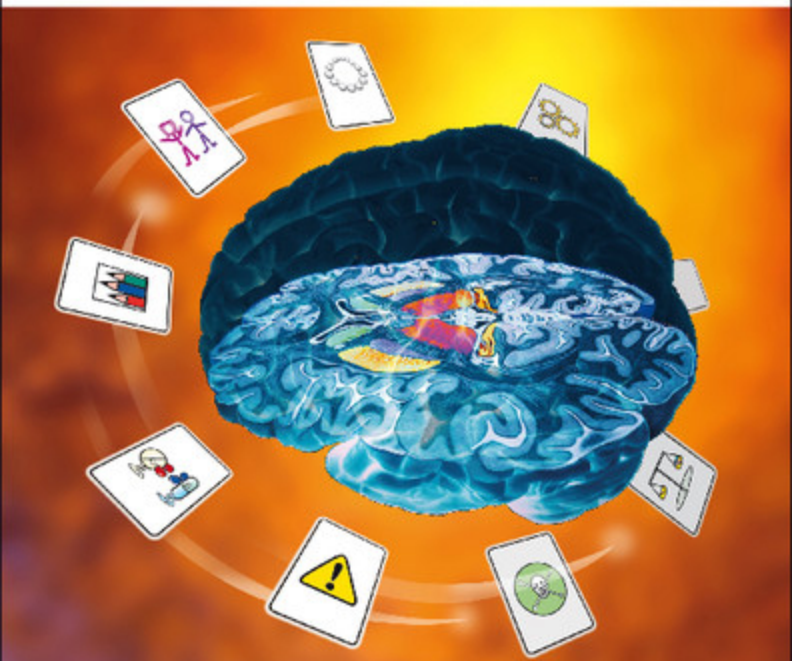
Stephen D. Silberstein, Michael J. Marmura, and Hsiangkuo Yuan

Consultant Editor Stephen M. Stahl

Essential Neuropharmacology

The Prescriber's Guide

SECOND EDITION



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Essential Neuropharmacology

The Prescriber's Guide

Second edition

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neurotoxin

NMDA receptor antagonist

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psychostimulant

selective serotonin reuptake inhibitor

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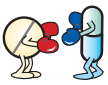
Life-threatening or dangerous adverse effects

Weight Gain: Degrees of weight gain associated with the drug, with unusual signifying that weight gain is not expected; not unusual signifying that weight gain occurs in a significant minority; common signifying that many experience weight gain and/or it can be significant in amount; and problematic signifying that weight gain occurs frequently, can be significant in amount, and may be a health problem in some patients

Sedation: Degrees of sedation associated with the drug, with unusual signifying that sedation is not expected; not unusual signifying that sedation occurs in a significant minority; common signifying that many experience sedation and/or it can be significant in amount; and problematic signifying that sedation occurs frequently, can be significant in amount, and may be a health problem in some patients

Tips for dosing based on the clinical expertise of the author



Drug interactions that may occur

Warnings and precautions regarding use of the drug

Information regarding use of the drug during pregnancy

Clinical pearls of information based on the clinical expertise of the author

Suggested reading

Preface

The past few years have been extremely exciting for both neuroscientists and clinicians. We are unlocking the mysteries of the human mind and applying these discoveries to create better treatment for those affected with neurological disorders, leading to more effective therapies. A new patient-centered medicine approach will hopefully lead to fewer side effects and increased efficacy.

This edition of *Essential Neuropharmacology* focuses on pharmacological treatment; however, substantial improvements in surgical and medical device treatments for neurological disorders have occurred. These include surgical treatments for epilepsy, deep brain stimulation, transcranial magnetic stimulation, vagal nerve stimulation, and occipital and other nerve stimulators for pain. Due to improvements in safety and proven efficacy, some of these procedures may now be considered earlier, rather than as a last resort.

Given the expanding role of neurologists, we also decided to widen the focus of the textbook to include areas such as sleep and neuro-oncology. The practice of sleep medicine has expanded and chemotherapy has been established as effective when combined with other treatments for the treatment of some brain cancers, such as glioblastoma and CNS lymphoma, and neurologists increasingly are working with neurosurgeons and radiation oncologists to manage these challenging disorders.

Like most neurologists, we became interested in neurology due to our fascination with the nervous system and by the fact that there is so much more to learn. The scope of neurological practice continues to expand, with increasing degrees of specialization. Although we practice based on available evidence, often we must revert to trial and error for our difficult cases. Keeping track of the newest medications and developments in our expanding field is a challenge. We have all had the experience of running into a complicated patient, and we know how important it is to discuss the case with an expert. We hope that this text will help those who don't have immediate access to such expertise and will lead to better care for patients with neurological disorders.

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Hsiangkuo Yuan would like to thank his parents Grace and John, brother Sean, wife Jie Ren, and daughters Deanna and Adelyn for their love and support.

ACETAZOLAMIDE

THERAPEUTICS

Brands
- Diamox, Diamox-Sequels, Azomid, AZM, Dazamide, Novo-Zolamide

Generic?
- Yes

Class
- Antiepileptic drug (AED)

Commonly Prescribed for
(FDA approved in bold)
- **Adjunctive treatment for centrencephalic epilepsies (petit mal, unlocalized)**
- **Acute mountain sickness**
- **Edema due to congestive heart failure or medication**
- **Glaucoma**
- Adjunctive treatment for generalized tonic-clonic and partial seizures
- Idiopathic intracranial hypertension (IIH) (pseudotumor cerebrii)
- Episodic ataxias type 1 and 2
- Hemiplegic migraine
- Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS)
- Marfan syndrome
- Sleep apnea

How the Drug Works
- Blocks the carbonic anhydrase enzyme, which is responsible for converting carbon dioxide and water to bicarbonate. This increases excretion of sodium, potassium, bicarbonate, and water, producing alkaline diuresis. In epilepsy, it decreases excessive neuronal discharge in CNS due to either slight degree of acidosis or perhaps reduction of extracellular calcium. It also reduces production of CSF and aqueous humor

How Long Until It Works
- Seizures: within a few days
- IIH: maximum benefit in 4–6 weeks

If It Works
- Seizures: goal is the remission of seizures. Continue as long as effective and well tolerated. Consider tapering and slowly stopping after 2 years seizure-free, depending on the type of epilepsy
- IIH: monitor visual fields and papilledema and symptoms such as visual obscurations and headache

If It Doesn't Work
- Increase to highest tolerated dose
- Seizures: consider changing to another agent, adding a second agent, using a medical device, or a referral for epilepsy surgery evaluation. When adding a second agent, keep drug interactions in mind
- IIH: eliminate symptomatic causes such as drugs or toxins, encourage weight loss if patient is obese, consider loop diuretics or topiramate. Lumbar puncture often provides short-term relief of symptoms. For visual loss, optic nerve defenestration or CSF shunting (lumboperitoneal or ventriculoperitoneal) may be needed

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Epilepsy: acetazolamide itself is usually an augmenting agent. Relatively few interactions with other AEDs. Topiramate and zonisamide have similar mechanisms of action, so acetazolamide is not usually combined with these agents
- IIH: furosemide and topiramate may be helpful. Combine with caution due to risk of kidney stone formation

Tests
- Obtain a CBC when starting drug and during therapy. Check bicarbonate, potassium, and sodium levels if symptoms of metabolic acidosis develop

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Related to carbonic anhydrase inhibition, which can cause metabolic acidosis and electrolyte imbalances

Notable AEs
- Paresthesias, tinnitus, sedation, GI disturbance (anorexia, nausea/vomiting, diarrhea, taste alteration, appetite suppression, weight loss), myopia

(transient), renal calculi, frequent urination, and photosensitivity

Life-Threatening or Dangerous AEs

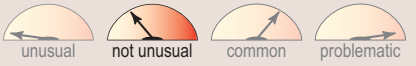
- Blood dyscrasias (agranulocytosis, hemolytic anemia, leukopenia, thrombocytopenia). Hypokalemia. Rash including Stevens-Johnson syndrome. Fulminant hepatic necrosis

Weight Gain

- Unusual

Sedation

- Not unusual



What to Do About AEs

- Lower dose when used for epilepsy or IIH. If AEs are significant, discontinue and change to another agent. Paresthesias may respond to high-potassium diets or potassium supplements

Best Augmenting Agents to Reduce AEs

- Concomitant topiramate, zonisamide, ketogenic diet predisposes to metabolic acidosis and kidney stones. Metformin may also promote acidosis

DOSING AND USE

Usual Dosage Range

- Epilepsy: age > 12: 375–1000 mg daily. Age < 12: 10–20 mg/kg/day. catamenial: 8~30 mg/kg/day
- IIH: 250–2000 mg daily
- Edema: 250–375 mg every other day
- Mountain sickness: 500–1000 mg daily

Dosage Forms

- Tablets: 125, 250 mg. Sustained release 500 mg
- Injection: 500 mg vials

How to Dose

- Epilepsy: start at 125–250 mg twice daily, with a lower starting dose (250 mg daily) for patients already on other AEDs. Occasionally used at higher doses, but not necessarily more effective
- IIH: start at 250–500 mg/day in 2 divided doses. Increase as tolerated to 1000 mg/day. Occasionally used at higher doses, depending on tolerability and effect on visual symptoms
- Acute mountain sickness: start 24–48 hours before ascent and continue for 48 hours or as long as needed to control symptoms. Usual dose 250–1000 mg/day
- Congestive heart failure: 250–375 mg daily, skipping doses every 2–3 days to maintain effect

Dosing Tips

- Citrus juice and fluids may help decrease risk of kidney stone formation. Taking with food can decrease AEs

Overdose

- Ataxia, anorexia, nausea, paresthesias, vomiting, tremor, and tinnitus. Induce emesis or gastric lavage. Supplement with bicarbonate or potassium as necessary

Long-Term Use

- Safe for long-term use. Tolerance due to increased carbonic anhydrase production in glial cells

Habit Forming

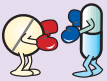
- No

How to Stop

- Taper slowly
- Abrupt withdrawal can lead to seizures in patients with epilepsy
- Papilledema or headaches may recur within days to months of stopping

Pharmacokinetics

- Tablets have peak effect at 2–4 hours, with 8–12 hours duration of action. Sustained-release tablets have peak effect at 3–6 hours and duration of 18–24 hours. 70–90% protein bound. Not metabolized and excreted unchanged by kidneys



Drug Interactions

- Not affected by other AEDs
- Decreases levels of primidone, lithium
- Increases levels of cyclosporine, carbamazepine, phenytoin, phenobarbital
- Concurrent use with salicylates can increase AEs of both
- Prolongs effects of amphetamines, quinidine

Do Not Use

- Known hypersensitivity to the drug. Depressed potassium or sodium levels, significant kidney or hepatic disease, hyperchloremic acidosis, adrenocortical insufficiency, and suprarenal gland dysfunction

Other Warnings/ Precautions

- Carbonic anhydrase inhibitors are sulfonamides. There may be cross-sensitivity with antibacterial sulfonamides. Increased risk of hyponatremia when combined with carbamazepine or oxcarbazepine

SPECIAL POPULATIONS

Renal Impairment

- Renal insufficiency can lead to increased toxicity. Use with caution

Hepatic Impairment

- Use with caution. Patients with severe disease have an increased risk of hyperammonemia or bleeding complications

