Alzheimer's Disease Clinical – from the WS

DIAGNOSIS

FIRST: Rule out organic causes of cognitive decline before considering AD

- Check electrolyte imbalances all U&E (renal failure or hyperuraemia can cause confusion)
- Assess metabolic disturbances
    - Low B12 and folate (low levels can cause memory impairment and mood changes
    - Thyroid function test (TFT) rules out hyperthyroidism which can cause dementia like presentation
    - Blood glucose (diabetes itself is risk, hypo can caus confusion
    - Liver function test (LFT) to rule out metabolic dysfunction e.g., hyperammonaemia in liver cirrhosis
- Infective screening
    - CRP – C reactive protein
    - FBC – full blood count
    - Temperature
    - Urine MSU (not dipstick for patients above 65 when assessing UTI)
- Refer for imaging
    - Full medical history to identify risk factors e.g., FH, genetics, alcoholism
    - ADLs (activities of daily living) check
    - CT brain to rule out stroke/tumour
    - Help identify small vessel disease suggestive of vascular dementia

SECOND: when all organic causes are ruled out refer to a specialist memory service

- Start behavioural and cognitive assessment
- AMTS (abbreviated mental test score) to determine memory problems present (10Q)
- MMSE (mini mental state examination score) to assess severity
    - 21-26 mild, 10-20 moderate, 10-14 moderately severe, less than 10 severe

TREATMENT

Acetylcholinesterase inhibitors are licensed for treatment of mild-moderate dementia of AD type

- No CVD issues
- No swallowing difficulties suggesting he would need a non-solid formulation
- Donepezil, rivastigmine, galantamine – all clinically fine
- NICE endorse to start with the drug with the lowest acquisition cost
- Most cost-effective choice is donepezil tablet 5mg OD (considering administration and acquisition – they are all available in generic)

Donepezil 5mg OD counselling:

- Tablet should be taken in the evening
- At least a month at 5mg OD will be needed to determine if its working
- Could be titrated up after a month
- Continued reassessment needed every 3 months to check therapeutic effects
- S/E common: nausea, diarrhoea, headache
- nausea: stick to simple foods, avoid fatty or spicy meal
- For Diarrhoea – drink plenty of fluid
- Headache – simple analgesia may help
- Changes in mood, behaviour, sleep (strange dreams)
- **donepezil should only be started if a caregiver is available to regularly monitor drug intake
- Due to pro-cholinergic effects, urinary incontinence is a common side effect it would be resolved upon withdrawal

Ebixa is memantine, a glutamate receptor antagonist - for moderate to severe AD

➔ Monotherapy is recommended for AD patients who are intolerant or C/I to AChE inhibitors or severe AD

Will the drugs work?

- Explain realistically AD is neurodegenerative and patients do deteriorate over time, it is impossible to predict the rate of decline, social interactions important
- On average about half the patients that take it tend to decline slower

Oxybutynin 5mg TDS

- Oxybutynin crosses the BBB and counteract any effects of donepezil on UT, but also remove cognitive support from donepezil
- Anticholinergic action in blocking the muscarinic effects of AChE on smooth muscle
- An anticholinergic would counter act effects of pro-cholinergic effects of donepezil
- Instead prescribe mirabegron – a beta-3-adrenergic drug with less cholinergic burden, less risk of confusion, helps with urinary incontinence as well as not interacting with donepezil

Use of antipsychotics

- Challenging for AD patients as it can significantly increase their risk of stroke
- To treat aggression in patients with moderate to severe AD – ONLY Risperidone is licensed
    - For a maximum of 6weeks, max dose at 1mg BD
- If patient prescribed with other antipsychotics e.g., lorazepam check:
    - How their symptoms are
    - How are the drugs being used
    - Are the symptoms worse at night or during the day – sundowning?
    - Is the carer getting enough rest and support?
    - Assess severity of patient via neuropsychiatric inventory (NPI)
    - Assess carer givers distress test

MANAGEMENT

Sleep: sleep hygiene methods, zopiclone short-term sleeping aid + monitor risk of falls in elderly

Non-pharmacological therapy

- Behaviour management techniques
- Cognitive/emotion-oriented interventions: reminiscence therapy, stimulated presence therapy (SPT), validation therapy, reality orientation therapy
- Sensory stimulation interventions: acupuncture, aromatherapy, light therapy, massage and touch therapy, music therapy, Snoezelen multisensory stimulation therapy, transcutaneous electrical nerve stimulation (TENS)
- Other psychosocial interventions: animal assisted therapy (AAT), exercise
- Various interventions targeting a specific behavioural symptom such as wandering, agitation, inappropriate sexual behaviour

Support for carers:

- Dementia UK, Alzheimer's society, NHS website, carers UK, talking to carers

Epilepsy Clinical – from the WS

Diagnosis of epilepsy

- Refer to specialist
- Record seizure attack to determine if it was epileptic
- EEG (gold standard), blood tests, MRI/CT (structural abnormalities), ECG (arrythmia), U&E, neuropsychological assessment, antibody testing (autoimmune encephalitis?)

Risk Factors: head trauma, stroke, brain tumour, infections e.g., meningitis, encephalitis, multiple sclerosis (degenerative brain disorder)

Generalised Seizure					
Increased neuronal activity that is widespread across both hemisphere of the brain – majority of patients have impaired awareness					
Motor					Non-motor
Tonic	Atonic	Myoclonic	Clonic	Tonic-clonic	Absence seizure
Stiffness and extension of limbs Consciousness impaired Seizures are brief and only last seconds	Sudden loss of muscle tone Seizures are brief	Abrupt muscle jerks affecting upper limbs Consciousness not affected	Loss of consciousness Rhythmic symmetrical shaking of limbs, face and neck due to rapidly alternating muscle contraction and relaxation	Initial tonic phase (loss of consciousness) Becomes rigid and falls Clonic phase of jerking Convulsions last 2-3minutes Person remains unconscious up to a few hours – tired confused	Person will stop moving and have a fixated stare for at least 10 seconds

Focal Seizure		
Increased neuronal activity originating and remaining in one hemisphere of the brain.		
Simple focal (awareness)		Complex focal (impaired awareness)
Motor onset	Changes in muscle activity • Jerking (clonic) • Stiffness (tonic) • Loss of muscle tone (atonic) • Quick involuntary muscle jerk (myoclonic) • Automatism (repeated movements: lip smacking, repetition of words, pacing) • Hyperkinetic – irregular big movements • Epileptic spasms – sudden flexing, extending of trunk NO TONIC CLONIC	
Non-motor onset	• Autonomic - changes in HR, breathing or colour (autonomic) • Behavioural arrest - blank stare, stop talking, stop moving • Cognitive changes - confusion, slowed thinking, problems talking, understanding • Emotional – sudden fear, dread anxiety/pleasure Sensory – changes in hearing, vision, taste, tingling or pain	

