CNS, Anaesthetics, Analgesia VIVAs (Pharmacology)

shakEM

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2015.1A

Question 2 Local Anaesthetics **Subject:** Pharm LOA: 1	Describe the mechanism of action of lignocaine? What factor affect systemic absorption after local infiltration What are the toxic effects of Lignocaine	Na channel blocker, Class 1B. **Blocks** (activated & inactivated) **Na channels = Blocks nerve conduction**. Less effect in infected tissue Dose/ Site of injection/ Drug tissue binding/ Tissue blood flow/ Vaso constrictors (combine preparation) **CNS -** Early: **tongue/oral numbness/metallic taste**, parathesia, sedation. Moderate: nystagmus, muscle twitching, N&V, Tinnitus, visual disturbance Severe: **Seizures**, sedation **CVS- Cardiovascular collapse** Hypotension, bradycardia, rarely arrhythmia, worsen CCF or conduction blocks GIT Anorexia, N&V (thru CNS effects)	Bold 3 of 5 Bold

2015.1B

Question 3 Propofol **Subject:** Pharm LOA: 1	Q1. Please outline the pharmakokinetics of propofol	IV administration only, **Distribution half life 2 - 4 minutes**, **Elimination half life 4 -23 minutes,** Duration of action 3 - 8 minutes - **Rapid onset and recovery due to redistribution of drug** from brain to skeletal muscle and then fat (rather than metabolism), Rapidly metabolised in the liver but as total body plasma clearance > hepatic flow, likely some extrahepatic mechanism (mostly lung), Excretion in the urine as glucuronides and sulphates < 1% unchanged	**Bold, reasonable understanding of redistribution of drug**
	Q2. What dose of propofol is used for induction of general anaesthesia? How does this differ from a procedural sedation dose?	PROCEDURAL SEDATION DOSE: 0.5 - 1.0 mg/kg single bolus dose or titrate in 10 - 20 mg aliquots particularly in conjunction with morphine, INDUCTION DOSE: **1 - 2.5mg/kg (adults)** and 2.5-3.5mg/kg in kids	**Bold**
	Q3. What clinical effects should be anticipated when using propofol?	anaesthesia/sedation, respiratory depression, transient **apnoea**, **hypotension** through vaso and venodilation, no analgesic properties, potential allergic reaction (soy, eggs), pain at injection site, metabolic acidosis when given as an infusion, antiemetic properties	**Bold + 2 more**
	Q4. How can you limit adverse effects when administering propofol?	smaller total doses, titrated doses, no opiates or benzodiazepines given simultaneously, IV fluid bolus, caution in the elderly and in those with poor cardiovascular reserve	**2**

2015.1B

Question 2 Lithium **Subject:** Pharm LOA: 1	Q1. What are the adverse and/or toxic effects of lithium?	Neuro - tremor, choreoathetosis, **ataxia,** dysarthria, hyperactivity, **confusion,** withdrawal. Thyroid - reversible **hypothyroidism.** Renal - **polyuria, polydipsia** (nephrogenic diabetes insipidus), chronic interstitial nephritis, nephrotic syndrome. Cardiovascular - oedema, worsening of sick sinus syndrome	**At least 3 bold**
	Q2. Describe the pharmacokinetics of lithium	**Oral absorption** (peak 0.5-2 h but complete 6-8 h). **Distributes in TBW. Excreted unchanged in urine.** Plasma half-life 20 h. Therapeutic concentration 0.6-1.4 mmol/L	**Bold, plus some appreciation of longer half-life.**
	Q3. How can you assess lithium toxicity and how do you treat it?	**Measure levels** (should be 10-12 h after last dose) >2 mmol/L should be considered toxic. Treatment is supportive and haemodialysis (Prompt that Li is an ion).	**Bold, plus some concept that levels should be measured well after last dose.**

2015.1C

Question 1 Benztropine Subject: Pharm LOA: 1	How does metoclopramide cause a dystonic reaction? You treat the dystonic reaction with benztropine. What is its mechanism of action? What are the potential side effects of benztropine?	Metoclopramide is a **dopamine antagonist** and causes an imbalance in the anticholinergic/ dopamine transmission in the basal ganglia. **Blocks the** muscarinic **cholinergic receptors**; an antimuscarinic agent. Tachycardia, sedation, mydriasis, urinary retention, dry mouth	Bold Bold **Knows 3**

2015.1D

Question 1 Ketamine (pp 444-445) **Subject:** Pharm LOA: 1	1. What is the mechanism of action of ketamine? 2. What are its clinical effects? 3. What are its adverse effects? [Prompt- Are there any airway concerns?] 4. Give an appropriate route and dose for procedural sedation in this child? [What other routes are available?]	**Antagonism of NMDA (**subtype of glutamate) **receptors**. Inhibits reuptake of catecholamines and serotonin **Dissociative anaesthetics**. Profound analgesia, stimulate sympathetic nervous system, bronchodilatation, minimal respiratory depression, stable CVS. increased Cerebral bd flow, partial amnesia, nystagmus **Unpleasant emergence reaction (**eg vivid dreams or hallucination)**, laryngospasm**, increased salivation, vomiting, myoclonus **1-2 mg/kg IV, 4-10 mg/kg IMI**	Bold Bold +2 Bold Can state either IV or IM dose

2015.1D

Question 4 Phenytoin Subject: Pharm LOA: 1	1. What is the mechanism of action of phenytoin? 2. What are the risks associated with intravenous phenytoin administration? 3. Describe the elimination kinetics of phenytoin and why it is important clinically? 4. What are the common features of acute overdose/intoxication with phenytoin?	Primarily **Na+ channel blockade/reduced neuronal Na+ conductance** and prolongation of inactivated state of Na+ channel. Reduces Ca++ influx into cells and decreases glutamate release and enhances GABA release. Inhibit the generation of rapidly repetitive action potentials **Hypotension and bradycardia with rapid infusion** (due to diluent). Allergic reactions. Limit rate of infusion to maximum 50mg/min (30-60 minutes). Less likely with fosphenytoin.. Local necrosis if extravasation **Dose-dependent elimination.** First order elimination at low serum concentrations, however elimination **becomes zero-order as concentration rises** with prolongation of elimination half-life. Implication- Small recurrent dose increase may => toxicity Sedation, coma, nystagmus, ataxia, cerebellar toxicity. No cardiac toxicity with ingested overdoses of phenytoin.	Bold Bold to pass. Explains concepts 2 to pass

2014.2C

Question 4 Olanzapine & atypical antipsychotics (Chp 29) **Subject:** Pharm LOA: 2	1. By what routes can Olanzapine be administered? 2. What dose, and route would you use in this situation? 3. What are the advantages of olanzapine over older "typical" antipsychotics? Prompt: e.g. chlorpromazine 4. What are some of its disadvantages? Prompt if needed – what about longer term effects	**1. Oral** (Tab or wafer); **Parenteral-** IMI, Depot IMI 2. Gives dose (10-20mg), same for each route 3. less hypotension; less tachycardia; **less extrapyramidal effect**; high clinical potency; less effect on prolactin; more effective vs neg&pos psychotic symptoms and cognition; multiple routes of admin 4. Anticholinergic effects; lowered seizure threshold; weight gain; DM; Hyperlipidaemia; expense	**Bold** **Reasonable answer** **Bold** **2 disadvantages**

2014.2C

Question 2 Haloperidol (pp 503-513) **Subject:** Pharm LOA: 2	What are the pharmacodynamics of haloperidol?	Butyrophenone- **high potency D2 receptor effects (dopamine antagonist), high extra-pyramidal side effects, low sedative**, low hypotensive, minimal anticholinergic effects, minimal 5-HT and H1 blockade effects.	**2/3 Bold**
	How does olanzapine differ?	Thienobenzodiazepine- less D2 receptor effects, **high 5-HT receptor blockade effects, low extrapyramidal effects, medium sedative**, low hypotensive and anticholinergic effects, low H1 blockade effects	**2/3 Bold**

2014.2D

Question 1 Oxycodone (p 558) **Subject:** Pharm LOA: 1-2	Describe the pharmacokinetics of oxycodone? Prompt: Describe the pharmacokinetics of opiates. What adverse effects might you anticipate? When prescribing oxycodone what prescribing strategies may help in reducing the development of, dependence.	**Oral commonly** Good oral absorption High Vd **Low first pass metabolism CW others** 10 morphine = 4.5mg oxycodone duration 3-4h, longer if CR formulation. Hepatic met Sedation/Respiratory depression/N+V/hypotension/dysphoria/biliary colic/pruritis/caution in renal failure **Smaller doses at longer intervals**/establish goals at start of Rx/**limit doses/use of other analgesics**/frequent evaluation of ongoing need/**use of modified CR formulations**	Bold plus one more N+V a particular concern in context of penetrating eye injury 3 to pass 2 to pass