Cardiac Impairment

- Severe hypokalemia causes cardiac arrhythmias. Chronic metabolic acidosis may lead to hyperventilation and decreases left ventricular function – use with caution in patients on β-blocker or calcium channel therapy

Elderly

- Use with caution

Children and Adolescents

- Safety and effectiveness in the pediatric population is unknown. Suggested daily dose is 8–30 mg/kg

Pregnancy

- Category C. Risks of stopping medication must outweigh risk to fetus for patients with epilepsy. Seizures and potential status epilepticus place the woman and fetus at risk and can cause reduced oxygen and blood supply to the womb
- In IIH, consider lumbar puncture as an alternative to medication, especially in the first few months of pregnancy, and monitor closely for visual changes
- Supplementation with 0.4 mg of folic acid before and during pregnancy is recommended

Breast Feeding

- A small percentage is excreted in breast milk. Monitor infant for sedation, poor feeding, or irritability

THE ART OF NEUROPHARMACOLOGY

Potential Advantages

- Inexpensive adjunctive medication for epilepsy and useful in the treatment of IIH and episodic ataxias. Rapid onset of action

Potential Disadvantages

- Not a first-line drug in epilepsy or migraine due to ineffectiveness and AEs. Tolerance

Primary Target Symptoms

- Seizure frequency and severity; headache or papilledema in IIH

Pearls

- In epilepsy, appears most effective in children with petit mal epilepsy, but may be effective in patients with grand mal, mixed, or myoclonic seizures
- Acetazolamide was used for migraine aura status in case reports

- Acetazolamide is occasionally used for treatment of migraine. Large, double-blind, placebo-controlled trials did not indicate effectiveness
- First-line for IIH by lowering the CSF production. In a recent trial comparing 6 months of acetazolamide (up to 4 g/day) to placebo, significant improvements were found in visual field function and papilledema but with 19% dropout. It did not appear to reduce associated headache
- In an open-label study on IIH, topiramate was as effective as acetazolamide but with prominent weight loss, which is beneficial for treating IIH
- In patients under topiramate or metformin, spironolactone can be an alternative
- First-line agent for treatment of episodic ataxias at an average dose of 500–750 mg/day. Type 2 responds better than type 1 in most cases
- Similar to episodic ataxia type 2, familial hemiplegic migraine type 1 is a channelopathy caused by a mutation of the *CACNA1A* gene. Case reports suggest acetazolamide can be used to treat hemiplegic migraine
- Found to be dramatically effective in a subset of MELAS patients with episodic weakness associated with specific mitochondrial DNA mutations
- As a diuretic, increased doses do not increase effect. Results are often improved with alternating days of treatment
- The acetazolamide challenge test is used to decide indications for CSF shunting
- Good for intermittent use, such as in catamenial epilepsy

Suggested Reading

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ALEMTUZUMAB

THERAPEUTICS

Brands
- Lemtrada, Campath, MabCampath, Campath-1H

Generic?
- No

Class
- Immunosuppressant

Commonly Prescribed for
(FDA approved in bold)
- **Relapsing forms of multiple sclerosis (MS)**
- **B-cell chronic lymphocytic leukemia (B-CLL)**
- Induction therapy in organ transplantation
- Sporadic inclusion body myositis (sIBM)

How the Drug Works
- It is a humanized IgG_1 kappa antibody that targets cell-surface glycoprotein CD52, which is expressed at a high level on T and B lymphocytes. Upon binding, it induces antibody-dependent cellular cytolysis and complement-mediated lysis of T and B lymphocytes. It particularly targets CD4+ naïve and CD8+ naïve T cells, and mature naïve B cells with proportional increase in regulatory T cells and memory T/B cells. Lymphocyte counts decrease after each course of treatment. Cells that escaped depletion may cause secondary autoimmunity. It also has prolonged decrease in the secretion of proinflammatory cytokines (interleukin [IL]-17, IL-22)

How Long Until It Works
- Months to years. In trials, treated patients had fewer relapses up to 2–5 years

If It Works
- Continue to use until ineffective. Screen for AEs

If It Doesn't Work
- It is the third-line treatment for relapsing forms of MS. If it fails, consider combination therapy with other disease-modifying agents

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Acute MS attacks are often treated with glucocorticoids, especially if there is functional impairment due to vision loss, weakness, or cerebellar symptoms
- Treat common clinical symptoms with appropriate medication for spasticity (baclofen, tizanidine), neuropathic pain, and fatigue (modafinil)
- It is uncertain whether combined use of 2 types of antibodies or adding another disease-modifying agent is beneficial to MS

Tests
- CBC and platelet counts (monthly), thyroid function tests (every 3 months), and renal function (regularly) until 4 years after the last infusion. Yearly skin exams

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Most AEs are likely related to immunosuppression or hypersensitivity

Notable AEs
- Rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes infection, thyroid gland disorder, fungal infection, arthralgia, back pain, diarrhea, paresthesia, dizziness, abdominal pain, flushing, vomiting

Life-Threatening or Dangerous AEs
- Thyroid disorders (20%)
- Immune thrombocytopenic purpura
- Anti-glomerular basement membrane disease
- Leukopenia, pancytopenia
- Severe infection
- Anaphylaxis
- Increased risk of malignancy (thyroid cancer, melanoma, lymphoproliferative disorder)

Weight Gain
- Unusual

Sedation
- Unusual

What to Do About AEs
- Control infection. Supportive treatment

Best Augmenting Agents to Reduce AEs
- Most AEs will not respond to augmenting agents

DOSING AND USE

Usual Dosage Range
- A total of 96 mg is the standard dose for MS

Dosage Forms
- Injection: 12 mg/1.2 mL, 30 mg/1 mL in a single-use vial

How to Dose
Lemtrada (for MS)
- First course: 12 mg/day on 5 consecutive days. IV infusion over 4 hours
- Second course (1 year after): 12 mg/day on 3 consecutive days
- It is available only through a restricted distribution program called the Lemtrada Risk Evaluation and Mitigation Strategy (REMS) Program
- Premedicate with corticosteroid for the first 3 days of each course
- Herpes prophylaxis for a minimum of 2 months after each course or until CD4+ lymphocyte count is $> 200/mm^3$, whichever occurs later

Campath (for B-CLL)
- Escalate to recommended dose of 30 mg/day 3 times per week for 12 weeks. IV infusion over 2 hours
- Premedicate with oral antihistamine and acetaminophen prior to dosing
- Administer prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) and herpes virus infections

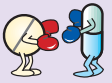
Overdose
- Doses greater than those recommended may increase the intensity and/or duration of infusion reactions or its immune effects. There is no known antidote for alemtuzumab overdosage

Long-Term Use
- Risk of infection, autoimmunity, and malignancy. Use beyond the approved dose or term is not recommended

Habit Forming
- No

How to Stop
- No need to taper

Pharmacokinetics
- Alemtuzumab serum concentrations reach maximum at the last day of infusion. It is largely confined to the blood and interstitial space. It is degraded by widely distributed proteolytic enzymes. Half-life 2 weeks



Drug Interactions
- No formal drug interaction studies have been conducted. Increases risk of serious infection when used with other immunosuppressants (e.g., azathioprine, cyclosporine, methotrexate, and 6-mercaptopurine) or inhibitors of tumor necrosis factor-α (TNF-α)

Other Warnings/ Precautions
- Infusion reactions usually occur within 2 hours but some reactions were reported after 24 hours
- Because of risk of autoimmunity, infusion reactions, and the risk of some kinds of cancers, Lemtrada is only available through the Lemtrada REMS Program

Do Not Use
- Hypersensitivity to drug. Severe infection. HIV

SPECIAL POPULATIONS

Renal Impairment
- May cause anti-glomerular basement membrane disease

Hepatic Impairment
- Not studied

Cardiac Impairment
- Does not prolong QTc interval

Elderly
- Not studied

Children and Adolescents
- It is not known if it is safe and effective for use in children under 17 years of age

Pregnancy
- Category C. Placental transfer of antithyroid antibodies resulting in neonatal Graves' disease has been reported. Use only if benefit of preventing MS relapse outweighs risk. Women of childbearing potential should use effective contraceptive measures when receiving a course of treatment with alemtuzumab and for 4 months following that course of treatment

Breast Feeding
- It is excreted in breast milk. Do not breast feed on drug

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
- Effective treatment for some of the most disabled MS patients including those failing first-line agents. Efficacy may be superior to other disease-modifying agents

Potential Disadvantages
- Rare but potentially fatal AEs of autoimmunity, opportunistic infection, and malignancy. Only available through specific infusion centers as IV infusion. Need for long-term monitoring

Primary Target Symptoms
- Decrease in relapse rate, prevention of disability, and slower accumulation of lesions on MRI

Pearls
- At this point, due to potentially severe AEs, it is usually reserved for patients with a very severe form of relapsing MS who have failed 2 types of disease-modifying treatments and are not candidates for natalizumab
- May be an alternative to natalizumab in patients with JC virus antibodies
- In clinical trials, the lowest cell counts occurred 1 month after a course of treatment at the time of the first post-treatment blood count. Lymphocyte counts then increased over time: B-cell counts usually recovered within 6 months; T-cell counts increased more slowly and usually remained below baseline 12 months after treatment. Approximately 60% of patients had total lymphocyte counts below the lower limit of normal 6 months after each treatment course and 20% had counts below the lower limit of normal after 12 months
- It is also approved for relapsing-remitting MS with superior 2-year relapse-free rate and reduced disability progression than interferon-β (INFβ)-1a in previously treated patients; superior 2-year relapse-free rate than INFβ-1a in treatment-naïve patients. The efficacy appears to continue beyond treatment period. However, it was associated with greater side effects (infection, malignancy, thyroid disorder, autoimmunity, thrombocytopenic purpura)
- Given higher rates of remission compared to INFβ-1a and -1b, might eventually have a place as an induction therapy prior to initiation of other agents
- In successfully treated patients consider initiating other treatment only after lymphocyte counts have normalized
- CAMMS223: alemtuzumab remained significantly more efficacious than INFβ-1a up to 5 years of study period
- In a small trial of 13 sIBM patients, alemtuzumab 0.3 mg/kg/day for 4 days slows the disease progression up to 6 months, improves the strength of some patients, and reduces endomysial inflammation and stressor molecules. Bimagrumab (activin receptor II antibody) is another investigational drug showing promising results on increasing muscle mass and function

Suggested Reading

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ALMOTRIPTAN

THERAPEUTICS

Brands
- Axert, Almogran

Generic?
- Yes

Class
- Triptan

Commonly Prescribed for
(FDA approved in bold)
- **Acute treatment of migraine in adults and adolescents (> 12 years old)**
- Menstrual migraine

How the Drug Works:
- Selective 5-$HT_{1B/1D/1F}$ receptor agonist. In addition to vasoconstriction on meningeal vessels, its antinociceptive effect is likely due to blocking the transmission of pain signals at trigeminal nerve terminals (preventing the release of inflammatory neuropeptides) and synapses of second-order neurons in trigeminal nucleus caudalis. Although it generally does not penetrate BBB, it has been postulated that transient permeability may occur during a migraine attack

How Long Until It Works
- 1–2 hours or less

If It Works
- Continue to take as needed. Patients taking acute treatment more than 2 days/week are at risk for medication-overuse headache, especially if they have migraine

