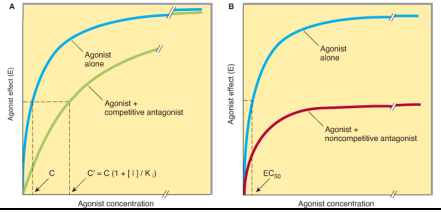
ACEM PRIMARY 2011.2 PHARMACOLOGY VIVA Day Thurs morning ***Candidate Number*…… AGREED MARK……**

TOPIC	QUESTION	KNOWLEDGE	Pass Criteria
Question 1 Competitive and non-competitive antagonists	a) What is an antagonist? b) What is the difference between a competitive and non-competitive antagonist?	a) Receptor antagonists bind to receptors but **do not activate** them. The primary action of antagonists is to prevent agonists from activating receptors. b)<u>Competitive antagonist</u> In the presence of increasing concentration of antagonist, **higher concentrations of agonist will produce a given effect**. Eg propanolol and noradrenaline / adrenaline Shift agonist vs effect curve to right. **Higher concentrations of agonist can overcome competitive antagonist** <u>Irreversible or non competitive antagonist</u> Bind via covalent bonds or just binding so tightly to receptor **so receptor unavailable for agonist**. Duration of action of antagonist depend on rate of turnover of receptor-antagonist molecules. **Reduces maximal effect of agonist** but may not affect its EC50. eg phenoxybenzamine vs adrenaline 	Must have good understanding of what happens with increasing agonist doses in both cases.
Question 2: Valproate	a) What are the proposed mechanisms of action of valproate? b) Describe the toxic effects of valproate? *c) What interactions does valproate have with other anti-seizure drugs?*	a)**Blocks Na channels** thereby blocking sustained high frequency firing of neurones. Blockade of NMDA receptor mediated excitation. Increase GABA levels 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 *c) Phenytoin inhibits metabolism and displaces from plasma proteins* *Phenobarbitore & carbamazapine inhib metab* *Lamotrigine decreases clearance*	Bolded Bold +1 to pass Supplementary
Question 3 Penicillin	a) What is the mechanism of action of penicillins? b) What are the important mechanisms of resistance to pencillins?	a)B-lactam antibiotic. **Inhibits bacterial cell wall synthesis by** interfering with trans-peptidation reaction of bacterial cell wall synthesis; bacteriocidal Structural analogue of D-Ala-D-Ala substrate present in cell wall. Covalently binds to the active site **of Penicillin-binding protein (PBP)** b) 1. inactivation **by B-lactamase** 2. modification of target PBPs (eg MRSA) 3. Reduced penetration (Gram neg organisms) 4. Efflux pump (Gram neg organisms)	Bold to pass bold + one other

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
Question 5 Antivenoms	a) What is an antivenom? b) What antivenoms are used in Australasia? c) What are the side effects of antivenom? d)What animals are used in the production of different antivenoms?	a) Immunoglobulin or **antibody** (specifically IgG FAB) produced by another **animal** in response to a venom. Used in humans IV or IM to neutralise venom after an envenomation. **b) Snake –polyvalent and monovalent** (black, brown, death adder, tiger, taipan, sea snake); stonefish, redback spider, box jellyfish, funnelweb spider c) Allergy, **anaphylaxis, serum sickness** **d) Horse –snake**, stonefish, redback; Sheep –box jellyfish; Rabbit –funnel web	Must get Ab or Ig produced by animal Must get Snake – polyvalent & monovalent & 2 others Must get bold Must get horse/snake and 1 other

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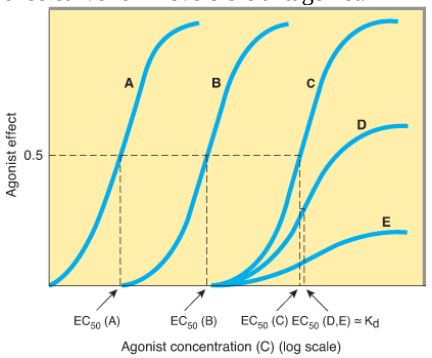
TOPIC	QUESTION	KNOWLEDGE	PASS CRITERIA
Question 1 Drug concentration and response	a) In relation to drug concentration and responses, what is the EC50? b) What are spare receptors?	a) EC50 is the **concentration at which an agonist produces half its maximal effect**. **b) Need to understand concept of spare receptors.** The concentration of agonist producing a maximum response may not result in occupancy of full complement of receptors. These receptors are said to be "spare." Temporal or in number Dose-response curve for irreversible antagonist.  A = no antagonist B = low dose antagonist. Still get maximum effect because receptors still in excess of required for effect C = Largest concentration of antagonist to produce maximum effect. Therefore no spare receptors. D + E = high concentrations of antagonist which diminish maximum response	Good understanding of bolded
Question 2: Calcium channel blockers	a) What are the effects of Ca channel blockers on smooth muscle? *(Prompt: tissue level)* b) By what mechanisms do Ca channel blockers control angina? c) Why is verapamil more efficacious than dihydropyridines in the treatment of arrhythmias?	a) **Relax smooth muscle esp vascular smooth muscle** Arterioles more sensitive than veins Does effect bronchiolar GIT and uterine b) **Decrease myocardial contractility** Decrease oxygen demand **Decrease afterload by relaxing vascular smooth muscle** Verapamil/ diltiazem have a non-specific antiadrenergic effect and decrease heart rate Relieve and prevent coronary artery spasm c) Blockade of L-channels more marked in tissues that fire frequently More marked effects on tissues that depend on Ca channels for activation, SA & AV nodes More marked on tissues with tissues less polarised at rest	Bolded Bolded Supplementary