2014.2D

Question 1 Tricyclics including Volume of distribution (Chp 30) **Subject:** Pharm LOA: 1	Which factors determine the volume of distribution of a drug? Describe the volume of distribution of tricyclic antidepressants How does this influence their toxicity? What therapies for tricyclic toxicity might reduce their tissue distribution?	**Drug factors**; lipid solubility (high in TCA), pKa, pH, protein binding (high in TCA). **Patient factors**; age, gender, comorbid disease (eg. Oedema or ascites), body fat, blood flow to tissues. TCAs have a **large Vd** (5-30L/kg), tissue **concentrations are high** especially in well perfused organs such as **the brain and heart.** **Alkalinisation** (Bicarbonate or hyperventilation) increases **plasma protein binding of the free drug** removing it from the tissues reducing its tox	At least 2 from each group bold bold

2014.1A

Question 4 Bupivicaine **Subject:** Pharm LOA: 1	1. What is the mechanism of action of bupivacaine? 2. How long will a bupivacaine block last? 3. What are the potential adverse effects from bupivacaine? 4. How can the risk of these effects be minimised in the ED?	1. **Blocks** voltage-gated **sodium channels in nerve.** Threshold for excitation increases, conduction slows, AP rise declines, AP generation abolished. If Na current blocked over length of nerve, propagation is ceased. 2. **3-6 hours** 3. **CNS toxicity** (sedation/light headedness/visual&auditory/tongue&mouth numbness/metallic taste/nystagmus/restlessness/ muscle twitches/seizure/resp depression), **Cardiac toxicity** (arrhythmias/cardiovascular collapse/cardiac arrest), Local toxicity (trauma/neurotoxicity) Allergy 4. Ask re Hx of allergy, Use safe max dose (<2mg/kg), withdraw pre injection, avoid vessels-anatomical consideration (above rib below) & use USS. Ask pt to flag Sx e.g. taste/tongue numb. Avoid hypoxia/acidosis.	Bold Approximate or long duration Bold Extra

2014.1B

Question 3 Morphine (Katzung 12th edition pp543-556) – pharmacokinetics; pharmacodynamics – in particular, receptors bound to; adverse reactions **Subject:** Pharm LOA: 1	1. What is its mechanism of action? 2. How is morphine metabolised and excreted? 3. What are the possible acute adverse reactions with morphine? Prompt: why are we more cautious in using morphine in renal failure patients?	**1.**Brain and Spinal cord **receptors: mu, delta, kappa.** (Subtypes: 2 mu and delta, 3 kappa). Binding to receptor (particularly mu) >> **reduction of neurotransmitter release from presynaptic nerve terminals** (especially glutamate), and **inhibit postsynaptic neurons** (by opening K channels).Central thalamic action and activation of descending inhibitory pain neurons. **2.** Mostly liver conjugated to morphine-3-glucuronide which has neuroexcitatory properties. 10% is metabolised to morphine-6-glucuronide with 4-6x increased analgesic potency. Excreted renally. **3. Sedation/ resp depression, nausea and vomiting**, hypotension if predisposed, histamine release, dysphoria, biliary colic, pruritis, allergy. In renal failure it can cause seizures, or prolonged analgesia.	Must name mu and 1 other types of receptors, and the 2 bold actions. Liver metabolism & metabolites are renally excreted Bold and 2 more.

2014.1B

Question 3 Valproate **Subject:** Pharm LOA: 1	1.What are the possible pharmacodynamic mechanisms of Na Valproate? Prompt: what ion channels/ neurotransmitters are most likely involved? 2.What are the adverse effects?	**GABA** increased presynaptically by reduced GABA breakdown to succinate (ABAT/ GAT1), (> Cl- inh post synaptic GABR channel)/ possible increased production (GAD) Direct inh actions on post synaptic **Na Channel** particularly high freq gates and Ca+ (membrane stabilisation-reduces voltage gated outflow), Blocked NMDA receptor activation effects? Nausea/vomiting/ GI (v common); **Severe hepatotoxicity**- liver failure (> young/ other hep tox drugs/ liver damaged); Marked fetal abnormality rates (8-9%)/ reduced IQ + other possible developmental effects; Thrombocytopaenia/ bruising; Pancreatitis; alopecia, neuro (asthenia, tremor, nystagmus etc); Hypersensitivity reactions	Bold Bold and 1 other

2014.1D

Question 1 Potency & efficacy with reference to morphine / fentanyl **Subject:** Pharm LOA: 1	(a) What is drug potency? (b) Draw and explain dose-response curves comparing morphine with fentanyl. (c) What are the pharmacokinetics of fentanyl?	(a) **Dose or concentration to achieve 50% maximal effect** (EC_{50} or ED_{50}) (b) **Must graph dose or log dose (X axis) versus response (Y axis).** (c) Highly lipid soluble, Half-life 5 mins, duration 1-1.5 h, low bioavailability, hepatic metabolism	(a) Bold to pass (b) Display differences and explain on graph (c) 3 of 5 to pass

2013.2A

Pharmacology Suxamethonium MOA, adverse effects	What is suxamethonium	**depolarising muscle relaxant** producing rapid neuromuscular blockade at **motor endplate nicotinic receptors.** Structurally two acetylcholine molecules linked end to end	Pass = bold
	Describe the mechanism of action of suxamethonium	**Phase I (depolarizing)** binds to nicotinic receptor; **opens channel** and causes **depolarisation of motor end plate**; spreads to adjacent membranes causing contractions of muscle motor units (fasciculations); **depolarised membranes remain depolarised (& unresponsive to subsequent impulses)** causing flaccid paralysis Phase 2 (desensitising) With continued exposure, the initial end plate depolarisation decreases & membrane becomes repolarised; membrane cannot be depolarised again as it is *desensitised* (mechanism unclear however ? due to channel block becoming more important than agonist action at receptor)	Pass = bold
	What are the important adverse effects of suxamethonium?	**hyperkalaemia** (eg burns, trauma patient); cardiac arrhythmias (eg if given with halothane) / **bradycardia** (repeat doses); increased IOP; increased intragastric pressure; muscle pain (likely related to fasciculation); malignant hyperthermia, prolonged paralysis	Pass 2 bold + 2 others

2013.2C

Question 2 **PHARMACOLOGY PROPOFOL** LOA: 1 (Katzung 12th ed p 438-440)	1. Describe the pharmacokinetics of propofol.	**1. Distribution half life 2-4 minutes** **Elimination half life 4-23 minutes** **Rapid onset and recovery**. Termination of drug effect due to **redistribution** from brain to sk muscle and then fat (rather than metabolism). Duration of action 3-8min Rapidly metabolised in liver and extrahepatic sites (lungs). Water soluble metabolites excreted in urine.	**Bold**
	2. What is the usual induction dose of propofol?	**2. 1-2.5mg/kg adults,** 2.5-3.5mg/kg in kids	**Bold**
	3. What clinical effects are expected after this dose of propofol is administered.	**3. Anaesthesia / Sedation**. Respiratory depression. Transient **apnoea. Decreased blood pressure** through vaso and venodilation (most pronounced of induction drugs). Does NOT have analgesic properties Anti-emesis, Metabolic acidosis, Pain at injection site	**Bold**
	4. List some drug interactions of propofol important in the setting of sedation/anaesthesia	**4.** Opioids – enhance respiratory depression Benzodiazepines - enhanced sedation and respiratory depression	**1 of 2**

2013.1.1

Question 4 **KETAMINE** LOA: 1	What are the indications for ketamine	**Induction agent, procedural sedation, analgesia**	**2 of bolded**
	What are the routes of administration?	**IV, IM,** IN, epidural, PO, PR, SC	**IV, IM + 1 other**
	What is the IV dose used for induction of general anaesthesia?	**1-2 mg/kg**	**Bolded**
	Name some of the adverse effects.	**Hypersalivation, larygospasm(peds), vomiting(recovery phase), emergence reactions, Hypertension, tachycardia, raised ICP**	**Emergence reactions + 2 other**

2013.1.2

Question 4 **MIDAZOLAM** LOA: 1	What are the clinical indications for the use of midazolam?	Anxiolysis**, sedation, anticonvulsant,** antiemetic	**Bold to pass**
	What are the advantages and disadvantages of the various routes of administration?	PO, IV, IM, PR, IN, Buccal	**Reasonable discussion of IV + 1 other**
	What are the adverse effects?	**Excess sedation, respiratory depression,** decreased motor skills, impaired judgment, hypotension + occasionally rashes	**Bold to pass**

2013.1.3

Question 4 PROPOFOL LOA: 1	What are the indications for the use of Propofol?	**Induction agent, maintenance of anaesthesia procedural sedation**	**2 bold to pass**
	What properties of Propofol make it suitable for procedural sedation?	**Rapid onset and offset**	
	What are adverse effects of Propofol?	Localised pain with bolus administration. Dose related **depression of respiratory drive** (central effect) and apnoea. Muscle movements, hypotonus and rarely tremor. **Hypotension** (reduced arterial resistance venodilation and negative inotropism).	**Bold to pass**

