CENTRAL NERVOUS SYSTEM

PHAN6014B

Time allowed: 2 hours

Part ONE

Answer ALL questions. For each question, there is ONE correct answer. Use the answer grid provided for ALL your answers.

Part TWO

Answer TWO of the THREE questions. Use a SEPARATE answer book for EACH question in Part TWO.

All questions have equal weighting. Answer ALL parts of each of the individual questions you select.

The mark allocation for the paper is:
- Part ONE carries 50% of the total mark
- Part TWO carries 50% of the total mark

This paper consists of 13 pages in total.

The following is provided: Multiple choice answer grid.

Notes are not permitted in this examination.

Do not turn over until you are told to do so by the Invigilator.

Do not take this question paper out of the examinations room.
PART ONE
SECTION A – TYPE 1 MCQ (Single Best Answer)

Answer ALL questions. For each question there is ONE correct answer. Use the answer grid provided for ALL your answers.

1. In terms of volume, which ONE of the following is the largest region of the human brain?
   (A) Brainstem  
   (B) Cerebellum  
   (C) Cerebrum  
   (D) Corpus callosum  
   (E) Diencephalon

2. Which ONE of the following is INCORRECT regarding 5-hydroxytryptamine (5-HT) in the human brain?
   (A) It is a neurotransmitter associated with neurons of the Raphe nuclei  
   (B) Its synaptic activity is enhanced by selective serotonin reuptake inhibitors (SSRIs)  
   (C) It is synthesized in the pre-synaptic terminal of the neuron  
   (D) 5-HT pathways are a major target of drugs used in treatment of epilepsy  
   (E) 5-HT signalling is a major target of drugs used in treatment of migraine

3. Which ONE of the following is INCORRECT regarding the N-methyl-D-aspartate (NMDA) receptor?
   (A) It has a glutamate binding site  
   (B) It has a glycine binding site  
   (C) It has a GABA binding site  
   (D) It has a Mg²⁺ binding site  
   (E) It has a polyamine binding site

4. Which ONE of the following is INCORRECT about the choroid plexus?
   (A) The choroid plexus is composed of epithelial cells  
   (B) The choroid plexus is found only in the lateral ventricles  
   (C) The choroid plexus serves as a barrier between the blood and the cerebrospinal fluid (CSF)  
   (D) The choroid plexus displays tight junctional networks  
   (E) The choroid plexus prevents passive protein leakage from the blood into the intraventricular spaces
5. Which **ONE** of the following best describes the composition of a functional LAT1 transporter?

(A) 4F2 heavy chain and CD98 light chain  
(B) 4F2 light chain and CD98 light chain  
(C) 4F2 light chain and 4F2 heavy chain  
(D) CD98 light chain and IgG heavy chain Fc domain  
(E) IgG heavy chain Fc domain and CD98 light chain

6. Which **ONE** of the following is **NOT** associated with the pathophysiology of Alzheimer's disease?

(A) Amyloidogenesis  
(B) Hyperphosphorylation of Tau  
(C) Neurodegeneration in the basal ganglia  
(D) Neurofibrillary tangles  
(E) Plaque formation

7. In terms of renal and hepatic impairment, which **ONE** of the following is **LEAST** appropriate regarding the use of memantine in treatment of Alzheimer’s disease?

(A) In patients with mildly impaired renal function, no dose adjustment is required  
(B) In patients with moderate renal impairment, the recommended daily dose is 10mg/day. If tolerated well after at least 7 days of treatment, the dose could be increased to 20mg/day according to the standard titration scheme  
(C) In patients with severe renal impairment, the recommended daily dose is 10mg/day  
(D) Due to possible increased exposure in mild to moderate hepatic impairment, dose escalation should be performed according to individual tolerability  
(E) Administration is not recommended in patients with severe hepatic impairment

8. Which **ONE** of the following has **NOT** been investigated as a drug discovery target for Alzheimer’s disease?

(A) β-secretase (BACE) inhibitors  
(B) Histone deacetylase (HDAC) inhibitors  
(C) Monoamine oxidase (MAO) inhibitors  
(D) N-Methyl-D-aspartic acid (NMDA) receptor  
(E) Proton pump inhibitors
9. Which **ONE** of the following is a motor symptom commonly associated with Parkinson’s disease?

(A) Depression
(B) Dementia
(C) Micrographia
(D) Sleep disturbance
(E) Sialorrhoea

10. Which **ONE** of the following best describes the pharmacological mechanism of action of rasagiline, a drug used in the treatment of Parkinson’s disease?