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
Question 4 Noradrenaline	a) What is the adrenoreceptor selectivity of noradrenaline? (prompt "what receptors does it act on") b) Describe the cardiovascular effects of infused noradrenaline	a) **alpha1 = alpha2; Beta1** >> Beta2 alpha 1: post-synaptic effector cells, especially smooth muscle alpha 2: presynaptic nerve terminals, platelets, lipocytes, smooth muscle beta 1: post synaptic effector cells, especially heart, lipocytes, brain b) 1. **Increases peripheral vascular resistance** 2. **Increases SBP and DBP** 3. Little chronotropy 4. **Positive inotropy**	all 3 bold to pass 2 of 3 bold to pass
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.

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TOPIC	QUESTION	ESSENTIAL KNOWLEDGE	NOTES
Question 1 Bioavailability	a) Define bioavailability b) What factors affect bioavailability c) How can you overcome the effects of high first pass metabolism?	**a) Fraction of unchanged drug reaching systemic circulation following administration by any route.** AUC (conc-time) is a common measure of the extent of bioavailability. b) 3 Factors **a) Extent of Absorption** i) Too Hydrophilic or too lipophilic ii) Reverse transporter associated with P-glycoprotein – pumps drug back to gut lumen iii) Gut wall metabolism **b) First Pass Elimination** i) Metabolism by liver before it reaches systemic circulation ii) Small additional affect if drug has biliary excretion c) Rate of Absorption i) Determined by site of administration and drug formulation c) **Change route of admin to**: Sublingual, transdermal, rectal, inhalation, IV, IM ; increase dose	Bolded Bolded **(Need 2 routes of admin)**
Question 2 Loop Diuretics	a) What are the mechanisms of action of FRUSEMIDE? b) What are the toxic effects of FRUSEMIDE?	a) • inhibits NKCC2 = a luminal $Na^+/K^+/2Cl$ co-transporter of **thick ascending limb of Loop of Henle** => **decreased reabsorption of NaCl** => diuresis • increased prostaglandin synthesis => a) inhibition of salt transport in thick ascending limb => b) increased renal blood flow, decreased pulmonary congestion, decreased LV filling pressures b) • **decreased K** metabolic alkalosis • ototoxicity • hyperuricaemia • hypomagnesaemia • Allergy - rash, eosinophilia, interstitial nephritis • dehydration • hyponatraemia	**bold** to pass 4+ to pass - must include **decr K** & one non-electrolyte

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*
Question 4 Macrolides	a) Give some examples of macrolide antibiotics b) What is their mechanism of action? c) What are the adverse effects of erythromycin? *(prompt if has not mentioned in question1: " Erythromycin is a macrolide antibiotic. Do you know any adverse effects of erythromycin?")*	a) **erythromycin (prototype drug), roxithromycin, azithromycin, clarithromycin,** b) **inhibit protein synthesis by binding to 50S ribosomal RNA** which blocks aminoacyl translocation reaction and formation of initiation complexes. Erythromycin may be inhibitory or bacteriocidal at higher concentrations c) 1. **gastrointestinal** (anorexia, nausea, vomiting, diarrhoea) 2. liver toxicity (acute cholestatic hepatitis, particularly with estolate) 3. allergic reaction (fever, eosinophilia, rash) 4. drug interactions (inhibits cyt P450)	Must give at least 2 examples Pass = bold Bold + one other
Question 5 Adrenocorticoids (Hydrocortisone)	a) What are the effects of hydrocortisone? (Prompt: *Describe the anti-inflammatory and immunosuppressant effects of hydrocortisone)* b) What are the effects of chronic steroid use?	a) Mediated by glucocorticoid receptors Physiologic + permissive effects Metabolic effects Catabolic and anti-anabolic effects Anti-inflammatory + immunosuppressive effects Other effects: CNS, pituitary axis, psychiatric, renal, neonatal lung Effect concentration, distribution + **function of peripheral leukocytes** **Suppress inflammatory mediators** (cytokines + chemokines, as well as PGs + leukotrienes) Inhibit tissue macrophages + APCs Suppress mast cell degranulation Reduce antibody production (in large doses) **c) Cushings Syndrome** Metabolic effects (moon face, fat redistribution, striae, weight gain, myopathy, muscle wasting, thin skin, bruising, hyperglycaemia, osteoporosis, diabetes, aseptic necrosis, wound healing impaired Other effects (peptic ulcers, psychosis, depression, cataracts, glaucoma, salt retention, hypertension) **Adrenal suppression** (> 2 weeks dosage)	Bolded + one other Bolded + 3 others