If It Doesn't Work
- Treat early in the attack – triptans are less likely to work after the headache becomes moderate or severe, regardless of cutaneous allodynia, which is a marker of central sensitization
- Address life style issues (e.g., stress, sleep hygiene), medication use issues (e.g., compliance, overuse), and other underlying medical conditions
- Change to higher dosage, another triptan, another administration route, or combination of other medications. Add preventive medication when needed
- For patients with partial response or reoccurrence, other rescue medications include NSAIDs (e.g., ketorolac, naproxen), antiemetic (e.g., prochlorperazine, metoclopramide), neuroleptics (e.g., haloperidol, chlorpromazine), ergots, antihistamine, or corticosteroid

Best Augmenting Combos for Partial Response or Treatment-Resistance
- NSAIDs or antiemetics/neuroleptics are often used to augment response

Tests
- None required

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Direct effect on systemic serotonin receptors (e.g., 5-HT_{1B} agonism on vasoconstriction)

Notable AEs
- Tingling, flushing, sensation of burning, vertigo, sensation of pressure, heaviness, nausea

Life-Threatening or Dangerous AEs
- Serotonin syndrome. Rare cardiac events including acute myocardial infarction and vasospasm have been reported with almotriptan. Life-threatening cardiac arrhythmias have been reported with other triptans

Weight Gain
- Unusual

Sedation
- Unusual

What to Do About AEs
- In most cases, only reassurance is needed. Lower dose, change to another

triptan, or use an alternative headache treatment

Best Augmenting Agents to Reduce AEs

- Treatment of nausea with antiemetics is acceptable. Other AEs decrease with time

DOSING AND USE

Usual Dosage Range

- 6.25–12.5 mg

Dosage Forms

- Tablets: 6.25 and 12.5 mg

How to Dose

- Most adult patients respond best at 12.5 mg oral dose and 6.25 mg for adolescents. Give 1 pill at the onset of an attack and repeat in 2 hours for a partial response or if the headache returns. Maximum 25 mg/day. The safety of treating > 4 migraine in a 30-day period has not been studied. Limit 10 days/month

Dosing Tips

- Treat early in attack

Overdose

- May cause hypertension, cardiovascular symptoms. Other possible symptoms include seizure, tremor, extremity erythema, cyanosis, or ataxia. For patients with angina, perform ECG and monitor for ischemia for at least 20 hours

Long-Term Use

- Monitor for cardiac risk factors with continued use

Habit Forming

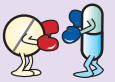
- No

How to Stop

- No need to taper. Patients who overuse triptans often experience withdrawal headaches lasting up to several days

Pharmacokinetics

- Half-life about 3–4 hours. T_{max} orally 1–4 hours. Bioavailability is 80%. Metabolized by monoamine oxidase (MAO)-A (27%; inactive indoleacetic acid metabolites) and CYP3A4/2D6 (12%; inactive GABA derivatives). 35% protein binding. Eliminated primarily by renal excretion (75%)



Drug Interactions

- MAO-A inhibitors may make it difficult for drug to be metabolized
- Minimal increase in concentration with CYP3A4 inhibitors – no need for dose adjustment

Do Not Use

- Patients with proven hypersensitivity
- Within 2 weeks of MAO-A inhibitors, or within 24 hours of ergot-containing medications such as dihydroergotamine
- History of stroke, transient ischemic attack, hemiplegic/basilar migraine, Wolff-Parkinson-White syndrome, peripheral vascular disease, ischemic heart disease, coronary artery vasospasm, ischemic bowel disease, and uncontrolled hypertension

SPECIAL POPULATIONS

Renal Impairment

- Start at 6.25 mg in those with moderate to severe renal impairment (CrCl < 30 mL/min). May be at increased cardiovascular risk. Avoid concomitant use of CYP3A4 inhibitors in patients with renal impairment

Hepatic Impairment

- Drug metabolism may be decreased. Do not use with severe hepatic impairment. Avoid concomitant use of CYP3A4 inhibitors in patients with hepatic impairment

Cardiac Impairment

- Do not use in patients with known cardiovascular or peripheral vascular disease. May have increased risk for vascular event

Elderly

- At an increased risk for cardiovascular incident. Most studies were done in patients

< 65 years old. In elderly with no other coronary artery disease risk factors beside age (male > 45, female > 55), it is generally safe

Children and Adolescents

- Safety and efficacy have not been established in children. Among triptans, almotriptan has the highest response rate in adolescents. Triptan trials in children were negative, due to higher placebo response

Pregnancy

- Category C. Use only if potential benefit outweighs risk to the fetus. Migraine often improves in pregnancy, and other acute agents (opioids, neuroleptics, prednisone) have more proven safety

Breast Feeding

- Almotriptan is found in breast milk. Use with caution

THE ART OF NEUROPHARMACOLOGY

Potential Advantages

- Effective with good consistency and excellent tolerability, even compared to other oral triptans. Less risk of overuse than opioids or barbiturate-containing treatments

Potential Disadvantages

- Cost, and the potential for medication-overuse headache. May not be as effective as other triptans

Primary Target Symptoms

- Headache pain, nausea, photo- and phonophobia

Pearls

- Early treatment of migraine is most effective
- Lower AEs compared to other triptans. Good consistency and pain-free response, making it a good choice for patients with anxiety prone to medication side effects
- May not be effective when taken during the aura, or once headache begins
- In patients with "status migrainosus" (migraine lasting more than 72 hours) neuroleptics and dihydroergotamine are more effective
- Triptans were not originally studied for use in the treatment of basilar or hemiplegic migraine
- Triptans can be used to treat tension-type headache in migraineurs but not in patients with pure tension-type headache
- Patients taking triptans more than 10 days/month are at increased risk of medication-overuse headache, which is less responsive to treatment
- Chest and throat tightness are usually benign and may be related to esophageal spasm rather than cardiac ischemia. These symptoms occur more commonly in patients without cardiac risk factors
- Combination use of SNRI and triptans does not lead to serotonin syndrome, which requires activation of 5-HT_{2A} receptors and a possible limited role of 5-HT_{1A}. However, triptans are agonists at the 5-$HT_{1B/1D/1F}$ receptor subtypes, with weak affinity for 5-HT_{1A} receptors and no activity at the 5-HT_2 receptors. Given the seriousness of serotonin syndrome, caution is certainly warranted and clinicians should be vigilant for serotonin toxicity symptoms and signs to insure prompt treatment

Suggested Reading

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ALTEPLASE

THERAPEUTICS

Brands
- Activase, Cathflo Activase

Generic?
- Yes

Class
- Thrombolytic agent

Commonly Prescribed for
(FDA approved in bold)
- **Acute ischemic stroke (AIS)**
- **Acute myocardial infarction (AMI)**
- **Pulmonary embolism (PE)**
- **Restoration of function to central venous access device**

How the Drug Works
- Alteplase is a tissue plasminogen activator (tPA). It binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin, initiating a local fibrinolysis with little systemic effect

How Long Until It Works
- Less than 1 hour, often earlier

If It Works
- After administration, monitor in intensive care – preferably in an acute stroke or cardiac unit

If It Doesn't Work
- Alteplase is not always effective and has risks. After initial monitoring period in intensive care, continue standard AIS, AMI, or PE care

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Alteplase with heparin may improve the clinical course of PE

Tests
- Ensure no contraindications are present before administering drug. For all patients with suspected AIS with onset less than 3 hours prior, immediately type and screen, obtain CBC, glucose, coagulation tests, and ensure no intracranial bleeding (usually with head CT)

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Activating plasminogen increases bleeding risk

Notable AEs
- Superficial bleeding (e.g., at puncture sites), fever, hypotension, dyspnea, nausea, urticaria, and flushing

Life-Threatening or Dangerous AEs
- Internal bleeding (intracranial, GI, GU, or retroperitoneal), anaphylactic reaction, reperfusion arrhythmias, and thrombocytopenia

Weight Gain
- Unusual

Sedation
- Unusual

What to Do About AEs
- Stop infusion for any serious bleeding. Can use fresh frozen plasma if needed

Best Augmenting Agents to Reduce AEs
- Most AEs cannot be reduced by an augmenting agent

DOSING AND USE

Usual Dosage Range
- 90 mg or less for AIS, 100 mg or less for AMI or PE

Dosage Forms
- Lyophilized powder for injection: 2 mg in 2 mL, 50 mg in 50 mL, 100 mg in 100 mL

How to Dose

- AIS: give 0.9 mg/kg (not to exceed 90 mg) in 1 hour, with 10% of the dose given in the first 1 minute
- AMI: give 15 mg as a bolus for all patients. For patients weighing more than 67 kg, then give another 50 mg over 30 minutes and then 35 mg over the next 60 minutes. For patients less than 67 kg, give 0.75 mg/kg over the 30 minutes after the bolus and then 0.50 mg/kg over the next 60 minutes
- PE: 100 mg over 2 hours and restart heparin once partial thromboplastin or thrombin time is less than twice normal
- Central venous access restoration: instill 2 mg into catheter

Dosing Tips

- Give alteplase as soon after AIS as possible (< 3–4.5 hours) to achieve best functional outcome once it has been determined that there are no contraindications

Overdose

- Bleeding complications are common. Treat, if needed, with fresh frozen plasma. Bradycardia, flushing, dyspnea, or hypotension can occur

Long-Term Use

- May be repeated after weeks of previous use if indicated. Not used for prophylaxis

Habit Forming

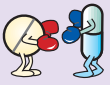
- No

How to Stop

- Not applicable

Pharmacokinetics

- Rapid hepatic metabolism by hydrolysis in liver. 80% of drug is cleared within 10 minutes after ending infusion



Drug Interactions

- Anticoagulants such as heparin, vitamin K antagonists increase bleeding risk
- Antiplatelet agents such as aspirin, dipyridamole, clopidogrel, and abciximab may increase bleeding risk when given prior to or soon after alteplase therapy
- NSAIDs may increase risk of GI bleed
- Nitroglycerin decreases alteplase concentrations. Avoid using
- Valproate may increase concentrations
- Dopamine may reduce activity and cause particulate formation

Other Warnings/ Precautions

- Cholesterol embolism causing renal failure, pancreatitis, bowel infarction, gangrenous digits, or AMI is a rare complication of thrombolysis

Do Not Use

- Evidence of intracranial hemorrhage or suspected subarachnoid hemorrhage
- Serious head trauma
- History of intracranial bleeding, neoplasm, or arteriovenous malformation
- Active internal bleeding
- Recent intracranial or intraspinal surgery
- Seizure at the onset of stroke
- Bleeding diathesis (PT INR > 1.7, heparin within 48 hours [aPTT < 40], platelet count < 100 000/mm^3)
- Uncontrolled hypertension at the time of treatment (greater than 185 systolic or 110 diastolic)

SPECIAL POPULATIONS

Renal Impairment

- Reduce dose and use with caution with severe renal disease

Hepatic Impairment

- Reduce dose and use with caution with severe hepatic disease

Cardiac Impairment

- No known effects

Elderly

- Patients over 75 are more likely to have bleeding complications

Children and Adolescents

- Not studied in children

Pregnancy

- Category C. Use if potential benefit outweighs risks. Increased risk of hemorrhage when given less than 10 days post-partum

