Essential PsychopharmaSTAHLogy
The Mechanism of Drug-induced Akathisia

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Issue
Akathisia is a movement disorder characterized by an inner sense of unease, unrest, and dysphoria. It can result in an inability to stand, sit, or lie still and an intense urge to move around. It is a common side effect of drugs, such as antipsychotics and serotonin selective reuptake inhibitors (SSRIs), but it also occurs spontaneously in patients with Parkinson’s disease. Several lines of evidence suggest that akathisia can be attributed to low activity of dopaminergic projections from the midbrain to the ventral striatum. However, the exact pathophysiological mechanism of this extrapyramidal symptom remains unclear. This article describes a possible mechanism for drug-induced akathisia based on the differential functions of the core and shell portions of the nucleus accumbens. These ideas arise from contemporary concepts regarding the mechanisms of compulsion, impulsivity, and depression.

Akathisia is a Neuropsychologically-induced Movement Disorder
Akathisia is a movement disorder characterized by an urge to move, unpleasant sensations in the legs, and inner restlessness. The core symptom is the subjective feeling of discomfort that results in objective signs of motor activity and an inability to remain still.¹ A specific variant presents itself primarily as tedious behavior in which the patient shows a compulsion to repeat the same questions and seeks constant reassurance from nearby individuals. It should be emphasized that unlike other extrapyramidal disorders, such as parkinsonism and dyskinesia, akathisia is primarily a psychological symptom and not just a movement disorder; patients experience the urge to move, and motor and behavioral symptoms result from this phenomenon.²,³

Akathisia is observed in patients who are undergoing treatment with antipsychotics, antiemetics, and antidepressants. Incidence rates for acute akathisia with conventional neuroleptics vary from 8% to 76%, with 20% to 30% being a conservative estimate.⁴ Akathisia is less prevalent with second-generation antipsychotics, but it remains a clinically relevant extrapyramidal side effect even with these newer drugs.⁵ Lipinski and colleagues⁶ described it in 9.8% to 25% of patients receiving the antidepressant fluoxetine. Akathisia also occurs spontaneously in Parkinson’s disease and is very similar in appearance to restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) in sleep.²,³,⁷ However, RLS and PLMD primarily occur at night, while akathisia occurs mostly in the daytime.⁸

Dopaminergic Hypoactivity Causes Akathisia
Akathisia is believed to be caused by an extensive (>80%) decrease in dopamine (D)2 receptor stimulation.¹ This is in accordance with its occurrence in patients suffering from Parkinson’s disease and the evidence that RLS and PLMD can be treated with levodopa and dopamine agonists.⁷,⁸ Antipsychotics and certain antiemetics are potent antagonists of the D2 receptor. However, not all of the published observations are in line with the dopamine deficiency hypothesis.⁹ For example, a direct relationship has not been found between parkinsonism—the extrapyramidal side effect most directly related to D2 antagonism—and akathisia.¹ The atypical antipsychotics clozapine and quetiapine bind loosely to the D2 receptor and cause little or no parkinson-like symptoms in therapeutic dosages.¹⁰ However, they cause far more akathisia,⁹,¹¹ although less than haloperidol.¹²

There are several drugs that have no affinity for the D2 receptor but cause akathisia. The best known are the SSRIs. It has been
suggested that SSRIs induce akathisia (and parkinsonism) by indirectly stimulating serotonin (5-HT)2A receptors, resulting in the inhibition of DA release.\textsuperscript{1,11} This accords with the hypothesis that atypical antipsychotics give rise to less akathisia than classic drugs by blocking these serotonin 5-HT2A receptors.\textsuperscript{1,11,13}

In addition to the blocking of 5-HT2A receptors, the blocking of cholinergic muscarinic receptors and β-adrenoceptors is known to result in therapeutic effects.\textsuperscript{1,9,11} The blocking of cholinergic muscarinic receptors is in line with the idea that a deficiency of dopamine and an excess of dopamine in the striatum causes akathisia.\textsuperscript{3} In the striatum, D2 receptors are largely present on cholinergic interneurons, which influence the medium-sized spiny neuron (MSN) of the direct extrapyramidal pathway.\textsuperscript{14} When the influence of these cholinergic interneurons is blocked, the D2 receptor is no longer able to influence the activity of the extrapyramidal circuit.

