

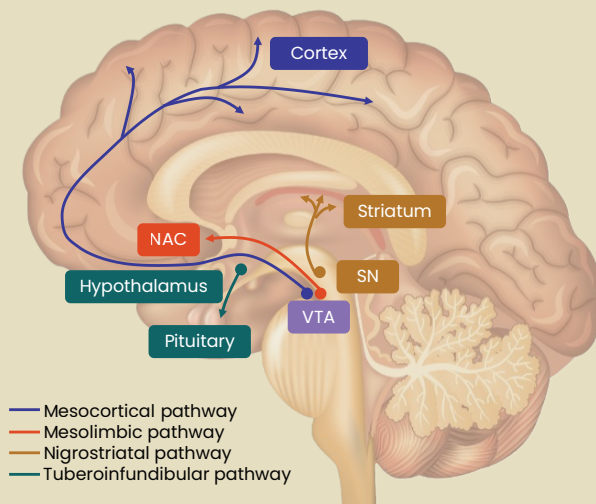
What's New in Schizophrenia Treatments?

What we knew about the dopamine hypothesis of schizophrenia has been updated. Early pharmacologic models (1960s–1970s) proposed that psychosis results from excess dopamine activity in the mesolimbic pathway (from the ventral tegmental area to the ventral striatum). This is supported by rodent models. However, imaging studies suggest that presynaptic dopamine dysregulation is most prominent in the associative/dorsal striatum which is thought to be refining the older mesolimbic-centered model. The end result is the same: Too much dopamine in the striatum results in psychotic symptoms.

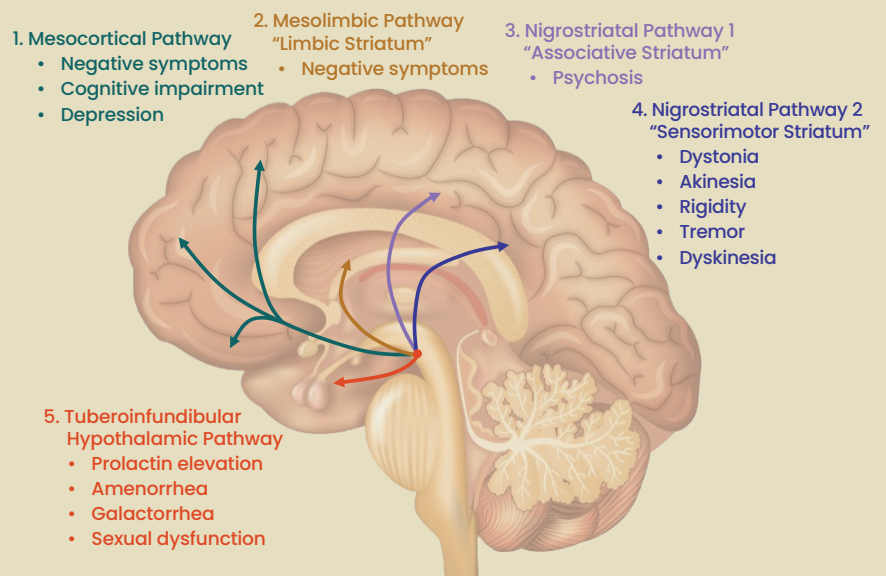
Blocking the dopamine D2 receptors in the associative striatum will address the hallucinations and delusions of schizophrenia, but collateral damage in that blockade of D2 receptors also occurs in the dorsal striatum, causing drug-induced movement disorders, and in the tuberoinfundibular hypothalamic pathway, causing hyperprolactinemia.

With the antipsychotic medications in current use, other receptors are blocked as well. For example, blockade of α -1 adrenergic receptors can lead to postural hypotension, histamine H1 receptor antagonism is associated with sedation, and serotonin 5-HT_{2C} antagonism is associated with an increase in appetite.

What we thought were the pathways, based on rodent models.



What we think are the pathways in humans, based on new imaging studies.



Disclaimer: Model inferred from murine models.

However, a different approach to treating schizophrenia involves decreasing the release of dopamine in the first place, instead of blocking the receptors after the fact. If done selectively in those circuits involved in dopamine signaling in the associative striatum, the collateral damage caused by dopamine blockade can be avoided. Moreover, a molecule free of other secondary binding affinities to adrenergic, serotonergic, and histaminergic receptors could potentially avoid the myriad of adverse effects that can be seen with second-generation antipsychotics.

