Overview of Dopamine Pharmacology in Bipolar I Disorder

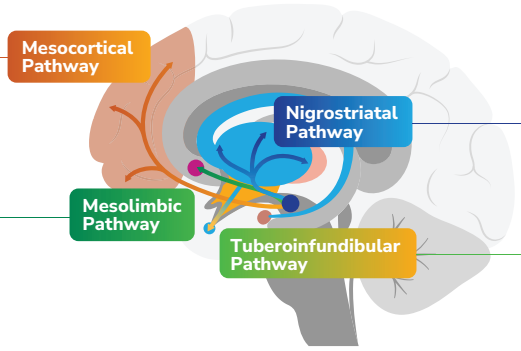
While the exact mechanisms underlying the etiology of bipolar I disorder (BP-1) are not fully understood, changes in dopaminergic activity are thought to be linked to the transitions between manic and depressive episodes in BP-1. The dopamine hypothesis of bipolar disorder suggests that during manic episodes, increased dopamine activity may contribute to some BP-1 symptoms such as hyperactivity, impulsivity, and euphoria. In contrast, decreased dopamine activity may be associated with symptoms including anhedonia and low motivation observed in depressive episodes.[1]

Dopamine Pathways in the Brain

There are four major dopamine pathways in the brain. Dysregulation of these pathways can often be implicated in psychiatric disorders.[2]

The **mesocortical pathway**, which projects from the ventral tegmental area to the prefrontal cortex, is thought to help regulate cognition, executive functions, and emotions.

The **mesolimbic pathway**, which projects from the ventral tegmental area to the nucleus accumbens in the ventral striatum, may play a role in the regulation of motivation, reward-seeking behavior, compulsion, desire, positive reinforcement, and aversions.



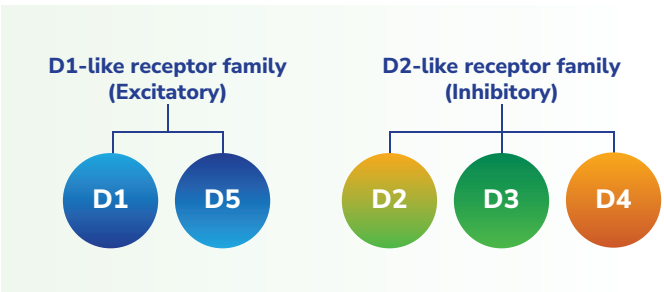
The **nigrostriatal pathway**, which projects from the substantia nigra to the striatum or basal ganglia, is thought to control motor movements as part of the extrapyramidal nervous system. Dopamine deficiencies in this pathway may lead to movement disorders such as extrapyramidal symptoms (EPS).

The **tuberoinfundibular pathway**, which projects from the hypothalamus to the anterior pituitary, is thought to be involved in the inhibition of prolactin release. Dopamine deficiency in this pathway may lead to elevated prolactin levels.

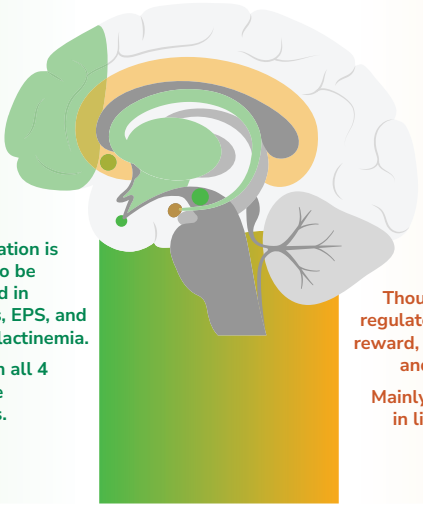
Dopamine Receptors in the Brain

Dopamine Receptor Subtypes

Dopamine exerts its effect through five known dopamine receptor subtypes, which are categorized into two subfamilies: the D1-like and D2-like receptors. D1-like receptors, which include D1 and D5 receptors, can have an excitatory effect on the postsynaptic neuron, while D2-like receptors, which include D2, D3, and D4 receptors, can have an inhibitory effect on the postsynaptic neuron. Of the five known dopamine receptor subtypes, D2 and D3 are thought to play an important role in mood regulation and have been the primary targets of some current therapies for BP-1.[3]



Hypothetical Functions Regulated by the D2 and D3 Receptors[2-5]



D2

Dysregulation is thought to be implicated in psychosis, EPS, and hyperprolactinemia.

Present in all 4 dopamine pathways.

D3

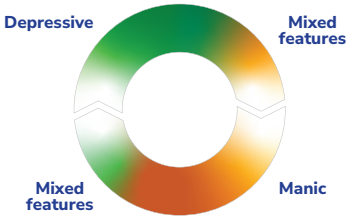
Thought to help regulate emotions, reward, motivation, and cognition.

