067

Chapter 13

Chapter 13

Pharmacology

Lipophilic antimuscarinic (good oral bioavailability and CNS penetration) (Tertiary amines) Drug Effect Indication • Atropine • ↑ Heart rate • ↓ Secretions of exocrine glands • ↓ Tone and motility of smooth muscles • ↓Cholinergic overactivity in CNS • Mydriasis and cycloplegia • Scopolamine(hyoscine) • ↓ Vestibular disturbances (antiemetic) • Homatropine • Mydriasis • Tropicamide • Impair accommodation • ↓ Cholinergic overactivity in CNS • Benztropine • Biperiden • Trihexyphenidyl • ↓ Tone and motility of smooth muscle cells • Oxybutynin • Tolterodine • Solifenacin • Dicyclomine • Darifenacin • ↑ Sphincter tone • Urinary urgency, urge incontinence, urinary frequency, and/or nocturia(symptoms resulting from, e.g., overactive bladder) Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• First drug of choice in unstable (symptomatic) sinus bradycardia (IV) • Premedication: prior to intubation to decrease salivary, respiratory, and gastric secretions • Ophthalmology: uveitis • Antidote for anticholinesterase poisoni ng • Scorpion stings • Motion sickness • Ophthalmology • Therapeutic use: in patients with uveitis • Diagnostic use: pupillary dilation to allow ocular fundus examination and cycloplegia to allow refractory testing • Antiparkisonian effect (Parkinson disease) • ↓ Extrapyramidal symptoms (EPS) caused by antipsychotics • Oxybutynin, tolterodine, and solifenacin: overactive bladder incontinence • Dicyclomine: irritable bowel syndrome

Hydrophilic (poor oral bioavailability and CNS penetration) (Quarternary amines) Drug Effect Indication • Glycopyrrolate • Decreases secretions of exocrine glands • Bronchodilation • COPD and bronchial asthma • Ipratropium bromide • Tiotropium bromide Anticholinergic syndrome (overdose) • Etiology Belladonna poisoning Jimson weed/Angel's trumpet (Datura stramonium) poisoning Medications Anticholinergic agents (e.g., atropine, benztropine, trihexyphenidyl) Drugs with anticholinergic properties Tricyclic antidepressives (predominantly doxepin, amitriptyline, imipramine, and trimipramine) Antipsychotics (e.g., clozapine, quetiapine) First-generation antihistamines (e.g., promethazine, dimenhydrinate) • Clinical features Dry mouth, warm, flushed skin, thirst, tachycardia, arrhythmias, mydriasis, confusion, and agitation Possibly anticholinergic delirium: Excessive use of tricyclic antidepressants (or other medications with significant anticholinergic effects) can cause lifethreatening delirium, hallucinations, and psychomotor symptoms. • Treatment: antidote for purely anticholinergic poisoning (e.g. atropine):

physostigmine One mnemonic used to remember the symptoms of anticholinergic toxicity is: Hot as a hare: increased body temperature Blind as a bat: mydriasis (dilated pupils) Dry as a bone: dry mouth, dry eyes, decreased sweat Red as a beet: flushed face Mad as a hatter: delirium Notes & Notes for MRCP
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• Peptic ulcer disease treatment • Ipratropium bromide: • COPD grade I and higher • Acute management of refractory asthma • Tiotropium bromide: • Longer duration of action • Long-term treatment of COPD (grade II and above)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 13

Pharmacology

Tiotropium Indications • Tiotropium is a specific long-acting antimuscarinic agent indicated as maintenance therapy for patients with (COPD) Cautions • Caution is advised in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction Side-effects • Dry mouth • Paradoxical bronchospasm • Rarer side-effects include tachycardia, blurred vision, urinary retention and constipation

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Doxapram Indications • Doxapram is a centrally acting respiratory stimulant, used in patients with severe respiratory disease who are deemed unsuitable for admission to the Intensive Therapy Unit • Intravenous doxapram only used if the patient is not suitable for either intubation or noninvasive ventilation. • The main purpose in using doxapram is to allow time for recovery from an acute respiratory event • The usual dosing regimen is 1-4 mg/min given as an intravenous infusion Contraindications • heart disease, • epilepsy, cerebral oedema, stroke, • status asthmaticus, • hypertension, hyperthyroidism and phaeochromocytoma Side-effects • hypertension, • exacerbation of apparent dyspnoea, • agitation, • confusion, • sweating, • cough, • headache, • dizziness, • nausea, vomiting • urinary retention

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Sodium cromoglicate • Sodium cromoglicate principally acts by reducing the degranulation of mast cells triggered by the interaction of antigen and IgE • The inhibitory effect on mast cells appears to be cell-type specific, since cromoglicate has little inhibitory effect on mediator release from human basophils • More recent research has also shown that cromoglicate may act on eosinophils to reduce their inflammatory response to inhaled allergens, but this is not the most probable mechanism of action of sodium cromoglicate in the prophylaxis of asthma