The anti-akathisia effect of β-blockers has been attributed to an interaction between adrenergic neurons that originate in the locus coeruleus complex and dopaminergic neurons in the midbrain.\textsuperscript{1} However, this is contradicted by the fact that the interactions between adrenergic neurons from the locus coeruleus and dopaminergic neurons of the ventral tegmental area (VTA) in the midbrain are primarily mediated by α- and not β-adrenoceptors.\textsuperscript{15} β-Adrenoceptors are primarily present in the synapses of adrenergic neurons that run from the locus coeruleus complex to the cerebral cortex, the accumbens nucleus, and the dorsal striatum.\textsuperscript{16} The nucleus accumbens in particular is a good candidate for association with akathisia because it is involved in processes that motivate rewarding behaviors.

However, before an association between akathisia and dopamine deficiency in the ventral striatum can be assumed, an explanation must be found for the observation that dopamine hyperactivity in the accumbens results in agitation and dopamine hypoactivity in the accumbens results in akathisia. The different functions of the shell and core portions of the nucleus accumbens could account for this.\textsuperscript{17} It should be noted that agitation and akathisia differ by the absence and presence, respectively, of an urge to make movements.

Role of the Nucleus Accumbens

The nucleus accumbens is considered to be the area of the striatum that forms the interface between limbic and motor structures.\textsuperscript{18} Based on experimental work in animals, it is evident that the shell portion of the nucleus accumbens (NAcbS) is distinguished from the core (NAcbC) and the rest of the striatum by its promotion of general, unconditioned behaviors, such as feeding and defensive behavior. By stimulation of the shell subregion, individuals are motivated to display standard behavioral patterns that are cued by “novel” stimuli.\textsuperscript{19} The NAcbS facilitates new behavior that is not necessarily rewarding, but could lead to improvement in an individual's condition.

The NAcbC, on the other hand, seems to be preferentially involved in response-reinforcement learning. The shell is not involved in motor or response learning per se; rather, it integrates basic biological “drives.”\textsuperscript{18} Thus, the NAcbC can be considered to mediate inter alia curiosity and aggressive dominance. Both parts of the nucleus accumbens are stimulated by dopaminergic neurons from the VTA.

Normally, the prefrontal cortex inhibits the response to immediate reward-bringing stimuli, allowing an individual to opt for behavior that brings a postponed but larger reward. This inhibition is thought to be mediated through the NAcbC. When this system is damaged in experimental animals, impulsivity in favor of immediate reward occurs. Different parts of the prefrontal cortex appear to be involved in different forms of impulsivity (Figure 1).\textsuperscript{17} What should be apparent in Figure 1 is that different parts of the cerebral cortex (anterior cingulate cortex, orbitofrontal cortex, and infralimbic cortex) differentially affect the NAcbC and the NAcbS and that these latter structures are also differentially innervated with catecholaminergic fibers from the brainstem. The NAcbC and the NAcbS are both densely innervated by dopaminergic fibers, but only the NAcbS receives substantial noradrenergic innervation.

Figure 1. The nucleus accumbens core (NAcbC) and shell (NAcbS) both participate in the ventral cortico-striato-thalamo-cortical circuit and contain dopaminergic terminals that originate in the ventral tegmental area (VTA) of the midbrain.
Both portions are affected by glutamatergic terminals from the orbitofrontal cortex (OFC), but only the NAcbs is affected by the infralimbic cortex (IL, subgenual cingulate area, Cg25). Moreover, only the NAcbs is stimulated by alpha-adrenoceptors in the terminal synapses of adrenergic projections from the locus ceruleus complex. (Scheme adopted from Dalley et al. [17] with permission from the authors and publisher). Cg1: cingulate gyrus, 1. OFC: orbitofrontal cortex. IL: infralimbic cortex. NAcBC: nucleus accumbens core. NAcbs: nucleus accumbens shell. VTA: ventral tegmental area. LC: locus coeruleus.

