proven
- Available as a sublingual formulation because it is not absorbed if swallowed; must wait 10 minutes before eating or drinking
- Absorbed rapidly with sublingual administration, allowing for use as a rapid-acting PRN option
- Can be sedating, especially at first dose
- Also available as a transdermal formulation

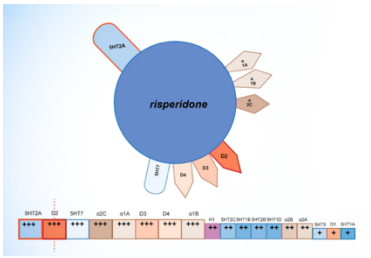
	Schizophrenia, Acute	Schizophrenia, Maint.	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X			X	X			

Zotepine



- do not use often, has binding like other "pines"
- Short acting so not used often (has to be given TID)
- Can cause seizures

Risperidone



- 5HT2A & D2 antagonist
- Approved for pediatric autism and bipolar in children 13-17
- Treats Irritability in ages 5-16
- Less weight gain & increased lipids than other atypicals
- For mania in children: FDA approved mania and mixed episodes: ages 10 and older. Monotherapy or adjunctive with lithium or valproate: Max dose: 4 mg children, 6mg adolescents

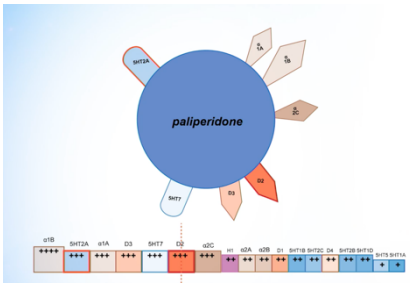
Risperidone: Expert Tips and Pearls

- Often preferred for children and adolescents (multiple approvals)
- Higher risk of prolactin elevation
- Risk of drug-induced parkinsonism increased with dose
- Available as two long-acting injectable formulations (2 weeks, 4 weeks)
- Plasma drug levels can be to guide dosing

	Schizophrenia, Acute	Schizophrenia, Maint.*	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X	X		X	X			X

*Delaying relapse
Also approved in "other psychotic disorders"

Paliperidone



- 5HT2A & D2 antagonist
- Alpha 1B

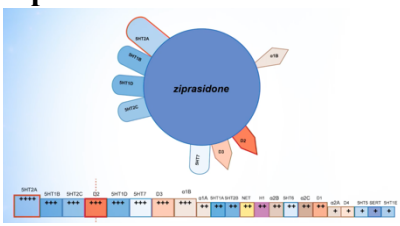
Paliperidone: Expert Tips and Pearls

- Metabolite of risperidone; not itself hepatically metabolized and thus few pharmacokinetic drug interactions
- Available as a sustained release oral formulation, which allows once daily dosing and may also reduce risk of some side effects compared to risperidone
- Can be underdosed in clinical practice
- Available as two long-acting injectable formulations (1 month, 3 month)
- Plasma levels can be used to guide dosing

	Schizophrenia, Acute	Schizophrenia, Maint.	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X	X						

Also approved in schizoaffective disorder

Ziprasidone



- 5HT2A antagonist
- QTc elongation

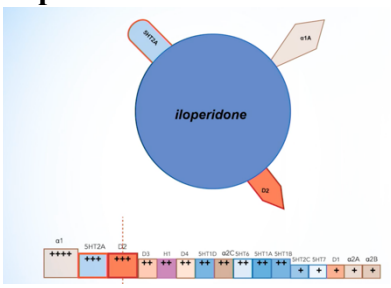
Ziprasidone: Expert Tips and Pearls

- Short acting, twice a day, helps negative symptoms
- Little or no propensity for weight gain or metabolic effects, no EPS
- Must be taken with food (or dose absorption is reduced by 50%)
- Earlier concerns about QTc prolongation now appear to be exaggerated

	Schizophrenia, Acute	Schizophrenia, Maint.*	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X	X	X (IM)	X	X			