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Magnesium treatment in asthma • Intravenous magnesium (1.2 - 2 g given over 20 minutes) is now indicated in the management of severe life threatening acute asthma attacks Its principal actions are to: • inhibit acetylcholine release at the neuromuscular junction

• relax bronchial smooth muscle • stabilise mast cells Unwanted effects are uncommon following single-dose therapy, although a slight decrease in blood pressure can be noticed and flushing can occur Symptoms of hypermagnesaemia include: nausea diarrhoea flushing hypertension confusion coma loss of tendon reflexes

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CNS & Psychiatric drugs

Anti-convulsants Remarkable side effects of anti-epileptic drugs are: • SIADH and rash (carbamazepine) • Liver toxicity (sodium valproate) • Severe rash (lamotrigine) • Retinal damage (vigabatrin) • Aplastic anaemia (felbamate). • Topiramate anticonvulsant ,most frequently prescribed for the prevention of migraines Side effects: Renal stones topiramate causes systemic metabolic acidosis, lowers urinary citrate excretion, and increases urinary pH. These changes increase the propensity to form calcium phosphate stones. weight loss (weight gain with sodium valproate), impaired taste sensation, cognitive dysfunction depression. Tingling in extremities. • Felbamate Because of its potentially fatal toxic effects (especially aplastic anemia and hepatic failure), the use of felbamate should be restricted to patients with severe partial epilepsy or Lennox-Gastaut syndrome who do not respond to other medications. • Lamotrigine Lamotrigine has a black box warning because of its association with StevensJohnson syndrome. the risk of tevens-Johnson syndrome increases if it is co-administered with valproate . When co-administered with valproate, the dosage of lamotrigine should be half that required in the absence of valproate and should be very slowly escalated.

Pharmacology Epilepsy medication in pregnancy • There is an increased risk of neural tube defects associated with anti-convulsants during pregnancy. • However, the risks associated with treatment are outweighed by the benefits in preventing seizures, so the drug should be continued. • The risks may be minimised through use of folate supplements. • If a patient is planning on pregnancy, then registry studies suggest that lamotrigine would be the best choice • Percentage of Congenital malformations associated with Anti-epileptics Valproate 6% (neural tube defects in the fetus) Valproate should be avoided in pregnancy if possible NICE guidance suggests that phenytoin should be avoided in women of child-bearing age because of the risk of congenital malformations. Topiramate 4.3% Phenytoin 3.5% (fetal hydantoin syndrome with facial dysmorphism) Carbamazepine 2.5% General population 1.5%
 Primidone and phenobarbital withdrawal symptoms in the newborn Contraception in epilepsy • Phenytoin induces liver enzymes, thereby increasing oestrogen breakdown and reducing the effectiveness of oestrogen-containing contraceptives • Where the combined contraceptive pill is used in conjunction with phenytoin, the contraceptive should contain high dose oestrogen: 50 mg ethinylestradiol or more • Lamotrigine is a suitable first-line treatment for partial epilepsy, and does not alter oestrogen metabolism • lamotrigine is the most appropriate choice in women of child-bearing age because: low risk of congenital malformations. it does not affect the

effectiveness of the oral contraceptive pill • Women taking lamotrigine monotherapy and oestrogen-containing contraceptives should be informed of the potential increase in seizures due to a fall in the levels of lamotrigine. • Whilst Carbamazepine is a potent enzyme inducer and therefore can't be used in combination with the pill Antiepileptic and weight (medical-masterclass.com 2017 part 2) • Two antiepileptic medications have been found to induce weight loss; topiramate and zonisamide. • Valproate, vigabatrin, gabapentin, carbamazepine, and pregabalin induce weight gain. • Levetiracetam, lamotrigine, and phenytoin are weight neutral.

Sodium valproate Indications • management of epilepsy and is first line therapy for generalised seizures.
• acute mania Action • blockage of voltage-gated sodium channels • increasing GABA activity (by inhibits GABA transaminase). Adverse effects • gastrointestinal: nausea • increased appetite and weight gain • alopecia: regrowth may be curly
(note that phenytoin → hirsutism while valporate → alopecia) • ataxia • tremor

Which enzyme does Valproic Acid inhibit? GABA Transaminase

What ion channel does valproic acid block? voltage-gated sodium channels

Sodium valproate can lead to severe hepatic toxicity. more commonly if the patient has a metabolic or degenerative disorder, organic brain disease or severe seizures associated with mental retardation. Usually this reaction occurs within the first three months of therapy.

