tonin ($5\text{-}HT_3$) antagonists are potent antiemetics, particularly useful for chemotherapy-induced nausea. A few cholinergic antagonists and histamine antagonists reduce emesis and control motion sickness (Table 3.4). The neural pathways influenced by these antagonists have not been clearly identified.

Anti-Parkinson Drugs

Parkinson's Disease affects a half million Americans. Symptoms include tremor (pill-rolling) at rest, bradykinesia (slow movements), and cogwheel rigidity.

The disease is caused by decreased dopamine neurotransmission in the nigrostriatal pathway secondary to degradation of dopaminergic neurons that project from the substantia nigra to the striatum (caudate and putamen). Figures 3.2 and 3.3 outline the neuropathology of Parkinson's Disease. Treatment consists of either increasing dopamine neurotransmission or blocking cholinergic neurotransmission (Table 3.5, Fig. 3.3).

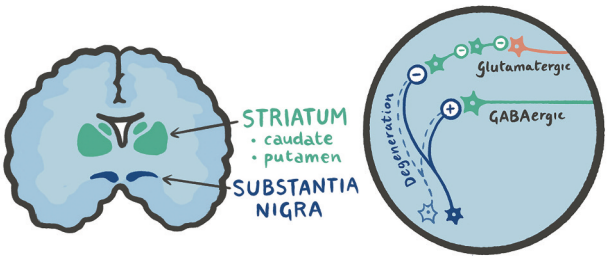

Figure 3.2 The symptoms of Parkinson's Disease are caused by degeneration of dopaminergic neurons in the nigrostriatal pathway. *Inhibitory dopaminergic neurons which project from the substantia nigra to the caudate and putamen are most affected. Cholinergic input (excitatory) to the caudate and putamen appears to be unaffected; thus the balance is tipped toward cholinergic input.*

Movement Disorder Drugs

Tardive dyskinesia is a serious side effect of antipsychotic medications that manifests as repetitive jerking movements of the tongue, face and neck. For many pa-

Table 3.6A Opioid Analgesics and Antagonists

DRUG	MECHANISM/ACTIONS	INDICATIONS	UNDESIRABLE EFFECTS
Full Agonists			
Morphine	Opiate receptor agonist. Induces analgesia, sedation, respiratory depression, nausea, vomiting, vertigo, miosis, ADH release, GI effects (decreased propulsion and secretions, tonic spasm). Increases tone in bile duct, bronchi, ureters, and bladder.	Severe pain which cannot be alleviated by non-narcotic analgesics or weaker narcotic analgesics. Drug of choice for treating severe pain of myocardial infarction.	Respiratory depression, constipation, CNS disturbances, orthostatic hypotension, cholestasis, nausea and vomiting with initial doses.
Levorphanol (Levo-dromoran) **Oxymorphone** **Oxycodone** (Oxycontin) **Hydromorphone** (Dilaudid) **Tramadol** (Ultram) **Hydrocodone** (Vicodin)	" "	Moderate to severe pain.	" "
Meperidine (Demerol)	" "	Also used to treat rigors such as those induced by amphotericin B.	Like morphine. Overdose causes convulsions due to excitatory actions of metabolite.
Methadone	Full morphine-like actions, weaker sedative.	Detoxification of narcotic addiction. Severe pain in hospitalized patients.	Similar to morphine.
Fentanyl (Sublimaze)	More potent than morphine.	Preoperative medication used in anesthesia.	Muscle rigidity, bradycardia.
Sufentanil	Potent analgesic.	Used in anesthesia.	Little data available.
Alfentanil	See Fentanyl.	" "	" "
Remifentanil (Ultiva)	" "	" "	May cause chest wall rigidity if infused rapidly.