2013.1.3

Question 5 **NALOXONE** LOA: 2	What is the mechanism of action of Naloxone?	Pure **opioid antagonist** binds to μ-opioid binding sites.	**Bold to pass**
	What is the time to onset and duration of action when administered intravenously?	**Rapid onset 1-3 minutes** **Duration 1-2 hours**	**Bold to pass**
	What problems may be associated with naloxone administration?	**Opioid withdrawal** **Resedation**	**Bold to pass**
	How can these problems be minimised or avoided?	**Smaller/titrated doses** Infusion Route of administration	**Bold to pass**

2012.1.1

Question 3 LOA: 1 **LITHIUM**	Describe the pharmacokinetics of Lithium	**Absorption; rapid and near complete**. peak levels in 30-120min **Distribution; total body water** Vol.D 0.5 to 0.9L/kg Slow distribution Metabolism; none T ½; @20 hours. **Elimination; renal excretion**	
	What are some of the drug interactions with lithium	**Thiazide diuretics**- 25% reduction in lithium clearance Newer NSAID's **–** similar reductions in clearance Neuroleptics (except clozapine) and antipsychotics- enhancement of extrapyramidal syndromes	
	What are the some side effects of lithium *Prompt: What other organ systems effects are there?*	**Neurological;** tremor, confusion, ataxia, dysarthria, new psychiatric symptoms Reduced thyroid function Nephrogenic diabetes insipidis **–** loss of responsiveness to ADH. Oedema Skin reactions; acneiform eruptions	2 neurologic symptoms

2012.1.1

QUESTION 5 LOA: 1 **DRUGS IN AGITATED PATIENTS**	List the drug classes which are used in management of acute agitation in the ED *Prompt: Can you give some specific examples?* What is the predominant mechanism of action of the atypical antipsychotics. Describe adverse effects of the atypical antipsychotics	**Benzodiazepenes** **Antipsychotics – Phenothiazines** eg chlorpromazine **Butyrophenones** eg haloperiodol **Atypicals** eg olanzapine , risperadone Barbiturates **–** phenobarbital **Serotonin** ($5HT_{2A}$) **receptor antagonism** Dopamine (D2) receptor antagonism (weaker effect) **Extrapyramidal reactions** - **–** less common than with older typical antipsychotics Tardive dyskinesia **Antimuscarinic effects –** dry mouth, urinary retention etc **Orthostatic hypotension** Weight gain Hyperglycemia Hyperprolactinemia Agranulocytosis (clozapine) Neuroleptic malignant syndrome	

2012.1.2

Question 3 LOA: 1 **CARBAMAZEPINE**	Outline the clinical uses of carbamazepine Describe the mechanism of its anticonvulsant activity Outline some of the side effects of carbamazepine *Prompt: What other organ systems can it effect?* **Optional**: Can you name some drug interactions involving carbamazepine	**Anticonvulsant;** partial and generalised tonic-clonic seizures Treatment of bipolar mood disorder Trigeminal neuralgia **Blocks sodium channels** Inhibits high-frequency repetitive firing of neurons Presynaptic blocker of synaptic transmission (similar to phenytoin) **Ataxia** and diplopia, **drowsiness** (dose related CNS) **GI upsets** and hepatic dysfunction Erythematous **skin rash** Hyponatraemia and water intoxication Blood dyscrasias, including leukopenia common), and rarely aplastic anaemia and agranulocytosis. **Enzyme induction** (all anticonvulsants including itself). Valproic acid + phenytoin may inhibit carbamazepine elimination	Anticonvulsant + 1 other use CNS + one other

2012.1.2

Question 5 LOA: 1 **DRUGS IN PROCEDURAL SEDATION**	List the classes of drugs used in emergency department procedural sedation *Prompt: for classes*	**Benzodiazepenes** **Dissociative anaesthetics (** ketamine**)** **Intravenous anaesthetics (** propofol**)** **Inhaled anaesthetics** (N2O ; volatile**)** **Opiates (** morphine**,** fentanyl)	**4 out of 5**
	Describe the elimination pharmacokinetics of propofol *Prompt: Why do patients wake up quickly?*	**Hepatic metabolism** producing inactive watersoluble compounds , excreted renally High plasma clearance exceeding hepatic clearance – thus extrahepatic clearance exists – probably via lungs. Termination of effect by **redistribution** from brain to skeletal muscle (waking after single induction dose at 8-10 mins) "Three compartment model" Short "half – life" making it suitable for infusions – rapid offset.	
	Describe the organ effects of propofol	**CNS: sedative/hypnotic – general depression of CNS activity**, reduced cerebral blood flow and reduction in ICP. Anti convulsant properties.Nil analgesic effect **Cardiovascular effects: hypotension secondary to arterial and venous vasodilatation** (reduced preload and afterload) – incr. effect with age and reduced intravascular volume. Some inhibition of baroreceptor reflex leading to small increase in heart rate response only **Respiratory effects: respiratory depression incl apnoea.** Reduction in tidal volume and rate Reduced response to hypercapnoea and hypoxia Reduction in upper airway reflexes. Other: Antiemetic	**One from CNS, CVS + Respiratory**
	Describe adverse effects of propofol	Effects related to organ system effects • Hypotension • Apnoea, respiratory depression • Loss of airway reflexes – obstruction and aspiration • Pain with injection Allergy – cross reactivity with egg allergy (emulsion) Propofol infusion syndrome (metabolic acidosis & tachycardia)	

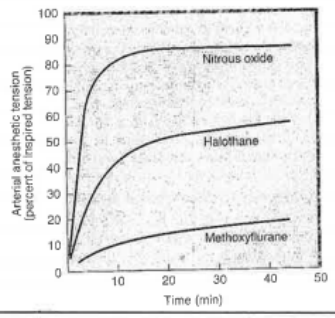
2012.2.1

Question 3 Non Depolarising Muscle Relaxants LOA: 1	What's the mechanism of action of Rocuronium? (Prompt: receptor level)	**Non-depolarising NM blocker**. In low doses it predominantly acts as a **competitive inhibitor of Acetylcholine** at nicotinic receptors. In larger doses it can enter the pore of the ion channel -> greater NM blockade. It can also block prejunctional sodium channels-> interference with the mobilisation of AChl at nerve endings.	Non-depolarising NM blocker. Initially acts as competitive inhibitor for Ach at nicotinic receptors
	Describe the pharmacokinetics of rocuronium. *Prompt: Describe rocuronium's distribution and elimination.*	Undergoes **rapid distribution.** Highly ionized - so small Vd (80-140ml/kg). Undergoes hepatic metabolism (75-90%) and renal excretion. Duration of action is 20-35mins.	Rapid distribution. **Short T1/2.**

2012.2.2

Question 2	Describe the central nervous effects of	1) central	**Bold to pass**
Morphine LOA: 1	Morphine	• **analgesia** • euphoria • **sedation** • **respiratory depression** • cough suppression • miosis • truncal rigidity • nausea / vomiting • temperature	candidate should be able To describe in detail of each one in bold
	Describe peripheral effects?	2) peripheral: • **cardiovascular** • GI- **constipation** • Biliary • Renal • Uterus • Neuroendocrine • Pruritis • immune	

2012.2.2

Question 3 Nitrous oxide	Explain the solubility characteristics of nitrous oxide	Nitrous oxide possesses **low solubility** in the blood, reaches **high arterial tension rapidly, Rapid equilibrium in the brain** and **fast onset of**	**Bolded concept to pass**
LOA: 1	Draw the arterial anaesthetic tension vs time for nitrous oxide vs halothane or Methoxyflurane	**action (rapid onset-rapid recovery)** 	A curve

2012.2.2

Question 5 Serotonin Syndrome LOA: 2	Describe the mechanism by which Serotonin Syndrome occurs. *Prompt: What receptors are involved in SS?* How do drugs cause excessive stimulation of serotonin receptors? *Prompt: Can you give an example*	**Excessive stimulation of serotonin receptors in the CNS** due to overdose of single drug or concurrent use of several drugs. Predictable, not idiosyncratic. Inhibition of serotonin metabolism: meclobemide, amphetamines Prevention of serotonin reuptake in nerve terminals: fluoxetine, paroxetine, sertraline, venlafaxine, tramadol, TCA Serotonin release or increased intake of serotonin precursors: tryptophan, lithium,	Must get bold items Must identify at least 1 mechanisms with corresponding example

2012.2.3

Question 3 Phenothiazines LOA 2	What are the side effects of chlorpromazine? (If required: What are the mechanisms of these side effects?)	**Hypotension – alpha blockade** Parkinson's, akthesia, **dystonic reactions – D2** Lactation – D2 Sedation – antihistamine Neuroleptic malignant syndrome – dopamine Confusion, tachycardia – anti muscarinic	Two bolded side effect any dyskinesia sufficient) and one correct mechanism.
	How do the newer atypical anti psychotic agents differ from chlorpromazine?	Newer agents have less side effects.	

