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Handbook of NEUROLOGICAL DRUGS



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Forewords
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JAYPEE

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SECTION 1

Drugs Used in Neurology

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Introduction

This section arranges drugs and biologicals in an alphabetical order with a brief description of the indications, contraindications, dosage, relevant pharmacokinetics, pharmacodynamics information, drug interaction where relevant, and use in special situations and populations.

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A

Section Outline

- Acenocoumarol
- Acetazolamide
- Acyclovir
- Aducanumab
- Albuterol
- Alemtuzumab
- Alglucosidase alfa
- Almotriptan
- Alpha-tocopherol
- Alprazolam
- Alteplase
- Amantadine
- Amifampridine
- Amitriptyline
- Ammonium tetrathiomolybdate
- Amphetamine
- Apixaban
- Apomorphine
- Aripiprazole
- Aspirin
- Ataluren
- Atogepant
- Atomoxetine
- Atorvastatin
- Azathioprine

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ACENOCOUMAROL

Introduction: Coumarin derivative and vitamin K antagonist.

Pharmacodynamics: Interfere with hepatic synthesis of vitamin K-dependent clotting factors II, VII, IX, and X as well as protein C and S; depletes vitamin K reserves, which in turn reduce synthesis of active clotting factors, by competitively inhibiting subunit 1 of the multiunit K epoxide reductase complex 1 (VKOR1).

Pharmacokinetics: It has oral bioavailability of 60%. Half-life (t½) is 8–11 hours and peak plasma concentration is reached in 1–3 hours. Duration of action is 48 hours. Metabolism is by hepatic P450 enzymes CYP2C9, CYP2C19, and CYP1A2. Elimination is by 60% renal and 20% fecal route.

Use: Cerebral venous thrombosis and some cases of cardioembolic stroke.

Dose: Available in 0.5, 1, 2, 3, and 4 mg strengths. If international normalized ratio (INR) is <1.3 start at 1 mg/day. Repeat INR after 1 week. If INR is 1.4–2 add 0.5 mg/day and repeat INR after 1 week. If INR is 2.1–3 continue with current dose.

Adverse effects: Bleeding—intracranial, gastrointestinal (GI), intraocular, and hemarthrosis.

Use in special population: Elderly patients are more prone to bleeding so should be closely monitored. In pregnant women with mechanical heart valve, it is category D drug and for all other it is category X drug. Breastfeeding women may take acenocoumarol as it poses very little risk to infant. Dose reduction is needed in renal impairment and no reduction in hepatic impairment.

ACETAZOLAMIDE

Introduction: Carbonic anhydrase inhibitor.

Pharmacodynamics: Inhibits enzyme carbonic anhydrase enzyme in proximal tubules (both membrane bound and cytoplasmic forms) resulting in near complete elimination of sodium bicarbonate reabsorption. Paresthesia and somnolence may suggest its action on central nervous system (CNS). Its efficacy in epilepsy can be attributed to production of metabolic acidosis.

Pharmacokinetics: It has 100% oral bioavailability and undergoes renal excretion unchanged. t½ is 6–9 hours.

Uses: High altitude sickness, periodic paralysis, idiopathic intracranial hypertension, and catamenial seizures.

Dose: Start at 500 mg/day in two divided doses and increase up to 2 g/day. Higher doses up to 3–4 g/day tried but most of them do not tolerate the adverse effects.

Adverse effects: Somnolence, paresthesia, metabolic acidosis, bone marrow depression, allergic reactions (as they belong to sulfonamides group), and metallic taste.

Use in special population: It belongs to pregnancy category C and risk benefit consideration is advised during lactation. It is contraindicated in chronic obstructive pulmonary disease (COPD), hepatic encephalopathy, those who are taking high dose salicylates, and renal calculus (due to precipitation of calcium phosphate salts in alkaline urine). Avoid in severe renal impairment and liver cirrhosis.

ACYCLOVIR

Introduction: Acyclic guanine nucleoside analog.

Pharmacodynamics: Its action is dependent on viral thymidine kinase in herpes virus. Phosphorylation of

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acyclovir occurs by viral thymidine kinase. Acyclovir triphosphate is incorporated in viral deoxyribonucleic acid (DNA) and causes suicidal inhibition of viral DNA polymerase.

Pharmacokinetics: t½ is 2.5 hours and has 10–30% oral bioavailability. Renal excretion and tubular secretion are the major routes of elimination.

