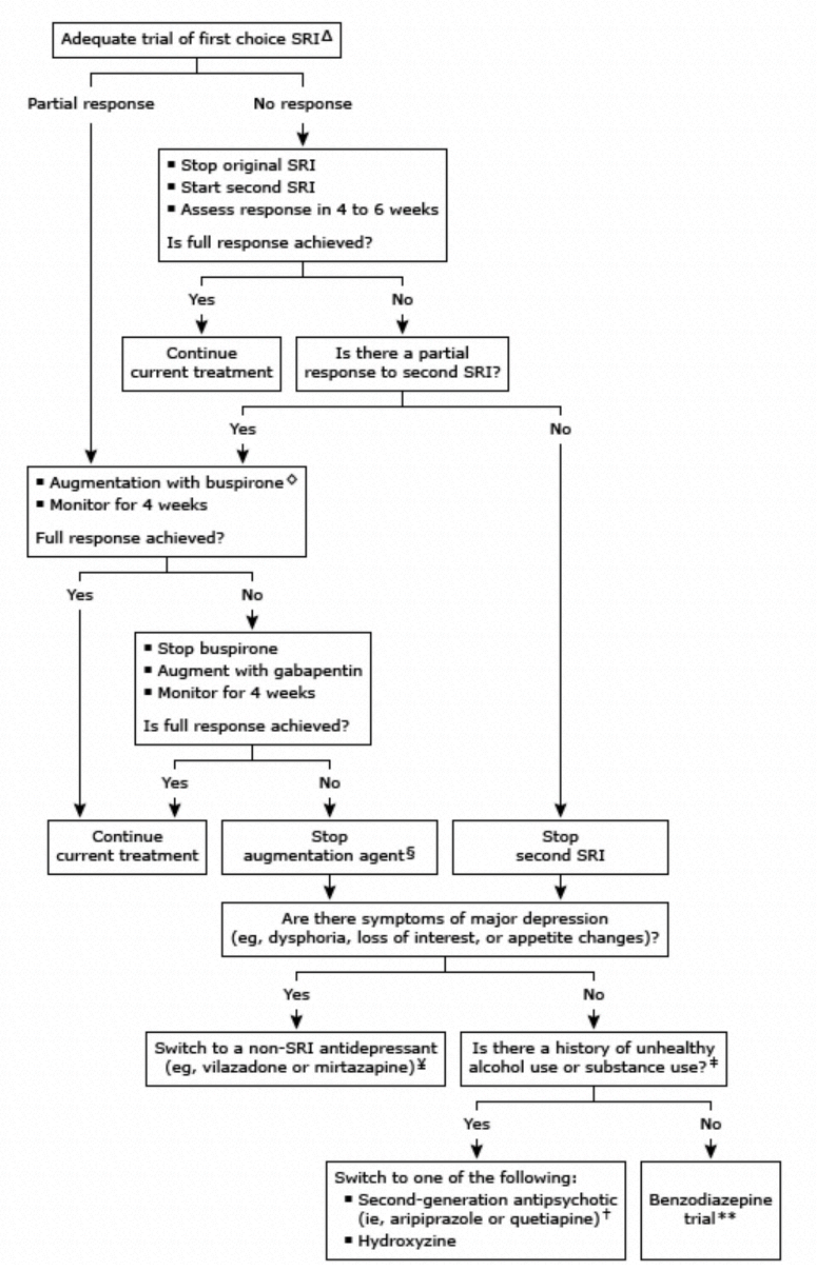
Pharmacologic Management of Generalized Anxiety Disorder (GAD)



GAD: generalized anxiety disorder; SRI: serotonin reuptake inhibitor; CBT: cognitive-behavioral therapy; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; EPS: extrapyramidal side effects.

* Augmentation with psychotherapy (ie, CBT) can be done at any point in the algorithm.

¶ SRI includes both SSRIs and SNRIs.

Δ Adequate trial is considered to be 6 weeks at therapeutic dose range for medication.

◇ Our first line for augmentation is buspirone; however, in individuals with significant mood fluctuation, irritability, or in those with diagnosis of bipolar disorder (with mania or hypomania), valproic acid or lamotrigine are acceptable alternatives.

§ We typically try augmentation with two different agents at therapeutic range for 4 weeks before considering the individual to not have acceptable response to augmentation efforts.

¥ Choice of antidepressant is based on symptoms present and potential side effects of medications. In individuals with decreased appetite or insomnia, we would use mirtazapine. In individuals sensitive to weight gain, we would use vilazodone.

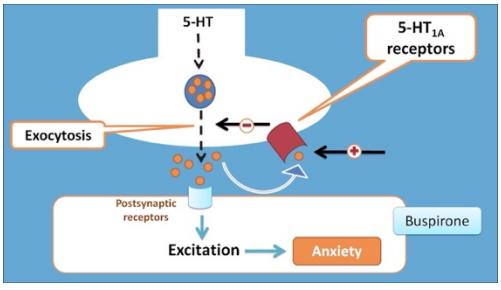
‡ For individuals with current unhealthy alcohol or substance use we address these concerns prior to treating generalized anxiety. In some cases, such as low-risk use of alcohol, we address them concurrently.