2012.2.3

Question 5 Seizure medications	Describe the pharmacokinetics of sodium valproate	Well absorbed PO, bioavailability >80% Food may delay abs for several hours. Peak plasma levels 2 hrs if empty stomach 90% **protein bound** (fraction bound reduces as	Highly protein bound and small Vd to pass
LOA: 1		total dose increases). Highly ionized and highly protein bound, therefore **Small VD**, essentially confined to extracellular water, approx. 0.15L/kg 95% hepatic metabolism, (some to active metabolites), 5% unchanged in urine Clearance is low and dose dependent, T1/2 is approx. 15/24 (9-18) and reduced if taking other antiepileptic drugs	
	Describe the toxic effects of sodium valproate.	Mild : Transient GI inc anorexia, nausea and vomiting. Rash, alopecia and increased appetite. Weight gain. Major Overdose: **CNS:** coma, cerebral oedema (potentially fatal) Bone marrow depression Metabolic effects: hyperNa, hypoCa, hyperammonaemia CVS, renal effects Severe and idiosyncratic 1. Hepatotoxicity – rarely fatal, usually in under 2 yo, or multiple meds. Elevation of LFTs in 40%. May be reversible 2. Thrombocytopaenia	CNS to pass

2011.1.1

Thiopentone	Describe the distribution of thiopentone following an IV bolus	To highly vascular tissue and rapidly crosses BBB. **High lipid solubility**. Then **rapidly redistributed** to body fat.	Bold
	What are the potential adverse effects of thiopentone? Prompts: What are the CNS effects? What are the CVS effects	Advantages: Rapid, Controllable, Amnesic, **Reduction of ICP**, anticonvulsant Disadvantages: **Hypotension,** Venous irritant, Myocardial depression, minimal muscle relaxation and analgesia, hepatic metabolism (vs inhalational agents)	Bold

2011.1.2

Lignocaine	Describe the mechanism of action of lignocaine on the heart.	Blocks activated & inactivated Na channels; greater effect on ischaemic tissue; no vagal effects. Class 1 B antiarraythmic action.	Na channel block and Class 1B
	Describe the adverse effects of lignocaine	CNS: dizzy, anorexia, N&V, tinnitus, tremor, visual disturbance, paraesthesia, slurred speech seizure, resp depression CVS: bradycardia, CVS collapse, uncommon proarrhythmia; can get SA arrest, impaired conduction may worsen/ precipitate pre existing CCF; ↓BP from myocardial depression Allergy GI as above	CNS & Cardiac with at least x 3 example total

2011.1.2

Anti-migraine medication	What drugs can be used in the treatment of an acute attack of migraine?	**simple analgesia** (eg paracetamol, aspirin, codeine); **metoclopramide**, **prochlorperazine**; ergot alkaloids eg ergotamine (+/- caffeine added); **chlorpromazine**; **triptans** eg sumatriptan (opoids can be used but not choice)	**3 bold**
	How do triptans work?	structural analogue of 5-HT; **selective agonists at 5-HT1 receptors; cause vasoconstriction, particularly on cerebral arteries**	**2 bold**
	Chlorpromazine can be used to treat acute migraine. What are the major side effects of chlorpromazine?	**hypotension; sedation; anticholinergic** (dry mouth, dry eyes, urinary retention, constipation); **extrapyramidal (eg acute dystonia)**; pain with IM injections, risk of muscle necrosis	**2 bold**

2011.1.3

Antipsychotic side effects and their treatment	What are the major side effects of phenothiazine antipsychotics?	**Anti-cholinergic:** dry mouth, dry eyes, urinary retention, constipation; Sedation; Weight gain; **Extra-pyramidal:** dystonia, Parkinson-like effects, akathisia, tardive dyskinesia; Hypotension; Neuroleptic malignant syndrome	Bold with 1 example of category
	What mechanisms of drug action are responsible for these side effects? Prompt: What receptors are involved?	Anti-muscarinic; Alpha blockade; D2 antagonism; Serotonin receptor antagonism; Anti-histamine (H1)	At least 3
	How could the extra-pyramidal side effects be managed? Prompt: What about acute EP side effects? Prompt if time for additional marks: What about chronic EP side effects	Lower dose; Switch to an atypical drug (lower incidence of extra-pyramidal effects); Administer **benztropine** or diazepam; No effective treatment for tardive dyskinesia: prevention vital; monitor for early signs and reduce or cease anti-psychotic asap	Bold

2011.2.1

Question 2: Valproate	a) What are the proposed mechanisms of action of valproate?	a)**Blocks Na channels** thereby blocking sustained high frequency firing of neurones. Blockade of NMDA receptor mediated excitation. Increase GABA levels	Bolded
	b) Describe the toxic effects of valproate?	b) **Hepatotoxicity**, Mostly within 4 months of initiation of treatment, Treat with intravenous L-carnitine. GI, tremor, weight gain, appetite, sedation, allergy Malformations in pregnancy	Bold +1 to pass
	c) What interactions does valproate have with other anti-seizure drugs?	*c) Phenytoin inhibits metabolism and displaces from plasma proteins* *Phenobarbitore & carbamazapine inhib metab* *Lamotrigine decreases clearance*	Supplementary

2011.2.1

Question 4 Local anaesthetics	a) What classes of local anaesthetics are used in the ED? *(Prompt for examples)* b) What factors affect the systemic absorption of lignocaine after local infiltration? c) What are the toxic effects of lignocaine?	**a)Amides**: lignocaine, prilocaine, bupivacaine, ropivicaine **Esters**: cocaine, benzocaine, procaine, tetracaine **b)** Absorption: **dose**, site of injection, drug-tissue binding, tissue blood-flow, vasoconstrictors, **c)** **CNS**: All can get: sleepiness, light-headed, visual, auditory disturbance, restlessness Early tox: circumoral/tongue numbness, metallic taste **Serious/higher**: Twitching, nystagmus, **seizures** Direct neurotoxicity – radicular irritation with spinals **CVS**: Na channel (depress abnormal pacemaker, excitability, conduction) v Ca channel effects at high doses – decrease myocardial contractility, arteriolar dilatation, hypotension, with bupivicaine can get idioventricular rhythm, broad QRS, EMD Haem: methaemoglobinemia Allergy: rare with amides as not metab'd to PABA	1 of each Bold + 1 CNS: seizures and 1 other CVS: arrhythmia

2011.2.2

Question 3 Benzodiazepines	a)What benzodiazepines are commonly used in the ED? b)What is the mechanism of action of benzodiazepines? (Prompt: describe how they interact with receptors) c) What are the clinical effects of benzodiazepines?	a)Diazepam, lorazepam, midazolam, clonazepam, temazepam, **b)** Agonist **at GABA $_A$ receptor** which is chloride ion channel binding between alpha1 & gamma2 subunit (BZ site) – more selective than barbs. Low affinity for $GABA_B$. GABA inhibition enhanced. **c) Sedation**, hypnosis, **anticonvulsant**, muscle relaxation, **resp depression** (esp if resp disease), CVS depression, decreased contractility, decr vasomotor tone (esp if CVS disease)	>= 2 Bolded Bolded

2011.2.2

Question 5 Addiction & drugs used in opiate addiction	a) Name some drugs that are used in the treatment of opiate addiction b) Outline the principles of how these agents work	**a) Methadone**, N acetylmethadol, buprenorphine clonidine, lofexidine, Naltrexone, naloxone ***b) Methadone*** **–**longer acting, opiate angonist, orally active **–**patient can be stabilised and gradually withdrawn but addictive also. *N acetylmethadol* **–**an even longer acting methadone analogue. *Buprenorphine* **–**partial opiod antagonist that can be given once daily, low doses for detoxification and higher doses for maintenance. *Clonidine* **–**central acting sympatholytic agent that mitigates signs of withdrawal sympathetic Overactivity. *Lofexidine* **–**clonidine analogue with less hypotensive effects *Naltrexone*-long acting orally active pure opiod antagonist, patients must be detoxified first Naloxone – rapid onset pure antagonist, short half-life, precipitate withdrawal	Must get methadone and 1 other Must get methadone principles and state that overall agents must be orally active and long acting. 1 other agents PD also.