Status epilepticus: prolonged convulsive seizure lasting 5 minutes or longer or recurrent seizures one after the other without recovery in between

- ➔ Triggered by head injury, metabolic disturbance (hypoglycaemia), cerebrovascular event (stroke), alcohol withdrawal
- ➔ Medical emergency: buccal midazolam or rectal diazepam given
- ➔ In hospital setting – give IV lorazepam max of 4mg or diazepam
- ➔ Give second line IV AED phenytoin, fosphenyotin sodium, phenobarbital

	Indications	S/E	Note	Monitoring
Sodium Valproate Cat 2 (involve GP)	1st line: generalised tonic clonic, myoclonic, tonic, atonic 2nd line add on: focal seizure	Nausea, weight gain (PCOS monitoring), LFT elevation, blood dyscrasias, alopecia, liver toxicity	Cause birth defects and developmental disorders, half life 8-20h, metabolised via liver, CYP inhibitor	LFT conducted before starting and w/i 6months Full blood count before starting Monitoring liver disorder and blood dyscrasias
Carbamazepine Cat 1 (need brand consistency)	2nd line: focal seizure Last line consideration for generalised tonic clonic Other indications: bipolar unresponsive to lithium, trigeminal neuralgia	Drowsiness, dry mouth, nausea, vision disorder, blood disorders (leucopenia, eosinophilia, thrombocytopenia), hyponatraemia (low sodium levels), skin disorders	CYP inducer, multiple formulations, Metabolised in the liver, autoinduction tf half life drug altered after continued administration	Pre-screening: Chinese or thai – allele HLA-B*1502 (due to increased risk of steven johnson syndrome in patients with this allele) Plasma concentration needs to be 4-12mg/L after 1-2 weeks - Oxcarbazepine - Eslicarbazepine ** interaction with quinolones antibiotics Use nitrofurantoin
Ethosuximide Cat 3 can switch but consider non clinical issues	1st line: absence, childhood absence, epilepsy syndrome Licensed for myoclonic seizure on SPC not NICE	Gi discomfort, anxiety, sleep disturbance, ataxia, drowsiness, blood disorders, rash (steven johnson syndrome)	Absorbed well orally, metabolised in the liver, soft capsule or syrup forms - Increased plasma concentration with phenytoin, carbamazepine	Monitor for blood dyscrasias (fever rash, mouth ulcers, bruising, bleeding), Monitor suicidal behaviour
Lamotrigine Cat 2 (involve GP)	1st line: focal, generalised tonic clonic, absence, tonic, atonic 2nd line: myoclonic	Dizzy, drowsiness, headache, dry mouth, diplopia, rash, hypersensitivity, suicide, blood disorder	Hepatic enzyme inducer or inhibitor, autoinduction (does not affect AED pharmacokinetics)	Skin reaction, bone marrow failure (anaemia, bruising, infection) COMBINED ORAL CONTRACEPTIVE AFFECT metabolism

Levetiracetam Cat 3 can switch but consider non clinical issues	1st line: focal, myoclonic 2nd line: absence, epilepsy syndrome Monotherapy for certain epilepsy unlicensed	Drowsy, dizzy, GI discomfort, asthenia, insomnia, behaviour abnormalities, rash, Rare suicidal, thrombocytopenia, leukopenia	Oral bioavailability 100% linear pharmacokinetic profile, plasma level predictable, not metabolised in the body and large proportion excreted through the kidney, does not involve CYP hepatic	General counselling for AED
Phenobarbital Cat 1 (need brand consistency)	NO 1st line Only 2nd line for tonic clonic, 3rd line for focal, myoclonic Absence seizure not licensed	AED hypersensitivity (steven johnsons syndrome), bone fractue, bone disorder, blood disorder, folate deficiency, drowsiness, suicidal, hepatic disorder	CYP450 inducer Present in breast milk, cross placenta, partly metabolised by liver, excreted through kidney	Optimum plasma conc: 15-40mg/L but due to tolerance not useful, monitor suicidal, skin reaction
Phenytoin Cat 1 (need brand consistency)	NO 1st line Add on 3rd line for focal seizures	Drowsy, confusion, hirsutism, gingival hyperplasia, bone marrow disorder Toxicity: nystagmus, dipolpia, slurred speech, ataxia, hyperglacaemia	Highly protein bound – albumin levels shd be checked First order elimination, non linear kinetics, CYP450 inducer	Pretreatment necessary for patients with HLAB*1502 allele increased risk of steven Johnson's syndrome Monitor for blood dyscrasias, skin disorders IV – monitor ECG, BP

Ketogenic diet (high fat, low protein, low carb) treatment for patient struggling to treat epilepsy

Pregnancy prevention due to childbirth defect, highly effective contraception essential for enzyme inducers, sodium valproate, lamotrigine

- Copper coil
- Levonorgestrel IUD
- Progesterone implant

Even after stopping AED – continue this for 4 months

Stop AED when 2years no seizure: discontinue in 2-3months

From WS

Levetiracetam or lamotrigine (first line choice) – safe in patients in childbearing potential

Zonisamide 100mg OD (2nd line monotherapy option)

- Requires women to be highly effective contraception (intrauterine devices e.g., copper coil, levonorgestrel IUD or progesterone implant) due to its teratogenic effect (risk of fetal abnormalities)
- Non-enzyme inducer AED tf, does not alter the efficacy of contraception
- S/E risk of heat stroke – adequate hydration crucial, hypersensitivity reaction, blood disorders

Carbamazepine 100mg BD counselling points (category 1 AED):

- Do not stop medication abruptly
- Needs to stay on the same brand of medication
- S/E drowsiness, fatigue, GI discomfort, leukopenia (not enough leukocyte), eosinophilia (increased number of eosinophil), thrombocytopenia (platelet deficiency)
- Risk of hypersensitivity syndrome: monitor for blood dyscrasias, seek medical attention if experience fever, rash, mouth ulcers, bruising, bleeding

Non-pharmaceutical advice:

