

**EXAMPLES OF DISORDERS ASSOCIATED WITH DEFECTS
 IN NEUROTRANSMISSION**

DISORDER	PATHOPHYSIOLOGY	TREATMENT
NEUROTRANSMITTER IMBALANCE		
Alzheimer's disease	Extracellular β -amyloid deposits, intracellular neurofibrillary tangles, and senile plaques, particularly in the limbic system (eg, hippocampus), in the association area of the cortex, and in neurons that synthesize and use acetylcholine (eg, in the basal nucleus of Meynert and its wide projections to the cortex)	Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) delay synaptic degradation of acetylcholine and thus modestly improve cognitive function and memory. Memantine, an NMDA-receptor antagonist, may slow progression of the disease and increase autonomy.
Anxiety	May reflect reduced activity of GABA, perhaps due to imbalance of endogenous inhibitors, stimulators of the GABA receptor, or both May also involve imbalances in norepinephrine and 5-HT responses	Benzodiazepines increase the probability of opening Cl^- channels modulated by GABA through GABA_A receptor activation. SSRIs are the drugs of choice for long-term treatment because tolerance to benzodiazepines can develop.
Autism	Possible hyperserotonemia, which occurs in 30–50% of autistic people, with no evidence of central 5-HT abnormalities	SSRIs and risperidone may be helpful.
Brain injury	Injury (eg, trauma, hypoxia, prolonged seizures) stimulating excessive release of excitatory neurotransmitters (eg, glutamate) and accumulation of intracellular Ca^{++} , which contribute to neuronal death	In experimental models of ischemia and injury, Ca channel blockers, glycine, and older NMDA-receptor antagonists (eg, dextromethorphan, ketamine) may reduce the extent of neuronal loss, but these drugs are not effective in people. Memantine, a newer NMDA-receptor antagonist, is under study.
Depression	Complex abnormalities in cholinergic, catecholaminergic (noradrenergic, dopaminergic), and serotonergic (5-HT) transmission Possible involvement of other hormones and neuropeptides (eg, substance P, dopamine, acetylcholine, GABA)	Antidepressants downregulate receptors indirectly or directly by inhibiting reuptake of 5-HT (as with SSRIs) and norepinephrine or dopamine or by blocking MAO. Blockade of 5-HT _{2A/2C} (a type of 5-HT receptor abundant in the prefrontal area) may increase the efficacy of SSRIs (eg, trazodone).

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DISORDER	PATHOPHYSIOLOGY	TREATMENT
Seizure disorders	Seizures consisting of sudden synchronous high-frequency firing by localized groups of neurons in certain brain areas, perhaps caused by increased activity of glutamate or reduced activity of GABA	<p>Phenytoin, lamotrigine, carbamazepine, valproate, topiramate, and some other anticonvulsants (eg, zonisamide, oxcarbazepine) stabilize voltage-dependent Na channels.</p> <p>Ethosuximide and gabapentin decrease certain Ca currents.</p> <p>Phenytoin also reduces excessive neurotransmitter release.</p> <p>Lamotrigine may decrease levels of glutamate and aspartate.</p> <p>Phenobarbital and benzodiazepines enhance GABA activation by affecting the GABA_A receptor–Cl channel complex.</p> <p>Tiagabine blocks GABA glial uptake.</p> <p>Valproate increases levels of GABA.</p> <p>Topiramate increases GABA activity.</p>
Huntington's disease (chorea)	Major neuronal damage in the cortex and striatum due to polyglutamine expansion (encoded by CAG repeat), produced by an abnormal gene on chromosome 4 (the abnormal gene overproduces the protein huntingtin, which may combine with molecules that induce excessive stimulation of cells by excitatory amino acid neurotransmitters such as glutamate)	<p>No specific treatment exists, but drugs that block NMDA receptors may block the toxic effects of excess glutamate.</p> <p>GABA-mimetic drugs are ineffective.</p>
Mania	Increased norepinephrine and dopamine activity, reduced 5-HT levels, and abnormal glutamate neurotransmission	<p>Lithium is the traditional first choice. It reduces norepinephrine release and increases 5-HT synthesis.</p> <p>Valproate and lamotrigine are beneficial, possibly by normalizing glutamate transmission.</p> <p>Other drugs used as mood stabilizers include topiramate, gabapentin, carbamazepine, and oxcarbazepine.</p> <p>Topiramate blocks voltage-dependent Na channels, augments GABA_A activity at some subtypes of the GABA_A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV. Gabapentin is thought to bind to the $\alpha 2\delta$ subunit (1 and 2) of the voltage-dependent Ca channel in the CNS. Carbamazepine and oxcarbazepine stabilize voltage dependent Na⁺ channels.</p>