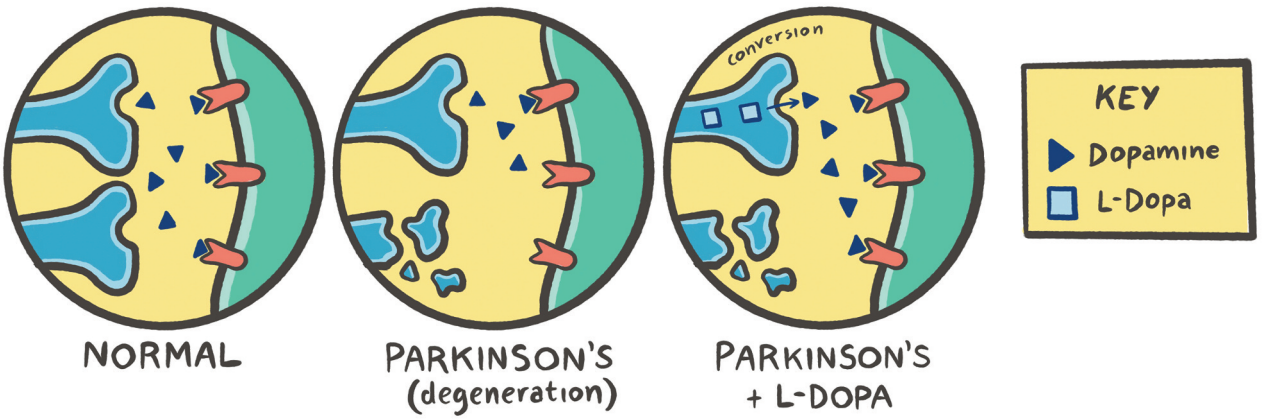

Figure 3.3 Synaptic view of Parkinson's Disease (PD) and therapy. *Dopaminergic terminals decay in PD, leading to decreased dopamine (DA, solid triangles). L-dopa, an amino acid precursor of DA crosses the blood brain barrier, enters surviving DA terminals and is converted to DA. Increased DA neurotransmission partially restores the dopamine-acetylcholine neurotransmission balance.*

tients, discontinuing the medication that causes tardive dyskinesia is not a good option because they rely on the medicine for mental health. **Valbenazine tosylate** (Ingrezza) and **Deutetrabenazine** (Austedo) are vesicular monoamine transporter 2 (VMAT2) inhibitors that reduce the movement symptoms of tardive dyskinesia.

PHARMACOKINETIC	TOLERANCE/DEPENDENCE	DRUG INTERACTIONS	NOTES
IM/PO/PR/SC/IV, epidural, intrathecal. Poorly absorbed, metabolized by conjugation w/glucuronic acid. 4–6 hr duration.	Tolerance develops to analgesic effects, but not to constipating effects. High abuse potential. Withdrawal leads to insomnia, pain, increased GI activity, restlessness.	Enhances actions of other CNS depressants. Increases neuromuscular blocker-induced respiratory depression. Additive with drugs that cause hypotension.	The analgesic actions of opioids are threefold. The perception of pain is reduced (increased threshold), the unpleasant psychological response is reduced, and sleep is induced even in the presence of pain.
Various. Better oral absorption than morphine.	" "	" "	" "
IM/SC/PO/IV. Shorter duration than morphine. Metabolite is excitatory to CNS.	" "	With MAO inhibitors, causes severe CNS excitation, respiratory depression, or hypotension.	" "
IM/SC/PO. Excreted more slowly than morphine (half-life = 25 h). Withdrawal symptoms are less intense, but prolonged.	Cross dependent with morphine (basis for narcotic detoxification). Tolerance develops readily. Less psychologically addicting than morphine.		Detoxification replaces heroin dependence with methadone dependence. Then slowly reducing methadone dose to zero.
IV. Rapid onset. Half-life = 4 h. Shorter duration than morphine.			Transdermal, transmucosal preparation available for chronic pain.
IV, sublingual	Little data available.		
IV. Fastest onset.	" "		
IV.	" "		IV tubing must be changed or cleared after remifentanil.

Huntington's disease (HD) is a neurodegenerative and movement disorder caused by an expansion of the triplet repeat "CAG" in the huntingtin gene. Deutetrabenazine (described immediately above) is also indicated for reducing the choreic movements of HD. Depression and suicide are risks of this drug in HD patients. **Xenazine** (tetrabenazine) is the first medication FDA has approved specifically for Huntington's. Like Deutetrabenazine, it is a VMAT2 inhibitor. It helps suppress jerky involuntary movements, but it may cause serious side effects, such as worsening depression.

Drugs to Treat Alzheimer's

Alzheimer's disease (AD) is the most common type of dementia. AD is thought to be caused by the abnormal build-up of proteins in and around brain cells. One of the proteins involved is called amyloid, deposits of which form plaques around brain cells. The other protein is called tau, deposits of which form tangles within brain cells. AD is a disease that progresses from mild to profound memory loss and diminished ability to converse or interact with the environment. AD involves parts of the brain that control thought, memory, and language. FDA approved drugs to treat Alzheimer's include two categories.

Monoclonal antibodies such as **Lecanemab** (Leqembi) and **Aducanumab** (Aduhelm) reduce beta amyloid plaques and are indicated for patients with mild disease. **Donepezil** (Aricept®), **Rivastigmine** (Exelon®), and **Galantamine** (Razadyne®) are drugs that inhibit the acetylcholinesterase enzyme, which normally breaks down acetylcholine. The main pharmacological actions of these drugs are believed to occur as the result of this enzyme inhibition, enhancing cholinergic transmission, which relieves the symptoms of Alzheimer's dementia.