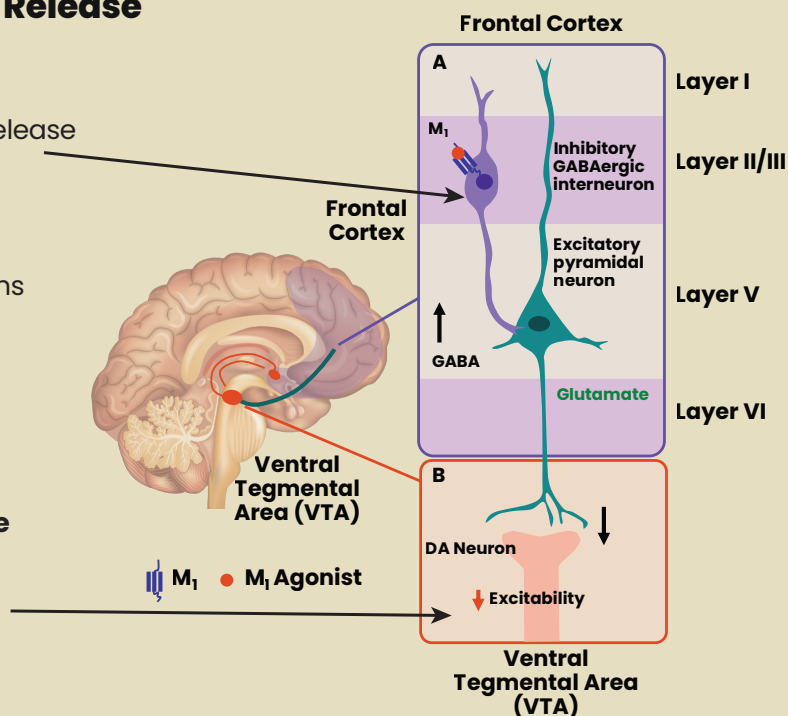
One such approach is muscarinic agonism at muscarinic M1 and M4 receptors. These 2 subtypes of muscarinic receptors are selectively involved in circuits in the brain associated with the regulation of dopamine signaling in the associative striatum. The precise downstream circuitry is still being refined in human models. Current descriptions of this in educational materials rely on the rodent model of dopamine pathways, but the end result is the same: less dopaminergic signaling only in that part of the striatum thought responsible for psychotic symptoms.

The “Top Down” M₁ Story: How Muscarinic Stimulation of PFC GABAergic Inhibitory Interneurons Decreases VTA Dopamine Release

GABAergic inhibitory interneurons control glutamate release from excitatory PFC pyramidal neurons

These pyramidal neurons have downstream projections to VTA **neurons where glutamate stimulates VTA dopamine release**

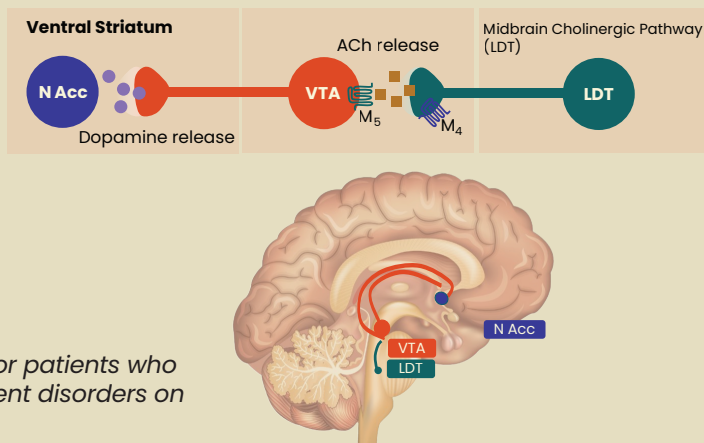
Stimulation of M₁ receptors on GABAergic inhibitory interneurons makes these interneurons release more GABA; this inhibitory signal reduces pyramidal cell glutamate release → net downstream effect is less striatal VTA dopamine release



“Bottom Up” M₄: Midbrain Input Decreases Dopamine Release in Psychosis Related Areas

- ▲ **LDT ACh release is modulated by the M₄ autoreceptor;** stimulation of M₄ autoreceptors on the LDT afferent decreases ACh release
- ▲ Net effect: decreased VTA neuron firing **and less VTA DA release**
- ▲ **Of importance,** the decreased DA outflow occurs in **areas related to psychosis, not motor systems**

Consider clinical implications of this for patients who have experienced significant movement disorders on traditional antipsychotic medications



Combination xanomeline-trospium is the first muscarinic agonist compound to be approved for the treatment of schizophrenia. Xanomeline has a higher agonist activity of muscarinic M₁ and M₄ receptors, leading to a reduction of dopamine release presynaptically. Xanomeline does not bind to dopamine, serotonin, α-adrenergic, or histamine receptors. The trospium component, by blocking peripheral muscarinic receptors, helps to decrease the occurrence and severity of procholinergic gastrointestinal adverse effects. Trospium does not cross the blood–brain barrier in any appreciable amount, so it cannot interfere with the therapeutic effects of xanomeline.

The clinical trial evidence for the efficacy of the xanomeline-trospium combination is robust, offering a viable treatment option that differs from second-generation antipsychotics. Moreover, the xanomeline-trospium combination showed low rates of weight gain, somnolence/sedation, or drug-induced movement disorders such as akathisia. The most common adverse events are nausea and vomiting (procholinergic and attributable to xanomeline) and constipation (anticholinergic and attributable to trospium).

Other muscarinic receptor–based treatments are being tested in clinical trials and may offer additional choices in the future.