*Delaying relapse

Iloperidone



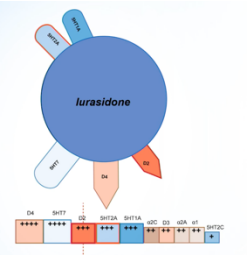
- Alpha 1 antagonist lowers blood pressure orthostatsis

Iloperidone: Expert Tips and Pearls

- Very low level of motor side effects
- Low level of dyslipidemia and moderate level weight gain
- Must be slowly titrated due to risk of orthostatic hypotension
- Generally dosed twice daily
- Often used as a switch agent in non-urgent situations
- Dose- dependent QTc prolongation (problem in overdose

	Schizophrenia, Acute	Schizophrenia, Maint.	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X	X						

Lurasidone



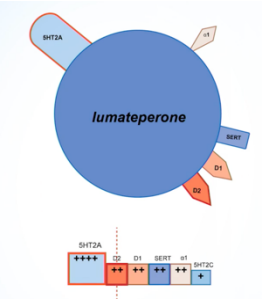
- D2, alpha 2, 5HT2A, & 5HT1A antagonist antidepressant

Lurasidone: Expert Tips and Pearls

- Use more in bipolar depression than in schizophrenia
- Low risk of weight gain or metabolic dysfunction
- Risk of motor side effects or sedation is reduced if dosed at night
- Should be taken with food (only 50% gets absorbed if not.

	Schizophrenia, Acute	Schizophrenia, Maint.	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X					X		

Lumateperone



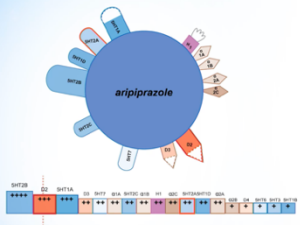
- 5HT2A
- SERT (serotonin transporter properties)

Lumateperone: Expert Tips and Pearls

- Agonist at the presynaptic receptor (presynaptic agonist will shut off some of the dopamine release so you do not have to block as many D2 postsynaptic receptors)
- Early clinical experience suggested efficacy for schizophrenia without dose titration
- Early clinical experiences also suggest little or no weight gain or metabolic disturbances
- Little or no drug-induced parkinsonism or akathisia

	Schizophrenia, Acute	Schizophrenia, Maint.	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X							

Aripiprazole



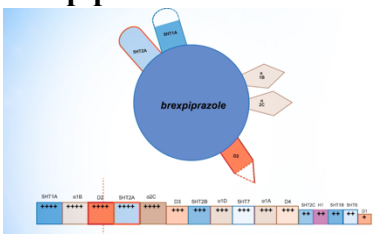
- first partial agonist
- D2 antagonist
- 5HT1A, 5HT2C, 5HT7 antidepressant
- Used often for unipolar depression with SSRI/SNRIs
- Not generally sedating due to no M1 or H1 activation
- Best for patients with metabolic or cardiac complications

Aripiprazole: Expert Tips and Pearls

- Used much more in depression than in schizophrenia
- Relatively low motor side effects: mostly akathisia
- Reduced prolactin rather than elevating it
- Little weight gain, except in children
- Peak plasma levels may not be reached for several days when starting and residual dose may remail for several days after discontinuing due to a very long (52 hour) half life
- Available as two long acting injectable formulations (4 week, 6w-8 week with loading injection)

	Schizophrenia, Acute	Schizophrenia, Maint.	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X	X	X (IM)	X	X		X	X
Also approved in Tourette's disorder (ages 6 to 18)								

Brexpiprazole



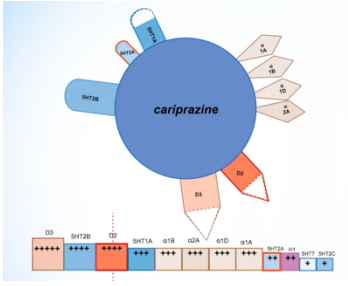
- 5HT1A & Alpha 2C antidepressant
- Works for agitation, PTSD, and Alzheimer's