Uses: Highly active against herpes virus type 1. Decreasing efficacy for herpes simplex virus 2 (HSV2), varicella-zoster virus (VZV), and Epstein–Barr virus (EBV). It is least active against cytomegalovirus (CMV). EBV-related oral hairy leukoplakia may improve with acyclovir. Oral acyclovir with systemic corticosteroids appears beneficial in treating Bell's palsy in some studies; varicella zoster and herpes zoster.

Dose: Intravenous (IV) dose is 10–15 mg/kg every 8 hours for 14–21 days. Oral dose is 800 mg five times a day for 10–14 days.

Adverse effects: Nausea, vomiting, and infusion site reactions. Major adverse effects include possible precipitation of acyclovir in renal tubules and subsequent acute renal failure, encephalopathy, and thrombocytopenic purpura (TTP) rarely.

Use in special population: Dose reduction is needed in renal failure. It belongs to pregnancy category B and caution warranted while breastfeeding. Safety for oral formulation is not established in children <2 years.

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ADUCANUMAB

Introduction: It is a monoclonal antibody targeting amyloid plaque aggregation. One of the controversial approval by the Food and Drug Administration (FDA) as the efficacy was not well-established. Under accelerated approval program drug was allowed in July 2021. But the manufacture had announced to withdraw the drug by January 2024 citing a "reprioritization" of the company's priorities in the Alzheimer's disease. Existing patients may receive till November 2024.

Pharmacodynamics: Human immunoglobulin G1 (IgG1) monoclonal antibody that targets aggregated forms of amyloid beta. Reduced plaque burden in a dose and time-dependent manner.

Pharmacokinetics: Half-life is 24.8 days. Maximum clinical benefits by 5 months of usage.

Uses: Alzheimer's disease at the mild cognitive impairment or mild dementia stage. Baseline MRI required prior to starting the drug. MRI should be done at 5th, 7th, 9th, and 12th infusions to detect amyloid-related imaging abnormalities (ARIAs).

Dose: Monthly infusions; available as IV formulation.

Initiation:
- Infusion 1 (at week 0) and infusion 2 (at week 4): 1 mg/kg
- Infusion 3 (at week 8) and infusion 4 (at week 12): 3 mg/kg
- Infusion 5 (at week 16) and infusion 6 (at week 20): 6 mg/kg
- Maintenance-infusion 7: 10 mg/kg every 4 weeks
- Dilution with normal saline 0.9% and given over an hour

Adverse effects: Most common adverse reactions (≥10%) include ARIAs—edema, headache, ARIA-H microhemorrhage, ARIA-H superficial siderosis, and fall. ARIAs are often asymptomatic and generally reversible with discontinuation of treatment but can cause headache, dizziness, and nausea.

Use in special population: No data is available in renal, hepatic impairment, pregnancy, or lactation.

ALBUTEROL

Introduction: It is a selective beta-2 adrenergic agonist which is approved for use in asthma and COPD.

Pharmacodynamics: Albuterol acts on beta-2 adrenergic receptors, inducing relaxation of bronchial smooth muscle and also inhibits immediate hypersensitivity mediator release, particularly from mast cells. Although albuterol also affects beta-1 adrenergic receptors, the impact is minimal, exerting little effect on the heart rate.

Pharmacokinetics: When inhaled only trace amounts of albuterol is found in bloodstream after 2–3 hours. It undergoes hepatic metabolism and renal excretion.

Uses: Primary use in neurology is in few forms of congenital myasthenic syndromes such as COLQ tail mutations, DOK7 mutation, and in agrin mutation.

Dose: The effective dose was found to be between 4 and 12 mg/day.

Adverse effects: Tremors, hypertension, cramps, and jitteriness.

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Special populations: No specific recommendations in renal and liver failure. Lack of well-controlled studies for use of albuterol in pregnancy. May be used in breastfeeding.

ALEMTUZUMAB

Introduction: It is a humanized anti-CD52 monoclonal antibody.

Pharmacodynamics: It binds to CD52 protein that is found in most of the B cells, T cells, natural killer cells, and macrophages. It then induces antibody-dependent lysis of cells it has binded and produces leukopenia which can last for more than a year.

Pharmacokinetics: Initial average t½ of 1 hour, but after multiple doses, The t½ extends to 12 days and steady-state plasma concentration reaches at approximately week 6 of treatment. It is metabolized probably by proteolytic degradation.

Uses: FDA approved for relapse remitting multiple sclerosis (those who failed two other disease modifying agents).

Dose: 12 mg IV over 4 hours daily IV infusion for 5 consecutive days, then again 12 months later for 3 consecutive days. Premedication with paracetamol and chlorpheniramine advised prior to infusion.

