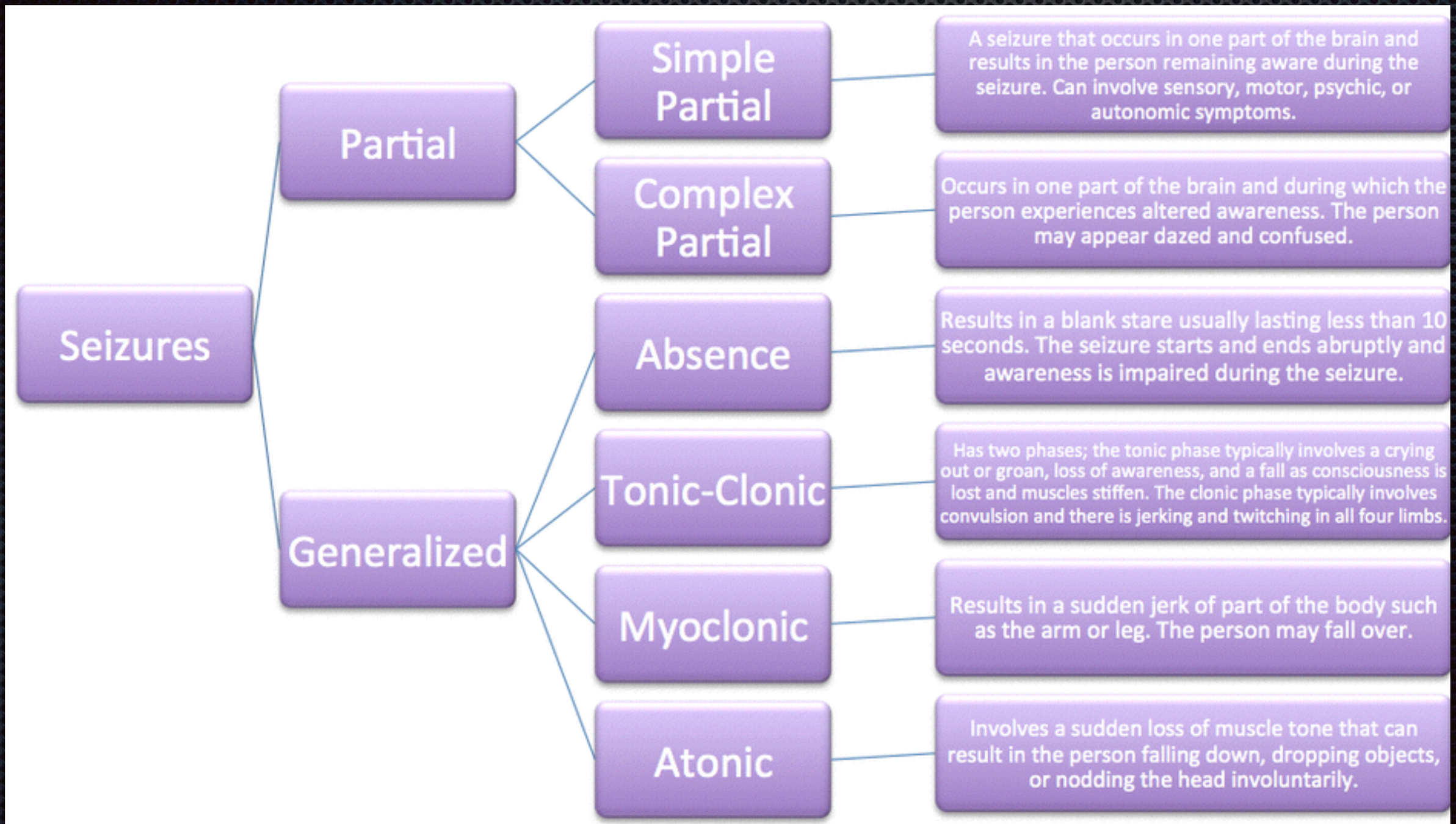
Westmead Primary Exams

Siezures


Seizures
Partial
Simple Partial
A seizure that occurs in one part of the brain and results in the person remaining aware during the seizure. Can involve sensory, motor, psychic, or autonomic symptoms.
Complex Partial
Occurs in one part of the brain and during which the person experiences altered awareness. The person may appear dazed and confused.
Generalized
Absence
Results in a blank stare usually lasting less than 10 seconds. The seizure starts and ends abruptly and awareness is impaired during the seizure.
Tonic-Clonic
Has two phases; the tonic phase typically involves a crying out or groan, loss of awareness, and a fall as consciousness is lost and muscles stiffen. The clonic phase typically involves convulsion and there is jerking and twitching in all four limbs.
Myoclonic
Results in a sudden jerk of part of the body such as the arm or leg. The person may fall over.
Atonic
Involves a sudden loss of muscle tone that can result in the person falling down, dropping objects, or nodding the head involuntarily.

Benzodiazepines

- Diazepam/Midazolam
  - MOA - GABA agonist, potentiates GABA-ergic inhibition in the CNS causing membrane hyperpolarisation
  - All benzodiazepines have hepatic metabolism and are excreted in the urine
    - Diazepam: Highly effective in stopping continuous seizure activity - tolerance develops if given long term
      - Pharmacokinetics:
        - A: well absorbed orally - over 90% bioavailability
        - D: Highly protein bound
        - M: metabolised into multiple active metabolites
        - E: Half life is 2 days, excreted in the urine

Clonazepam

- Long acting, effective against absence seizures and some myoclonic seizures
- Potent sedative
- No active metabolites but extensively metabolised by 1st pass
- PO bioavailability around 80%
- Half life 20 -50 hours