To properly explain the role of dopaminergic neurotransmission in the nucleus accumbens, we must first address its role in drug abuse and dependence.20 An essential part of addiction is the craving for the addictive substance, which leads to characteristic drug-seeking behavior. This is likely due to dysfunction in the mechanisms that induce reward-seeking or discomfort-avoiding behavior. Three anatomical structures are involved in inducing this behavior: the orbitofrontal cortex, the NAcBC (reward-seeking behavior), and the amygdala (fear-activated behavior). All three anatomical structures are richly supplied with dopaminergic terminals that originate in the VTA. In people with drug dependence, the orbitofrontal cortex in particular is believed to initiate the drug-seeking behavior. The promotion of this behavior is mediated through the NAcBC and the ventral pallidum (i.e., the ventral cortico-striato-thalamo-cortical re-entry circuit of the prefrontal cortex).20 This is strongly conditioned behavior that leads to habit formation, and it is more or less the same as the conditioned behavior that is found in obsessive-compulsive disorder.21,22

The infralimbic cortex activates behavioral, neuroendocrine, and sympathetic autonomic systems in response to acute stressful situations.23 This cortical region corresponds to Brodmann area 25 in rats, monkeys, and humans, and it appears to be the only prefrontal area that projects substantially to the NAcbs.24 It is also known to be metabolically overactive in treatment-resistant major depression, and it is the target of deep brain stimulation in this disorder.25 This corresponds with the feelings of discomfort and dysphoria that accompany akathisia.

The Mechanism of Akathisia

Although it was not intended for that purpose, the model of Dalley and colleagues17 offers some interesting clues regarding the mechanism of akathisia. Akathisia may result from efforts to compensate for dopaminergic underactivity in the nucleus accumbens. By decreasing the stimulation of the nucleus accumbens, a dopamine deficiency results in an inhibition of both the NAcBC and the NAcbs. When an individual is compensating for this deficiency by inter alia increasing the adrenergic input from the brainstem, only the NAcbs is stimulated. This motivates individuals to display seemingly purposeless, immediate reward-seeking behavior, and it results in the activation of the corresponding re-entry circuit. Moreover, through feedback mechanisms, the activity of dopaminergic projections from the VTA to the prefrontal cortex may result in increased activity, particularly of the orbitofrontal cortex. This is due to stimulation of the D1 receptors that are present in these terminals and that are not affected by dopamine antagonists. In cortical areas, D1 receptors are expressed almost exclusively; there are hardly any D2 receptors.26

Several findings support such a mechanism. First, β-blocking agents have therapeutic effects in akathisia. Adrenergic terminals that originate in the locus coeruleus complex and end in the NAcb and the prefrontal cortex stimulate β-adrenoceptors at their terminals.15,16
Moreover, as indicated previously, the NAcbS plays a key role in promoting unconditioned defensive behavior. There are numerous reports of an association between the occurrence of akathisia and different forms of aggression. Therefore, this could be related to or even part of the complex behavior of akathisia.

**Conclusion**

Much evidence exists to support the idea that akathisia is related to a decrease in dopaminergic neurotransmission. This likely results in decreased activity in the entire ventral striatum. It can be postulated that this decline results in compensatory enhancement of the activity of adrenergic projections from the locus coeruleus complex. Because these projections selectively stimulate the shell portion of the nucleus accumbens, a mismatch between the activities of the NAcbC and the NAcbS occurs. Relative overstimulation of the NAcbS results in the typical urge to display senseless "curious" or "defensive" behavior and is accompanied by dysphoric feelings.