† For individuals starting an antipsychotic medication, we monitor for EPS, prolonged QTc, and metabolic dysregulation. Refer to content in UpToDate.

** Benzodiazepines can be used as monotherapy in individuals who have not responded to any prior agents or as an adjunctive agent based on response to prior agent. Refer to UpToDate content.

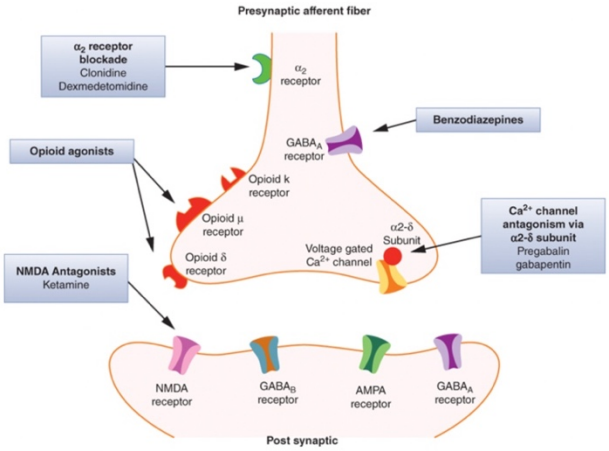
<u>Buspirone</u> (Buspar)

- Buspirone is a non-BZD anxiolytic agent and is not associated with abuse or dependence.
- MOA: buspirone acts as a $5HT_{1A}$ receptor agonist, reducing 5HT (serotonin) neurotransmission → reduces excitation → reduces anxiety.
- Buspirone has a delayed onset (4-6 weeks) and is not appropriate for "PRN" use.



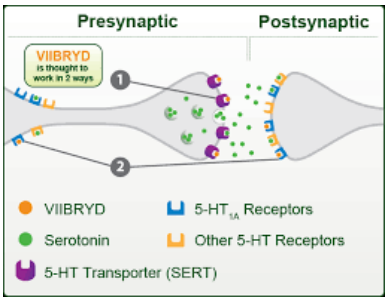
Gabapentin (Neurontin) and Pregabalin (Lyrica)

- MOA: bind to voltage-gated calcium channels at the alpha 2-delta subunit and inhibit neurotransmitter release.
- Gabapentin and pregabalin appear to be efficacious in managing somatic symptoms of GAD and are mostly used to augment SSRI/SNRI treatment in patients who show partial response to SSRI/SNRI treatment.
- Pregabalin has a potential for addiction and dependence (Schedule V).



Vilazodone (Viibryd)

- Vilazodone is a SSRI with 5-HT_{1A} "partial" receptor agonist property --> referred to as a "serotonin partial agonist-reuptake inhibitor (SPARI)."
- Vilazodone overall efficacy in GAD is similar to other SSRIs.
- Vilazodone should be taken with food to improve its bioavailability and efficacy.



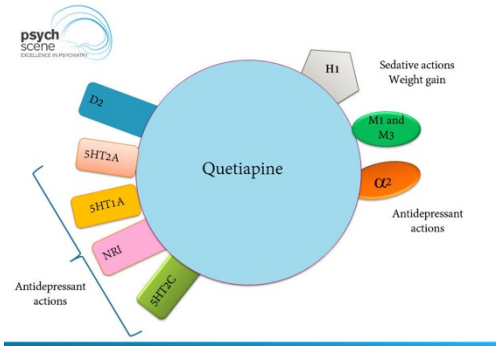
Hydroxyzine (Vistaril, Atarax)

- Hydroxyzine is a sedating antihistamine with anxiolytic properties.
- Hydroxyzine may also be used as an augmentation option for patients with insomnia.
- Anticholinergic side effects, especially with higher doses (e.g., 50-100 mg PO QID prn anxiety), are common.

Quetiapine (Seroquel) and Aripiprazole (Abilify)

- Quetiapine and aripiprazole are second-generation antipsychotic (SGA) agents used as monotherapy or adjuncts for augmentation of antidepressants.