2011.2.3

Question 3 Tri-cyclic anti-depressants	a)What are the pharmacokinetics of tricyclic anti-depressants? b) What are the toxic effects of tricyclics in overdose? *c)What drugs could be used in the treatment of tricyclic toxicity in overdose?*	a) Oral, well-absorbed, bioavail 40-50%, **long half-time**, high first pass metabolism, high tissue protein binding, high lipid solubility, **large VOD,** metabolised in liver, active metabolites **b)Sedation**- plus drug interactions, sympathomimetic tremor, insomnia, **antimuscarinic**- blurred vision, constipation, urinary, confusion, tachycardia cardiovascular- alpha-blocker, Na channel blocker, orthostatic **hypotension**, **arrhythmias**, psychiatric- psychosis, agitation, withdrawal **seizures**, weight gain *c)* *Supportive- dopamine/NA for hypotension* *Quinindine like cardiac toxicity- sodium bicarb 50-100 mEq IV, Intralipid*	Bold Bolded *supplementary*

2010.1.3

Question 2: Drugs in status epilepticus P374-92	1. Describe how phenytoin is administered in status epilepticus? *What's the mg/kg dose?* 2. Describe the adverse effects of phenytoin ? *What about short term vs long term effects?* *What about in iv administration?*	IV load 13-20mg/kg,, given diluted in saline (precipitates in glucose at max rate in adults of 50mg/min Continued 100mg Q6-8hrly Dose related nystagmus, ataxia, diplopia long term: gingival hypertrophy, hirsuitism mild facial coarsening & peripheral neuropathy abnormal Vit D levels (osteomalacia) low folate levels; megaloblastic anaemia; Foetal hydantoin syndrome. Idiosyncratic: skin rash; SJ syndrome; Lymphadenopathy; agranulocytosis. Rapid iv may cause hypotension/arrhythmia Drug interactions; reduced CL & binding in neonates	Dose mg/kg, iv route safe rate CNS + skin + CVS in iv admin

2010.1.3

Question 3: Morphine P489-98	1. Describe the effect of morphine on the different opiod receptors? 2. Describe the effects of morphine on different organ systems?	Morphine is a full agonist in the μ (mu) receptor→ analgesia, sedation, ↓respirations, ↓ GIT transit, modulation of hormone and neurotransmitter release ; also affects σ (delta) → analgesia, modulation of hormone and neurotransmitter release and Ќ (kappa)→analgesia, psychomimetic effects,↓ GIT transit CNS: Analgesia, euphoria, sedation, respiratory depression; miosis, hyperthermia, -stimulates release of ADH, prolactin and somatotrophin, -truncal rigidity, Resp: depression, Cough suppression, CVS: bradycardia GIT: constipation, contracting biliary smooth muscle, N&V, Renal: Depressed renal function Gynae: Decreases uterine tone Skin: Pruritis, urticaria	Agonist mu receptor + 1 receptor CNS + resp + 2 others

2010.2.1

3. a. What is pancuronium?	**Non-depolarising NM blocker** Quaternary ammonium compound Potent competitive antagonist of ACh at nicotinic receptors skeletal muscle motor end-plate Interruption of transmission requires > 70% occupancy; blockade requires > 95% occupancy	Nondepolarising NM blocker
b. Describe the pharmacokinetics of pancuronium?	Poorly absorbed after oral admin Rapidly and widely distributed after iv Rapid elimination ($T1_{/2}$ 30min) by urinary excretion unchanged drug (highly water soluble), and hepatic metabolism with biliary excretion **[Prompt: Describe its distribution and elimination]**	Rapid distribution Rapid elimination
c. What are the adverse effects of pancuronium?	Uncommon Minor tachycardia, hypertension, sl ↑ CO can occur Life-threatening anaphylaxis < 1:10,000	A cardiac and allergy effect

2010.2.1

4. a. Describe the pharmacokinetics of lithium	Rapidly absorbed (except SR preparations) with peak plasma concs in 1-3hrs. High bioavailability. Not metabolised Renally excreted unchanged with partial reabsorption from PT. Long T ½ of 24hrs in adults Steady state plasma concs not reached for 5-7 days **(PROMPT – How long does it take to reach steady state plasma conc?)**	Long T ½ so steady state plasma concs not reached for days. Renally excreted unchanged.
b. What are the adverse effects of Lithium at therapeutic levels?	Tremor, nausea, polydypsia /polyuria, diarrhoea, weight gain. Long-term: Acne / psoriasis, hypothyroidism, nephrogenic diabetes insipidus (inhibits the effect of ADH on the DT cells -> polyuria).	Polyuria & Polydipsia OR NDI.
c. What are the signs/symptoms of lithium toxicity?	GIT: Vomiting. Neuro: Tremors, confusion, slurred speech, ataxia, drowsiness, blurred vision, seizures.	CNS effects with at least 3 symptoms

2010.2.2

4. a. Describe the pharmacokinetics of phenytoin.	Oral absorption slow and variable: Time to peak levels 1.5-3hrs. Saturable hepatic metabolism leading to non-linear PK and variable T ½ of 7-42hrs. Metabolites excreted in the bile & urine.	Saturable metabolism/non-linear pharmacokinetics
b. What are the adverse effects of phenytoin?	Idiosyncratic: hirsuitism. gingival hyperplasia & overgrowth with bleeding, acne & facial coarsening. Dose related neurotoxic effects: drowsiness , dizziness, blurred vision, hallucinations, slurred speech, clumsiness, dizziness and confusion. Rapid IV administration associated with CV collapse. **PROMPT: Are there any specific problems with IV administration.**	Dose-related CNS effects Cardiac with IV administration & 1 other.

2010.2.3

5. a. What are the indications for benzodiazepine use?	Anxiety Disorders Preoperative Medication Insomnia Sleep Disturbances Seizure Disorders Panic Disorder Alcohol Withdrawal Muscle Spasm Induce amnesia during cardioversion/endoscopic procedures	Seizures and 2 others
b. Explain the rationale for use of benzodiazepines in alcohol withdrawal	Down-regulation of neuro-inhibitory GABA receptors in alcohol dependent individual leads to symptoms of GABA deficiency in withdrawal. BZD act at a modulatory site on the the $GABA_A$ receptor to facilitate GABA binding to the $GABA_A$ receptors, enhance chloride channel opening, and overcome neuroexcitatory symptoms of GABA deficiency.	Facilitate GABA binding to the $GABA_A$ receptors Control neuroexcitatory symptoms of alcohol withdrawal.

2010.2.3

4. a. Describe the general pharmacokinetic characteristics of antipsychotic drugs	Most are readily but incompletely absorbed. Many undergo significant first pass metabolism Most are lipid soluble (lipophilic) Most have high PPB (92-99%) Most are completely metabolised by hepatic enzymes (oxidation; demethylation) These are catalysed by liver enzymes. **PROMPT: Use chlorpromazine as an example**	Lipid soluble. Hepatic metabolism + 1 other
Define the term "atypical" antipsychotic and provide an example.	Newer antipsychotic agents with less propensity to cause extra-pyramidal side-effects. Better at treating negative features of schizophrenia. They share a greater ability to alter $5HT_{2A}$ receptor activity than to interfere with D_2-receptor action. Examples: olanzapine; clozapine; quetiapine; risperidone; loxapine	Less EPS One example
c. Describe the adverse drug reactions to olanzapine.	Weight gain Sedation (but less than typical antipsychotics) Minor orthostatic hypotension Minor anticholinergic effects (dry mouth, urine retention etc) (Extrapyramidal effects less prominent)	2 effects

2010.2.3

5. a. What is the mechanism of action of flumazenil?	Antagonist at the BZD binding site on the $GABA_A$ receptor (ligand-gated chloride channel). Decreases the binding of GABA. Blocks GABA-induced increase in Cl^- permeability and influx of Cl^- into the cell causing hyperpolarisation and decreased excitability of the neuron.	Specific BZD receptor antagonist at GABA receptor
b. What are the indications for flumazenil use	Avoid intubation or ICU admission in BZD overdose. Reverse BZD sedation after procedures Diagnostic role	Reverse the sedative effects of BZD
c. What potential problems should be anticipated when using flumazenil?	Precipitate seizures in mixed overdoses with BZD and proconvulsants Precipitate seizures in pts taking BZD to control epilepsy Precipitate withdrawal symptoms and seizures in BDZ-dependent Duration of action is only 1-3hrs thus repeated administration may be necessary Reversal of BZD-induced respiratory depression has not been demonstrated, so resp and cardiovasc support may be required Adverse Effects: headache, visual disturbance, increased anxiety, nausea, light-headedness	Precipitate fits Need for repeated doses

2009.1.1

Question 3: Carbamazepine	1. Describe the mechanism of action of carbamazepine.	Anticonvulsant: a) blocks Na channels b) Inhibits high-frequency repetitive firing of neurones c) Presynaptic blocker of synaptic transmission d) similar action to phenytoin	Pass: (a)
	2. How is carbamazepine metabolised?	a) Metabolised by microsomal enzymes b) enzyme induction occurs c) active metabolites (clinical significance uncertain)	Pass: (a)
	3. What is its effect of the metabolism of other drugs?	If (b) is not volunteered above – Enzyme induction increases the rate of metabolism of other drugs eg primidone, phenytoin, valproate, clonazepam. Some of these drugs also can inhibit carbamazepine metabolism	Pass: Enzyme induction

2009.1.2

Question 3: Chlorpromazine	1. What are the clinical uses of chlorpromazine?	**Antipsychotic** especially for schizophrenia Sedative for agitation Antiemetic	Antipsychotic and one other
	2. What are the phamacodynamic properties responsible for these effects?	Antipsychotic D_2 blockade in mesolimbic & mesofrontal systems Antiemetic dopamine receptor blockade in medullary chemoreceptor trigger zone & peripherally on receptors on stomach Sedation 5HT blockade	Dopamine blockade
	3. What are its adverse effects?	Autonomic loss of accommodation, dry mouth, **urinary retention**, constipation **orthostatic hypotension**, sexual dysfunction CNS **Parkinsonism**, akathisia, dystonia, **Neuroleptic Malignant Syndrome** Tardive Dyskinesia Confusion Seizures **Sedation** Endocrine **Hyperprolactinaemia** – Amenorrhoea, galactorrhoea, infertility, impotence Ocular Corneal deposits	Any 3 adverse effectss