Mainly expressed in limbic areas.

Pharmacologic Modulation of Dopamine Activity

Clinical Consideration for Treatment of BP-1

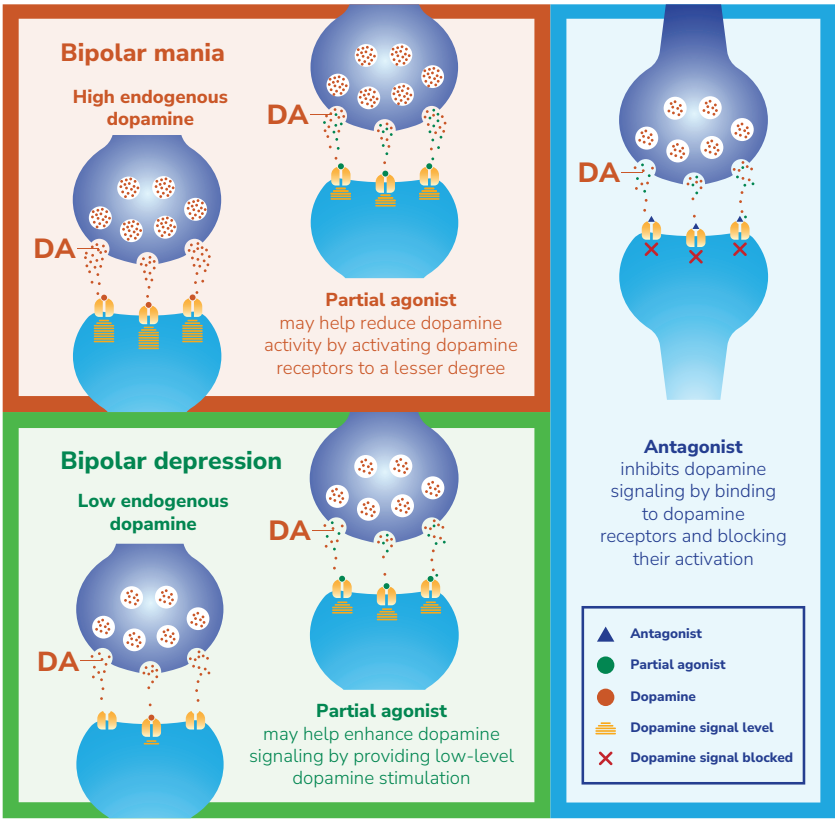
Modulation of dopamine signaling via atypical antipsychotics is an important component of the management of BP-1 and schizophrenia.[6,7] Some treatment options address either the depressive or manic pole of BP-1, while others address both poles of BP-1.[8,9]



Dopamine Receptor Partial Agonism

Atypical antipsychotics with **dopamine receptor antagonist** activity may help address the symptoms of mania or psychosis associated with hyperdopaminergic states by primarily blocking D2 receptors to help reduce dopamine activity.[10] However, D2 receptor antagonism may over-inhibit dopamine release and may be associated with adverse effects, such as EPS and hyperprolactinemia.[2]

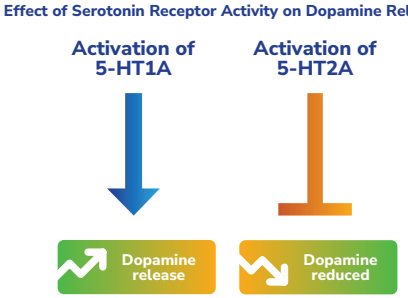
Atypical antipsychotics with **dopamine receptor partial agonist** activity may **help** modulate dopamine activity depending on the level and activity of endogenous dopamine. In a **hyperdopaminergic** state, such as in a manic episode, partial agonists may help reduce dopamine activity by competing with dopamine at receptor sites and activating them to a lesser degree than a full agonist would. In a **hypodopaminergic** state, such as in a depressive episode, partial agonists can help enhance dopamine signaling by providing low-level dopamine stimulation. Additionally, dopamine partial agonists are theorized to be associated with reduced EPS and hyperprolactinemia since they do not completely block dopamine activity.[11]



DA = dopamine

Interplay Between Dopamine and Serotonin Signaling

Dopamine signaling is believed to be closely connected with serotonin signaling, particularly in the prefrontal cortex, where serotonin receptors are thought to affect downstream dopamine release. Activation of the 5-HT1A receptor is thought to be associated with enhanced dopamine release, while activation of the 5-HT2A receptor is believed to inhibit dopamine release. Dysregulation of this balance, such as reduced 5-HT1A function or excessive 5-HT2A activity, has been implicated in the development of depressive symptoms of various mood disorders, including BP-1. Pharmacologic modulation of dopamine release with a 5-HT1A agonist or a 5-HT2A antagonist may help promote dopamine release and potentially improve depressive symptoms.[2]



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