Drugs to treat ALS

Amyotrophic lateral sclerosis (ALS) is an uncommon neurologic disorder that involves degeneration of the motor neurons that control voluntary muscle movement. As the disease progresses, individuals have increasing difficulty chewing, swallowing, walking, talking, and ultimately breathing. Onset of symptoms is typically between age 40 and age 70 and patients typically survive 2-10 years after diagnosis. In 8-23% of patients, the disorder is caused by a heritable mutation in the superoxide dismutase 1 (SOD1) gene. In others, no genetic defects can be identified. The FDA approved **Tofersen** (Qalsody) to treat patients with amyotrophic lateral sclerosis (ALS)

Table 3.6B Opioid Analgesics and Antagonist (cont.)

DRUG	MECHANISM/ACTIONS	INDICATIONS	UNDESIRABLE EFFECTS
Weak Agonists			
Codeine	A prodrug: 10% of dose is converted to morphine. Actions are due to morphine. Also an antitussive (suppresses coughing).	Minor pain relief. Cough.	Similar to morphine, but less intense at doses which relieve moderate pain. At high doses, toxicity is as severe as with morphine.
Mixed Agonist-antagonists—lower abuse potential			
Buprenorphine	In contrast to full opioid agonists, Buprenorphine is a partial agonist that does not cause the euphoric high.	Moderate to severe pain. Preoperative medicine, combination anesthesia.	Respiratory depression, sedation, dizziness, nausea, vomiting.
Pure Antagonists			
Naloxone (Narcan)	Surmountably blocks opioid receptors. Has no effect in narcotic-free persons.	Treatment of narcotic overdose. Diagnostic agent (for evaluation of addiction) in methadone programs. To reduce postoperative respiratory depression.	Induces narcotic withdrawal syndrome (appetite loss, muscle contraction, fever/chills, restlessness, cardiovascular and respiratory symptoms, nausea, vomiting, diarrhea.)
Naltrexone (ReVia)	Similar to naloxone, but longer duration.	" ". Also indicated for treatment of alcoholism.	" "

associated with a mutation in the superoxide dismutase 1 (SOD1) gene (SOD1-ALS). Tofersen is an antisense oligonucleotide that targets SOD1 mRNA to reduce the synthesis of SOD1 protein. The approval was based on a reduction in plasma neurofilament light (NfL), a blood-based biomarker of axonal (nerve) injury and neurodegeneration. Tofersen is administered intrathecally (through a spinal injection) by healthcare professionals. This drug is not approved for patients who lack a mutation in the SOD1 gene. **Edaravone** (Radicava) is an anti-oxidant that may scavenge oxygen free radicals and slow the progression of ALS. **Riluzole** (Rilutek, Tiglutik, Exervan) inhibits glutamate release and extends the life of ALS patients by about 3 months.

Central Analgesics

• The Opioid System

Opium, derived from poppies, relieves pain and induces euphoria by binding to "opiate receptors" in the brain. These opioid drugs mimic the actions of three peptide families in the brain known as the endorphins, the enkephalins, and the dynorphins. These peptides, along with several nonopioid peptides (MSH, ACTH, & lipotropin) are cleaved from the protein precursors pro-opiomelanocortin (POMC), proenkephalin, and prodynorphin (Fig. 3.4).

Three subtypes of receptors, mu, kappa and delta, mediate the effects of opioid drugs and peptides. The prototype agonist is morphine, which is a potent analgesic and sedative. Agonists with similar analgesic effects (full agonists) are described in Table 3.6A and partial agonists are described in Table 3.6B. Opioid agonists also reduce intestinal motility (antidiarrheals), reduce coughing (antitussives) and induce vomiting. Nonanalgesic agonists used for these purposes are listed in Table 3.6C.

Patients on morphine and related agonists must be monitored for signs of CNS-mediated respiratory depression, which is the dose-limiting side effect of opioid agonists.

Principles that should be kept in mind when prescribing pain relievers include:

- Narcotic analgesics should be employed only when pain cannot be relieved by non-narcotic analgesics (Chapter 9).
- Abuse and street-sales of narcotic agents are common. Monitor patients for drug-seeking behavior.
- Remind patients that constipation is a likely side effect and that a stool softener may be necessary.

PHARMACOKINETICS	TOLERANCE/DEPENDENCE	DRUG INTERACTIONS	NOTES
PO/SC/IM. Rapid absorption, half-life = 3 h. 10% demethylated to form morphine, the rest is conjugated in liver and excreted in urine.	Low risk of abuse.	Similar to morphine.	Included in a number of cough medicine preparations because of antitussive effects.
Various.	Abstinence syndrome upon withdrawal. Lower abuse potential than morphine.	Increase CNS depression caused by CNS depressants.	Antagonist activity: - Bupromorphine > Butorphanol > Desocine = Nalbuphine > Pentazocine.
IV. Rapid onset, short half-life (< 1 h).	Induces abstinence syndrome in narcotic-dependent patients.	Reverses narcotic-induced depression.	
PO. Duration > 24 h.	" "	" "	