2009.2.1

Question 3: **Propofol**	(a) Describe the pharmacokinetics of propofol?	Intravenous administration **Distribution $t_{1/2}$ 2-8 min**, redistribution $t_{1/2}$ 30-60 min **Metabolism- rapidly in liver**; total body clearance is greater than hepatic blood flow, suggesting extrahepatic mechanisms **Excretion- urine** as glucuronides and sulphates- <1% unchanged	Required for Pass: a) bold
	(b) What are the side effects of propofol?	Respiratory- dose-related **depression of central ventilatory drive**, apnoea, Cardiac- **Marked decrease in blood pressure** through decreased peripheral arterial resistance and venodilatation, and direct negative inotropic effect. Soy/egg allergy, Pain on injection	b) Knowledge of respiratory and cardiac effects of propofol

2009.2.2

Question 3: **Ketamine**	(a) How does ketamine affect the cardiovascular system?	HR, BP and cardiac output increase Stimulate central SNS, and inhibits re-uptake of noradrenaline at sympathetic nerve terminals	(a) Demonstrated understanding of CV effects of ketamine
	(b) What are the side effects of ketamine?	Sialorrhoea **Decreased RR** Postoperative disorientation Sensory and perceptual illusions **Emergence phenomenon** Vomiting **Raised ICP**- increases cerebral blood flow, oxygen consumption and ICP Rash	2 bold + 1 other

2009.2.3

Question 3: **Suxamethonium**	(a) Describe the mechanism of action of suxamethonium	Phase I (**depolarising**)- reacts with Nicotinic receptor, opens the channel, causing depolarisation of the motor end plate, not metabolised at the synapse, and so membranes remain unresponsive to subsequent impulses- lack of "repriming" leads to **flaccid paralysis**. Phase II (desensitising) Unclear, but channel block may be more important than agonist action. Action is terminated by diffusion away from the end plate into the extracellular fluid, where it is metabolised by plasma cholinesterase.	Demonstrated understanding of mechanism of action
	(b) What are the side effects of suxamethonium?	b) **Bradycardia**- negative inotropic and chronotropic effects (inc. second dose bradycardia)	3 bold to pass
		Hyperkalaemia (esp burns, nerve damage, NM disease, closed head injury) **Increased intra-ocular pressure** **Increased intragastric pressure** (inc. aspiration) **Muscle pain** (in up to 20%) **Malignant hyperthermia** (when combined with volatiles) ***Sux apnoea*** in susceptible patients	

2009.2.3

Question 5: Topical Anaesthetics	(a) What is the mechanism of action of local anaesthetics?	**- blockade of voltage-gated Na channels in neurones** - increasing doses lead to higher excitation threshold, slower impulse conduction, lower AP **- blocks conduction if 2-3 nodes of Ranvier in a myelinated nerve affected**	Blockage of Na channels and blocked conduction to pass.
	(b) Which local anaesthetics are used topically?	Lignocaine – oral spray for procedures, viscous for pharynx, with prilocaine in EMLA, other mixtures for wound and ENT care, eye drops EMLA (Eutectic Mixture of Local Anaesthetics – mixture of lignocaine and prilocaine) – skin anaesthesia for cannula insertion, etc. Cocaine – ENT procedures (combines vasoconstriction) Proxymetacaine, amethocaine, oxybuprocaine – eye drops Benzalkonium – oral gels	2 agents

2008.2.1

Question 3: Tricyclic antidepressants	1. What is the mechanism of action of the tricyclic antidepressants? Prompt: Name one amine? "Where does it happen? 2. Describe the toxic effects in overdose and how are they mediated?	Block amine (NAdr or Serotonin) reuptake pumps at presynaptic nerve endings prolongs duration of action of neurotransmitters at postsynaptic receptors. Most non selective Antimuscarinic. tachycardia, dry mouth, blurred vision, delirium, coma, Agitation; Urinary retention, reduced gastric motility, Respiratory depression; Neuromuscular irritability and seizures Sympathomimetic: tremor. Insomnia Sedation: additive effects alpha1-antiadrenergic – postural hypotension, Hypotension, dizziness fast sodium-channel blockade – reduced myocardial contractility, QT prolongation, cardiac arrhythmias;	Amine block, reuptake inhibitor some antimuscarinic cardiac (mix) Na channel block effects

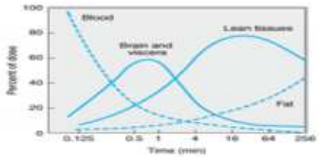
2008.2.2

Question 3: SSRIs	1 What is the mechanism of action of the SSRI drugs *Prompt selective serotonin reuptake inhibitors* *Prompt for delayed onset of action- possible mechanisms)* 2 What receptor/channel effects lead to the SSRI side effect profile *Prompt why are SSRIs safer than TCAs?*	i) **Amine hypothesis** – modulation of **NET + SERT** pathways by reuptake inhibition ? > serotonin response ii) Prolonged synaptic exposure to Serotonin leads to iii) prob **time frame 3-6 weeks** due to presynaptic/ post synaptic receptor / storage regulation iv) SSRIs **v HT specific** v TCA 300-7000:1 Very **specific for HT**(partic 1) receptors –therefore **serotonin syndrome/ restlessness. Minimal autonomic** NE activation + mild muscarinic / Na channel, **H1** block effects **(safety/ tolerance)**. Possibly some α block (sexual dysfunction)	**General understanding** knowledge of amine hypothesis and b) delayed response c) prob alteration in pre/post synaptic **specific HT + 1 other,** Serotonin syndrome Minimal autonomic = good tolerance/ safety modulation receptors and storage

2008.2.3

Question 3: Phenytoin	1. Describe the pharmacokinetics of phenytoin?	Weak acid pKa 8.3; oral abs almost complete 90%, with peak serum conc 3-12hrs later. Slow release formulation also. IMI: incomplete abs with drug precipitation in the muscle, fosP OK **Highly plasma protein bound,** metabolised to inactive metabolities with urinary excretion, < 2% exc unchanged in urine. **Dose dependant kinetics**; Vd 45L/70kg. t1/2 av 24 hours (conc dependant). Therapeutic level 10-20mg/L. Drug interactions via plasma protein binding or via enz induction (CYP2C19 & CYP2C9). Alters TFT results; reduced CL neonates; foetal hydantoin syndrome	Pass: highly protein bound and dose dependant kinetics
	2. Describe the pharmacodynamics of phenytoin? *Prompt: what is the effect on action potentials?*	**Block sodium channels** & inhibits the generation of repetitive APs blocks sustained high frequency repetitive firing of APs). Preferential binding to & prolongation of the inactivated state of the Na channel (use dependant effect on Na conductance). **Other electrolyte effects** -alters K conductance; alters Ca conductance ad decreases Ca permeability, inhibits Ca influx therefore affecting neurotransmitter & hormone release; -interacts with membrane lipids ? stabilising membranes; -paradoxical excitation in some neurones; -alters membrane potentials and the conc of amino acids; affects neurotransmitters NA, Ach & GABA. High conc inhibits serotonin and NA release, promotes uptake of DA & inhibits MAO activity.	Pass: Na channel, And one other effect

2008.1.2

Thiopentone	Describe the pharmacokinetics of thiopentone	After IV bolus, rapidly crosses the blood-brain barrier. Plasma:brain equilibrium occurs < 1 min because of high lipid solubility. Rapidly diffuses out of the brain and highly vascular tissues, and redistributed to muscle and fat. Metabolized at rate of 12–16% per hour. <1% of the administered dose excreted unchanged by kidney.  	
	What adverse effects does it cause when used as an anaesthetic induction agent ?	Drops BP, SV, CO due to myocardial depressant effect and increased venous capacitance. Apnoea. Rarely precipitates porphyric crisis by inducing ALA synthase in liver Pass – 2 phase concept, hypotension	

2008.1.3

Drugs Binding To Biogenic Amine Transporters	How do anti-depressants exert their action ?	Thought to enhance amine-dependent synaptic transmission (serotonin and noradrenalin) by: (1) Inhibition of metabolism within nerve terminal (MAOIs) (2) Inhibition of reuptake from synapse (TCAs, SSRIs) (3) Increased release due to antagonism of specific serotonin and alpha2 noradrenalin receptors (Mirtazapine)	2/3 mechanisms to pass
	What are the relative advantages of different classes of antidepressants ? (Direct to adverse effects if no response)	Adverse effect profile Cost Efficacy Risk of overdose Dosing schedule Drug interactions	Able to discuss pros and cons of at least two