Generic name	Trade name	Dose equival	Onset of action *	Elimin. t 1/2 hr	Starting dose (mg)	Maximum dose mg/d	Metabolism Excretion *
Long (25-100h)							
Chlordiazepoxide	Librium	10	I	6-20	25 bid-tid	300	K
Clonazepam	Klonopin	0.25	I	18-50	0.25-0.5 bid	20	LK
Clorazepate	Tranxene	7.5	R	30-100	7.5-15 qhs	60	K
Diazepam	Valium	5	R	30-100	2.5-5	40	K
Flurazepam	Dalmane	5	R-I	50-160	15-30 qhs	30	K
Medium (10-15h)							
Lorazepam	Ativan	1	I	10-20	0.5 tid	10	K
Estazolam	ProSom	0.33	I	10-24	0.5-1 qhs	3	K
Temazepam	Restoril	5	I	8-20	15-30 qhs	30	K
Short (<12h)							
Alprazolam	Xanax	0.5	I	6-20	0.25 tid	10	K
Midazolam	Versed	1.25-1.7	I	2-3	0.07/kg	5	L
Oxazepam	Serax	15	I-S	8-12	10-15 tid	120	K
Triazolam	Halcion	0.1	I	1.5-5	0.125 qhs	0.5	K

Phenytoin

- Pharmacodynamics
  - Alters Na (blocks Na channel), K, Ca conductance
  - Therefore interferes with membrane potentials, concentration and release of neurotransmitters
  - Blocks high frequency firing potentials
  - Used in partial and generalised tonic clonic siezures
  - Earliest non sedative anti-epileptic

Pharmacokinetics

- A: Complete gastro absorption, peak plasma concentration in 3 - 12 hours
  - Unreliable absoprtion with IM injection so the precursor fosphenytoin is used
  - 90% bound to plasma proteins
- D: Accumulates in multiple organ tissues - brain, fat, liver, muscle
- M: Metabolised by liver into inactive metabolites - half life is 12 - 36 hours, longer in high levels - takes 4 - 6 weeks for blood levels to stabilise
  - Theraputic range is 10 - 20mcg/ml
- E: Excreted in urine - a small proportion is excreted unchanged in urine
  - Dose dependent elimination (variable order kinetics)
    - At low concentrations it follows first order kinetics, which causes saturation of hepatic enzymes leading to…
    - Zero order kinetics at higher levels within the therapeutic dosing range so even a small rise in dose after this can increase plasma concentrations by large amounts and rapidly lead to toxicity