(A) It is an irreversible inhibitor of monoamine oxidase B (MAOB)
(B) It is a selective inhibitor of dopamine reuptake
(C) It is a selective catechol-O-methyl transferase (COMT) inhibitor
(D) It increases the enzymatic production of dopamine from L-DOPA
(E) It is a DOPA decarboxylase inhibitor

11. Which **ONE** of the following is **INCORRECT** about epilepsy?

(A) According to the World Health Organisation, it accounts for 0.75% of the global burden of disease
(B) Incidence rates are lowest in children
(C) The majority of cases are idiopathic
(D) It can be secondary to a brain tumour
(E) There can be a genetic component to the disease

12. Which **ONE** of the following is **CORRECT** regarding the biosynthesis of morphine?

(A) Demethylation of reticuline gives morphine
(B) Thebaine is a precursor of dopamine
(C) Dopamine is oxidised to papaverine
(D) Reticuline is a precursor of thebaine
(E) Tyramine is the precursor of tyrosine
13. Mr NM comes to the pharmacy to buy a packet of co-codamol 8/500 tablets for his headaches. The counter assistant tells you that he has been buying these every few days for the past two weeks. He takes no other medication and has no other medical conditions. Which ONE of the following would be the MOST appropriate action?

(A) Sell the co-codamol
(B) Recommend he tries co-codamol and ibuprofen
(C) Refer the patient to the doctor urgently
(D) Suggest he tries to go without using co-codamol for a while and then see the doctor if there is no improvement
(E) Recommend he tries sumatriptan

14. Which ONE of the following patients may NOT be able to safely receive epidural analgesia?

(A) A pregnant female patient
(B) A female patient with haemophilia
(C) A male patient who reports suffering from a severe headache following a previous epidural injection
(D) A female patient who has had a previous deep vein thrombosis (DVT)
(E) A male patient who takes medication to manage hypertension

15. Which ONE of the following is NOT an intravenous anaesthetic?

(A) Etomidate
(B) Isoflurane
(C) Ketamine
(D) Propofol
(E) Thiopental

16. Which ONE of the following classes of drugs would stimulate the production of aqueous humour?

(A) An α2-receptor agonist
(B) A β-receptor agonist
(C) A β-receptor antagonist
(D) A muscarinic agonist
(E) A muscarinic antagonist
17. The tear film is the first barrier encountered when considering drug delivery to the eye. Which **ONE** of the following statements is **INCORRECT** regarding the tear film?

(A) Human tear volume is estimated to be 7µl
(B) The cul-de-sac can transiently contain around 30µl of administered liquid formulations
(C) Most of any topically administered ocular drug solution is washed away in the time period 30-60 minutes following administration
(D) The tear film has a rapid restoration time of 2–3 minutes
(E) Mucin in the tear film forms a hydrophilic layer for clearing debris and pathogens
SECTION B – TYPE 2 MCQ (Extended matching questions)

Neurotransmitters

(A) Acetylcholine
(B) Dopamine
(C) γ-aminobutyric acid (GABA)
(D) Glutamate
(E) Glycine
(F) 5-hydroxytryptamine (5-HT)
(G) Noradrenaline

For each of the following statements, select the corresponding neurotransmitter from the list above. Each option may be used once, more than one, or not at all.

18. A neurotransmitter acting at ligand-gated Cl⁻ channels that are potentiated by benzodiazepines.

19. A neurotransmitter that is depleted in Parkinson’s disease from the neurons of the substantia nigra.

20. The major excitatory neurotransmitter in the central nervous system.

21. A neurotransmitter thought to cause the release of nitric oxide leading to the dilation of extracerebral blood vessels which result in throbbing pain in the head for a patient.
Epilepsy

(A) Carbamazepine
(B) Clonazepam
(C) Gabapentin
(D) Lamotrigine
(E) Lorazepam
(F) Sodium valproate
(G) Topiramate
(H) Vigabatrin

For each of the following statements, select the most appropriate anti-epileptic drug from the list above. Each option may be used once, more than once, or not at all.

22. A drug whose primary pharmacological action is to inhibit the conversion of γ-aminobutyric acid (GABA) to glutamate.

23. Mr TS is 46 years old and has requested a private conversation with you about his hair loss. He thought he was losing his hair because of his age, but it is now growing back curly. Which medication is most likely to be causing these side-effects?