- Driving – inform the DVLA – need to be 1 year seizure free before you can drive, if weaned of antiepileptics then patients should not drive during that period of a further 6 months
- Triggers – sleep deprivation, alcohol, flickering lights, recreational drugs (drugs e.g., tramadol, quinolone and carbapenems)
- Careful at home - seizures while taking a bath can be dangerous, risk of hitting a window during seizures should be prevented
- Consider age and discuss contraception and plans to have a baby

➔ Use of highly effective contraception: progesterone only injection, levongesterol IUD, Cu IUD

Drug interaction issues

EX1) carbamazepine 400mg BD + ciprofloxaxin 500mg BD for UTI

- Drug disease interaction exists (DOES NOT APPEAR ON BNF) – ciprofloxacin can lower the seizure threshold and thus should be avoided in epileptic patients
- Quinolones (antibiotics) generally known to induce seizures
- Multiple indications for carbamazepine, can be used for neuropathic pain, so first check
- Offer alternative antibiotic therapy – Trimethoprim (but can cause hyponatraemia with carbamazepine, Nitrofurantoin (best alternative depending on patient renal function)

EX2) Lamotrigine therapy and severe rash

- Check if anything new started or changed there could be other cause for rash
- Rash is rare but reported ADR of lamotrigine - urgent GP referral to consider alternative therapy

EX3) phenytoin 300mg OD -> phenytoin level 10mg/L

Before interpreting phenytoin levels check:

1) Has there been recent dose changes? It can take 5-14 days to reach steady state
2) Phenytoin interacts with many drugs check if there any new drugs
3) Check albumin level, as phenytoin is highly protein bound, if the patient has low albumin, then true free concentration not reflected
4) Check adherence – has the patient been taking their medication
5) Time of level – should be pre-dose trough level (bc of long-half life and helps ensure measurements are taken consistently at the same time when the serum concentrations are least likely to vary – usually w/I 1 hour of dose being due)
6) Check formulation, whether patient taking tablets or capsules bc difference in phenytoin base levels

➔ Phenytoin dose not display linear pharmacokinetics tf, would not expect a dose increase to result in predictable increase in therapeutic levels, so dose increase not recommended

EX4) NIL by mouth patient taking carbamazepine MR 200mg BD

- Available as a suppository but dose not equivalent
- 100mg tablet = 125mg suppository (BNF indication section) 25% increase (SPC)
- Thus, give suppository 125mg QDS and monitor clinical response or 250mg BD

EX5) Sodium valproate 1g BD for generalised tonic-clonic seizures wanting to add lamotrigine

- Higher risk of liver toxicity when more than one antiepileptic is used with sodium valproate
- Is it appropriate for patients' seizure type?
    - Lamotrigine is 1st line or add on for focal seizures, generalised tonic-clonic seizures, absence seizures and tonic, atonic seizures
- Valproate can increase plasma concentration of lamotrigine tf, need to consider dose titration
- Can sodium valproate be discontinued instead – reduced slowly?

Parkinson's Disease Clinical – from the WS

Sinemet – co-careldopa (100mg L dopa + 25mg carbidopa)
Co-beneldopa is different

Nausea vomiting and orthostatic hypotension are the most commonly encountered side effects of levodopa therapy -> increase levodopa more slowly or co-prescribe antiemetic domperidone

Levodopa therapy stimulates dopamine receptors found in the peripheral areas of the gut and vomiting centre

- ➔ Metoclopramide is contraindicated in PD as it blocks the dopaminergic transmission
- ➔ Domperidone 10mg TDS is an appropriate alternative antiemetic – it reduces dopaminergic transmission but does not pass the BBB tf, safe to use in PD

Refer patient to Parkinson's/neurology specialist – patient may have developed postural hypotension as a result of the increased levodopa dose so return to original dose
Tamsulosin causes postural hypotension – is it necessary?
Copcareldopa tablets – dispersible in water so thicken fluid
Dompeidone available as suspension
Stop statin
Aspirin stop

Treatment of Parkinson's Disease				
Type	Drug	Explanation	Monitoring parameters	Counselling points
	Levadopa			
Dopa decarboxylase inhibitor	Cabidopa			
	Benserazide			
COMT inhibitor	Entacapone			
	Tolcapone			
Dopamine Receptor Agonist (Non-ergot derived)	Ropinirole			
	Rotigotine			
	Pramipexole			
Dopamine Receptor Agonist (Ergot derived)	Bromocriptine			
	Cabergoline			
	Lisuride			
	Pergolide			
Monoamine oxidase B inhibitor	Selegeline			
	Rasagiline			
	Amantadine			

Pain Pharmacology - STOKES2591

Pain: protective response, raise awareness of damage and help immobilise damaged area to facilitate healing

- Unpleasant sensation perceived as arising from a specific region of the body and commonly produced by processes that damage or are capable of damaging, bodily tissue

Somatic pain – post operative, mild trauma / Visceral pain – post operative, cancer, trauma /
Neuropathic pain – amputation, DM2 (damage to nervous system) / Sympathetically maintained pain – CRPS
Nociception: detection of noxious stimuli

Difference between ascending pathways and descending pathways
1>Directionality 2>Starting and ending point 3>Neurotransmitters involved

Ascending pathways	Descending pathways
- Trauma is detected and chemical mediators are released e.g., ATP, bradykinin, prostaglandins, histamine, 5-HT and H+	- Originate in the brain, from distinct regions periaqueductal grey (PAG) in the midbrain and locus ceruleus (LC), project down to the spinal cord where they modulate the activity of central synapse in the spinal cord
- Starts in periphery where nociceptor ending is located, signal travels to the spinal cord where they terminate in dorsal horn of the spinal cord in different laminae (layers)	- Descending inhibitory neurons can directly inhibit transmission through the central synapse by releasing endorphins/enkephalins to act on opioid receptors – inhibitory GPCR which can inhibit neurotransmission by acting on NT release (inhibit CaV channel) or an action potential generation by activating K channels and increasing hyperpolarisation
- Synapse with second neurons which projects to the brain, ascends through spinothalamic tracts to the thalamus and the higher brain – somatosensory cortex, limbic system, cingulate and insular areas	- Activate short inhibitory interneurons in the spinal cord which will inhibit pain transmission
- Nociceptive fibres A delta and C fibres are involved A delta fibre – enters the dorsal into laminar I and V, involved in first pain, informative to move away ➔ myelinated C fibre – has polymodal stimuli and enters the dorsal into laminar I and II and V via dendrites, involved in second pain, dull and long lasting ➔ unmyelinated (Not a nociceptor but beta fibre enters the superficial layer of the dorsal horn and can dampen down pain e.g., by rubbing)	- Inhibitory interneurons are present throughout dorsal horn in lamina I and II - Pathway originating from PAG involves 5-HT NT - Pathway originating from LC involves NA NT
- This pathway is excitatory - Synapse uses glutamate as NT - Not a single pain centre in the brain - Instead, the somatosensory cortex processes the information/intensity and the amygdala affect the emotional response -> help direct away from danger	- Opioids have different actions on the pathways: • Inhibit ascending excitatory pathway • Potentiate descending inhibitory pathway