Toxicity

- Nystagmus - early
- Loss of smooth extraoccular pursuit movements
- Diplopia
- Ataxia
- Sedation
- Gingival hyperplasia
- Hirsutisim
- Coarsening of facial features
- Peripheral neuropathy - diminished deep tendon reflexes
- Osteomalacia
- Rash/fever/agranulocytosis

Interactions

- Protein binding
  - Other protein bound drugs can displace phenytoin
  - Hypoalbuminemia
  - Renal disease - can decrease plasma protein binding and result in elevated free drug concentrations
- Induces microsomal enzymes in liver —> warfarin

Carbemazepine

- Tricyclic anti-epiletic effective also in Bipolar depression, non sedative
  - Can also be used in trigemminal neuralgia and mania
- Pharmacodynamics
  - Blocks Na channels and inhibits high frequency repetitive firing neurones
  - Acts presynaptically to prevent synaptic transmission and neurotransmitter release

Pharmacokinetics

- A - variable rate of absorption, but complete, food slows absorption
- D - peak levels occur in 6 - 8 hours, distribution is slow, Vd 1L/kg
    - 70% bound to plasma protein - doesn't displace other drugs from the proteins
- M - low systemic clearance at start
    - half life 36 hours at start
    - 8 - 12 hours when on continuous therapy
    - induces microsomal enzymes of the liver
    - once completely metabolised it has one metabolite with anticonvulsant therapy
    - theraputic trough level 4 - 8 mcg/mL

Interactions

- Due to enzyme induction
  - Increases metabolism of phenytoin, ethosuxamide, valproate, clonazepam
    - These drugs can also induce enzymes and cause carbamazepine to have lower concentrations

Toxicity

- Diplopia, ataxia
- GI upset
- Unsteadiness
- Drowsy at high doses
- Idiosyncratic blood dyscrasia
- Rash

Sodium valproate

- Pharmacodynamics
  - Blocks sustained high frequency firing neurones
  - Affects sodium channel current - used in partial seizure prevention
  - Also has an element of NMDA blockade
  - Increased GABA levels - unclear mechanism
  - Effective in tonic clonic seizures
  - Also effective in absence seizures
  - Can also be used in migraine prophylaxis

Pharmacokinetics

- A - well absorbed, bioavailibility is > 80%
- D - Volume of distribution is limited to extracellular water 0.15L/kg
- M - Slow and dose dependent clearance
  - half life varies from 9 - 18 hours
- E - 20% excreted as a direct conjugate of valproate

Drug interaction

- Displaces phenytoin from plasma proteins
- Inhibits metabolism of phenytoin, carbamazepine, phenobarbital
- Decreases clearance of lamotragine
- Toxicity
  - Most common - N/V, abdominal pain, heart burn
  - Sedation
  - Tremor and weight gain, hair loss
  - Idiosyncratic hepatotoxicity especially in toddlers and so needs LFT monitoring
  - Teratogenicity - can cause spinabifida

Phenobarbitone

- Pharmcodynamics
  - Enhances phasic GABA - a receptor responses and reduces excitatory synaptic responses
- Uses - generalised tonic clonic seizures, partial and myoclonic seizures
- Pharmacokinetics - nearly complete absorption, NOT significantly plasma protein bound
  - peak concentrations 0.5 - 4 hours
  - no active metabolites
  - half life varies form 75 - 125 hours
- Toxicity
  - sedation, ataxia, hyperactivity in children

Lamotrigine

- Prolongs inactivation of Na channels
- Acts of presynaptic Ca channels and decreases glutamate release
- No significiant protein binding
- Half life - 25 - 35 hours
- No active metabolites
- Used in generalised, partial and absence seizures