**References**

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Invited Insights
Psychopharmaceuticals and your Licensing Board

Marvin Firestone, MD, JD, FCLM and Dan Tennenhouse, MD, JD, FCLM

The Issue. Prescribing is one of the most common bases for actions by licensing boards against clinicians. How can clinicians protect themselves?

Bases for licensing board actions
While licensing board actions differ from state to state, they generally require proof of gross (or extreme) negligence, incompetence, repeated negligent acts, or inadequate record keeping. The board establishes such proof by relying on expert witnesses who testify before the board or before an administrative law judge. The board may then suspend or revoke the clinician’s license, or place the clinician on probation for a period of years subject to conditions of probation set forth by the board. The process is difficult and expensive for the clinician.

Any clinician notified of an investigation by their licensing board should obtain consultation from a lawyer experienced in licensing board actions before responding to any query or accepting invitations for an investigator's visit from the licensing board. One naïve comment can make a licensing board action indefensible. Many clinicians believe that not seeking legal consultation will maintain a more friendly and cooperative relationship with their licensing board, and will increase the likelihood the board will not take further action. Wrong! Licensing boards are government agencies that want to prove their worth by revoking as many licenses as possible. Clinicians who do not take basic measures to defend themselves are easy prey. Being represented by a lawyer makes it more expensive and difficult for the board to prevail.

Prescribing requirements
Table 1 lists the ten requirements for prescribing:

<table>
<thead>
<tr>
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<th>Prescribing Requirements</th>
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<tbody>
<tr>
<td>1.</td>
<td>A prior good-faith evaluation of the patient. This must generally be done in person. Prescribing based only on a telephone call or Internet interaction with the patient is likely to result in a licensing board action.</td>
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<tr>
<td>2.</td>
<td>A diagnosis supporting the choice of medication. The benefits of the medication must warrant the risks. Off-label prescribing (for an indication not specifically approved by the FDA) is legal so long as the medical literature supports that use of the medication.</td>
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<tr>
<td>3.</td>
<td>Investigation for, and awareness of, any contra-indications to the medication. In most cases, a history from the patient or family and a review of prior medical records constitutes sufficient investigation.</td>
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<tr>
<td>4.</td>
<td>A safe dosage and frequency of administration.</td>
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<td>5.</td>
<td>Appropriate quantities in each prescription. Excessive quantities are especially risky for patients with increased suicide potential.</td>
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<tr>
<td>6.</td>
<td>Proper instructions to the patient about how to take the medication.</td>
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<td>7.</td>
<td>Adequate warnings about adverse effects of the medication and when to immediately contact a clinician.</td>
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<tr>
<td>8.</td>
<td>Sufficient monitoring of the patient while on the medication to detect therapeutic failure, adverse reactions, and patient non-compliance.</td>
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<td>9.</td>
<td>Proper methods of discontinuing the medication when necessary, such as tapering.</td>
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<tr>
<td>10.</td>
<td>Documentation showing that the above measures have been taken, and to assure safe continuity of the patient’s care.</td>
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**Controlled substances**

Additional regulations for controlled substances may limit who may prescribe, amount of medication in a prescription, conditions for refilling the medication, duration of time until the patient must be seen again, and more.

**Documentation**

While licensing board investigations may not turn up evidence of improper conduct that would support a licensing board action, inadequate documentation is often found. The action then proceeds on an accusation for inadequate documentation. Clinicians should take extra care when documenting prescriptions and subsequent monitoring of the medication. When a prescription is written, the medical record should always contain at least the information presented in the Table 2.

<table>
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<th>Table 2: Medical Record Documentation</th>
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<tr>
<td>1. The diagnosis for which the medication is prescribed</td>
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<td>2. The name of the medication</td>
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<tr>
<td>3. The dose and frequency of administration</td>
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<tr>
<td>4. The number prescribed</td>
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<tr>
<td>5. The number of refills, if any</td>
</tr>
<tr>
<td>6. The date of the prescription</td>
</tr>
<tr>
<td>7. A follow-up plan for the patient with reasonable time periods in order to monitor the patient for therapeutic efficacy, patient compliance, and for determining any adverse reactions.</td>
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In addition to the above, the clinician would be well-advised to briefly note that the patient was instructed on using the medication and given required warnings.