Brexpiprazole: Expert Tips and Pearls

- Chemically and pharmacologically related to aripiprazole
- In late-stage clinical testing development with positive studies for treatment of agitation in dementia
- Promising preliminary data in combination with sertraline for the treatment of PTSD

	Schizophrenia, Acute	Schizophrenia, Maint.	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X						X	

Cariprazine



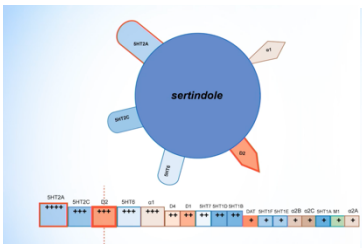
- powerful D3 partial agonist (blocking) properties
- Disinhibits (releases) dopamine in the cortex
- 5HT1A and Alpha 2A antidepressant action

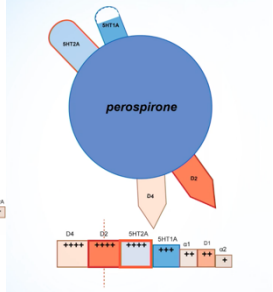
Cariprazine: Expert Tips and Pearls

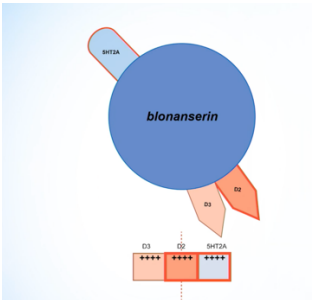
- Low incidence of drug induced parkinsonism; some akathisia which can be reduced with slow titration
- Low propensity for weight gain or metabolic disturbances
- Two long to very long-lasting active metabolites
- Highly effective and well tolerated in bipolar depression

	Schizophrenia, Acute	Schizophrenia, Maint.	Agitation	Bipolar Mania	Bipolar Maint.	Bipolar Depression	TRD (Adjunct)	Autism-related
Approval	X	X		X		X		

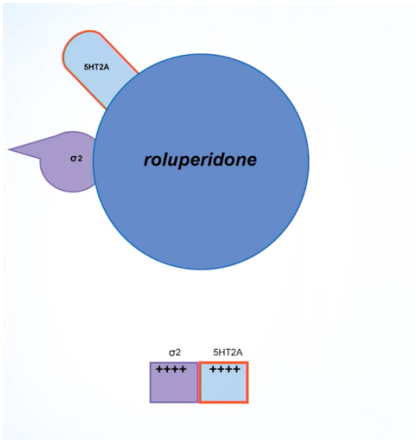
Others







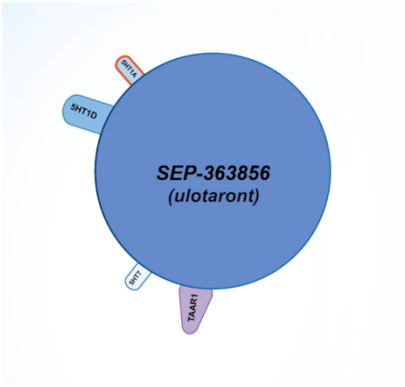
Future of treatments of Schizophrenia



New drug not yet approved

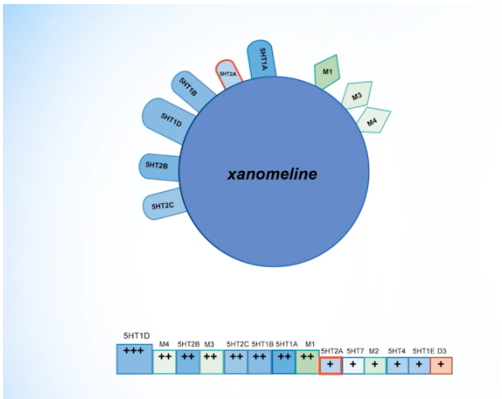
Trace Amines

- Five principal trace amines in humans
  - B-phenylethylamine (PEA)
  - P-Tyramine
  - Tryptamine
  - P-Octopamine
  - P-Synephrine
- Six human trace amine-associated receptors (TAARs)
  - TAAR1 (main TAAR in humans)
  - TAAR2
  - TAAR5
  - TAAR6
  - TAAR8
  - TAAR9