24. Mrs JM is currently taking carbamazepine for focal seizures, but is not well controlled. The clinician asks for advice regarding adjuvant medication. Which medication would be most suitable?
Migraine

(A) Co-codamol 8/500 tablets
(B) Eletriptan tablets
(C) Ibuprofen tablets
(D) Migraleve pink® tablets
(E) Naratriptan tablets
(F) Paracetamol tablets
(G) Sumatriptan nasal spray
(H) Zolmitriptan orodispersable tablets

For each of the patients described, select the most appropriate therapy from the list above. Each option may be used once, more than once, or not at all.

25. A migraine sufferer who has very intense, quick onset, headaches at the start of the attack, together with lots of nausea and vomiting.

26. A migraine sufferer who has slow onset migraine which lasts for two days with moderate intensity.

27. A migraine sufferer with uncontrolled blood pressure and allergy to aspirin.
Analgesia

(A) Amitriptyline
(B) Aspirin
(C) Codeine
(D) Diamorphine
(E) Fentanyl
(F) Methadone
(G) Naproxen

For each of the patients described, select the most suitable therapy from the list above. Each option maybe used once, more than once or not at all.

28. Mrs ST, a 55 year old lady with no previous medical history, has recently fractured her wrist. She has been taking paracetamol and ibuprofen for analgesia, though she tells you that the pain is not being managed.

29. Mr PH, a 65 year old man with no previous medical history, has been diagnosed with shingles and has been experiencing neuropathic pain.

30. Mrs WY, a 74 year old lady diagnosed with palliative oesophageal cancer, is currently taking paracetamol and oral morphine for her pain. She has been having trouble swallowing and the doctors want to switch her analgesia to a patch.

END OF PART ONE
PART TWO

Answer TWO of the THREE questions. Use a SEPARATE answer book for EACH question.

31. Answer ALL parts (a) to (c).

(a) Critically appraise the role of passive and active mechanisms for drug transport across the blood brain barrier. Use graphs and diagrams in your answer to illustrate your point. [50%]

You are a basic grade hospital pharmacist on your rotation of the neurology wards. You encounter Mr GH who was admitted earlier this morning for a chest infection which was due to aspiration. Mr GH is 75 years old with a diagnosis of Parkinson’s disease. His medication history is co-beneldopa 25/100, four capsules three times a day and metoclopramide 10mg tablets three times a day when required. The foundation year doctor would like to start him on metronidazole and amoxicillin three times a day for the chest infection.

(b) Co-beneldopa is a combination product of levodopa and benserazide. Explain why levodopa is administered in preference to dopamine and the role of benserazide in this combination product. [30%]

(c) Discuss the pharmaceutical issues that should be investigated to ensure that Mr GH’s medication is appropriately managed during his admission and that he is appropriately prepared for discharge. [20%]
32. Answer **ALL** parts (a) to (d).

(a) Describe the neurochemical changes that occur in relation to acetylcholine-dependent signalling in the pathophysiology of Alzheimer’s disease. [20%]

(b) How do acetylcholinesterase inhibitors affect cholinergic signalling? [15%]

(c) Donepezil is an acetylcholinesterase inhibitor that is used in the treatment of Alzheimer’s disease.

\[ \text{donepezil} \]

(i) Show reagents and conditions for the following two steps (A and B) in donepezil synthesis.

(ii) Suggest reasons why the drug is marketed as the racemate rather than a single enantiomer. [10%]

(d) Mrs CP is a 76 year old lady, who has received a new prescription for donepezil 10mg daily. She is also currently prescribed: Propranolol 10mg three times daily, Paracetamol 1g QDS prn.

(i) Mrs CP has been experiencing symptoms such as nausea, sickness, dizziness and fatigue since starting her new medication. What might be the cause? [20%]

(ii) Discuss your possible interventions. [15%]
33. Answer ALL parts (a) to (e).

(a) Describe the physiological transmission of a pain signal. [30%]

(b) Explain how states of hyperalgesia could develop. [10%]

(c) During pain signal transmission, explain where opioid drugs could exert their effect. [15%]

(d) For the following three molecules, discuss with reference to the Snyder theory, whether they would act as agonists or antagonists or show mixed behaviour at opioid receptors. Use diagrams to illustrate your answer.

![Diagram of molecules](image)

[20%]

(e) Compare and contrast, with examples, two different approaches currently being investigated to develop opioid analgesics with reduced side effects. [25%]

END OF PAPER