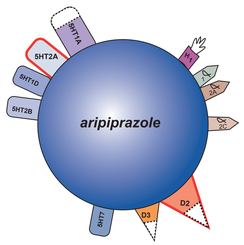
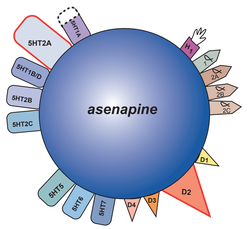
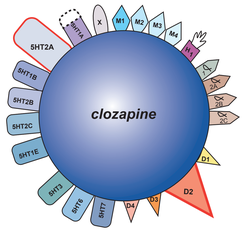
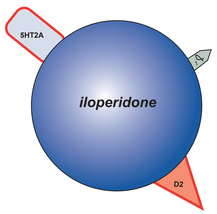
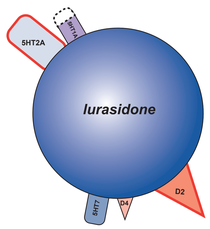
Receptor Binding Profiles of Atypical Antipsychotics:
Mechanisms of Therapeutic Actions and Adverse Side Effects











Mechanisms of Therapeutic Actions and Adverse Side Effects

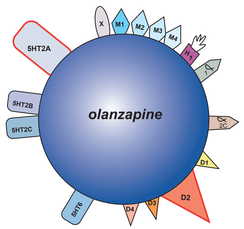
All antipsychotics (both conventional and atypical) bind to some degree at dopamine D_2 receptors. It is believed that D_2 antagonism mediates antipsychotics' ability to reduce positive symptoms of schizophrenia, including hallucinations and delusions. What sets the atypical antipsychotics apart from conventionals is the propensity of atypicals to bind additional receptors in antagonistic or agonistic manners. Binding to additional dopaminergic, serotonergic, adrenergic, and cholinergic receptors has additional consequences, such as lessening some of the symptoms of schizophrenia or mitigating side effects caused by D_2 antagonism. For example, in addition to D_2 antagonism, most atypical antipsychotics also act in an antagonistic fashion at serotonin $5HT_{2A}$ receptors. This $5HT_{2A}$ antagonism is theorized to reduce the extrapyramidal symptoms (EPS) and hyperprolactinemia caused by chronic D_2 antagonism.

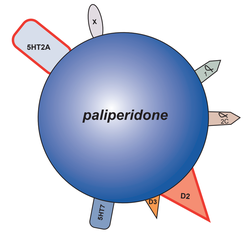
The vast molecular polypharmacy of atypical antipsychotics is associated not only with additional therapeutic benefits; binding to some receptor types increases a drug's propensity to cause adverse side effects. Chronic D_2 antagonism is linked with EPS, tardive dyskinesia, and hyerprolactinemia, which are common side effects associated with conventional antipsychotics. Although additional binding properties of atypical antipsychotics lower the risk of some D_2 antagonism-associated side effects, the more complex binding profiles of atypical antipsychotics can lead to other serious side effects. Most notably, the binding of atypical antipsychotics to $5HT_{2C}$, M_3, and/or H_1 receptors has been linked with cardiometabolic effects that can greatly compromise a patient's physical well-being

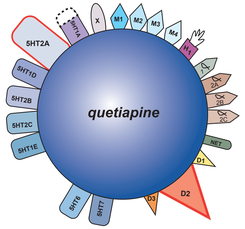
Each atypical antipsychotic agent has a binding profile that differs from other antipsychotics. An antipsychotic's binding profile is a summation of the receptors to which it binds, the strength of the binding to individual receptor types (binding affinity or Ki), and the action of the drug on that receptor type (antagonism, partial agonism, etc.). The unique binding profile lends each antipsychotic both efficacy in reducing symptoms and propensity to cause particular side effects. Two different antipsychotics may have similar adverse effects associated with them due to having similar binding properties for certain receptor types. Conversely, one antipsychotic may be more effective at reducing affective symptoms than another due to its ability to bind a particular receptor type with adequate affinity.

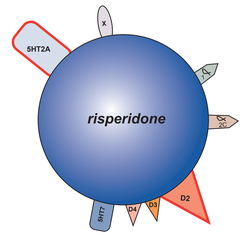
Drug	D_2 Antag	D_2 PA	D_3	$5HT_{1A}$	$5HT_{2A}$	$5HT_{2C}$	$5HT_7$	α_1	M_1	M_3	H_1
Aripiprazole		+++	+++	+++	++	++	+++	++			++
Asenapine	+++		+++	++	++++	++++	++++	+++	+		+++
Clozapine	+		+	+	++	++	++	+++	+++	++	+++
Iloperidone	+++		++	++	+++	+	++	+++			++
Lurasidone	+++		?	+++	++	+	++++	++			
Olanzapine	++		++		+++	++	+	++	++	++	+++
Paliperidone	+++		+++	+	++++	++	+++	+++			++
Quetiapine	+		+	+*	++*	+*	++*	+++	++*	++*	+++*
Risperidone	+++		+++	+	++++	++	+++	+++			++
Ziprasidone	+++		+++	++	++++	++	+++	++			++
Therapeutic Effects	Reduced positive symptoms	Reduced positive symptoms	Reduced positive symptoms; Reduced negative symptoms; Procognitive; Antidepressant	Reduced EPS; Reduced hyperprolactinemia; Antidepressant; Anxiolytic	Reduced EPS; Reduced hyperprolactinemia	Antidepressant	Reduced circadian rhythm dysfunction; Reduced negative symptoms; Procognitive	Reduced nightmares	Reduced EPS	Reduced EPS	Hypnotic
Side Effects	EPS; Hyperprolactinemia; Increased negative symptoms; Increased negative symptoms; Increased cognitive deficits; Sedation	Relatively lower risk of EPS	Unknown	Unknown	Cardiometabolic	Cardiometabolic	Unknown	Dizziness; Sedation; Hypotension	Constipation; Sedation; Dry mouth; Blurred vision	Cardiometabolic; Constipation; Sedation; Dry mouth; Blurred vision	Cardiometabolic; Sedation

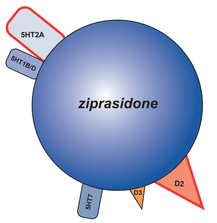
+ weak binding affinity (100>Ki<1000)
++ moderate binding affinity (10>Ki<100)
+++ strong binding affinity (1>Ki<10)
++++ very strong binding affinity (Ki<1)
? No data yet available
* Binding property due primarily to the metabolite norquetiapine











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Presented at the 2012 NEI Global Psychopharmacology Congress.
This poster is supported by an unrestricted educational grant from Sunovion Pharmaceuticals Inc.