- TAAR receptors and monoamine receptors are in the same places
- TAAR1 agonist attaches to TAAR 1 receptors which dimerizes the D2 receptor. Making the D2 want to follow the Gi pathway which turns off dopamine synthesis (alternative pathway is the B-arrestin pathway goes go GSK-3 which leads to overstimulation and psychosis)

Xanomeline



- pan-agonist at muscarinic receptors
- Unclear what is functional due to binding
- M1 and M4 preferring in the brain
  - a phase 2 study shows it's an antipsychotic

Art of switching Antipsychotics

- Two agents DA antagonist: sedating: cross titrate: one goes up the other goes down.
- Sedating to non-sedating: need benzo; introduce benzo, up-titrate non-sedating and maintain the full does of sedating: short term and can get SEs.
- Similar with switch from D2 antagonist to D2 partial agonist DPA.

Adverse Side Effects of Antipsychotics

Type	Manifestations	Mechanism
Autonomic nervous system	Loss of accommodation, dry mouth, difficulty urinating, constipation	Muscarinic cholinoceptor blockade
	Orthostatic hypotension, impotence, failure to ejaculate	α-Adrenoceptor blockade
Central nervous system	Parkinson's syndrome, akathisia, dystonias	Dopamine-receptor blockade
	Tardive dyskinesia	Supersensitivity of dopamine receptors
	Toxic-confusional state	Muscarinic blockade
Endocrine system	Amenorrhea-galactorrhea, infertility, impotence	Dopamine-receptor blockade resulting in hyperprolactinemia
Other	Weight gain	Possibly combined H_1 and 5-HT_2 blockade

Drug Class	Drug	Advantages	Disadvantages
Phenothiazines			
Aliphatic	Chlorpromazine[1]	Generic, inexpensive	Many adverse effects, especially autonomic
Piperidine	Thioridazine[2]	Slight extrapyramidal syndrome; generic	800 mg/d limit; no parenteral form; cardiotoxicity
Piperazine	Fluphenazine[3]	Depot form also available (enanthate, decanoate)	(?) Increased tardive dyskinesia
Thioxanthene	Thiothixene	Parenteral form also available; (?) decreased tardive dyskinesia	Uncertain
Butyrophenone	Haloperidol	Parenteral form also available; generic	Severe extrapyramidal syndrome
Dibenzoxazepine	Loxapine	(?) No weight gain	Uncertain
Dibenzodiazepine	Clozapine	May benefit treatment-resistant patients; little extrapyramidal toxicity	May cause agranulocytosis in up to 2% of patients; dose-related lowering of seizure threshold
Benzisoxazole	Risperidone	Broad efficacy; little or no extrapyramidal system dysfunction at low doses	Extrapyramidal system dysfunction and hypotension with higher doses
Thienobenzodiazepine	Olanzapine	Effective against negative as well as positive symptoms; little or no extrapyramidal system dysfunction	Weight gain; dose-related lowering of seizure threshold
Dibenzothiazepine	Quetiapine	Similar to olanzapine; perhaps less weight gain	May require high doses if there is associated hypotension; short $t_{1/2}$ and twice-daily dosing
Dihydroindolone	Ziprasidone	Perhaps less weight gain than clozapine, parenteral form available	QT_c prolongation
Dihydrocarbostyril	Aripiprazole	Lower weight gain liability, long half-life, novel mechanism potential	Uncertain, novel toxicities possible

[1]Other aliphatic phenothiazines: promazine, triflupromazine.

[2]Other piperidine phenothiazines: piperacetazine, mesoridazine.

[3]Other piperazine phenothiazines: acetophenazine, perphenazine, carphenazine, prochlorperazine, trifluoperazine.