	1st generation	2nd generation
A.K.A.	typical antipsychotics	atypical antipsychotics
MOA	Primarily block D2 receptors only	Primarily block D2 and 5HT2A receptors
Examples	• haloperidol • chlorpromazine	• aripiprazole • olanzapine • quetiapine • risperidone • clozapine
EPS	More likely to cause EPS (dystonia, akathisia, pseudoparkinsonism, and tardive dyskinesia)	Less likely to cause EPS and tardive dyskinesia (but can still occur)
Metabolic abnormalities	Less likely to have metabolic abnormalities	More likely to cause metabolic abnormalities (elevated glucose, lipids, and weight gain)



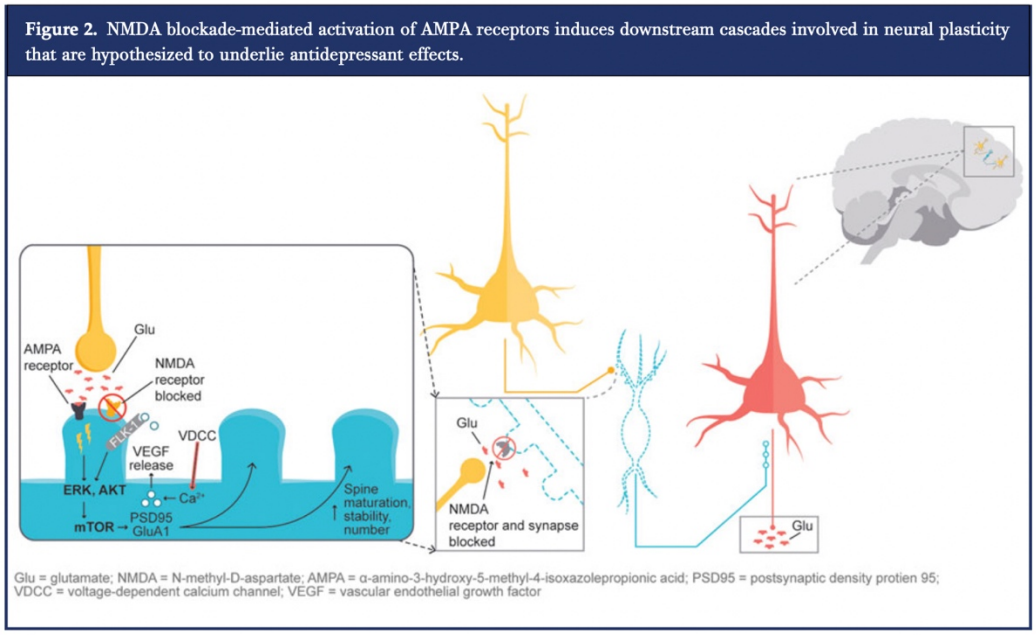
Benzodiazepines (BZDs)

- BZDs are used in select individuals with GAD who are refractory to multiple prior medication and augmentation trials.
- Avoid using BZDs in patients with a history of substance misuse.

UPDATE: New FDA-Approved Agents for the Treatment of Major Depressive Disorder

Dextromethorphan 45 mg / Bupropion 105 mg (Auvelity)

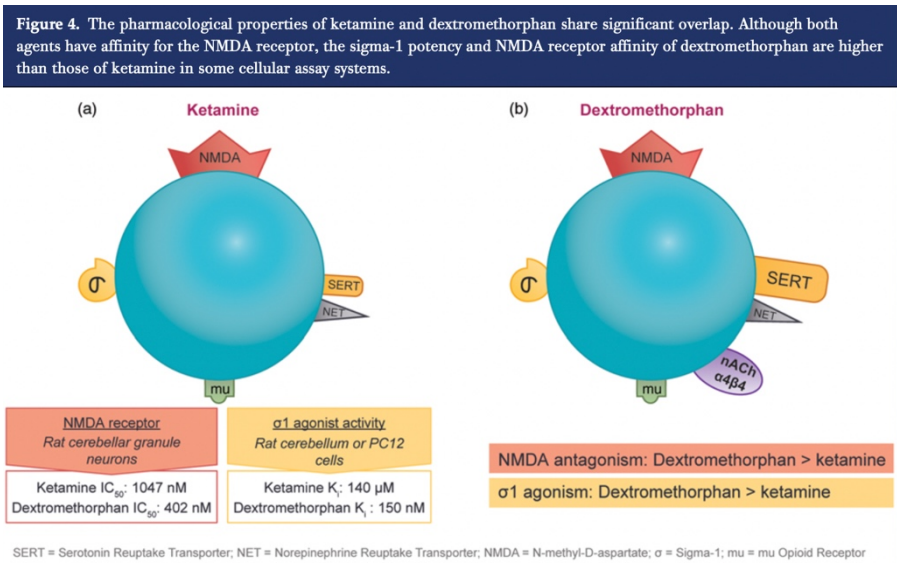
- Auvelity is a rapid-acting oral combination product consisting of dextromethorphan plus bupropion indicated for treatment of major depressive disorder (MDD) in adults.
- Dextromethorphan (DM) is a NMDA (N-methyl D-aspartate) receptor antagonist; and, bupropion primarily blocks the reuptake of dopamine (DA) with negligible serotonin (SE) reuptake blocking effects.
- Bupropion increases plasma levels of dextromethorphan (DM) by inhibiting the hepatic cytochrome P450 enzyme responsible for metabolizing DM --> increases the duration of action and pharmacologic activity of DM.