Co transmission – substance p, CGRP neurotransmitter released alongside with glutamate

Ways in which transmission of nociceptive signals can be altered at the spinal cord:

1. Activate inhibitory interneurons (gate control)
- Inhibitory interneurons regulate amount of transmission of nociceptors and how much of the signal is sent to the brain known as gate control
- Enkephalins are endogenous opiates that activate these short inhibitory interneurons at the spinal cord
- Activate local inhibitory interneurons – release GABA and dampen down transmission
2. Descending inhibitory pathway can be activated to reduce transmission
- PAG – 5-HT and LC – NA
- Enkephalins also stimulate these pathways
3. A beta fibre activation e.g., by rubbing reduce pain signal transmission and dampens the pain
4. Neuropathic pain is damage to the nerve fibres themselves
- Hyperalgesia: enhancement of pain signals (central sensitisation)
    - Anything that increases in NMDA receptor signalling, elevation of cytosolic calcium ions in the post synapse, works similarly to LTP and strengthening pain signals result in more pain
    - Shot inhibitory interneurons no longer control transmission, GABAergic or glycinergic inhibitory neurons lose its inhibitory effect and enhance depolarisation and cause excitation
    - Glial neurons e.g., microglial release inflammatory cytokines enhancing neuronal central sensitization, e.g., ATP acting on P2X4 release BDNF from microglia, alters effect of GABA and becomes excitatory, prolonged inflammation causes chronic pain
5. Opioids
- Reduce transmission at central synapse – presynaptic neuron will reduce NT release –this reduces excitation at the post synapse by inhibiting calcium ion channel and activating potassium ion channels leading to hyperpolarisation
- Opioid receptors all signal through GPCR Galpha i/o
- Mu opioid receptor (MOR), delta opioid receptor (DOR), kappa opioid receptor (KOR), orphan receptor (ORL1)

Nociceptor afferent terminal channels ->Initiate action potential in the nociceptors

TRPV1
- Non-selective cation ion channel activated by various stimuli
- Influx of sodium and calcium ion causes depolarisation

ASIC – tissue damage acidic environment
- Responds to high concentration of protons
- Cation selective ion channel
- Its activation will cause depolarisation

P2X receptor – ligand gated ion channels found on nociceptive endings (activation)
- Responds to high concentration of ATP
- Cation selective ion channel
- Its activation will cause depolarisation

NaV – if damaged cannot feel pain, important pharmacological
- Important in propagating action potential and releasing NT to pass message to central synapse
- Depolarisation within the cell activates the voltage gated sodium channel
- Contributes to depolarisation of the cell
- Leads to action potential generation

B2 receptor
- Responds to bradykinin an inflammatory mediator released by immune cells
- It is a PKC coupled receptor -> phosphorylate TRPV1 -> enhance depolarisation
- Also release prostaglandins that act on the prostanoid receptor, which is PKA coupled and activate various ion channels and inhibits potassium ion channels affecting the overall level of depolarisation

Drugs that could be used in the treatment of neuropathic pain:

1. Gabapentin/pregabalin – p/q voltage gated calcium channels – blocking – oscilliating subunit and interfere with how the channel works
    - Located in presynaptic terminal of the dorsal horn synapse regulate NT release, dampen down through central synapse
2. Ziconotide – peptide that target voltage gated calcium channel (not given orally) like pregabalin and gabapentin
3. Amitriptyline – TCA, act on SERT and NET, increase 5HT and NA levels, potentiate descending inhibition, and stop neuropathic signal
4. Lidocaine (topical lidocaine) inhibit voltage gated sodium channels and prevent nociceptor firing
5. Ketamine – act at NMDA receptor
6. Capsaisin patches – agonist at TRPV1 ion channel – regular administration cause desensitisation

Pain

➔ An unpleasant sensory and emotional experience associated with or resembling that associated with, actual or potential tissue damage

Measure pain by scale of 1 to 10 or pictorial scale for kids
Use WHO analgesic ladder
1) Non-opioid analgesia
2) Opioids
3) Adjuvant therapies

1) Chronic pain		
2) Musculoskeletal pain		
3) Lower back pain/ sciatica		
4) Osteoarthritis		
5) Rheumatoid arthritis		
6) Neuropathic pain		
7) Non-specific persistent pain		
8) Chronic headache		
9) Acute pain		
10) Pallative care		

Post Operative Pain – Patient controlled analgesia (PCA)

Epidural Anaesthesia

General Anaesthesia

➔ Act on brain to produce loss of sensation, affect synaptic transmission and neuronal excitability rather than axonal conduction, small lipid soluble molecules that readily get access to the brain by crossing the BBB

➔ Ideal general anaesthetic should be readily controllable so that induction and recovery of anaesthesia can be rapid

	Intravenous anaesthetics	Inhaled anaesthetics
Role	Induction Occurs quickly in seconds, as soon as the drug reaches the brain	Maintenance Pharmacokinetics important
Examples	Thiopental	Halothane
	Propofol	Isoflurane
	ketamine	Nitrous oxide
Notes		

➔ Mechanism of action of anaesthetic: anaesthetic molecules bind to hydrophobic pockets within specific membrane protein target

$GABA_A$ receptors		
Glutamate receptors		
Voltage gated ion channels	Sodium	
	Potassium	
	Calcium	

Define the effect of general anaesthetic drugs
Where they act to exert effect on physiology
Inhaled anaesthetics
Intravenous anaesthetics
Major factors that affect induction and recovery from anaesthesia
Minimal alveolar concentration is a measure of drug potency
Mechanism of action of anaesthetic drugs

Explain why the induction of anaesthesia with intravenous anaesthetic is rapid. (5%)
Discuss why there is slow elimination of thiopental from the body and suggest an alternative intravenous anaesthetic that could be used, stating its advantages (15%)
Describe the main stages of anaesthesia and how this affects normal physiological function (15%)
Discuss what regions of the brain are involved when a patient undergoes anaesthesia (10%)