**The bottom line**

Understanding the ramifications of licensing board investigations is important for all clinicians. Besides needing to be properly advised of their rights, clinicians also have the duty to protect themselves, and this starts by implementing a secure and solid system of documenting prescriptions and any follow-up including monitoring of the medication and the patient's compliance and well-being.
Polymorphisms in the gene for methylenetetrahydrofolate reductase (MTHFR) have been linked to several different psychiatric disorders.

This article discusses how genetic polymorphisms in MTHFR can influence folate metabolism and ultimately lead to increased susceptibility to psychiatric disorders. Several pharmacological treatments to correct aberrant folate metabolism and its downstream consequences are currently under investigation.

As personalized medicine becomes a reality, knowledge of the biochemical and molecular underpinnings of folate metabolism will be necessary for the optimal detection and treatment of psychiatric disorders associated with abnormal folate metabolism.

Folate is an important and necessary vitamin B complex found in leafy greens such as spinach. It is required for several important biological processes, including normal cell growth and replication, nucleic acid synthesis, DNA repair, and modulation of the amino acid homocysteine. In fact, maternal folate deficiency has such a detrimental effect on embryonic neural tube development that several countries, including the United States, now require supplementation of many grain products with folic acid (a synthetic form of folate). In addition to the more severe neural tube defects caused by extreme folate deficiency during development, folate deficiency has also been associated with several psychiatric diseases, including major depressive disorder (MDD), schizophrenia, and bipolar disorder (BP), indicating that folate deficiency may have more subtly damaging effects on brain development and maintenance throughout the lifetime of an individual.

Methylenetetrahydrofolate reductase (MTHFR) is the enzyme responsible for synthesizing L-methylfolate from dietary folate sources. L-methylfolate has several very important roles. First, L-methylfolate affects the synthesis of neurotransmitters by regulating levels of the cofactor bioppterin. Bioppterin is required by tyrosine hydroxylase and tryptophan hydroxylase in the synthesis of monoamines such as dopamine (DA) and norepinephrine (NE). Second, L-methylfolate is used in the conversion of the amino acid homocysteine to methionine and thus regulates homocysteine concentrations. Additionally, L-methylfolate is ultimately responsible for the regulation of gene expression. The methionine produced with the help of L-methylfolate is converted into s-adenosylmethionine (SAMe), the major methyl group (CH3) donator for several enzymes, including DNA and histone methyltransferases. DNA and histone methyltransferases tag DNA and histones, respectively, with methyl groups, and in doing so, turn off the expression of genes (Figure 1).

Two significant polymorphisms have been discovered in the MTHFR gene, and both lead to consequences that are similar to those of
reduced dietary folate intake. The first MTHFR polymorphism, known as the "T allele," is a transition of cytosine to thymine at codon 677. The second common MTHFR polymorphism, known as the "C allele," involves a transversion of adenine to cytosine at codon 2398. Both of these polymorphisms result in the reduced activity of MTHFR, and the consequences of this reduced enzymatic activity include the diminished production of L-methylfolate, the reduced availability of methyl groups, and elevated homocysteine levels (i.e., hyperhomocysteinemia). The reduced production of L-methylfolate gives rise to a paucity of monoamine production, whereas the diminished availability of methyl groups is believed to have epigenetic effects on the expression of many genes. Reduced methylation also results in the aberrant building of cell membranes and has detrimental effects on myelin structure, leading to impaired nerve conduction. Hypercysteinemia has been shown to modulate the activity of N-methyl-D-aspartate receptors (NMDAR), which play an integral role in the long-term potentiation that underlies learning and memory. The actions of homocysteine on NMDAR therefore impair learning and memory and can even be excitotoxic, resulting in cell death. Given the effects of MTHFR polymorphisms on decreased neurotransmitter production, aberrant gene expression, and synaptic transmission, it is not surprising that MTHFR polymorphisms have been linked to several psychiatric disorders, including MDD, schizophrenia, and BD. Inheritance of the MTHFR T or C allele increases the susceptibility of an individual to psychiatric disorders, but the determination of whether one develops a psychiatric disorder is most likely also influenced by the inheritance of polymorphisms in other genes that affect folate metabolism as well as environmental influences on folate availability (e.g., smoking).