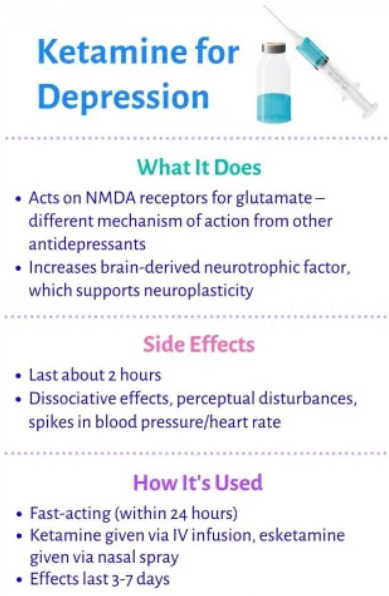


Bv

Esketamine (Spravato) Nasal Spray (C-III)

- Esketamine is FDA-approved for treatment of resistant depression



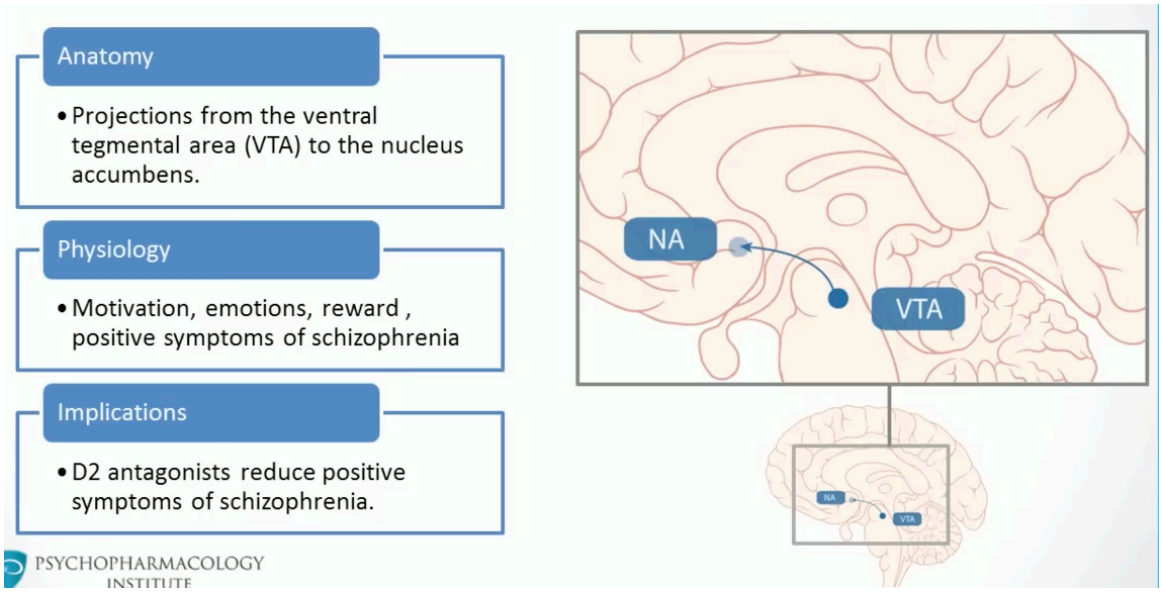


ANTIPSYCHOTIC AGENTS & SCHIZOPHRENIA

I. Dopamine Pathways in the CNS

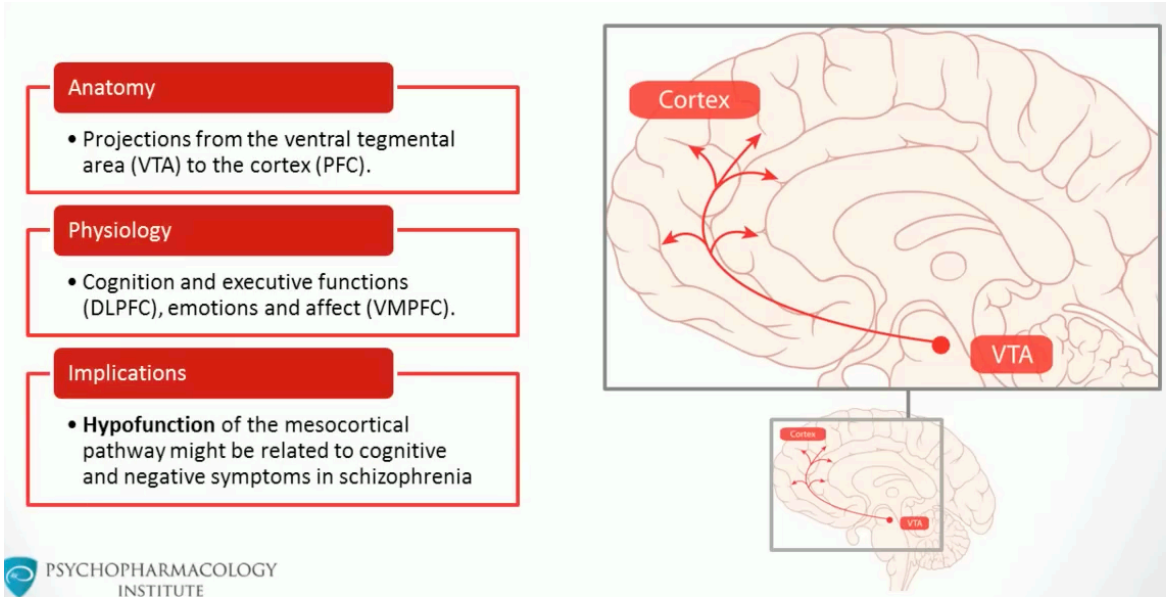
A. Mesolimbic Pathway & Symptoms of Schizophrenia