Nausea and Vomiting

1. Stimulation of back of throat
2. Noxious chemicals
3. Distension or irritation of stomach or duodenum
4. Rotation or acceleration of the head
5. Elevated intracranial pressure
6. Emotional factors

3 major inputs to NTS (nucleus solitary tract in medulla 'vomiting centre')

1> Chemoreceptor trigger zone (CTZ)/Area Postrema (AP) same thing

- Located at the base of 4th ventricle
- D2 receptors on CTZ/AP (dopamine agonists have pro-emetic effects)
- No BBB, the gaps between allow substances in blood to pass through vascular endothelial cells
- Detects noxious chemical such as bacterial toxins from food, poisonous alkaloids, and drugs to trigger nausea and the vomit reflex
- Dendrites from NTS connects to CTZ/AP coordinating the vomit reflex

2> Vestibular system

- H1 histamine receptors
- Muscarinic 3 and 5 receptors

3> GI tract – enterochromaffin cells

-

2 outputs from NTS:

1> Nausea:

- Learned aversion to casual agents to avoid in future – new behaviour formation
- Vasopressin (ADH) is released during nausea – could be a drug target in future

Vomit reflex – motor pathways	
Autonomic response	Somatomotor response

CAUSES

Types

***Referral required when:

- Severe symptoms: projectile vomiting, sour smelling vomit (both pyloric stenosis: narrow of outlet from stomach risking blockage), blood in vomit, severe diarrhoea, weight loss, abdominal pain (maybe appendicitis, hernias), vertigo (may be meningitis, head injury or meniere's)
- Duration of symptoms too long leading to dehydration, renal impairment, electrolyte abnormal

Antiemetic drugs				
	Target	Examples	S/E	Notes
H1 antagonist (antihistamine)		Cinnarizine, promethazine, cyclizine		
Muscarinic antagonist (anticholinergic)	Motion sickness involved in vestibular pathways	Hyoscine	Anti-muscarinic: dry mouth, dry skin bc	
D2 antagonist		Prochlorperazine		
		Metoclopramide		
		Domperidone		
5-HT3 antagonist		Ondansetron, granisetron, palonosetron		
NK1 antagonist		Aprepitant, fosaprepitant		
CB1 agonist		Nabilone		
Corticosteroids		dexamethasone		
Other treatments				

Muscle Relaxants

- Target nicotinic receptors, which are cation ligand gated ion channels (mediate fast excitatory synaptic transmission) – located at muscle, autonomic ganglia and CNS
- Nicotine mimics the action of endogenous agonist acetylcholine (a non-selective agonist)
- Selective agonist: succinylcholine is selective for muscle nAChR
- Five subunits, all nicotinic receptors have 2 alpha subunits acting as binding pockets
- Four transmembrane domain, M2 domain lining the pore (with negatively charged AA) selective for cations to pass through
- Opened channel allow sodium ions inside causing depolarisation leading to action potential fire and contraction of skeletal muscle

Methods of neuromuscular blocking		
	1> Non-depolarising block	2> Depolarising block
Explained		
Method		
Clinical use		
Note		

Headaches – Migraine

Headaches: symptom not disease	
Tension Headaches	Cluster Headaches
Most common, due to muscle spasm in neck/scalp, could be caused by emotional stress. Pain is mild to moderate, non-throbbing, feeling of tightness or squeezing or weight on the head Affect both side of head	More common in men (x6-9), excruciating severe unilateral pain, affect nasal eye symptoms e.g., droopy eyelid, eyelid oedema, nasal congestion ➔ Mistaken for eye injury Sudden onset, intermittent onset (multiple times x8 a day), last between 10min to 3H

WHO pain ladder:

1> Pain score 1 (mild): paracetamol (1g 4-6hrly) max 8

2> Pain score 2 (moderate): paracetamol + codeine 30-60mg 4-6H could + ibuprofen 400mg 6-8H
   a. Weak opioid of max 24mg at OTC not EBM

3> Pain score 3 (severe): paracetamol + appropriate opiate/opioid e.g. morphine, fentanyl, oxycodone -> need break through dose
   a. Need break through dose of 1/6th of opioid for stable pain management

Migraine		
Epidemiology	Pathophysiology	Types of migraine
Common condition – 3x in women 190,000 attacks in the UK each day Under diagnosed and under treated Pharmacist important role Less migraines with age	- Genetic link of chromosomal 19 and 1 - Familial hemiplegic migraine: migraine with aura + motor weakness on one side of body ➔ Chromosomal defects present from 10 genetic polymorphism that impair calcium channels involved in 5HT release ➔ 5HT implicated in pathogenesis	1. Classical migraine (15%) - Has aura, visual disturbance, photoneurological disturbance
	Theory 1 – Vascular theory (disproved) - Vasoconstriction = aura - Vasodilation = headache	2. Common migraine (80%) - w/o aura, prodrome then headache, N&V, dislike light/sound
	Theory 2 – Brain hypothesis - Increased extracellular potassium decrease blood flow - Spreading neuronal inhibition	3. Abdominal migraine - In children, have GI symptoms
	Theory 3 – Sensory nerve hypothesis - Activation of trigeminal nerve goes to meninges and inflammatory mediators are released	***childhood travel sickness leads to migraine – not fully understood
KEY SYMPTOMS		
1) Prodrome – before headache, heightened sensation, foreboding 2) Aura – fortification spectra (zigzag lights), flashing lights, scotoma (blind patch in visual field), paraesthesia (pins&needles) 3) Headache – unilateral or pulsatile 4) Others: photophobia, phonophobia, N&V, speech difficulties (less common)		

Diagnosis		
International Headache society diagnosis	NEED at least 2 +	NEED at least 1
	Unilateral pain	N&V
	Throbbing pain	
	Aggravated by movement	Phono or photophobia
	Moderate or severe intensity	
	+ five or more attack lasting 4-72H meet the criteria to diagnose as migraineur	
	Suspected meningitis e.g., non-blanching rash, neck stiffness (neck to chest test)	

Differential diagnosis		
	Red flag	Subarachnoid haemorrhage (loss of blood flow) – worst ever headache, occipital area
		History of trauma/fall with loss of consciousness
		Suspected temporal arteritis: temple/scalp painful to touch usually in age >55 (steroid need)
	Refer to GP	Headache lasting more than 24H w/o ease
		Headache ease as day progress – effortless vomiting in the morning (can be brain tumour)
		Headache with unsteadiness/clumsiness esp in children
		Children under 12 – if headache not ease
		Suspected ADR (w/ nitrates, GTN, CCB etc) to look at alternative