Breast Feeding

- Unknown if present in breast milk, use with caution

THE ART OF NEUROPHARMACOLOGY

Potential Advantages

- Proven treatment for acute stroke in adults

Potential Disadvantages

- Must be used within the acute window. Multiple potential complications (intracranial hemorrhage 5.8–6.8% within 7 days)

Primary Target Symptoms

- Improving neurological function and reducing disability resulting from ischemic stroke

Pearls

- Must meet National Institute of Neurological Disorders and Stroke (NINDS) inclusion/exclusion criteria
- NINDS (1995) found IV tPA effective for AIS within 3 hours. ECASS-3 trial (2009) demonstrated IV tPA effective within 4.5 hours in appropriate patients. In IST-3 trial (2014), IV tPA within 3–6 hours had excess 7-day mortality over control (3.5%) and did not improve 18-month mortality over control. MR CLEAN trial (2014) suggested intra-arterial therapy (tPA or mechanical, with or without prior IV tPA) within 6 hours for AIS due to proximal intracranial (A1, A2, M1, M2) occlusion. Overall mortality rate (90th day) is around 20–30%
- Effective in improving disability when given in 4.5–6-hour window. The benefit is greatest when given within 3 hours. Later treatment is less beneficial due to less tissue to salvage, rather than more hazards
- If treated within 3 hours, 9% reach independence (modified Rankin score 0–2)
- The relative and absolute benefits of tPA are at least as large in older as in younger people but overall severe IS morbidity is still very high in elderly patients with large strokes
- Pediatric studies using alteplase for pediatric stroke are lacking. The appropriate dose may be 0.75 mg/kg rather than the 0.9 mg/kg used in adults. There is no evidence for intra-arterial thrombolysis in children with IS
- No coadministration of heparin and aspirin during the first 24 hours
- Control blood pressure and maintain below 185/110 mm Hg during treatment. Blood pressures are often elevated in AIS
- Less likely to be effective for larger artery AIS (i.e., carotid occlusion)
- Recent studies suggest that alteplase is likely safe when given for "stroke mimics" such as seizure or migraine. Given that alteplase is less likely to work when delayed, giving alteplase after ruling out hemorrhage is probably better than waiting for imaging to confirm the diagnosis (i.e., MRI)

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AMANTADINE

THERAPEUTICS

Brands
- Symmetrel, Symadine

Generic?
- Yes

Class
- Antiparkinson agent

Commonly Prescribed for
(FDA approved in bold)
- **Parkinson's disease (PD)**
- **Drug-induced extrapyramidal reactions**
- **Influenza-A prophylaxis/treatment**
- Post-encephalitic parkinsonism
- Vascular parkinsonism
- Fatigue in multiple sclerosis (MS)
- Accelerate recovery after traumatic brain injury
- Attention deficit hyperactivity disorder
- SSRI-related sexual dysfunction
- Tardive dyskinesia

How the Drug Works
- The mechanism of action in PD is poorly understood but animal studies suggest either that it induces release or decreases reuptake of dopamine. Also is a weak NMDA receptor antagonist that in animals decreases release of acetylcholine from the striatum. Treats and prevents influenza-A by preventing the release of viral nucleic acid into the host cell by interfering with the function of a viral M2 protein. It may also prevent virus assembly during replication

How Long Until It Works
- PD: 48 hours or less

If It Works
- PD: most patients require dose adjustment over time and will need to take other agents, such as levodopa

If It Doesn't Work
- PD: motor symptoms, such as bradykinesia, gait, and tremor should improve. Reduces extrapyramidal reactions, such as dyskinesias, and can allow reduction of carbidopa-levodopa doses. Non-motor symptoms, including autonomic symptoms such as postural hypotension, depression, and bladder dysfunction, do not improve. If the patient has significantly impaired functioning, add levodopa or a dopamine agonist
- Fatigue: MS-related fatigue may respond to stimulants or modafinil

Best Augmenting Combos for Partial Response or Treatment-Resistance
- For suboptimal effectiveness add carbidopa-levodopa with or without a catechol-*O*-methyltransferase (COMT) inhibitor or dopamine agonist depending on disease severity. Monoamine oxidase (MAO)-B inhibitors may also be beneficial
- For younger patients with bothersome tremor anticholinergics may help
- For severe motor fluctuations and/or dyskinesias with good "on" time, functional neurosurgery is an option
- Depression is common in PD and may respond to low-dose SSRIs
- Cognitive impairment/dementia is common in mid- to late-stage PD and may improve with acetylcholinesterase inhibitors
- For patients with late-stage PD experiencing hallucinations or delusions, withdraw amantadine and consider oral atypical neuroleptics (quetiapine, olanzapine, clozapine). Acute psychosis is a medical emergency that may require hospitalization

Tests
- None required

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Effects on dopamine concentrations and possible anticholinergic effects

Notable AEs
- Nausea, dizziness, insomnia, and blurry vision most common. Depression, anxiety, confusion, livedo reticularis, dry mouth, constipation, peripheral edema, orthostatic hypotension, nervousness, and headache can occur. Can exacerbate preexisting seizure disorders

Life-Threatening or Dangerous AEs

- Abrupt discontinuation has been associated with the development of neuroleptic malignant syndrome
- Rare suicide attempts or ideation, even in those with no history of psychiatric disorders

Weight Gain

- Unusual

Sedation

- Common

What to Do About AEs

- Titrate slowly to avoid GI side effects. Most AEs require reducing dose or stopping medication

Best Augmenting Agents to Reduce AEs

- Most AEs cannot be reduced by use of an augmenting agent

DOSING AND USE

Usual Dosage Range

- PD: 100–200 mg in divided doses. Occasionally up to 400 mg/day

Dosage Forms

- Tablets/capsules: 100 mg
- Syrup: 50 mg/5 mL

How to Dose

- Start at 100 mg daily or 100 mg twice daily in patients on no other PD medications with no other major medical problems. In 1 week or more can increase by 100 mg
- Occasionally patients will require doses of 300 mg or 400 mg in divided doses to achieve optimal clinical effect

Dosing Tips

- Initial sedation may improve with time or dividing doses

Overdose

- Symptoms relate to anticholinergic effects. May include renal, respiratory, or CNS AEs or cardiac effects, including arrhythmia, tachycardia, or hypertension. Deaths have been reported with as little as 1 g

Long-Term Use

- Safe for long-term use. Effectiveness may decrease over time

Habit Forming

- No

How to Stop

- Taper slowly and monitor for parkinsonian crisis. Abrupt withdrawal may also precipitate delirium, hallucinations, agitation, depression, pressured speech, anxiety, stupor, or paranoia

Pharmacokinetics

- Most drug is excreted unchanged in the urine. Peak effect is at 1.5–8 hours and half-life an average of 17 hours. Doses over 200 mg may cause greater than proportional increases in levels

Drug Interactions

- Anticholinergics can increase the mild anticholinergic effects of amantadine
- Quinidine, triamterene, thiazide diuretics, and trimethoprim/sulfamethoxazole impair renal clearance of amantadine and can increase plasma concentrations
- Thioridazine with amantadine can increase PD tremor

Other Warning/ Precautions

- May cause mydriasis due to anticholinergic AEs. Do not give to patients with untreated angle-closure glaucoma

Do Not Use

- Known hypersensitivity to the drug

SPECIAL POPULATIONS

Renal Impairment

- Decrease dose for impaired function. CrCl 30–50 mL/min: 200 mg day 1 then 100 mg daily. 15–29 mL/min: 200 mg day 1 then

100 mg every other day. < 15 mL/min or hemodialysis: 200 mg every 7 days

Hepatic Impairment

- May cause elevation of liver enzymes. Use with caution

Cardiac Impairment

- Infrequently causes congestive heart failure or peripheral edema. Use with caution

Elderly

- There is reduced drug clearance, but no dose adjustment needed as the dose used is the lowest that provides clinical improvement

Children and Adolescents

- Use for influenza treatment in children aged 1 or greater (PD is rare in pediatrics)

Pregnancy

- Category C. Teratogenic in some animal studies. Risks may include cardiovascular maldevelopment. Use only if benefits of medication outweigh risks

Breast Feeding

- Excreted in breast milk. Do not use

THE ART OF NEUROPHARMACOLOGY

Potential Advantages

- Relief of dyskinesias in PD. Relatively quick-acting and less sedation than other treatments. Useful in some patients for fatigue

Potential Disadvantages

- Usually not a first-line treatment for PD. No evidence of neuroprotection against PD. Generally less effective than levodopa and risks significant CNS AEs including hallucinations

Primary Target Symptoms

- PD: motor dysfunction and dyskinesias

Pearls

- Useful for PD patients with dyskinesias. Level C evidence for its use in tardive dyskinesia
- Can cause anticholinergic AEs (dry mouth, urinary retention) despite no known action on receptors. This and hallucinations may limit treatment
- Use with caution in patients with heart failure, arrhythmia, and seizure
- Used for the treatment of MS-related fatigue at doses of 200–400 mg/day. However, its use was not substantiated by a Cochrane review
- May be useful in the treatment of traumatic brain injury, including children, at doses of 200–400 mg/day
- Amantadine accelerated the pace of functional recovery during active treatment in patients with post-traumatic disorders of consciousness. In theory, may be effective for chronic pain disorders such as migraine, but not studied in large placebo-controlled trials

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AMIFAMPRIDINE

THERAPEUTICS

Brands
- 3,4-diaminopyridine, Firdapse, Zenas

Generic?
- Yes

Class
- Potassium channel blocker

Commonly Prescribed for
(FDA approved in bold)
- Lambert-Eaton myasthenic syndrome (LEMS)
- Congenital myasthenia gravis (CMG)
- Multiple sclerosis (MS)
- Downbeat nystagmus, cerebellar gait disorder

How the Drug Works
- Potassium channel blocker. Reduces flow of potassium across nerve terminal membranes and increases calcium influx with prolongation of action potential. This promotes presynaptic release of acetylcholine and may improve weakness and autonomic dysfunction

How Long Until It Works
- About 20 minutes, but maximum effect might take a few days

If It Works
- Continue to use to reduce symptoms of LEMS or CMG at lowest required dose. In LEMS, disease-modifying treatments, such as plasma exchange, IV immune globulin, corticosteroids, and immunosuppressives such as azathioprine are useful. Identifying malignancy such as small-cell lung cancer is essential

If It Doesn't Work
- LEMS: treat with immunological therapy. Removal of neoplasm may improve symptoms
- CMG: establish the type. Presynaptic forms may respond to 3,4-diaminopyridine. Acetylcholinesterase inhibitors may improve or worsen symptoms, depending on the disorder

Best Augmenting Combos for Partial Response or Treatment-Resistance
- May be combined with pyridostigmine, which increases the available amount of acetylcholine for receptor binding and may allow reduction of dose

Tests
- Obtain baseline CBC, electrolytes, glucose, blood urea nitrogen, creatinine, liver function tests. Repeat monthly for 3 months, then every 6 months while on treatment

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Some AEs are related to acetylcholine release, others are unknown

Notable AEs
- Paresthesias, perioral numbness, insomnia, abdominal pain

Life-Threatening or Dangerous AEs
- Seizures, delirium: most common at doses of 100 mg or greater

Weight Gain
- Unusual

Sedation
- Unusual

What to Do About AEs
- Lower dose, supplement with pyridostigmine in LEMS. For first seizure, lower dose or discontinue and evaluate for metastatic brain tumor. For recurrent seizure, discontinue