Adverse effects: Acute infusion reactions, (myelosuppression) neutropenia, thrombocytopenia, and anemia. Patents are at risk for autoimmune hemolytic anemia, autoimmune thyroiditis, and other autoimmune diseases (probably due to immune reconstitution after a profound leukopenia). Risk of immunosuppression leads to various opportunistic infections. Particularly CMV infection is to be monitored. *Pneumocystis carinii* and herpes virus prophylaxis should be given for at least 2 months following treatment. CD4 count may be below 200 cells/μL for at least a year.

Use in special population: It is contraindicated in pregnancy. Live vaccines are not to be given to patients on treatment with alemtuzumab. Combining this drug with anticancer drugs may increase immunosuppression. No adequate data regarding its usage in renal and hepatic impairment, lactation, and pediatric safety.

ALGLUCOSIDASE ALFA

Introduction: Biosynthetic (recombinant DNA origin) form of human acid α-glucosidase (GAA).

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Pharmacodynamics: It is an enzyme that catalyzes the hydrolysis of α-1,4- and α-1,6-glycosidic linkages of lysosomal glycogen. It provides an exogenous source of GAA in Pompe's disease.

Pharmacokinetics: t½ is 2–3 hours. Those who develop antibody titers of ≥12,800 at week 12 of treatment have increased clearance by about 50%.

Uses: Management of infantile-onset Pompe's disease. It is designated as orphan drug by the FDA for this condition.

Dose: Infants and children 1 month to 3.5 years of age—20 mg/kg by IV infusion once every 2 weeks. Do not exceed infusion rate > 7 mg/kg/hour.

Adverse effects: Fever, pharyngitis, respiratory distress, pneumonia, tachypnea, bronchiolitis, rash, urticaria, and other hypersensitivity reactions.

Use in special population: No recommendations at this time for special population.

ALMOTRIPTAN

Discussed under triptans.

ALPHA-TOCOPHEROL

Introduction: It also known as vitamin E, a fat-soluble vitamin. It is not produced in our body. Vitamin E is formed from photosynthetic processes of plants. It is found abundantly in avocados, wheat, green leafy vegetables, nuts, soybeans, olive oils, and sunflower oil. Alpha form of tocopherol is usually found in abundance.

Pharmacodynamics: It is a free radical scavenger and also inhibits the aggregation of platelets and monocyte adhesion.

Pharmacokinetics: It undergoes hepatic metabolism and excreted in bile and feces. It is stored in fat cells.

Uses: Ataxia with vitamin E deficiency.

Dose: Vitamin E dose ranges from 800 to 1,500 mg (or 40 mg/kg body weight in children).

Adverse effects: Nausea, headache, blurred vision, and GI upset.

Use in special population: It can be used in pregnancy and lactation. It is safe in pediatric population, renal, and hepatic failure patients.

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ALPRAZOLAM

Introduction: Benzodiazepine and anxiolytic.

Pharmacodynamics: It binds to GABA-A receptor and increases the frequency of opening of chloride channels resulting in hyperpolarization and neuronal inhibition.

Pharmacokinetics: It undergoes CYP metabolism in liver. CYP3A4 inhibitors like itraconazole increase the toxicity of the drug. CYP3A4 inducer like carbamazepine decreases the levels of alprazolam. Oral bioavailability is 90%. Peak plasma concentration in 1–2 hours. Metabolites are excreted in urine. t½ is 11–12 hours. Asians have 25% greater t½ compared to Caucasians.

Uses: Anxiety and panic disorders.

Dose: 0.25–0.5 mg three times a day. Maximum is 4 mg/day for anxiety. For panic disorders 5–6 mg average dose is required and maximum dose of 10 mg may be required. Conventional and extended release are available.

Adverse effects: Withdrawal effects, drowsiness, depression, headache, constipation, diarrhea, incoordination, and fatigue.

Use in special population: In hepatic impairment and in geriatric population, use smallest effective dose. Concomitant use with opioid not recommended. It is contraindicated in pregnancy. Discontinue nursing or the drug regarding lactation.

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ALTEPLASE

Introduction: Biosynthetic (recombinant DNA origin) form of human tissue-type plasminogen activator (t-PA) which is a thrombolytic agent.

Pharmacodynamics: It catalyzes the conversion of plasminogen to the proteolytic enzyme plasmin, which lyses fibrin as well as fibrinogen.

Pharmacokinetics: It is metabolized in liver and excreted in urine. It has an initial t½ of fewer than 5 minutes and a terminal t½ of 72 minutes.

Uses: Reperfusion therapy in acute ischemic stroke within a window period of 4.5 hours (after excluding bleed in the brain).