Trigger Factor Management – use point system	
Anxiety/emotions	Relaxation, coping strategy – exercise, yoga, meditation
Changes of habit	Usually eating and sleeping habit maintained
Specific food triggers	Chocolate, coffee, alcohol, dairy products avoided (consult dietitian if necessary)
Bright lights and noise	AKA photophobia, phonophobia – avoid
Hormonal changes	HRT, contraceptive pill, pregnancy (decrease)

Treatment of Migraine				
	When is it used?	Drugs		Note
Simple analgesic	Help control pain • Reach shared agreement • Patient specific strategy	Aspirin 900mg Ibuprofen 400mg Paracetamol 1000mg		Could recommend dispersible of effervescent BC with nausea, GI tract not working and need product that can rapidly be absorbed *Higher salt content – CVD risk, salt restricted diet patient warning * Can be with caffeine (help absorb, but trigger) or codeine
		Migraleve		Pink tablet (onset of attack) Buclizine (antihistamine) + paracetamol + codeine
				Yellow tablet (during attack) Paracetamol + codeine
		Buccastem M		3mg Buccal prochloperazine – work on chemorecptor trigger zone
Abort or treat acute attack	Used to abort or treat an acute attack *If symptoms disappear after but then reappear take 2nd dose after 2H * Symptoms do not disappear, not going to work for this attack, do NOT take 2nd dose	POM & P – 5HT1 agonist specific for 5HT1B, 5HT1D		- Constricts blood vessel back to normal - C/I in IHD, uncontrolled increased BP, >65years - S/E tiredness & dizziness (common) Heaviness on chest + throat ➔ Looks like CVD event
		Triptans	Sumatriptan	50-100mg normal dose Poorly absorbed by mouth + S/C v. fast acting + Nasal fast acting (under18)
			Zolmitriptan	Orange flavour
			Naratriptan	Less effective at 2H + prolonged half-life Not for intense but drawn-out migraines
Anti-emetics	Reduce symptoms of N&V			
Prophylaxis	Reduce frequency of attacks • Off work 2-3 days a	Propranolol	B-blocker, may already be taking for CVD S/E of fatigue, bronchoconstriction (asthma X)	Check patient's expectation - Will not provide

	month – functional impairment • Headaches frequency >2/week • Amount of acute medication used • Can patient comply w/ treatment	Pizotifen	S/E v.BAD	5-HT2 antagonist, antihistaminic S/E of weight gain, sedation	migraine free living - Side effects of weight gain and nausea + may need contraceptive for women - Takes 6months to a year for full effect - Could be withdrawn in the future
		Methysergide		H-HT2 antagonist S/E of N&V, fibrotic (rare)	
		Amitriptyline		Antidepressant	
		Anticonvulsants: Valporate or Topiramate		Good for prolonged or atypical migraine aura (no headache), not good for young women – need contraception+S/E hair grow	
		Botulinum toxin type A (Botox)		Non systemic med – S/E minimal with needle injection in head/neck Relax muscle and block pain?	
		Calcitonin gene-related peptide (CGRP)		CGRP antagonist: no vasoconstrictor effect CVD ok Liver toxicity concern	
		Serotonin receptor agonist		5-HT (1D/1F) target only No vasoconstrictor effect	
		NO antagonist		Vasodilator produced through NO synthase	

Medication overuse headaches
1 in 50 ppl affect at some point - Taking too much meds for tension type headaches - Brain wants medication creates symptoms, pain oppressive, worse in morning - STOP current therapy cold turkey – worse first before better RISK patients: using analgesic/triptans >15 days/month or refer request for more than 4 imigran/month To PREVENT: 1. Take less than 15 days on meds/month, 2. 2-4 doses over 1-2 days ok, 3. No more than 2 consecutive days, 4. Avoid codeine contain products

Eye Physiology

Aqueous humour (AH) of the eye has constant turnover of the fluids to maintain its intraocular pressure, it also has a role to provide nutrients and oxygen to the cornea

➔ Ciliary body secretes this AH into the posterior chamber and drains it through the trabecular meshwork (TM) into the Schlemm canal (SC) out the episcleral vein (conventional, 70-90%)

➔ AH leaves non-conventionally, the uveoscleral pathway – between cellular spaces (10-30%)

Vitreous humour is in a large chamber and it is viscous to absorb energy and to protect delicate structure of the eye e.g., the neural retina that is light sensitive

Control of Pupil Size	
Iris smooth muscle 1 **Circular muscle (outer layer)**	**Iris smooth muscle 2** **Radial muscle (inner layer)**
With parasympathetic stimulation (rest and digest) In the light for less light to enter	With sympathetic stimulation (fight or flight) In the dark for more light to enter
Circular muscle that runs circularly constricts causing pupillary constriction	Radial muscle that runs radially constricts causing pupillary dilation

Focussing light on the retina (accommodation)	
First point of focus is the cornea, where there is the greatest degree of refraction Circular smooth muscle of the ciliary body contract and relax to alter the curvature of the lens Suspensory ligaments connect the lens to the ciliary muscle	
Far vision	**Near vision**
Ciliary muscle is relaxed Lens is pulled taut by intraocular pressure Lens FLAT and THIN	Ciliary muscle is contracted Lens not under tension as suspensory ligaments slack and can focus on close objets Lens ROUND with greater refraction of light
Sympathetic nervous system (but more off of para)	Parasympathetic nervous system

Vision Problems	
Astigmatism (난시)	Surface of the cornea uneven causing blurred vision ➔ LASIK to change curvature of cornea
Presbyopia (노안)	Lens less flexible, no longer able to become rounded, thus cannot focus on near object
Short-sightedness (myopia) (근시)	Eyeball too long, parallel light is focussed on the front of retina
Longsightedness (hyperopia) Hypermetropic (long sighted eyes)	Eyeball too short, near objects brought to a focus behind the retina

Structure of Retina

- Made up of layers of neuronal cells with the photoreceptors at the back of the retina
- Direction of retinal visual processing is the opposite of the direction of light
- Amacrine and horizontal cells that goes across the retina is important in lateral processing

Fibres of optic nerves	**Ganglion cell**	**Bipolar cells**	**Photoreceptor cells (cones and rods)**	**Pigment epithelial layer**	**Choroid layer**	**Sclera**	**Back of retina**