Older

FIRST QUESTION	Describe the pharmacokinetics of propofol	
	Distribution after IV with t ½ 2-8 mins, **elimination** t ½ 30-60 mins Rapidly metabolized in liver (10x faster than thio) by conjugation to glucuronide and S04 Excreted in urine, <1% excreted unchanged Total body clearance greater than hepatic blood flow (extrahepatic mechanisms must also be at work)	
SECOND QUESTION	What are the adverse effects of propofol	
	Resp. – apnea **CV – marked decrease in BP during induction (decr. peripheral resistance)** - **greater neg.inotropic effects on heart** Pain at site of injection	

FIRST QUESTION	What are the pharmacokinetics of suxamethonium?	
	Short half life Plasma cholinesterase hydrolysis	
SbECOND QUESTION	What are the adverse effects of suxamethonium	
	1.Cardiac arrythmias – low dose negative inotropic/chronotropic response, bradycardia when 2nd dose 5 mins after first 2.Hyperkalemia – burns, nerve damage, NM disease, CHI, peritoneal infections, RF 3.Incr. IOP 4.Incr.intragastric press – risk emesis 5.Muscle pain	Hyperkalemia Increased press (1)

Indirect acting Cholino-mimetics pp98-105	1.What is the mechanism of action of indirectly acting cholinomimetics?	**Inhibition of the enzyme acetylcholinesterase thereby increasing the concentration of endogenous acetylcholine in the vicinity of cholinoreceptors** Action on both nicotinic and muscarinic receptors. Action on the neuromuscular end plate and autonomic ganglion cells	To pass: must get bold item	
	2.What types of indirectly acting cholinomimetics are there? Please give examples.	Reversible: Group 1.Alcohols – edrophonium Group 2.Carbamates – neostigmine, physostigmine, pyridostigmine Irreversible: Group 3. Organophosphates – Ecothiophate, insecticides	To pass: Must either delineate reversible and irreversible groups or give two well explained examples	
	3.What are the cardiovascular effects of these groups of drugs?	Both sympathetic and parasympathetic ganglia can be activated **Parasympathetic effects generally predominate Bradycardia, decreased CO, decreases contractility, no change or modest decrease in BP.** OD may cause tachycardia and hypotension.	To pass: Must at least get bold items	

Muscarinic blockers	1.Can you describe the basic machanism of action of atropine. Prompt: ask about specific receptor if just say anticholinergic	Anti-cholinergic Anti-muscarinic at all three types of muscarinic receptors No significant nicotinic effect	Must say anti -muscarinic	
	2. What are the therapeutic applications of drugs that block muscarinic receptors?	Heart Gut Eye Organophosphate poisoning Parkinsons Motion Sickness Respiratory (IB) Urinary disorders	Any 4	
	3.What are the toxic effects of antimuscarinic overdose?	Delirium Hyperpyrexia Mydriasis Tachycardia Dry mouth Urinary retention Dry as a bone Red as a beet	5 out of 8	

Midazolam	What is the mechanism of action of midazolam ? What is the drug antagonist for midazolam OD ? What adverse events may be associated with the use of flumazenil for midazolam toxicity ?	GABA complex binding Cl channel opening , inhibitory effect on CNS Flumazenil Resedation Withdrawal/seizures	

H1 receptor anatagonists	How do you classify H1 antagonists ? Describe the pharmacodynamics of promethazine ? What are the important adverse reactions associated with this drug?	Sedating/non sedating or 1st/2nd generation H1 antagonist Antidopaminergic **AT LEAST 3** Alpha blockade Na channel blockade Anticholinergic Antiserotinergic Sedation Hypotension	

Local anaesthetics	Explain the chemical classification of local anaesthetics Explain tachyphylaxis associated with LA use	Amides and esters Increased ionisation	

Lignocaine	Describe the mechanism of action of lignocaine on the heart Describe the adverse effects of lignocaine	Na channel blockade Stepwise CNS effects Cardiovascular Na blockade	

Valproate	Describe the mechanism of action of sodium valproate? What potential drug interactions can occur with sodium valproate?	**Three possible mechanisms:** • **Effect on sodium channels (blocker)** • **Effect on K+ channels (enhance efflux)** • **Increase in GABA via inhibition of GABA T, and decrease GABA breakdown via conversion to succinic semialdehyde (seen at high doses)** **(2 of 3 mechanisms)** • **Inhibition of its own metabolism at low doses.** • **Decreases metabolism of phenobarbitone, phenytoin and carbamzepine** • **Displaces phenytoin from plasma proteins** **(1 of 3)**	

Nitric oxide	What are the effects of nitric oxide? What are potential therapeutic applications of nitric oxide.	**Smooth muscle relaxant** **Platelet inhibitor** **Immune regulator** **Neurotransmitter** **(1of 4)** .**Vascular effects** - on vascular smooth muscle tone and B.P. - may play a role in normal regulation of vascular tone -vasodilator action -inhibits neutrophil adhesion to vascular endothelium 2.**Hypertension associated with pregnancy** - resemble deficiency of NO and PG - possible role of enhancing NO levels via nutritional supp.w/L-arginine 3.**Respiratory disorders** - used via inhalation to newborns w/pulmonary hypertension and ARDS - decreases pulmonary arterial pressure and inproves blood oxygenation - also used in open trials in adults with ARDS - may act also act as bronchodilator by relaxing airway smooth muscle 4.**Septic shock** -Urinary excretion of N03, oxidative product of nitric oxide in G- bacterial infection 5.**Atherosclerosis** - may act as antioxidant, blocking oxidation of LDL, preventing foam cell formation in the vascular wall **6.Platelets** -nitric oxide = potent inhibitor of platelet adhesion and aggregation — as in vascular sm.muscle, cGMP mediates protective effect of NO in platelets -may have additional effect on blood coagulation by enhancing fibrinolysis via effect on plasminogen **7.Organ transplantation** -. N0 reduces free radical toxicity, inhibits platelet and neutrophil aggregation and adhesion to vascular wall - too high concentration of NO may be detrimental – so need to inhibit synthesis to prolong graft survival **8.CNS** -modifies neurotransmitter release in different areas of the brain --also may have role in epileptic seizures - also has negative effects - causes destruction of photoreceptor cells in retina – prolonged increase in cGMP formation **9. Peripheral nervous system** - NO promotes relaxation of sm.muscle in corpora cavernosa – impotence trials with NTG ointment and NTG patch **(any 1))**	

Antipsychotic agents – side effects	What adverse reactions can be associated with the use of antipsychotic agents?	.Anticholinergic .Disturbance of Ach/Dopamine balance leading to EPS (extrapyramidal Syndrome) Parkinsonism Akathisia Dystonia Long term effects – tardive dyskinesia .NMS, Neuroleptic malignant syndrome .Antialpha .Antihistaminic .Jaundice .Endocrine **(Bold x 3 + 1 of the other)**	bold

5. Benztropine	1. What is benztropine? 2. What are the adverse effects of benztropine? (1 FROM EACH CATEGORY)	Centrally acting anti-muscarinic **CNS** – drowsy, confusion, hallucinations **PNS** –dry mouth, blurred vision, mydriasis, retention, N/V, constipation Cardiac – tachycardia, palpitations	

3. Ketamine	What type of anaesthesia does ketamine produce? Which receptor action produces the anaesthesia? What are the cardiorespiratory effects of ketamine? (1 CVS, 1 RESP FOR PASS)	Dissociative anaesthetic: analgesia, amnesia, catatonia +/- LOC Blockade of glutamic acid (excitatory neurotransmitter) at NMDA receptor CVS: HR, BP, CO increase central SNS excitation Resp: decreased rate, airway reflexes remain intact, bronchodilator	

Succinylcholine	Describe succinylcholine and its metabolism?	**Depolarizing neuromuscular blocking drug** **Hydrolyzed by plasma cholinesterase** to succinic acid & choline	Two linked acetylcholine molecules Action at motor end plate terminated by diffusion away into ECF
	What are the adverse effects of depolarising neuromuscular blockade?	**Hyperkalaemia** Renal Failure Burns > 24 hours Demyelination Spinal Cord Injury Muscular Dystrophies CVA **Increased IOP, intragastric & ICP (1 of)**	Paralysis & prolonged Apnoea CVS - negative inotrope & chronotrope Muscle Pain

Olanzapine	What are the advantages of olanzapine over the older antipsychotics? *Prompt with* How does Olanzapine compare with haloperidol in terms of sedation, hypotensive effect and extrapyramidal toxicity? **2 out of 3, prompts allowed**	Can be given as tablet, wafer or injection (wider **Less unwanted dopamine effects**, eg tardive dyskinesia, NMS

Drug	Usual daily oral dose range (mg)	Sedation	Postural hypotension	Anticholinergic	Extrapyramidal	Weight gain
haloperidol	1-7.5	+	+	+	+++	++
olanzapine	5-20	+++	+	++	+	+++

Like clozapine, olanzapine has a wide range of receptor affinities. It is relatively well tolerated but drowsiness and dizziness can occur. Excessive weight gain may precipitate type 2 diabetes. Transient elevation of liver enzymes has been associated with olanzapine, but this does not appear to be of clinical significance.