- Hyperactivation from the VTA (ventral tegmental area (VTA) areas is related to positive symptoms of schizophrenia.
- Positive symptoms of schizophrenia include delusions, hallucinations, thought disorder.



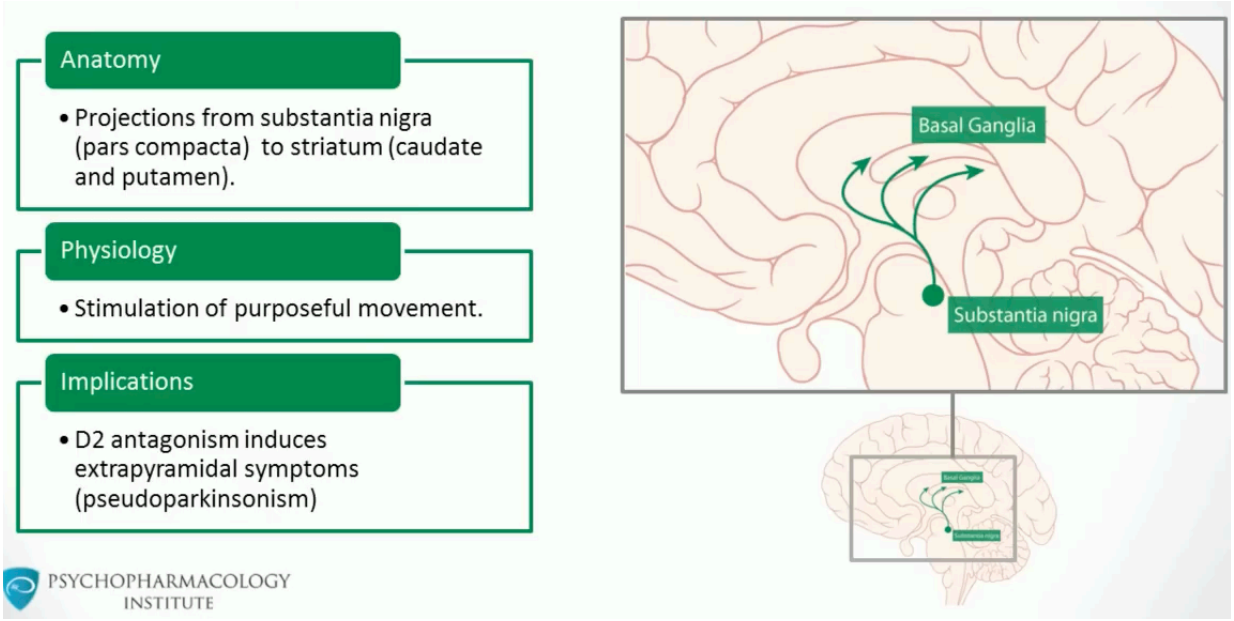
B. Mesocortical Pathway: Negative & Cognitive Symptoms

- Hypofunction of the mesocortical pathway may explain cognitive and negative symptoms of schizophrenia.
- Negative symptoms include apathy, social withdrawal, restricted affect, and anhedonia.
- Cognitive symptoms include deficits in attention, memory, and executive function.