Photoreceptors		
Outer segment	**Inner segment**	**Synaptic terminal**
*Detects light stimulus with light absorbing photopigment *Consists of flattened, stacked membranous discs *There are turnover of these discs to prevent accumulated damage from the light – by the cells of retinal pigment epithelium (RPE cells)	*Metabolic centre *Contains nucleus, mitochondria, ribosomes	*Release neurotransmitters *Synapse with the bipolar cells

Cones – 6million	**Rods – 10million**
Low sensitivity to light – bright light for colour vision	High sensitivity to light – enables night vision
Abundant in the fovea (colour vision) - Fovea is the area where the lens focuses the image - Visual acuity in the fovea is highest with fine resolution 1) More cones: 1 to 1 coupling (no convergence) 2) Lateral inhibition – if one photoreceptor is stimulated, it can switch the next photoreceptor off 3) Other areas of retinal are moved aside, so light does not travel	Abundant in the periphery (black and white vision) - Grey scale vision - Highly convergent - Wider receptive field - Very sensitive to movement and flashes of light
No convergence: 1:1 ratio of cone to ganglion cells	Highly convergent: up to 100 rods feeding into one ganglion cell
High resolution	Increased sensitivity

Visual transduction
- Photoreceptors change light energy into an electrical signal
1. Photoreceptors contain photopigments in the outer segment membranes that capture light energy Photopigments consist of: a. Opsin – GPCR protein b. Retinal – the chromophore (molecule that absorb light), opsin receptors ligand, derived from vit A (carrot) 2. When retinal is activated by light it changes shape from 11-cis-retinal to all-trans-retinal 3. This causes a conformational change in the opsin receptor 4. Resulting in hyperpolarization (+) of the photoreceptor membrane potential (activated)

Phototransduction	
In the dark	In the light
➔ Outer segment of photoreceptor contain cGMP gated cation channel 1. Guanylate cyclase converts GTP to cGMP 2. cGMP activated cGMP gated cation channels 3. Influx of sodium and calcium ions into the cell 4. Causes depolarization (-40mV) and release of NT glutamate	1. Light activates retinal (11-cis-retinal to all-trans-retinal) 2. This conformational change of opsin activate transducin 3. Transducin stimulates phosphodiesterase activity 4. This enzyme breakdown of cGMP, conc of cGMP low 5. cGMP gated ion channels close 6. Hyperpolarization (+) occurs
➔ Retinal ganglion cells are inactive	➔ Turned into the depolarization in the retinal ganglion cells to enable action potential generation to the brain
• Brighter the light (bigger hyperpolarization), the less neurotransmitter will be released – able to detect light • Sensitive system: 5 photons can be detected for us to see (only little light required) • After activation photopigments are bleached and remain unresponsive until recycling of retinal – converts all-trans-retinal back to 11-cis-retinal by RPE cells	

How we see colour:

There are **four photopigments**:

1) One rod – rhodopsin: sensitive to wavelengths of visible light (greyscale, not colour)
2) There are 3 cones responsive to blue, red, and green (wavelength from 400 to 700)

- Different cones with different opsins in them will respond to different wave lengths of light
- We can see whole range of colours
- Colour blindness is lacking one of these cones and the colour perception is altered

Visual Pathways

- Right side of the visual field goes to the left side of the brain for processing
- Left side of the visual field goes to the right side of the brain for processing
- Axons cross the optic chiasm -> lateral geniculate nucleus of thalamus -> occipital lobe -> visual cortex

Glaucoma

➔ Irreversible, progressive disease of the optic nerve associated with characteristic nerve head changes and visual field defects, which untreated results in tunnel vision and eventual blindness

Anatomy

The optic nerve head is where the optic nerve exits the eye via the lamina cribrosa
There are no photoreceptors at the optic nerve head
The optic nerve head is the cause of the normal blind spot

Symptoms

Vision from the patient's eye starts to blur from the outside, slowly dimming the outer vision until peripheral vision is gone and only a focused central vision is present.

➔ **Arcuate visual field defect**

Glaucomatous optic neuropathy – nerve tissue on the outer part of the optic nerve becomes damaged and there is a glaucomatous insult where the retinal nerve fibre layers are thin and the cup is enlarged

➔ Increasing cup and decreasing rim
➔ Normal field: normal blind spot, central area of fixation
➔ Defects join up with the blind spot and become arcuate

Types of glaucoma	
1 Congenital type	2 Acquired type (common)
3 Primary glaucoma (common)	4 Secondary to other ocular condition
5 Open angle glaucoma – Damage in the angle between the cornea and the iris	6 Closed angle glaucoma – Usually occurs due to pupil block
Edge of the iris rest on the lens, blocking the flow of aqueous and the elevated pressure in the posterior chamber pushes iris forward to close the angle, nowhere for the fluid to exist the eye the pressure rises and cause glaucoma	

➔ All result in damage to optic nerve
➔ Most associated with elevated intraocular pressure (IOP) – major risk factor
➔ Normal range of IOP – 11~21 (24?) mmHg (24) measured by non-contact tonometry

Primary angle closure – due to iridocorneal angle occlusion
- Classically affects hypermetropic eyes (long sighted)

Classification		Management	
PACS (suspect)		Laser iridotomy	Small hole made in iris, when pupil block and aqueous cannot move from posterior to anterior chamber, it can com through the iridotomy and prevent onset of angle closure
PAC (established)		Cataract surgery	Remove cataract and preventing pupil block
PACG (glaucoma)	Acute	Medicine	Lower IOP associated glaucoma
	Chronic	Glaucoma surgery	
ACUTE ANGLE CLOSURE (AAC) - Medical emergency		Signs and symptoms: Painful red eye, blurred vision/haloes, N&V, mid dilated pupil (most risk of block), cloudy cornea (elevated pressure), shallow anterior chamber, elevated IOP, closed angle at gonioscopy (look cornea), glaukomflecken (small white fleck in front of lens), fellow eye PACs (suspicion of PAC in other eye)	
DRUG INDUCED ANGLE CLOSURE (DAC) - Medical emergency		Topical mydriatic drugs: topicamide, atropine Nebulised drugs: ipratropium bromide, salbutamol Oral or intravenous drugs: amitriptyline, SSRI citalopram Other (very rare): topiramate, over the counter flu remedies	