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DISORDER	PATHOPHYSIOLOGY	TREATMENT
Neuroleptic malignant syndrome	Blockage of dopamine (D ₂) receptors by drugs (eg, antipsychotic drugs, methylphenidate) or abrupt withdrawal of a dopaminergic agonist, resulting in muscle rigidity, fever, change in mental status, and autonomic instability	Treatment with a D ₂ agonist (eg, bromocriptine) reverses the disordered neurotransmission. Other drugs are also used as needed (eg, dantrolene, a direct muscular blocker, is used to block the muscle spasms).
Pain	Tissue injury, which causes release of substance P and glutamate in the posterior horn of the spinal cord and release of other macromolecules that mediate pain signals, such as calcitonin gene-related protein, neurokinin A, and bradykinin, which are localized primarily in the lamina II and IV of the spinal cord Further modulation of these signals by endorphins (in the spinal cord) and by 5-HT and norepinephrine (in the descending pathways that originate in the brain)	NSAIDs inhibit prostaglandin synthesis selectively (with COX-2 inhibitors—eg, celecoxib, parecoxib) or nonselectively (with COX-1 and -2 inhibitors—eg, ibuprofen, naproxen) and reduce pain impulse formation. Opioid analgesics (eg, morphine) activate endorphin-enkephalin (μ, δ, and κ) receptors, reducing pain impulse transmission.
Parkinsonism	Inhibition of the dopaminergic system due to blockage of dopaminergic receptors by antipsychotic drugs	Anticholinergic drugs reduce cholinergic activity and restore balance between cholinergic and dopaminergic systems.
Parkinson's disease	Loss of dopaminergic neurons of the pars compacta in the substantia nigra and other areas, with reduced levels of dopamine and met-enkephalin, altering the dopamine/acetylcholine balance and resulting in striatal acetylcholine overactivity	L-dopa reaches the synaptic cleft, is taken up by the axon, and is decarboxylated to dopamine, which is secreted into the cleft to activate dendritic dopamine receptors. Amantadine increases the pre-synaptic release of dopamine; dopamine agonists stimulate dopamine receptors, although bromocriptine, pramipexole, and ropinirole bind only to D ₂ , D ₃ , and D ₄ dopamine receptor subtypes. Anticholinergic drugs reduce activity of the cholinergic system, restoring the balance of dopamine and acetylcholine. MAO-B inhibitors prevent reuptake of dopamine, increasing its levels. Selegiline, an MAO-B inhibitor, blocks dopamine breakdown and thus prolongs the response to levodopa and allows the dosage of carbidopa/levodopa to be reduced. Catechol <i>O</i> -methyltransferase (COMT) inhibitors also inhibit dopamine breakdown.

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DISORDER	PATHOPHYSIOLOGY	TREATMENT
Schizophrenia	Increased presynaptic release, synthesis of dopamine, sensitivity or density of postsynaptic dopamine receptors, or a combination	Antipsychotic drugs block dopamine receptors and reduce dopaminergic overactivity to normal. Haloperidol preferentially blocks D ₂ and D ₃ receptors (high affinity) and D ₄ receptors (low affinity) in mesocortical areas. Clozapine has a high affinity for binding D ₄ and 5-HT ₂ receptors, suggesting 5-HT system involvement in the pathogenesis of schizophrenia and its response to treatment. Clozapine has a significant risk of leukopenia. Olanzapine and risperidone, similar to haloperidol, also have high affinity for 5-HT ₂ and D ₂ receptors.
Tardive dyskinesia	Hypersensitive dopamine receptors due to chronic blockade by antipsychotic drugs	Reducing doses of antipsychotics may reduce hypersensitivity of dopamine receptors; however, in some cases, changes can be irreversible.