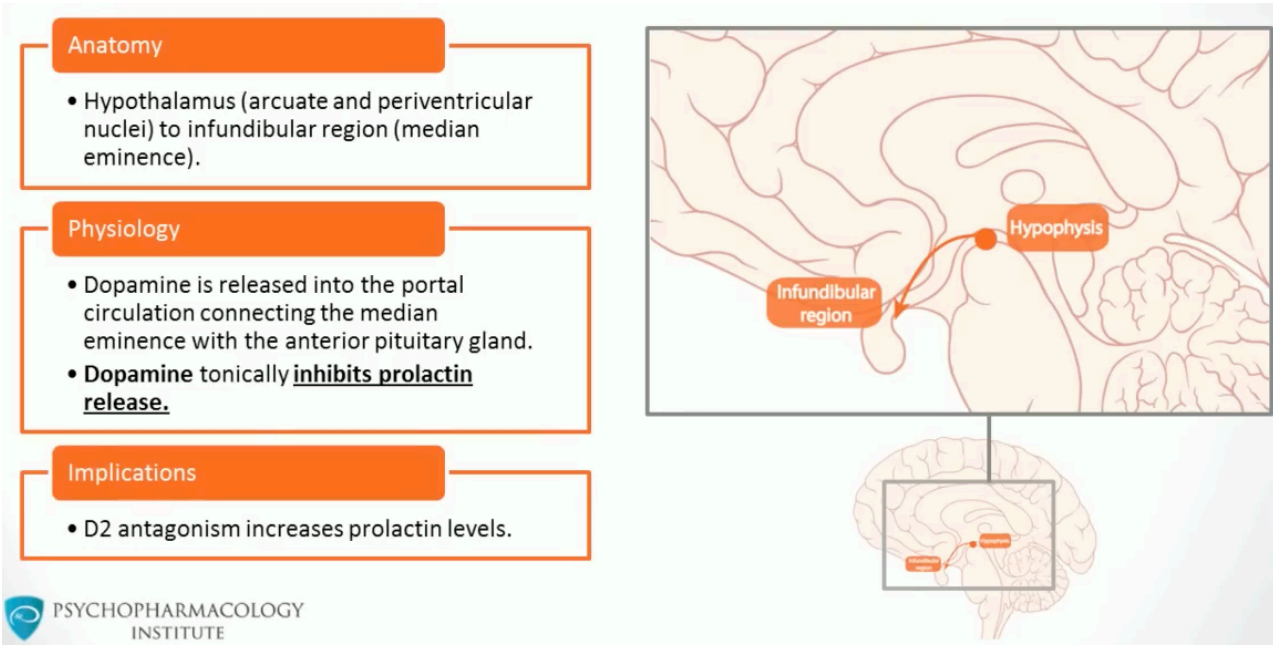
C. Nigrostriatal Pathway & EPS

- D2 blockade of the nigrostriatal pathway may cause EPS (extrapyramidal symptoms).



D. Tuberoinfundibular Pathway & Prolactin Release

- D2 blockade of the tuberoinfundibular Pathway increases prolactin blood levels.
- Hyperprolactemia in females results in milky nipple discharge, milk production when no pregnant or breastfeeding, menstrual irregularities, and vaginal dryness (painful intercourse). In men, hyperprolacemia may cause erectile dysfunction, gynecomastia, and decreases muscle mass and body hair.



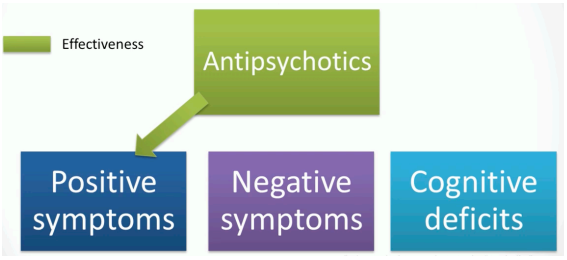
II. Schizophrenia: Positive, Negative, and Cognitive Symptoms

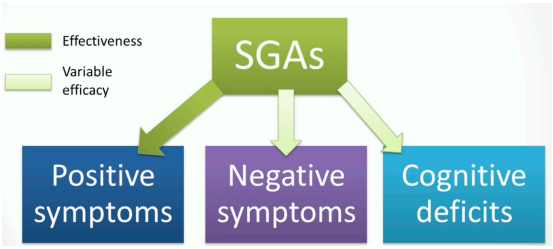
Schizophrenia has multiple psychopathologic dimensions …

Positive symptoms	Negative symptoms	Cognitive deficits	Mood symptoms	Other
• Dellusions • Hallucinations • Thought disorder	• Apathy • Social withdrawal • Restricted affect • Anhedonia	• Attention • Memory • Executive function	• Dysphoria • Depression	• Agitation/ excitement

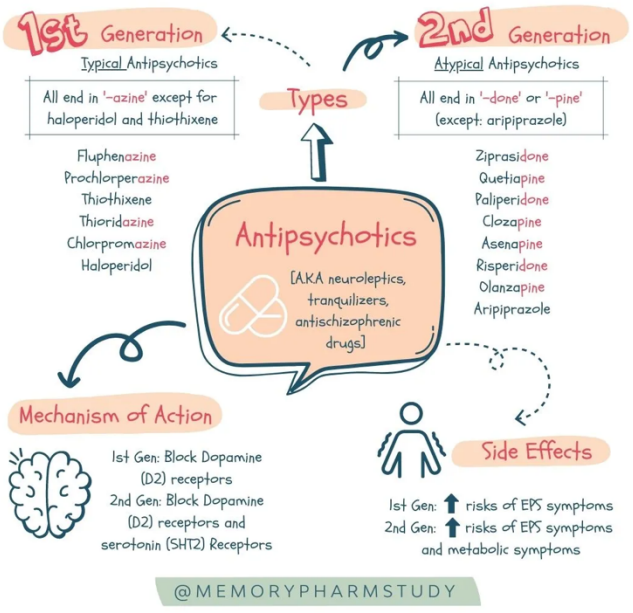
FGAs improve positive symptoms.