Best Augmenting Agents to Reduce AEs
- Cannot be reduced with augmenting agents

DOSING AND USE

Usual Dosage Range
- 15–80 g/day

Dosage Forms
- Tablets: 5 mg

How to Dose
- Start at 10 mg orally 3–4 times daily or as tolerated. Increase every 1–2 weeks by 5 mg until maximum benefit, up to 80 mg/day. For suboptimal benefit in LEMS, add pyridostigmine

Dosing Tips
- Dose requirements may change over time. Periodically attempt to lower dose

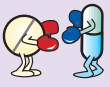
Overdose
- Seizures and encephalopathy have been reported

Long-Term Use
- Requires frequent monitoring for hematological or renal complications

Habit Forming
- No

How to Stop
- No need to taper, but LEMS symptoms may worsen

Pharmacokinetics
- Bioavailability 30%. The pharmacokinetics and systemic exposure to amifampridine are notably influenced by the overall metabolic acetylation activity of *N*-acetyl transferase (NAT) enzymes and NAT2 genotype, which is subject to genetic variation. The plasma elimination half-life is approximately 2.5 hours for the amifampridine and 4 hours for the 3-*N*-acetylated amifampridine metabolite



Drug Interactions
- No significant drug interactions via CYP450 due to lack of metabolism
- The concomitant use of amifampridine and a cholinergic drug may increase the effect of both products. Do not combine with acetylcholinesterase inhibitors other than pyridostigmine

Other Warnings/ Precautions
- The use of amifampridine in pateints with the non-paraneoplastic form of LEMS should only be commenced following a thorough assessment of the risk–benefit to the patient. Asthma patients should be monitored

Do Not Use
- Hypersensitivity to drug

SPECIAL POPULATIONS

Renal Impairment
- No known effects. Upward dose titration should be discontinued if any adverse reaction occurs

Hepatic Impairment
- No known effects. Upward dose titration should be discontinued if any adverse reaction occurs

Cardiac Impairment
- May prolong QTc. Clinical and ECG monitoring are indicated at the initiation of the treatment and yearly thereafter

Elderly
- Unknown

Children and Adolescents
- Unknown

Pregnancy
- Unknown. Use only if benefits of medication outweigh risks

Breast Feeding
- Unknown if excreted in breast milk. Do not use

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
- Fewer AEs than other symptomatic agents for LEMS

Potential Disadvantages

- Does not alter disease outcome in LEMS. Limited availability

Primary Target Symptoms

- Weakness associated with LEMS, CMG, or MG

Pearls

- Unlike MG, LEMS is a presynaptic disorder of neuromuscular transmission. LEMS is an autoimmune disease with antibodies directed against the voltage-gated calcium channels. LEMS is usually associated with small-cell lung cancer
- Not approved in the US but available on a compassionate-use basis
- Effective in the majority of LEMS patients, with or without malignancy
- In studies improved both strength and resting compound muscle amplitude
- Pyridostigmine or other acetylcholinesterase inhibitors alone are usually not effective in LEMS
- CMG is a group of disorders that are genetic – immunotherapy is not effective, so symptomatic treatment is the rule. Ptosis and ophthalmoplegia are common and age of presentation is variable. Some variants may respond to acetylcholinesterase inhibitors
- In small clinical trials, effective for improving motor symptoms and fatigue in MS. Experimental studies suggest enhancement of excitatory synaptic transmission
- Compared to 4-aminopyridine, more effective with fewer AEs in LEMS because of lack of CNS penetration, but 4-aminopyridine is likely superior for treating MS symptoms and is FDA approved to improve walking speed in MS

Suggested Reading

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AMITRIPTYLINE

THERAPEUTICS

Brands

- Elavil, Amitid, Amitril, Endep, Elatrol, Laroxyl, Saroten, Redomex, Triptafen, Tryptanol, Tryptizol, Trepiline, Triptyl

Generic?

- Yes

Class

- **Tricyclic** antidepressant (TCA)

Commonly Prescribed for

(FDA approved in bold)

- **Depression**
- Migraine prophylaxis
- Tension-type headache prophylaxis
- Fibromyalgia
- Neuropathic pain
- Post-herpetic neuralgia
- Bulimia nervosa
- Insomnia
- Anxiety
- Nocturnal enuresis
- Pseudobulbar affect
- Arthritic pain

How the Drug Works

- The mechanism of action of amitriptyline and its active metabolite (nortriptyline) is probably related to reuptake inhibition of serotonin and norepinephrine at the synaptic clefts of brain and spinal cord
- It also exhibits antagonism on 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, 5-HT_7, α_1-adrenergic, muscarinic, H_1, and NMDA receptors, and agonism on opioid (σ_1, σ_2) receptors
- Antinociceptive and antidepressive effects are more likely related to adaptive changes in serotonin and norepinephrine receptor systems over time

How Long Until It Works

- Migraines: effective in as little as 2 weeks, but can take up to 3 months on a stable dose to see full effect
- Neuropathic pain: usually some effect within 4 weeks
- Insomnia, anxiety, depression: may be effective immediately, but full effects often delayed 2–4 weeks

If It Works

- Migraine: goal is a 50% or greater reduction in migraine frequency or severity. Consider tapering or stopping if headaches remit for more than 6 months or if considering pregnancy
- Neuropathic pain: the goal is to reduce pain intensity and symptoms, but usually does not produce remission
- Insomnia: continue to use if tolerated and encourage good sleep hygiene

If It Doesn't Work

- Increase to highest tolerated dose
- Migraine: address other issues, such as medication overuse, other coexisting medical disorders, such as anxiety, and consider changing to another agent or adding a second agent
- Neuropathic pain: either change to another agent or add a second agent
- Insomnia: if no sedation occurs despite adequate dosing, stop and change to another agent

Best Augmenting Combos for Partial Response or Treatment-Resistance

- Migraine: for some patients, low-dose polytherapy with 2 or more drugs may be better tolerated and more effective than high-dose monotherapy. May use in combination with AEDs, antihypertensives, natural products, and non-medication treatments, such as biofeedback, to improve headache control
- Neuropathic pain: TCAs, AEDs (gabapentin, pregabalin, carbamazepine, lamotrigine), SNRIs (duloxetine, venlafaxine, milnacipran, mirtazapine, bupropion), capsaicin, and mexiletine are agents used for neuropathic pain. Opioids (morphine, tramadol) may be appropriate for long-term use in some cases but require careful monitoring

Tests

- Check ECG for QTc prolongation at baseline and when increasing dose, especially in those with a personal or family history of QTc prolongation, cardiac arrhythmia, heart failure, or recent myocardial infarction. If patient is on diuretics, measure calcium, potassium, and magnesium at baseline and periodically

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs

- Anticholinergic and antihistaminic properties are causes of most common AEs. Blockade of α_1-adrenergic receptors may cause orthostatic hypotension and sedation

Notable AEs

- Constipation, dry mouth, blurry vision, increased appetite, nausea, diarrhea, heartburn, weight gain, urinary retention, sexual dysfunction, sweating, itching, rash, fatigue, weakness, sedation, nervousness, restlessness

Life-Threatening or Dangerous AEs

- Orthostatic hypotension, tachycardia, QTc prolongation, and rarely death
- Increased intraocular pressure
- Paralytic ileus, hyperthermia
- Rare activation of mania or suicidal ideation
- Rare worsening of existing seizure disorder

Weight Gain

- Problematic

Sedation

- Common

What to Do About AEs

- For minor AEs, lower dose or switch to another agent. If tiredness/sedation are bothersome, change to a secondary amine (i.e., nortriptyline, desipramine). For serious AEs, lower dose and consider stopping

Best Augmenting Agents to Reduce AEs

- Try magnesium for constipation. For migraine, consider using with agents that cause weight loss (i.e., topiramate)

DOSING AND USE

Usual Dosage Range

- Depression, anxiety: 50–150 mg/day
- Migraine/pain: 10–100 mg/day
- Tension-type headache: 35–75 mg/day

Dosage Forms

- Tablets: 10, 25, 50, 75, 100, and 150 mg

How to Dose

- Initial dose 10–25 mg/day taken about 1 hour before sleep. Effective range from 10 to 400 mg but typically 150 mg or less

Dosing Tips

- Start at a low dose, usually 10 mg, and titrate up every few days as tolerated. Low doses are often effective for pain even though they are below the usual effective antidepressant dose

Overdose

- Cardiac arrhythmias and ECG changes; death can occur. CNS depression, convulsions, severe hypotension, and coma are not rare. Patients should be hospitalized. Sodium bicarbonate can treat arrhythmia and hypotension. Treat shock with vasopressors, oxygen, or corticosteroids

Long-Term Use

- Safe for long-term use

Habit Forming

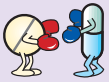
- No

How to Stop

- Taper slowly to avoid withdrawal symptoms, including headache, nausea, and rebound insomnia. Withdrawal symptoms usually last less than 2 weeks. For patients with well-controlled pain disorders, taper very slowly (over months) and monitor for recurrence of symptoms

Pharmacokinetics

- Metabolized primarily by CYP2D6 and CYP1A2. Half-life 10–28 hours and metabolized to nortriptyline. 90–95% protein bound. Steady state typically reached in 1–3 weeks (slow hydroxylators may take longer period)



Drug Interactions

- CYP2D6 inhibitors (e.g., duloxetine, paroxetine, fluoxetine, bupropion, cimetidine, quinidine, phenothiazines,

propafenone), CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin), and valproic acid can prevent its metabolism to nortriptyline and increase amitriptyline concentrations
- Phenothiazines (e.g., chlorpromazine, prochlorperazine, promethazine) increase TCA levels
- Enzyme inducers (e.g., rifampin, smoking, dexamethasone) can lower levels
- Tertiary amine TCAs (amitriptyline, imipramine) inhibit drugs that are metabolized by CYP2C19 (e.g., proton pump inhibitors, phenytoin, citalopram, clopidogrel) and CYP2D6 (e.g., β-blockers, antidepressants, antipsychotics, tramadol)
- Tramadol increases risk of seizures in patients taking TCAs
- Use with clonidine has been associated with increases in blood pressure and hypertensive crisis
- May reduce absorption and bioavailability of levodopa
- May alter effects of antihypertensive medications and cause prolongation of QTc, especially problematic in patients taking drugs that induce bradycardia
- Use together with anticholinergics can increase AEs (e.g., risk of ileus)
- Methylphenidate may inhibit metabolism and increase AEs
- Use within 2 weeks of MAOIs may risk serotonin syndrome

Other Warnings/ Precautions

- May increase risk of seizure

Do Not Use

- Proven hypersensitivity to drug or other TCAs
- Concomitant use of MAOIs
- In acute recovery after myocardial infarction or uncompensated heart failure
- In conjunction with antiarrhythmics that prolong QTc interval
- In conjunction with medications that inhibit CYP2D6

SPECIAL POPULATIONS

Renal Impairment

- Use with caution. May need to lower dose

Hepatic Impairment

- Use with caution. May need to lower dose

Cardiac Impairment

- Do not use in patients with recent myocardial infarction, severe heart failure, history of QTc prolongation, orthostatic hypotension, or electrolyte imbalance (hypocalcemia, hypokalemia, hypomagnesemia)

Elderly

- More sensitive to AEs, such as sedation, hypotension. At risk for anticholinergic crisis. Start with lower doses