**Folate in the Treatment of Psychiatric Disorders**

It seems clear that folate metabolism, which is influenced by MTHFR and other polymorphisms as well as environmental factors, has a major influence on neurobiological development and regulation. Abnormal folate metabolism may therefore greatly affect an individual's susceptibility to psychiatric disorders. It seems plausible that the modulation of folate levels may be useful as a potential treatment for many psychiatric disorders. Indeed, several studies have indicated the effectiveness of using folate and its metabolites or downstream effectors in the treatment of various psychiatric disorders. For example, treatment with L-methylfolate has been shown to improve positive, negative, and cognitive symptoms in schizophrenia, and treatment with SAMe reduces depressive symptoms in Parkinson disease patients.

**Figure 1. Folate Metabolism**

A. In normal folate metabolism, the production of L-methylfolate from folate is mediated by the enzyme methylenetetrahydrofolate reductase (MTHFR). L-methylfolate regulates the production of biopterin, a cofactor required by tyrosine and tryptophan hydroxylases for the production of monoaminergic neurotransmitters, such as dopamine and norepinephrine. L-methylfolate also converts the amino acid homocysteine (Hcy) into methionine, reducing homocysteine levels and leading to the production of s-adenosylmethionine (SAMe), the major methyl (CH3) donor in the brain. Along with modulated levels of homocysteine, the production of SAMe allows for normal nerve conduction, plasma membrane formation, and the synaptic transmission that underlies long-term potentiation. SAMe also provides methyl groups to the DNA and histone methyltransferase enzymes that mediate the epigenetic control of gene expression.
B. When folate metabolism is abnormal due to folate deficiency and/or genetic polymorphisms, such as the T and C polymorphisms in MTHFR, less L-methylfolate is produced. Ultimately, this may lead to reduced monoaminergic neurotransmitter production; the reduced conversion of homocysteine to methionine, leading to a buildup up homocysteine; and reduced SAKe concentration. The buildup of homocysteine and the decreased availability of methyl groups from SAMe bring about impairments in neural transmission and the aberrant expression of genes that should be silenced. Together, these changes in folate metabolism may increase an individual’s risk for developing a psychiatric disorder.

The bottom line
Both dietary folate deficiency and genetic polymorphisms that affect folate metabolism, including the MTHFR T and C alleles, have wide-ranging consequences for the epigenetic regulation of gene expression, neurotransmitter production, and neural transmission. Combinations of genetic and environmental factors that affect folate metabolism likely underlie the susceptibility and development of various psychiatric disorders, including MDD, schizophrenia, and BD. It is possible that optimal treatment of these disorders may include addressing abnormal folate metabolism through the administration of folate or one of its metabolites or manipulating the epigenetic mechanisms of aberrant gene expression.

References

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The neuroanatomy of dopamine neuronal pathways in the brain can explain the symptoms of schizophrenia as well as the therapeutic and side effects of antipsychotic drugs. (a) The **nigrostriatal dopamine pathway**, which projects from the substantia nigra to the basal ganglia or the striatum, is part of the extrapyramidal nervous system and controls motor function and movement. (b) The **mesolimbic dopamine pathway** projects from the midbrain ventral tegmental area to the nucleus accumbens, a part of the limbic system of the brain that is thought to be involved in many behaviors, such as pleasurable sensations, the powerful euphoria of drugs of abuse, and the delusions and hallucinations of psychosis. (c) A pathway related to the mesolimbic dopamine pathway is the **mesocortical dopamine pathway**. It also projects from the midbrain ventral tegmental area, but it sends its axons to areas of the prefrontal cortex, where they may play a role in mediating the cognitive (dorsolateral prefrontal cortex) and affective (ventromedial prefrontal cortex) symptoms of schizophrenia. (d) The fourth dopamine pathway of interest, the **tubero-infundibular dopamine pathway**, projects from the hypothalamus to the anterior pituitary gland and controls prolactin secretion. (e) The **fifth dopamine pathway** arises from multiple sites, including the periaqueductal gray, the ventral mesencephalon, hypothalamic nuclei, and the lateral parabrachial nucleus, and it projects to the thalamus. Its function is not currently well known.