SGAs are effective for positive symptoms and may be effective for negative symptoms, with less EPS.



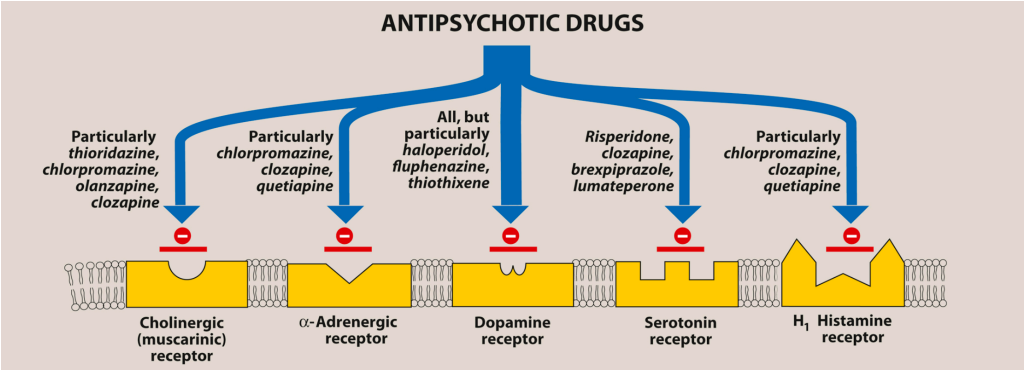


III. Antipsychotic Drugs: FGAs and SGAs



FIRST-GENERATION ANTIPSYCHOTIC (low potency)
Chlorpromazine GENERIC ONLY
Thioridazine GENERIC ONLY
FIRST-GENERATION ANTIPSYCHOTIC (high potency)
Fluphenazine GENERIC ONLY
Haloperidol HALDOL
Loxapine GENERIC ONLY
Molindone GENERIC ONLY
Perphenazine GENERIC ONLY
Pimozide ORAP
Prochlorperazine COMPRO, PROCOMP
Thiothixene GENERIC ONLY
Trifluoperazine GENERIC ONLY
SECOND-GENERATION ANTIPSYCHOTIC
Aripiprazole ABILIFY, ARISTADA
Asenapine SAPHRIS, SECUADO
Brexpiprazole REXULTI
Cariprazine VRAYLAR
Clozapine CLOZARIL
Iloperidone FANAPT
Lumateperone CAPLYTA
Lurasidone LATUDA
Olanzapine ZYPREXA
Paliperidone INVEGA
Pimavanserin NUPLAZID
Quetiapine SEROQUEL
Risperidone PERSERIS, RISPERDAL
Ziprasidone GEODON

IV. Selective Adverse Effects of Antipsychotic Drugs in Schizophrenia



DRUG NAME	INDICATIONS	SEDATION	EPS	ANTI-CHOLINERGIC	ORTHOSTASIS	THERAPEUTIC NOTES & SPECIAL SIDE EFFECTS
First generation						
Chlorpromazine	Psychosis, mania, N/V, intractable hiccups	++++	+++	+++	++++	
Fluphenazine	Schizophrenia	+	++++	+	+	LAI for patients with a history of nonadherence with oral regimens
Haloperidol	Schizophrenia, Tourette syndrome, severe behavior problems in children	+	++++	0	+	LAI for patients with a history of nonadherence with oral regimens; low potential for weight gain
Loxapine	Schizophrenia	+++	+++	++	++	Metabolite is *amoxapine* (antidepressant)
Molindone	Schizophrenia	+	+++	++	++	Weight loss
Perphenazine	Schizophrenia, N/V	++	+++	++	++	
Prochlorperazine	Schizophrenia, anxiety, N/V	++	+++	+	+	IM and suppository formulation available; commonly used for N/V
Thioridazine	Schizophrenia	++++	++	++++	++++	QTc interval prolongation - avoid in combination with other drugs known to prolong the QTc interval and in patients with congenital long QT syndrome or a history of cardiac arrhythmias; pigmentary retinopathy
Thiothixene	Schizophrenia	+	+++	+	+	
Trifluoperazine	Schizophrenia, anxiety	++	+++	++	++	
Second generation						
Aripiprazole	Schizophrenia, bipolar mania, irritability secondary to autistic disorder, adjunctive treatment of MDD, bipolar maintenance	+	+	0	+	Two LAI formulations available; N/V likely due to D_2 partial agonism; low risk for prolactin-related problems
Asenapine	Schizophrenia, acute mania	++	++	0	+	Transdermal and SL formulation available; dysgeusia and oral hypoesthesia with SL formulation; low potential for weight gain
Brexpiprazole	Schizophrenia, adjunctive treatment of MDD	+	+	0	+	N/V likely due to D_2 partial agonism; low risk for prolactin-related problems; low potential for weight gain
Cariprazine	Schizophrenia, bipolar mania, bipolar depression	+	++	0	0	N/V likely due to D_2 partial agonism; low risk for prolactin-related problems; low potential for weight gain
Clozapine	Treatment-resistant schizophrenia, recurrent suicidal behavior in schizophrenia or schizoaffective disorder	++++	–/+	++++	++++	High risk for blood dyscrasias, orthostasis, seizures, weight gain, sialorrhea; myocarditis
Iloperidone	Schizophrenia	+	+	+	++	QTc interval prolongation
Lumateperone	Schizophrenia	++	–/+	0	+	Low potential for weight gain
Lurasidone	Schizophrenia, bipolar depression	+	+	0	+	Food increases absorption; low potential for weight gain
Olanzapine	Schizophrenia, bipolar mania	+++	++	++	++	LAI formulation available; high potential for weight gain
Paliperidone	Schizophrenia, schizoaffective disorder	+	+	0	++	LAI formulation available; high risk for increase in prolactin level; active metabolite of *risperidone*
Quetiapine	Schizophrenia, acute mania, bipolar depression, adjunctive treatment of MDD	+++	+	+	++	High potential for weight gain
Risperidone	Schizophrenia, acute mania, irritability secondary to autistic disorder, bipolar maintenance	+	++	0	++	LAI formulation available; high risk for increase in prolactin level; moderate potential for weight gain
Ziprasidone	Schizophrenia, bipolar mania	+	+	0	+	Contraindicated in patients with a known history of QT prolongation, a recent acute myocardial infarction, and with uncompensated heart failure; low potential for weight gain