Children and Adolescents

- Some data for children over 12 and an appropriate treatment for adolescents with migraine, especially children with insomnia who are not overweight. In children less than 12, most commonly used at low dose for treatment of enuresis

Pregnancy

- Category C. Crosses the placenta and may cause fetal malformations or withdrawal symptoms. Generally not recommended for the treatment of pain or insomnia during pregnancy. For patients with depression or anxiety, SSRIs may be safer than TCAs

Breast Feeding

- Some drug is found in breast milk and use while breast feeding is not recommended

THE ART OF NEUROPHARMACOLOGY

Potential Advantages

- Proven effectiveness in multiple pain disorders. Can treat insomnia and depression, which are common in patients with chronic pain

Potential Disadvantages

- AEs are often greater than with SSRIs or SNRIs and many AEDs. More anticholinergic AEs than other TCAs. Weight gain and sedation can be problematic

Primary Target Symptoms

- Headache frequency and severity
- Reduction in neuropathic pain

Pearls

- Level A recommendation for use in prophylaxis of tension-type headache, and treatment of fibromyalgia
- Level B recommendation for efficacy in migraine prophylaxis, post-traumatic neuropathic pain, and cancer neuropathic pain but inefficacy in HIV neuropathic pain and phantom limb pain
- Based on a Cochrane review on TCA and phantom limb pain, morphine, gabapentin, and ketamine demonstrate trends towards short-term analgesic efficacy. Memantine and amitriptyline were ineffective for phantom limb pain. Results, however, are to be interpreted with caution as these were based mostly on a small number of studies with limited sample sizes that varied considerably and also lacked long-term efficacy and safety outcomes
- In patients with neuropathic pain or headache, offers relief at doses below usual antidepressant doses, and can treat coexisting insomnia
- The number of patients needed to treat is 3.6 with relative risk of 2.1 for achieving at least moderate pain relief
- Based on a recent Cochrane review on amitriptyline and neuropathic pain, amitriptyline should continue to be used as part of the treatment of neuropathic pain or fibromyalgia, but only a minority of patients will achieve satisfactory pain relief
- For patients with significant anxiety or depressive disorders, not as effective as newer drugs but with more AEs. Consider treatment of depression or anxiety with another agent together with a low dose of amitriptyline or other TCA for pain
- Norepinephrine:serotonin transporter binding ratio = 1.5:1
- TCAs can often precipitate mania in patients with bipolar disorder. Use with caution
- Despite interactions, expert psychiatrists may use with MAOIs for refractory depression
- Increases non-REM sleep time and decreases sleep latency
- Effective for nocturnal enuresis in children. Usual dose is 25 mg for children 6–10 and 50 mg for those 11 and older
- May be used to treat pathological laughing or crying due to forebrain disease at doses of 30–75 mg/day
- Previously used for ADHD before new treatments became available. May be useful as an adjunct for patients with pain and coexisting ADHD
- From a recent Cochrane review on TCAs and ADHD, most evidence on TCAs relates to desipramine. Findings suggest that, in the short term, desipramine improves the core symptoms of ADHD, but its effect on the cardiovascular system remains an important clinical concern. Thus, evidence supporting the clinical use of desipramine for the treatment of children with ADHD is low

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APIXABAN

THERAPEUTICS

Brands
- Eliquis

Generic?
- No

Class
- Anticoagulant

Commonly Prescribed for
(FDA approved in bold)
- **Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF)**
- **Primary prevention of venous thromboembolic (VTE) events in adult patients who have undergone elective total hip arthroplasty (THA) or total knee arthroplasty (TKA)**
- Treatment of cerebral venous thromboembolism

How the Drug Works
- Apixaban is a selective reversible inhibitor of both free and clot-bound factor Xa, and prothrombinase activity, thereby reducing the conversion of prothrombin to thrombin and thrombus formation. Thrombin-induced platelet aggregation is also inhibited

How Long Until It Works
- Peak concentration in 3–4 hours

If It Works
- Monitor for signs of bleeding. Assess liver function periodically as clinically indicated

If It Doesn't Work
- Correct the underlying disorder. Use a higher dose or switch to different anticoagulant

Best Augmenting Combos for Partial Response or Treatment-Resistance
- None

Tests
- The degree of anticoagulation does not need to be assessed

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Reduced coagulation due to inhibited thrombin formation

Notable AEs
- Bleeding, nausea/vomiting, constipation

Life-Threatening or Dangerous AEs
- The yearly incidence of life-threatening bleed is 0.11 %, intracranial hemorrhage 0.3 %, and major GI bleed 0.83 %

Weight Gain
- Unusual

Sedation
- Unusual

What to Do About AEs
- Discontinue treatment, supportive care. Active charcoal reduces absorption. Not effective: vitamin K, protamine sulfate, hemodialysis

Best Augmenting Agents to Reduce AEs
- In most cases discontinuation and changing to another medication is more practical than trying to reduce AEs with another medication

DOSING AND USE

Usual Dosage Range
- 2.5–5 mg twice daily

Dosage Forms
- Tablet. 2.5 and 5 mg

How to Dose
For NVAF
- 2.5 mg twice daily for patients with any 2 of the following 3 factors: > 80 years old, body weight < 60 kg, serum Cr > 1.5 mg/dL

- If 1 or fewer of the above factors is present, use 5 mg twice daily for stroke prevention
- 2.5 mg twice daily if used with strong CYP3A4 and P-glycoprotein (P-gp) inhibitor

For deep vein thrombosis prophylaxis
- 2.5 mg twice daily

Conversion between other anticoagulants
- Converting from warfarin: discontinue warfarin and start apixaban when INR < 2
- Converting to warfarin: discontinue apixaban and bridge with parenteral anticoagulant until INR 2–3
- Converting from heparin/low molecular weight heparin (LMWH): start at the time of discontinuation (heparin) or 2 hours before the next scheduled time (LMWH)
- Converting to heparin/LMWH: add heparin at the time of next dose of apixaban

Dosing Tips

- Crushed or single tablet have similar effects

Overdose

- May lead to hemorrhagic complications.

Long-Term Use

- Safe for long-term use

Habit Forming

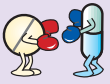
- No

How to Stop

- A specific antidote for apixaban is not available. It is not dialyzable due to high protein binding. Investigational antidotes include aripazine and andexanet

Pharmacokinetics

- Metabolized mainly via CYP3A4. Eliminated in urine (27%) and feces (63%). Half-life 10–14 hours



Drug Interactions

- Anticoagulants such as heparin, vitamin K antagonists increase bleeding risk. Concomitant usage of apixaban and enoxaparin resulted in a ~50% increase in peak anti-Xa activity
- Antiplatelet agents such as aspirin, dipyridamole, clopidogrel, and abciximab may increase bleeding risk
- Long-term NSAIDs may increase risk of GI bleed
- CYP3A4 or P-gp inhibitors (e.g., amiodarone, ketoconazole, clarithromycin, fluoxetine, naproxen) increase drug concentration
- CYP3A4 or P-gp inducers (rifamycin, carbamazepine, phenytoin, St. John's wort) lower drug concentration

Other Warnings/ Precautions

- Procedure with minor bleeding risk: stop 1 day before procedure and start 12~24 hours after procedure. If CrCl < 50 mL/min stop 2 days before
- Procedure with major bleeding risk: stop 2 days before procedure and start 2–3 days after procedure. If CrCl < 50 mL/min stop 3 days before

Do Not Use

- History of mechanical heart valve replacement
- Hypersensitivity to the drug
- Evidence of major bleeding (e.g., intracranial, intra-abdominal, retroperitoneal, intra-articular, etc.)
- Serious trauma
- Prior to major surgery

SPECIAL POPULATIONS

Renal Impairment

- Patients with end-stage renal disease maintained on stable hemodialysis with the recommended dose of 5 mg twice daily
- Reduction in dose to 2.5 mg twice daily for either ≥ 80 years of age or body weight ≤ 60 kg

Hepatic Impairment

- No adjustment needed in mild impairment. No information on moderate impairment. Contraindicated in severe hepatic impairment

Cardiac Impairment

- Safety information is lacking for use in patients with mechanical valve. Use is not recommended

Elderly

- 2.5 mg twice daily for either $\geq$ 80 years of age or body weight $\leq$ 60 kg or serum Cr $\geq$ 1.5 mg/dL

Children and Adolescents

- Not studied in children

Pregnancy

- Category B. May increase hemorrhage during pregnancy and delivery

Breast Feeding

- Unknown if present in breast milk. Discontinue use

THE ART OF NEUROPHARMACOLOGY

Potential Advantages

- Proven treatment for stroke and systemic embolism prevention in adults with AF
- Better than aspirin, non-inferior to warfarin in reducing rate of stroke and systemic embolism from AF
- Has a lower risk than warfarin for hemorrhagic stroke and major bleeding, and marginally lower risk of death from any cause

Potential Disadvantages

- Increased risk of bleeding although less than warfarin. Lack of antidote or monitoring lab test. Not dialyzable

Primary Target Symptoms

- Reduce recurrent attacks of cerebral embolism caused by cardiogenic thrombi due to AF. Reduce venothromboembolism following TKA or THA

Pearls

- Effective in patients with NVAF with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater (Level of Evidence B)
- Compared to warfarin, fewer serious AEs and equal effectiveness in preventing ischemic stroke
- No large head-to-head comparisons with other newer agents in clinical trials
- Recommended in patients with NVAF unable to maintain a therapeutic INR level with warfarin. (Level of Evidence C)
- Has the lowest bleeding risk among the 3 new anticoagulants
- Compared to enoxaparin 40 mg/day has a lower incidence of all-cause death and major venothromboembolism
- For cerebral venous thrombosis, despite a lack of evidence, it is often recommended to use vitamin K antagonist for 3–12 months. Longer duration is reserved for those with severe coagulopathies or recurrent VTE. For newer anticoagulants, although no evidence available, their lower intracranial bleeding rate might offer them a potential role for cerebral venous thrombosis

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APOMORPHINE

THERAPEUTICS

Brands
- Apokyn, Apo-go, Uprima

Generic?
- No

Class
- Antiparkinson agent

Commonly Prescribed for
(FDA approved in bold)
- **Parkinson's disease (PD): acute intermittent treatment of "off" episodes**

How the Drug Works
- It is a dopamine partial agonist to $D_{2\text{-}4}$ receptors. D_2 agonism is likely the main reason for effectiveness in PD. Despite its name, does not actually contain morphine or act on morphine receptors

How Long Until It Works
- PD: 10–60 minutes

If It Works
- PD: this is an adjunctive medication designed for use with other PD treatments. Continue to adjust other PD treatments to achieve maximum functionality

If It Doesn't Work
- PD: adjust PD medication regimen, determine compliance with medications, and reconsider the diagnosis

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Patients requiring frequent injections will need an improved treatment plan to avoid severe "off" periods. Strategies include shortening the interval of levodopa dosing, adding catechol-*O*-methyltransferase (COMT) inhibitors, or adding longer-acting dopamine agonists

Tests
- None required

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Direct effect on dopamine receptors

Notable AEs
- Injection site reactions, drowsiness, nausea or vomiting, dizziness, postural hypotension, hallucinations, edema. Less common hypersexuality or erections

Life-Threatening or Dangerous AEs
- May cause somnolence or sudden-onset sleep. Severe orthostatic hypotension and nausea/vomiting, even when compared to other PD treatments