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Tips and Pearls
Aripiprazole

**Brands**
Abilify

**Class**
Atypical antipsychotic; serotonin-dopamine antagonist

**Approved For:**
- Schizophrenia (ages 13 and older)
- Maintaining stability in schizophrenia
- Acute mania/mixed mania (ages 10 and older)
- Bipolar maintenance
- Depression (adjunct)
- Autism-related irritability in children (ages 6 to 17)

**Dosing**

**Formulation:**
- Tablet 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg
- Orally disintegrating tablet 10 mg, 15 mg
- Oral solution 1 mg/mL
- Injection 9.75 mg/1.3 mL

**Dosage range:**
15–30 mg/day

**Pearls**
Well accepted in clinical practice when wanting to avoid weight gain or sedation because it generally causes these side effects less than most other antipsychotics
Can even be activating, which can be reduced by lowering the dose or starting at a lower dose
If sedation is desired, a benzodiazepine can be added either short term at the initiation of treatment until symptoms of agitation and insomnia are stabilized or intermittently as needed

**Dosing tips:**
Patients who are not acutely psychotic may need to be dosed lower (e.g., 2.5–10 mg/day) in order to avoid akathisia and activation and for maximum tolerability
Consider cutting 5 mg tablet in half (tablets are not scored) or administering 1–5 mg as the oral solution for children, adolescents, and
adults who are very sensitive to side effects
Although studies suggest that patients switching to aripiprazole from another antipsychotic can do well with rapid switch or cross-titration, clinical experience suggests that many patients do best by adding a full dose of aripiprazole to the maintenance dose of the first antipsychotic for at least several days and possibly as long as 3 or 4 weeks prior to slow down-titration of the first antipsychotic
Due to its very long half-life, aripiprazole will take longer to reach steady state when initiating dosing and longer to wash out when stopping dosing than other atypical antipsychotics

**Children and adolescents:**
Approved for use in schizophrenia (ages 13 and older), manic/mixed episodes (ages 10 and older), and irritability associated with autism (ages 6–17)
Children and adolescents using aripiprazole may need to be monitored more often than adults and may tolerate lower doses better
May be more risk of weight gain in children than in adults

**Pregnancy:**
Risk Category C [some animal studies show adverse effects; no controlled studies in humans]

**Side Effects**

**Weight gain:**

**Sedation:**

**Notable or dangerous side effects:**
Dizziness, insomnia, akathisia, activation, nausea, vomiting
Theoretical risk of tardive dyskinesia, rare neuroleptic malignant syndrome, rare seizures
Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis

**Drug interactions:**
Ketoconazole and possibly other CYP450 3A4 inhibitors, such as nefazodone, fluvoxamine, and fluoxetine may increase plasma levels of aripiprazole
Carbamazepine and possibly other inducers of CYP450 3A4 may decrease plasma levels of aripiprazole
Quinidine and possibly other inhibitors of CYP450 2D6, such as paroxetine, fluoxetine, and duloxetine, may increase plasma levels of aripiprazole
Aripiprazole may enhance the effects of antihypertensive drugs
Aripiprazole may antagonize levodopa and dopamine agonists

**Cardiac impairment:**
Use with caution because of risk of orthostatic hypotension

**Renal impairment:**
Dose adjustment not necessary
Hepatic impairment:
Dose adjustment not necessary


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