Dose: 0.9 mg/kg. 10% given as IV bolus. Rest is given as infusion over an hour. Dilute with 0.9% sodium chloride solution. Maximum dose is 90 mg.

Adverse effects: Hemorrhage (sometimes serious bleeds like intracranial hemorrhage). Increased risk of bleeding when used along with antiplatelets and anticoagulants.

Use in special population: Some of the absolute contraindications include patients with intracranial hemorrhage, neoplasm, suspected aortic dissection, active bleeding diathesis, prothrombin time (PT) INR > 1.7, uncontrolled blood pressure (BP), serious head injury, or stroke within 3 months. Safety and efficacy not established in pediatrics. Category C in pregnancy. Can be used if benefits outweigh the risk. Lactation data not available. Elimination t½ prolonged in liver failure patients hence caution warranted.

AMANTADINE

Introduction: This drug has antiparkinsonian action in addition to its use as an antiviral agent against influenza.

Pharmacodynamics: It blocks N-methyl-D-aspartate (NMDA) receptors, increases dopamine signal in striatum, and has got anticholinergic activity too.

Pharmacokinetics: It is well absorbed in gastrointestinal tract. Its half-life is 9–37 hours. There is no appreciable metabolism. The drug is eliminated by kidneys unchanged.

Uses: Can be started as an initial therapy in mild Parkinson's disease. Also used as an adjunct therapy in levodopa dose-related motor fluctuations and dyskinesia.

- *Huntington chorea*: 100 mg orally three to four times daily.
- *Multiple sclerosis-related fatigues*: 100 mg orally twice daily, increasing to 200 mg twice daily as needed.
- *Restless leg syndrome*: 100 mg orally daily, increasing to 300 mg/day as needed.
- *Traumatic brain injury*: 100 mg orally twice daily, increasing to 200 mg twice daily as needed.

Dose: 100 mg twice per day and od formulations.

- For the treatment of Parkinson disease, amantadine is also given orally at 100 mg twice daily and increased to 200 mg twice daily as needed. Dosing should begin at 100 mg once daily for patients taking other parkinsonian drugs.
- It is important not to discontinue amantadine abruptly as it can cause neuroleptic malignant syndrome (NMS)-like symptoms.

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Adverse effects: Dizziness, nausea, and vomiting (mild and reversible), orthostatic hypotension, syncope, peripheral edema, dizziness, delusions, hallucinations, falls, xerostomia, and constipation. Livedo reticularis is a less common side effect. This side effect is reversible with the withdrawal of medication. Serious adverse effects include NMS, psychosis, suicidal ideation, and CNS depression.

Use in special population: It belongs to the FDA pregnancy category C. Discontinue nursing or drug during lactation. When administering amantadine, monitor BP, renal function, and mental statuses, such as depression/suicidality, and psychosis. Those with seizure disorders have to be monitored for seizure activity. Patients with heart failure require vigilance for increased water retention and lower leg edema. The clearance of amantadine greatly diminishes in elderly patients and patients with renal impairment. Therefore, dose modification merits consideration in such cases.

AMIFAMPRIDINE

Introduction: Voltage-gated potassium channel blocker. Orphan drug for Lambert–Eaton myasthenic syndrome (LEMS).

Pharmacodynamics: Blocks voltage-gated potassium channel and prevents efflux of K^+ thereby prolonging depolarization. This leads to prolonged calcium entry and enhanced acetylcholine release which improves the neuromuscular function.

Pharmacokinetics: Liver metabolism by N-acetyltransferase 2 (NAT2). Amifampridine and its inactive metabolite eliminated in urine. Orally well absorbed and peak concentration reaches in 20 minutes to 1 hour.

Uses: LEMS in children ≥ 6 years of age and in adults. To improve muscle strength (symptomatic treatment).

Dose: Begin with 15–30 mg daily in three to five divided doses. Increase 5 mg every 4 days till desired clinical response not to exceed 100 mg/day. Half the above dosing recommended in patients weighing < 45 kg.

Adverse effects: Nausea, vomiting, headache and diarrhea, paresthesia, and respiratory tract infection.

Use in special population: 5 mg in three to five divided doses in patients weighing <45 kg with hepatic impairment or creatinine clearance of 15–90 mL/min. 15 mg in three to

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Handbook of NEUROLOGICAL DRUGS

Salient Features

- Provides a comprehensive alphabetical list of drugs which are specifically used in neurology with pharmacological details in the first section
- Section 2 provides disease/condition-based drug lists which can be cross referenced in Section 1
- Ready reckoner and easy-to-use for the practicing neurologists and the trainees/postgraduates alike

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