Weight Gain
- Unusual

Sedation
- Common

What to Do About AEs
- Orthostatic hypotension: the first dose should be given in a monitored setting (such as a physician's office). Check supine and standing blood pressure predose and 20, 40, and 60 minutes after injection. If there is no clinical improvement and no AEs, a dose of 4 mg can be given, no earlier than 2 hours after the initial dose

Best Augmenting Agents to Reduce AEs
- Nausea/vomiting: at least 3 days before initiating therapy, start trimethobenzamide 300 mg 3 times a day and continue this for at least 2 months. When given alone, apomorphine causes severe nausea and vomiting. Domperidone, an antidopaminergic drug that does not cross the BBB, is an alternative treatment for nausea – typically starting at 10 mg 3–4 times a day

DOSING AND USE

Usual Dosage Range
- PD: 2–6 mg per dose, up to 20 mg/day

Dosage Forms
- SC injection: 10 mg/mL in 3 mL cartridges

How to Dose
- PD: before starting therapy, monitor for orthostatic hypotension
- The usual starting dose for acute "off" episodes is 1 mg less than the tolerated test dose. If the patient tolerates the 4 mg test dose, start at 3 mg. If the patient tolerates 3 mg, start at 2 mg and so on

Dosing Tips
- Start with low dose and increase as needed and based on response and side effects
- For patients resuming therapy after an interruption of 1 week or more, start at the 2 mg dose. The dose may then be increased by 1 mg every few days as an outpatient to a maximum of 6 mg per dose and total daily dose of 20 mg/day. The average number of daily doses in clinical trials was 3 per patient

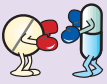
Overdose
- Symptoms include severe orthostatic hypotension, nausea, and vomiting. Somnolence, agitation, chest and abdominal pain, or dyskinesias can occur

Long-Term Use
- Safe for long-term use

Habit Forming
- No

How to Stop
- Designed for acute use only

Pharmacokinetics
- Peak plasma levels in 10–60 minutes



Drug Interactions
- Serotonin 5-HT_3 antagonists used to treat nausea such as ondansetron, dolasetron can cause profound hypotension and loss of consciousness
- Use with caution with antihypertensives (due to risk of orthostatic hypotension) or QTc prolonging medications
- Dopamine antagonists reduce drug effectiveness

Other Warnings/ Precautions
- Sodium metabisulfite is a metabolite and can cause reactions in patients allergic to sulfites

Do Not Use
- Hypersensitivity to the drug
- Concomitant use with 5-HT_3 antagonists

SPECIAL POPULATIONS

Renal Impairment
- Mild to moderate impairment: start at 1 instead of 2 mg

Hepatic Impairment
- Increased concentrations can occur with mild to moderate impairment. Use with caution

Cardiac Impairment
- No known effects

Elderly
- No dose adjustment needed with normal renal function. The dose used is the lowest that provides clinical improvement

Children and Adolescents
- Not studied in children (PD is rare in pediatrics)

Pregnancy
- Category C. Use only if benefits of medication outweigh risks

Breast Feeding
- Unknown if excreted in breast milk

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
- The only drug approved for emergency treatment of "off" episodes in PD. Rapid onset of action

Potential Disadvantages

- Severe nausea. Cost. Advanced PD patients often have difficulty using SC injection during "off" periods and a caregiver may be needed to administer

Primary Target Symptoms

- PD: acute freezing and "off episodes" with markedly impaired motor dysfunction including bradykinesia, hand function, gait and resting tremor

Pearls

- Efficacious for treatment of motor fluctuation and as symptomatic adjunct to levodopa
- For patients with advanced PD, make sure to ask about "off" periods: how often they occur, severity, and how the patient or caregiver manages them
- In advanced PD, "freezing" becomes more unpredictable over time despite well-designed medication regimens, and apomorphine can be a useful adjunct
- May be particularly helpful for nighttime symptoms, including pain and restless leg syndrome
- Daytime apomorphine continuous infusion (12–16 hours/day) has been used to avoid pulsatile medication and reduce oral medication. It also improves non-motor symptoms (e.g., hyperhidrosis, nocturia, urgency of micturition, and fatigue) but with visual hallucination and paranoid ideations
- Both apomorphine and deep brain stimulation (DBS) decrease daily off time. Only DBS reduces dyskinesia duration and severity but with more neuropsychiatric side effects
- Previously used off-label for erectile dysfunction but now being replaced by sildenafil and others. It may exert anti-Alzheimer's disease effect by enhancing the degradation of intracellular amyloid β (activation of proteasome and insulin-degrading enzyme) or antioxidation (upregulated glutathione peroxidase). Both are independent from dopamine signaling pathway

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Ohyagi Y. Apomorphine: a novel efficacy for Alzheimer's disease and its mechanisms. *J Alzheimers Dis Parkinsonism*. 2012;2(4):1000e122.

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APREPITANT

THERAPEUTICS

Brands
- Emend

Generic?
- No

Class
- Antiemetic

Commonly Prescribed for
(FDA approved in bold)
- **Prevention of nausea and vomiting (chemotherapy, postoperative)**
- Nausea and vomiting (gastroenteritis, pregnancy)
- Pruritus

How the Drug Works
- Selective blocking agent of substance P/neurokinin 1 (NK_1) receptors. No affinity for 5-HT_3, dopamine, and corticosteroid receptors. It augments the antiemetic activity of the 5-HT_3 antagonist ondansetron and corticosteroid dexamethasone

How Long Until It Works
- Less than an hour

If It Works
- Use at lowest effective dose

If It Doesn't Work
- Increase dose, or discontinue and change to another agent

Best Augmenting Combos for Partial Response or Treatment-Resistance
- May add D_2 antagonist, 5-HT_3 antagonist, antihistamine, benzodiazepine, or corticosteroid

Tests
- None required

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Not known

Notable AEs
- Asthenia, diarrhea, hiccup, pruritus, hair loss

Life-Threatening or Dangerous AEs
- Hypersensitivity reactions such as angioedema and Stevens-Johnson syndrome have been reported

Weight Gain
- Unusual

Sedation
- Unusual

What to Do About AEs
- Reduce dose or discontinuation

Best Augmenting Agents to Reduce AEs
- Symptomatic management

DOSING AND USE

Usual Dosage Range
- 40–150 mg

Dosage Forms
- Capsule: 40, 80, 125 mg
- Injection (fosaprepitant dimeglumine): 115, 150 mg

How to Dose
- For chemotherapy-induced nausea/vomiting: 125 mg 1 hour prior to chemotherapy (day 1) and 80 mg daily (day 2–3), with or without 5-HT_3 antagonist and corticosteroid
- For postoperative nausea/vomiting: 40 mg within 3 hours prior to anesthesia induction

Dosing Tips
- Can be taken with or without food. Only for short-term use

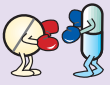
Overdose
- May develop drowsiness or headache

Long-Term Use
- Not been studied

Habit Forming
- No

How to Stop
- No need to taper

Pharmacokinetics
- Bioavailability 60–65%. > 95% protein bound. Metabolized predominantly by CYP3A4. Not renally excreted. Half-life 9–12 hours



Drug Interactions
- Increased level by CYP3A4 inhibitor (ketoconazole, clarithromycin, antiviral, diltiazem, cisapride, etc.)
- Decreased level by CYP3A4 inducer (rifampin, carbamazepine, phenytoin, etc.)
- As a CYP2C9 inducer, lowers the concentration of warfarin, naproxen, fluoxetine, etc.
- As a CYP3A4 inhibitor, increases the concentration of many drugs
- May reduce the efficacy of hormonal contraceptives

Other Warnings/ Precautions
- May mask a progressive ileus or gastric obstruction

Do Not Use
- Known hypersensitivity

SPECIAL POPULATIONS

Renal Impairment
- No adjustment necessary

Hepatic Impairment
- No dose adjustment needed for mild to moderate impairment

Cardiac Impairment
- Typically needs no adjustment

Elderly
- Typically needs no adjustment

Children and Adolescents
- Safety and effectiveness have not been established

Pregnancy
- Category B. Use for significant migraine or nausea during pregnancy if needed

Breast Feeding
- Found in breast milk. Little information is available. Bottle feed if possible

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
- Novel mechanism

Potential Disadvantages
- Drug interaction with CYP3A4 inhibitor/ inducer

Primary Target Symptoms
- Nausea and vomiting

Pearls
- Commonly used in combination with dexamethasone and ondansetron for chemotherapy-induced nausea and vomiting
- May be effective for patients with chronic pruritus
- Not effective in major depressive disorder or generalized anxiety disorder
- Theoretically useful in treatment of chronic pain and inflammation but not established in human trials

Suggested Reading

Aapro MS, Schmoll HJ, Jahn F, Carides AD, Webb RT. Review of the efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in a range of tumor types. *Cancer Treat Rev*. 2013;39(1):113–17.

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Ständer S, Siepmann D, Herrgott I, Sunderkötter C, Luger TA. Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. *PLoS One*. 2010;5(6):e10968.

ARIPIPRAZOLE

THERAPEUTICS

Brands
- Abilify, Abilify Discmelt, Abilify Maintena

Generic?
- No

Class
- Atypical antipsychotic

Commonly Prescribed for
(FDA approved in bold)
- **Schizophrenia in adults and adolescents**
- **Bipolar I disorder (mixed and manic episodes) as monotherapy or adjunct to lithium or valproate**
- **Irritability associated with autistic disorder**
- **Adjunctive therapy for major depressive disorder**
- **Gilles de la Tourette syndrome (GTS; 6–18 years old)**
- Agitation in patients with Alzheimer's dementia (AD)
- Augmentation for refractory obsessive-compulsive disorder
- Anxiety disorder
- Insomnia

How the Drug Works
- It is a phenylpiperazine derivative that acts as partial agonist with high affinity towards 5-HT_{1A}, 5-HT_7, and $D_{2\text{-}3}$ receptors, and moderate affinity towards 5-HT_{1D}, 5-HT_{2C}, and D_4 receptors. As a partial agonist, it blocks receptors at high dopamine and serotonin levels, but activates receptors at low levels. It also exerts moderate antagonism on 5-$HT_{2A/2B}$, H_1, and $\alpha_{1,2}$-adrenergic receptors but with no effect on muscarinic receptors. Antagonism on D_2 receptors relieves positive symptoms; antagonism on 5-HT_{2A} relieves negative symptoms

How Long Until It Works
- Schizophrenia/bipolar: may be effective in days, more commonly takes weeks or months to determine best dose and achieve best clinical effect. Usually 4–6 weeks
- Agitation/insomnia: may be effective immediately

If It Works
- Continue to use at lowest required dose. Most patients with schizophrenia see a reduction in psychosis with neuroleptics. However, it may worsen psychosis in patients with Parkinson's disease (PD) or dementia with Lewy bodies (DLB)

If It Doesn't Work
- Increase dose
- Psychosis related to PD or DLB: clozapine is more efficacious for acute treatment only
- Insomnia: if no sedation occurs despite adequate dosing, change to another agent

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Patients with affective disorders, such as bipolar disorder, may respond to mood-stabilizing AEDs, lithium, or benzodiazepines

Tests
- Prior to starting treatment and periodically during treatment, monitor weight, blood pressure, lipids, and fasting glucose due to risk of metabolic syndrome