NORMAL NEUROTRANSMITTERS BUT NONFUNCTIONAL RECEPTORS

Myasthenia gravis	Reflects inactivation of acetylcholine receptors and postsynaptic histochemical changes at the neuromuscular junction due to autoimmune reactions	Anticholinesterase drugs inhibit acetylcholinesterase, increase acetylcholine levels at the junction, and stimulate remaining receptors, increasing muscle activity.
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DECREASED NEURONAL UPTAKE OF NEUROTRANSMITTERS

Amyotrophic lateral sclerosis	Destruction of upper and lower motor neurons, possibly caused in part by glutamate neurotoxicity	Riluzole, which inhibits glutamate transmission, modestly extends survival.
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NORMAL NEUROTRANSMITTERS BUT ION CHANNEL DEFECTS

Episodic ataxias	Defective voltage-gated K channels, causing distal rippling and incoordination (myokymia)	Treatment with acetazolamide is effective in some types of episodic ataxia.
Hyperkalemic periodic paralysis	Decreased Na channel inactivation	Severe attacks may be terminated by Ca gluconate, glucose, and insulin.
Hypokalemic periodic paralysis	Defective voltage-gated Ca channels	Acute attacks can be terminated by K salts. Acetazolamide is effective for prevention.

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Lambert-Eaton syndrome*	Antibodies that decrease presynaptic release of acetylcholine	Corticosteroids, 3,4-diaminopyridine (DAP), guanidine, IVIG, and plasmapheresis can be helpful.
Paramyotonia congenita	Defective voltage-gated Na channels, causing cold-induced myotonia and episodic weakness	Mexiletine (a Na channel blocker) and acetazolamide (a carbonic anhydrase inhibitor) may be helpful.
Rasmussen's encephalitis	Postviral production of antibodies to glutamate receptors, affecting glutamate-gated channels Most distinctive form of epilepsy partialis continua	Corticosteroids and antiviral drugs are usually ineffective. Functional hemispherectomy can control seizures if spontaneous remission does not occur.
Startle disease (hyperreflexia, stiff baby syndrome)	Mutation in the gene for the $\alpha 1$ subunit of the glycine-gated channel Characterized by stiffness, nocturnal myoclonus, and an exaggerated startle reflex, with hyperreflexia and falling	Clonazepam or certain other anti-convulsants (eg, phenytoin, phenobarbital, diazepam, valproate) may result in improvement.
POISONING		
Botulism	Inhibition of acetylcholine release from motor neurons by toxin from <i>Clostridium botulinum</i>	No specific drug therapy exists. Tiny amounts of the toxin are used to treat certain dystonias, spasticity, neuropathic pain, and migraines or cosmetically to reduce skin wrinkles.
Mushroom poisoning	<i>Amanita muscaria</i> : Contains ibotenic acid (which has effects similar to those of glutamate) and a metabolite similar to muscimol (which has effects similar to those of GABA) <i>Inocybe</i> and <i>Clitocybe</i> spp: Stimulation of muscarinic receptors by muscarine and related compounds	Treatment is supportive because no drugs reverse the effects on neurotransmission. Atropine helps reverse muscarinic manifestations.
Organophosphates	Irreversible inhibition of acetylcholinesterase and marked increase in acetylcholine levels in synaptic cleft	Pralidoxime removes toxin from acetylcholinesterase and helps reverse nicotinic as well as muscarinic manifestations. Atropine helps rapidly reverse muscarinic effects.
Snake venom from <i>Bungarus multicinctus</i> (Taiwanese banded krait)	Acetylcholine receptors at neuromuscular junction blocked by α - <i>Bungarus</i> toxin	Antivenom appears to be effective and is available.

*Easton-Lambert syndrome is an antibody-mediated paraneoplastic syndrome that typically occurs in small cell lung cancer. It can be present before the tumor manifests.

GABA = γ -aminobutyric acid; 5-HT = serotonin; IVIG = IV immune globulin; MAO = monoamine oxidase; MAO-B = MAO type B; NMDA = *N*-methyl-D-aspartate.