Detailed Adverse Effects of Antipsychotic Drugs in Schizophrenia (UpToDate, 2024)

	Weight gain	Glucose abnormalities	Hyperlipidemia	Akathisia	Parkinsonism	Dystonia	Tardive dyskinesia	Prolactin elevation	Sedation	Anticholinergic	Orthostatic hypotension	QTc prolongation
Second-generation agents												
Aripiprazole	+	+	+	++	+	+	+	+	+	+	+	*
Asenapine	++	++	++	++	+	++	++	++	++	+	++	+
Brexpiprazole¶	+	+	++	++	+	+	+	+	++	+	+	*
Cariprazine¶	++	+	+	++	+	+	+	+	++	++	+	*
Clozapine$^{\Delta}$	+++	+++	+++	+	+	+	+	+	+++	+++	+++	++
Iloperidone	++	++	+	+	+	+	+	++	++	+	+++	+
Lumateperone¶	+	+	+	+	+	+	+	+	+	+	+	*
Lurasidone	+	++	++	++	++	++	++	+	++	+	+	*
Olanzapine	+++	+++	+++	++	++	+	+	++	+++	++	++	++
Paliperidone	++	+	++	++	++	++	++	+++	+	+	++	+
Pimavanserin	–	+	+	+	+	+	+	+	+	+	++	+
Quetiapine	++	++	+++	+	+	+	+	+	+++	++	++	++
Risperidone	++	++	+	++	++	++	++	+++	++	+	++	++
Ziprasidone	+	+	+	++	+	+	+	++	++	+	++	+++
First-generation agents												
Chlorpromazine	++	++	+	++	++	++	+++	+	+++	+++	+++	+++
Fluphenazine	++	+	+	+++	+++	+++	+++	+++	+	+	+	+
Haloperidol	++	+	+	+++	+++	+++	+++	+++	+	+	+	Oral: ++ IV: +++
Loxapine	+	+	+	++	++	++	++	++	++	++	++	*
Molindone	+	+	+	++	++	++	++	++	++	+	+	*
Perphenazine	++	+	+	++	++	++	++	++	++	++	++	*
Pimozide	+	+	+	+++	+++	++	+++	+++	+	+	+	++$^{\diamond}$
Thioridazine§	++	+	+	+	+	+	+	++	+++	+++	+++	++
Thiothixene	+	+	+	+++	+++	+++	+++	+++	+	+	+	*
Trifluoperazine	++	+	+	++	++	++	++	++	+	++	+	*

Adverse effect rankings, with the exception of the QTc classifications, are consistent with American Psychiatric Association practice guidelines for the treatment of schizophrenia.[1] The QTc classifications are determined by UpToDate Lexidrug according to US Food & Drug Administration guidance.[2,3] Other sources may use different classification systems resulting in some agents being classified differently.

IV: intravenous.

* Clinically significant QTc prolongation was not detected in preliminary studies or reported in the manufacturer's labeling.

¶ Based upon limited experience.

Δ Clozapine also causes granulocytopenia or agranulocytosis in approximately 1% of patients requiring regular blood cell count monitoring. Clozapine has been associated with excess risk of myocarditis and venous thromboembolic events including fatal pulmonary embolism. These issues are addressed in the UpToDate topic review of guidelines for prescribing clozapine section on adverse effects.

V. Supplemental Illustrations: Mechanism of Action of Atypical Antipsychotics