Primary open angle glaucoma (POAG) -most common - Initially asymptomatic, slow progression, late presentation	
Epidemiology	67 million cases (10% blind), 1% at 50, 4% at 80 and 15% >80 1:1 of diagnosed and undiagnosed
Cause	Poorly understood
	Associated with raised IOP
	Mechanical pathogenesis: due to movement of lamina cribrosa causing direct trauma to the retinal ganglion cell axons as they exit the eye
	Ischaemic pathogenesis: due to ischaemic problems at the optic nerve
Risk factor	Age, genetics, FH, type of optic nerve head, vascular/haematological, neurogenic (some optic nerve more susceptible to glaucoma
	IOP >30mmHg certain to develop glaucoma in life ➔ Treatable but not good for screening glaucoma ➔ Some patients have normal tension glaucoma (glaucoma w/o raised IOP) ➔ Some patients have ocular hypertension w/o glaucomatous damage

Screening methods	
1) Optic nerve head examination/imaging	
2) Visual field testing	
3) Risk factor assessment	IOP, central corneal thickness (can have influence on which pressure is read from device used to measure pressure), CVD risks
4) Slit-lamp examination	To exclude secondary cause of glaucoma
5) Gonioscopy	Iridial corneal angle is directly viewed to define whether the glaucoma is either open angle or closed
Diagnostic spectrum	
Normal (just congenital abnormality of optic nerve), non-glaucomatous disorder (temporal hemianopia filed defects can be detected – indicated of pituitary tumours), ocular hypertension, glaucoma suspect, POAG either HTG or NTG	

Medical therapy of Glaucoma – topical anti-glaucoma

Hopefully in the future there are systemic drugs that are easier to take than eye-drops

Preservatives used: benzalkonium chloride (BAC), polyquaternium -1 (PQ-1) and others w/o as single use

Mode of action 1:
Increased outflow of aqueous (rate of production = rate of outflow, but increased outflow decreases IOP)
a) Conventional route (70-90%) – inhibited by dilation of pupil, facilitated by contraction of the ciliary muscle
Parasympathetic autonomic nervous system: Ach via muscarinic (M3) receptors (muscarinic agonist target)
- Constricts iris circular SM, causing pupillary constriction, allowing good flow of AH
- Contract ciliary SM, causing round lens for near vision– blurred vision (important in accommodation)

Sympathetic autonomic nervous system: NA via alpha1 adrenergic receptors
- Constricts radial muscle, causing pupillary dilation, restricting flow of AH

b) Uveo-scleral outflow (10-30%) (prostaglandin analogues target)

Types	Drugs	Notes	Pharmacology
Prostaglandin analogues	Latanoprost 0.005% ON	Analogues of PGF2alpha	Increase outflow via the uveoscleral pathway to decrease IOP Most recently introduced therapy, now initial therapy in POAG S/E: conjunctival hyperaemia (bloodshot eyes), foreign body sensation, ocular irritation – due to drugs themselves not preservatives, eyelash lengthening, thickening, iris hyperpigmentation
	Travoprost 0.004% ON		
	Bimatoprost 0.01% ON	No an agonist at PGF receptors (mechanism unknown) V.potent	
	Tafluprost 0.0015% ON	First available w/o preservatives	
Muscarinic agonist	Pilocarpine	Stimulate M3 receptors cause pupil constriction (myotic effect), contraction of ciliary muscle facilitates drainage of AH decreasing IOP Not used much due to ocular S/E of blurred vision	

Mode of action 2:
Reduced production of aqueous (usually produced at rate of 2-3ul/min from ciliary body)
Under autonomic sympathetic control AH is actively secreted

a) Stimulation of post-synaptic beta2 receptors via ligand binding NA stimulates Na+K+ ATPase, moving the ions against the electrical gradient causing downstream actions, increasing production of AH (B blocker target)
Alpha 2 adrenoreceptors in the pre-synapse uptake NA decreasing AH production via negative feedback (alpha agonist target)

b) Carbonic anhydrase activity in the ciliary epithelial cells takes CO2 + H20 to form bicarbonate ions, which is transported across membrane into AH assisting its secretion, however by inhibiting carbonic anhydrase, it decreases bicarbonate availability hence decreasing AH (carbonic anhydrase inhibitor target)

Types	Drugs	Notes	Pharmacology
Beta-blockers	Timolol 0.1,0.25,0.5%	Nonselective	B2 receptor cause increased AH production so via inhibition S/E: Ocular – stinging, dry eye, itching, pain, erythema (red eye), corneal disorders Systemic – bradycardia, breathlessness, C/I in bradycardia, HB (more in elderly) • If used OD, avoid using at night due to hypotensive dips that may occur
	Levobunolol 0.5%		
	Carteolol	Nonselective, has intrinsic sympathomimetic activity (help with S/E)	
	Betaxolol 0.25,0.5%	Selective to B1R (less therapeutic effect)	
Carbonic anhydrase inhibitors	Acetazolamide	Not an eye drop (not recommended long term)	Reduces production of AH (least potent, but fewer S/E) C/I in sulphonamide sensitivity Usually TDS due to less potent – cause poor adherence
	Dorzolamide 2%	Stings due to pH	
	Brinzolamide 10mg/ml	Doesn't sting bc oily suspension	
Alpha agonists	Brimonidine 0.2% BD	Can be allergic, S/E of taste perversion, can cause bad nightmares (CNS) But can be used long term	Stimulate pre-synaptic alpha 2 adrenoceptors, decreasing NA in turn decreasing AH secretion *** avoid MAOIs and TCA use due to interactions
	Apraclonidine 0.1, 1% BD	Only short-term use after laser procedure	
Combination therapy	Most are with timolol (beta blocker) E.g., cosopt, azarga, eylamdo, xalacom, duotrav, ganfort, taptiqom, gixapost, eyzeetan, combigan, simbrinza (no beta blocker)		

Laser therapy		Surgery
Selective laser trabeculoplasty	Cyclodiode laser therapy	Trabeculectomy
Improves aqueous drainage - Better at lowering IOP than topical therapy - May be more cost effective	Reduces aqueous production ➔ Last resort	Forms by-pass of aqueous through a small sclerectomy under a flap of sclera to form a bleb under the conjunctiva so that the aqueous is by-passed from anterior chamber into the sub-conjunctival space (could be first line for severe glaucoma in future)

KEY WS QUESTIONS:

1) Explain muscarinic antagonist (atropine, tropicamide) and muscarinic agonist (pilocarpine) effects on pupil size and accommodation.
2) How can ipratropium (COPD, anticholinergic) and amitriptyline (tricyclic antidepressant) cause acute angle closure glaucoma?
3) How beta-blockers such as timolol cause breathlessness and red eyes
4) Why could memantine used in AD may be use full in treatment of glaucoma?