	What are the clinical conditions Olanzapine is prescribed for?	Wide Spectrum of use: Autism spectrum disorders. Behavioural emergencies Delirium: mood and behavioural disturbances; palliative care; AIDS Dementia: General; Sleep disorder in patients with dementia (palliative care) Acute treatment of mania: Olanzapine Schizophrenia **2 of list**

Nitrous oxide	What are the organ effects of nitrous oxide?	CNS: Analgesic, amnesic. Inc CBF Renal: Decreased GFR, inc filtration fraction & inc renal vasc resistance CVS: Dose dependant myocardial depression Resp: Reduced resp response to CO2 & hypoxia **1 CNS and 1 non CNS**	
	What is the mechanism of action of nitrous oxide? *How does NO affect GABA* *Any other mechanisms by which NO works?*	**Directly activate GABA A receptors**	-GABA A receptor Cl channel. Facilitate GABA mediated inhibition at GABA receptor sites -membrane hyperpolarisation -decreased duration of opening of nicotinic receptor activated channels. Decreased excitatory effect of ACh

Topical anaesthetics	What is the mechanism of action of local anaesthetics?	**Sodium channel blocker** **Voltage gated**	Interfere with propagation of AP by blocking the increase in sodium permeability during depolarization. Provide pain relief by blocking nociceptive fibers. Other fibers are affected as well. Sensitivity depends on: fiber diameter, fiber type, degree of myelination. Sensory modalities are affected in the following order: pain, cold, warmth, touch, and pressure. Most local anesthetics are weak bases, pKa 7.5-9.0.
	How are local anaesthetics classified? Give an example of each group?	**Esters and Amides:** Esters are hydrolyzed by plasma and liver esterases. Amides are metabolized in the liver. Patients with severe hepatic damage or advanced congestive heart failure may be unusually sensitive to these drugs. Some amides are partially excreted unchanged in the urine Esters: cocaine, procaine, amethocaine and chloroprocaine, amides lignocaine, prilocaine, mepivacaine and bupivacaine. **1 example of each**	Allergic reactions are rare, especially with amide local anesthetics.
	Describe the ideal local anaesthetic for topical application? *What clinical situations would you use topical anaesthesia for?* *What are the contraindications to using topical Las?*	Ease of application (Not messy; No dressing; Well tolerated by kids; Not painful) Rapid Onset of action Low (nil) systemic toxicity eg MetHb with EMLA in neonates High analgesic efficacy Reasonable duration of action Not allergenic May be applied to the skin, the eye, the ear, the nose and the mouth as well as other mucous membranes. EMLA cream a eutectic mixture of LAs provides surface anaesthesia of the skin (partic paeds). A mixture of base forms of lignocaine & prilocaine in equal proportions in an emulsion. Cutaneous contact (usually under an occlusive dressing) should be maintained for at least 60 min prior to venipuncture Other LA agents may be abs in significant amounts particularly after topical application to the more vascular areas, fatalities have occurred after application of these agents to mucosal surfaces.	Absorption of LAs through intact skin is usually slow and unreliable and high concentrations (e.g. 20% benzocaine or 40% lignocaine) are required. In general, cocaine, amethocaine, lignocaine and prilocaine are the most useful and effective local anaesthetics for this purpose. When used to produce topical anaesthesia, they usually have a rapid onset of action (5-10mins) and a moderate duration of action (30-60 mins).

2.3 Midazolam	What is the mechanism of action of midazolam? What are the pharmacokinetics of Midazolam? What are the pharmacodynamics of Midazolam?	**Binds to GABA-A Chloride channels**, potentiates GABAergic inhibition through hyperpolarisation , acts throughout brain **Water soluble** hence oral/IM/intranasal but crosses BB barrier easily at body pH. **Short elimination half-life** 2-4 hours. (Note for examiners who may have forgotten- 56% renal excretion!) Strong amnestic effect, **anticonvulsant**, anxiolytic, **sedative-hypnotic**	/2

2.5 Olanzepine	What the pharmacological characteristics of olanzepine? How does it differ from haloperidol?	Olanzepine = Thienobenzodiazepine, most D4, alpha-1, 5-HT receptor effects, also H1 effect, high potency, very low extrapyramidal effects, medium sedative, low hypotensive effects, causes weight gain long term **(must get 2)** Haloperidol = Butyrophenone, most D2 receptor effects, high potency, very high extrapyramidal effects, low sedative, low hypotensive effects, cheap. **(must get 1)**	/2

3.3 Prilocaine	What is the mechanism of action of prilocaine Describe the adverse effects of prilocaine How is prilocaine metabolized?	Blockade of voltage-gated **Na channels** CNS: sleepy, light-headed, circumoral numbness, seizures Cardiovascular: direct and indirect, depress pacemaker, excitability and conduction Haematology: Methemoglobinaemia (accumulation of 0 –toluidine) Neurotoxicity Allergy **(must get 2)** Prompt adverse effects of local anaesthetics in general Amide link hydrolysed by P 450 **in liver** and then renal excretion	/2

2.2 H1 blockers (BF)	What are the clinical uses of H1 antagonists?	1 Allergic reactions; rhinitis,urticaria, possible role in type 1 2 Motion sickness (best as preventers) 3 Vestibular disturbance 4 Nausea and vomiting (esp in pregnancy) 5 Sedation (mentioned as SFX in book) 6 Serotonin antagonist (cyproheptadine) 7 Drug induced Parkinsonism	
	What are the major adverse effects?	1 Sedation, 2 Antimuscarinic effects, 3 Seizures, 4 Postural hypotension, 5 Drug allergy	
	What are the significant potential drug interactions	• Additive effect with other sedatives • Additive effect with Muscarinic and alpha-blocking drugs • Grapefruit juice inhibits same p450 group	

2.3 Morphine	How is Morphine metabolised?	Converts to polar metabolites in form of glucuronides in liver Primarily conjugated to morphine-3-glucuronide (M3G)→neuro-excitatory properties. 10% of morphine conjugated to morphine-6-glucuronide (M6G)→analgesic effect	
	What opioid receptor sites does it act on?	Full agonist at μ receptor. But also acts on κ and δ receptor sites	
	What is the mechanism of action at the cellular level?	By binding to specific G protein-coupled receptors in brain and spinal cord 1. Close voltage-gated Ca channels → ↓ Ca influx on presynaptic nerve terminals and ↓ transmitter release 2. Hyperpolarise postsynaptic neurones by ↑ K conductance → inhibitory postsynaptic potential	

2.4 Levodopa	Why is levodopa used in combination with carbidopa?	Carbidopa is a peripheral dopa decarboxylase inhibitor. Because it doesn't penetrate the blood brain barrier, it reduces the peripheral metabolism of levodopa → ↑ levodopa levels, ↑ half-life resulting in more dopa being available for entry into brain to exert its effects.	
	What are the adverse affects of levodopa?	GIT: Anorexia, nausea and vomiting in up to 80% of patients. Due to stimulation of emetic centre in brainstem. Incidence ↓ to < 20% if a peripheral decarboxylase inhibitor is added. CVS: Arrhythmias-tachycardia, ventricular ectopics, AF. Due to ↑ catecholamine formation peripherally. Postural hypotension Dyskinesias: Up to 80% of those receiving levodopa for long periods. Behavioural effects: Depression, anxiety, agitation, insomnia, nightmares, euphoria and mood changes. More common if taking a levodopa with a decarboxylase inhibitor. Due to higher levels presenting to the brain. Fluctuations in clinical response occurs with increasing frequency as treatment continues. Miscellaneous: Mydriasis, acute glaucoma, Coombs positive haemolytic anaemia, gout, abnormalities of taste and smell, Brownish discolouration of saliva, urine or vaginal secretions, priapism, abn urea, LFTs. Drug Interactions: Pyridoxine enhances metabolism of levodopa. Hence effect ↓. **3 systems to pass**	

3.2 Clonazepam (BD)	What is the mechanism of action of clonazepam?	**Binds to GABA-**A , potentiates GABAergic **inhibition through hyperpolarisation** (does not act as direct GABA analogue), increases frequency of chloride channel opening, acts throughout brain but the distribution of the different GABA A receptor isoforms varies across the CNS	
	What are the clinical uses of clonazepam?	Strong amnestic effect, **anticonvulsant**, anxiolytic, **sedative-hypnotic**	
	What properties make clonazepam an effective anticonvulsant.	Lipid soluble/**blood brain barrier**, acts on alpha 1 GABA receptor isoform, potentiates inhibitory interneurones	/2

3.5 Dantrolene (SB)	Describe the actions of Dantrolene	ACTIONS • Interferes with release of Ca^{++} from SER, by binding to the SER Ca^{++} channel ("ryanodine receptor"), hence reducing excitation coupling. • Motor units that contract rapidly are more sensitive (hence only slight depression of cardiac and smooth muscle)	
	What are the uses?	USES: • Spasmolysis (cerebral palsy, MS, stroke) • Malignant hyperthermia (hereditary impairment of SER to sequester/reuptake calcium that has been released into the cell)	
	What is the dose for acute management of malignant hyperthermia?	DOSE for MH: 1 mg/kg IV, repeat as needed to 10 mg/kg	/2