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- Antagonism on H_1, 5-HT_{2C}, and D_2 may cause weight gain; antagonism on α_1 can cause orthostatic hypotension; antagonism on H_1 and 5-HT_{2A} can cause sedation

Notable AEs
- CNS: dizziness, personality disorder, akathisia, sedation, fatigue, asthenia, tremor, insomnia
- Autonomic: dry mouth, postural hypotension, blurred vision
- Gastrointestinal: constipation, drooling, decreased appetite, nausea

Life-Threatening or Dangerous AEs
- Tardive dyskinesia (lower risk than conventional neuroleptics)
- Metabolic syndrome

- Neuroleptic malignant syndrome (rare compared with conventional antipsychotics)
- Agranulocytosis (very rare)
- Seizure

Weight Gain

- Not unusual

Sedation

- Common

What to Do About AEs

- Take at night: for many disorders there is no need for daytime dosing

Best Augmenting Agents to Reduce AEs

- Most AEs cannot be reduced with an augmenting agent

DOSING AND USE

Usual Dosage Range

- Bipolar disorder/schizophrenia: 10–15 mg/day

Dosage Forms

- Tablets: 2, 5, 10, 15, 20 mg
- Tablet, orally disintegrating: 10, 15 mg
- Solution, oral: 1 mg/mL
- Injection: 9.75 mg/1.3 mL
- Injection (extended release): 300, 400 mg/syringe

How to Dose

- Schizophrenia/bipolar I: 10–15 mg/day. May increase to 30 mg/day
- Adjunct for depression: 2–15 mg/day. Titrate 2–5 mg/day every week
- Agitation: 5.25–15 mg IM every 2 hours, up to 30 mg/day
- GTS: 2 mg/day. Titrate every 2 days to 5 mg/day ($<$ 50 kg) or 10 mg/day ($\geq$ 50 kg)

Dosing Tips

- For injection, do not administer IV or SC. For oral form, can be taken with food. Use at night if sedation is a problem. Elderly and children often need lower doses

Overdose

- Vomiting, somnolence, tremor. Standard management with activated charcoal. Hemodialysis not effective

Long-Term Use

- Safe for long-term use with appropriate monitoring

Habit Forming

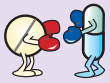
- No

How to Stop

- Gradual withdrawal is advised

Pharmacokinetics

- T_{max} 3–5 hours (oral) and 1–3 hours (IM). Hepatic metabolism to active metabolites via CYP2D6 and CYP3A4. Half-life 75–94 hours. $>$ 99% protein bound. Reach steady state in 2 weeks



Drug Interactions

- Strong CYP3A4 inhibitor (e.g., protease inhibitor, macrolide, azole antifungals, nefazodone) and moderate CYP3A4 inhibitor (e.g., aprepitant, verapamil, grapefruit juice) can increase drug levels; reduce aripiprazole dose
- Strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine, bupropion, quinidine, ritonavir) and moderate CYP2D6 inhibitor (e.g., sertraline, duloxetine) can increase drug levels; reduce aripiprazole dose
- CYP enzyme inducer (e.g., dexamethasone, rifampin, carbamazepine, phenytoin, barbiturate, St. John's wort) can lower drug level
- It does not affect the level of valproate, lithium, lamotrigine, warfarin, lorazapem, and most SSRIs

Other Warnings/ Precautions

- Increased mortality from aripiprazole use in elderly patients with dementia-related psychosis

Do Not Use

- Proven hypersensitivity to aripiprazole

SPECIAL POPULATIONS

Renal Impairment
- No dose adjustment needed

Hepatic Impairment
- No dose adjustment needed

Cardiac Impairment
- May worsen orthostatic hypotension. Use with caution. No known risk of QTc prolongation

Elderly
- Start with lower doses. Greater risk for infection, stroke, and other AEs in those with dementia-related psychosis

Children and Adolescents
- Schizophrenia (13–17 years): start at 2 mg/day. Titrate to 5 and 10 mg/day every 2 days. Long-term efficacy unknown
- Irritability associated with autism (6–17 years): start at 2 mg/day. Titrate 5 mg/day every week until 10–15 mg/day. Long-term efficacy unknown
- Bipolar I (10–17 years): start at 2 mg/day. Titrate to 5 and 10 mg/day every 2 days

Pregnancy
- Category C. Probably safer than AEDs during pregnancy for bipolar disorder. Use only if benefit outweighs risks

Breast Feeding
- It is found in breast milk. Use while breast feeding is generally not recommended

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
- Partial agonist effect with lower risk of dyskinesia. No known risk of QTc prolongation. More weight neutral than other atypical antipsychotics. Proven efficacy for depression

Potential Disadvantages
- Probably less effective than clozapine. Drug interaction by CYP450

Primary Target Symptoms
- Psychosis, depression, mania, and insomnia

Pearls
- May be useful for migraine refractory to standard treatment
- May improve psychosis in treating vascular parkinsonism
- Risperidone, olanzapine, and aripiprazole are recommended for treating agitation associated with dementia, although with potential harms (e.g., infection, cardiovascular event). Quetiapine, SSRIs, and trazodone remain investigational. Valproate is not advised. Olanzapine 10 mg IM (number needed to treat [NNT] 3), aripiprazole 9.75 mg IM (NNT 5), ziprasidone 10–20 mg IM (NNT 3)
- Aripiprazole can worsen parkinsonian symptoms in treating psychosis associated with PD or DLB. Only clozapine has A-level support. Quetiapine may also be considered
- From a Cochrane review on antipsychotics for schizophrenia, aripiprazole is less effective than olanzapine but has fewer side effects. It is similar to risperidone and may be better than ziprasidone. It has fewer side effects than olanzapine and risperidone
- Patients with BMI < 23 kg/m^2 are likely to gain weight; those with BMI > 27 kg/m^2 are likely to lose weight
- Less weight gain than risperidone and olanzapine. May lower the metabolic effect from clozapine
- For GTS requiring medication, consider α agonist (clonidine, guanfacine), antipsychotics (haloperidol, pimozide, risperidone), dopamine depletor (tetrabenazine). FDA currently approves haloperidol, pimozide, and aripiprazole

Suggested Reading

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ARMODAFINIL

THERAPEUTICS

Brands
- Nuvigil

Generic?
- No

Class
- Psychostimulant

Commonly Prescribed for
(FDA approved in bold)
- **Reducing excessive sleepiness in patients with narcolepsy or shift work disorder**
- **Reducing excessive sleepiness in patients with obstructive sleep apnea (OSA)/ hypopnea syndrome**
- Attention deficit hyperactivity disorder
- Fatigue in multiple sclerosis (MS), depression, cancer, HIV, fibromyalgia, or post-stroke patients
- Bipolar depression

How the Drug Works
- Armodafinil is the R-enantiomer of modafinil (a mixture of R- and S-enantiomers). R-modafinil binds to the dopamine transporter (DAT) with 3-fold higher affinity than S-modafinil
- No binding to serotonin transporter or norepinephrine transporter
- It may act on the hypothalamus by stimulating wake-promoting areas, or inhibiting sleep-promoting areas. Increases neuronal activity selectively in the hypothalamus and activates tuberomammillary nucleus neurons that release histamine
- It also activates hypothalamic neurons that release orexin/hypocretin

How Long Until It Works
- Typically 2 hours, although maximal benefit may take days to weeks

If It Works
- Continue to use indefinitely as long as symptoms persist. Complete resolution of symptoms is unusual. Does not cause insomnia when dosed correctly

If It Doesn't Work
- Change to most effective dose or alternative agent. Re-evaluate treatment of underlying cause (e.g., OSA) of fatigue. Consider other causes of fatigue (e.g., anemia, heart disease) as appropriate. Screen for use of CNS depressants that can interfere with sleep (e.g., opioids or alcohol)

Best Augmenting Combos for Partial Response or Treatment-Resistance
- In treating OSA, armodafinil is an adjunct to standard treatments such as continuous positive airway pressure (CPAP), weight loss, and treatment of obstruction when possible
- In narcolepsy with cataplexy, TCAs or SNRIs may be of some help on cataplexy. Sleep hygiene is also important. As a last resort, sodium oxybate can be used for both narcolepsy and cataplexy

Tests
- None required

ADVERSE EFFECTS (AEs)

How the Drug Causes AEs
- AEs are probably related to drug actions on CNS neurotransmitters

Notable AEs
- Nervousness, insomnia, headache, nausea, anorexia, palpitations, dry mouth, diarrhea, hypertension

Life-Threatening or Dangerous AEs
- Transient ECG changes have been reported in patients with preexisting heart disease (left ventricular hypertrophy, mitral valve prolapse)
- Rare psychiatric reactions (activation of mania, anxiety)
- Rare severe dermatological reactions

Weight Gain
- Unusual

Sedation

- Unusual

What to Do About AEs

- Try lowering the dose. If insomnia, do not take later in the day

Best Augmenting Agents to Reduce AEs

- Most AEs do not respond to adding other medications

DOSING AND USE

Usual Dosage Range

- 50–250 mg daily

Dosage Forms

- Tablets: 50, 150, 200, 250 mg

How to Dose

- Start at 150 mg in the morning
- Patients with narcolepsy are more likely to require a higher dose (250 mg)

Dosing Tips

- Dose requirements can escalate over time due to autoinduction. A drug holiday may restore effectiveness of lower dose
- In patients with shift work disorder, take 1 hour prior to beginning a shift

Overdose

- No reported deaths. Insomnia, restlessness, agitation, anxiety, tachycardia, nausea, and hypertension have been reported

Long-Term Use

- Although most initial trials were only a few months, appears safe. Periodically re-evaluate need for use

Habit Forming

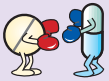
- Class IV medication, but rarely abused in clinical practice

How to Stop

- Withdrawal is not problematic, unlike traditional stimulants. Symptoms of sleepiness may recur

Pharmacokinetics

- Metabolized by amide hydrolysis and CYP3A4/5 in the liver. T_{max} 2–4 hours. 60% protein bound. Elimination predominantly in urine and the half-life is 15 hours. Reaches steady state at 7 days. Although having similar half-life and T_{max} to modafinil, the average plasma concentration of armodafinil is higher than that of modafinil



Drug Interactions

- It weakly induces CYP1A2 and 3A and inhibits CYP2C19. Dose reduction may be required for CYP2C19 substrate (e.g., phenytoin, diazepam, propranolol, omeprazole, TCAs)
- Strong CYP3A4 inhibitor (e.g., protease inhibitors, macrolides, azole antifungals, nefazodone) can increase armodafinil concentration
- Strong CYP3A4 inducer (e.g., carbamazepine, phenytoin, phenobarbital, rifampin, glucocorticoid, St. John's wort) can decrease armodafinil concentration
- Armodafinil can affect warfarin effectiveness, requiring closer monitoring of PTINR
- May interact with MAOIs

Other warnings/ precautions

- May adversely affect mood. Can cause activation of psychosis or mania

Do Not Use

- Known hypersensitivity to the drug, severe hypertension or cardiac arrhythmias

SPECIAL POPULATIONS

Renal Impairment

- No known effect. May require lower dose

Hepatic Impairment

- Reduce dose in patients with severe impairment

Cardiac Impairment

- Do not use in patients with ischemic ECG changes, chest pain, left ventricular hypertrophy, or recent myocardial infarction

Elderly

- No known effects