Phenytoin Indications • management of seizures. • used as an antidote for Digitalis-induced arrhythmias. Action • blockage of voltage gated Na+ channels.
• refractory period of voltage-gated Na+ channels decreasing the sodium influx into neurons which in turn decreases excitability Side effects • Acute initially: dizziness, diplopia, nystagmus, slurred speech, ataxia later: confusion, seizures • Chronic common: gingival hyperplasia (secondary to increased expression of platelet derived growth factor, PDGF), hirsutism, coarsening of facial features, drowsiness megaloblastic anaemia (secondary to altered folate metabolism) Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• hepatitis • pancreatitis • thromobcytopaenia • teratogenic • hyponatraemia • polycystic ovarian (PCOS) syndrome • strong inhibitor of CYP450s.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 13

Pharmacology

 peripheral neuropathy enhanced vitamin D metabolism causing osteomalacia lymphadenopathy dyskinesia • Idiosyncratic fever rashes, including severe reactions such as toxic epidermal necrolysis hepatitis Dupuytren's contracture (although not listed in the BNF) aplastic anaemia drug-induced lupus Hypocalcaemia Pseudolymphoma or, rarely,

malignant lymphoma and mycosis-fungoides-like lesions. • Teratogenic associated with cleft palate and congenital heart disease Interaction • Phenytoin would speed up metabolism of ethinyloestradiol making the pill less effective. strong inducer of CYP450 enzymes.
• Cimetidine increases the efficacy of phenytoin by reducing its hepatic metabolism • Sucralfate may decrease the pharmacological effects of phenytoin when administered concurrently • Effect on other anti-epileptic: Phenytoin usually lowers the serum concentration of carbamazepine, clonazepam, topiramate and sodium valproate,
 elevates the serum level of phenobarbitone.
 Phenytoin does not appear to influence the serum concentration of levetiracetam. In renal failure Renal failure ↓ drug affinity for protein binding ↑ free drug toxicity (drug level may be within the therapeutic range)
• In patients with renal failure, dose reduction of phenytoin is therefore required. • Other drugs where this may be a problem include sodium valproate and warfarin.

There is no oral preparation of fosphenytoin; it is used in status epilepticus only.

Phenytoin toxicity typically gives rise to a cerebellar-like syndrome. Nystagmus is present even in mild toxicity.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Carbamazepine Carbamazepine is chemically similar to the tricyclic antidepressant drugs. Indications: • most commonly used in the treatment of epilepsy, particularly partial seizures, where carbamazepine remains a first-line medication.
• Other uses include neuropathic pain (e.g. trigeminal neuralgia, diabetic neuropathy) bipolar disorder Mechanism of action • binds to sodium channels increases their refractory period Adverse effects • P450 enzyme inducer Auto-induction of carbamazepine metabolism need to increase the dose to achieve a therapeutic plasma concentration. In patients on carbamazepine who develop Hashimoto's thyroiditis the dose of thyroxine should be increased to maintain therapeutic levels • dizziness and ataxia • drowsiness • headache • nystagmus • visual disturbances (especially diplopia) The most common dose-related adverse effects of carbamazepine are diplopia and ataxia • Steven-Johnson syndrome HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine.*
 *The prevalence of the HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine • leucopenia and agranulocytosis • syndrome of inappropriate ADH secretion • Carbamazepine is nephrotoxic and may cause proteinuria. Carbamazepine overdose presents with: • Drowsiness • Slurred speech • Ataxia • Hallucinations • Nausea • Vomiting • Tremor • Blurred vision • Seizures • Oliguria, and • Bullous skin lesions.

Contraindications: • atrioventricular (AV) conduction abnormalities • porphyria • history of bone marrow depression

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 13

Pharmacology

Vigabatrin

Action • Inhibition of GABA Transaminase, thereby increasing GABA levels Indication: • Vigabatrin should be used only in combination with other anti-epileptic drugs for patients with resistant partial epilepsy when all other appropriate drug combinations have proved inadequate or have not been tolerated.
• Vigabatrin is the drug of choice for infantile spasms, is not generally used outside the situation of infantile spasms Adverse effects: • reduced peripheral vision 40% of patients develop visual field defects, which may be irreversible The pattern of the field defect is typically a bilateral, absolute concentric constriction of the visual field, the severity of which varies from mild to severe.
 Vigabatrin-associated field defects are typically nasal more so than temporal, visual fields should be checked before the start of treatment and every 6 months • aggression • alopecia • retinal atrophy

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Topiramate

• Action blocks voltage-gated Na+ channels ↑ GABA action • advantages Topiramate is one of the few antiepileptic drugs (also including gabapentin) with almost exclusively renal metabolism It would be less likely to cause worsening of hepatic function • adverse effects of topiramate include renal stones weight loss
 and neuropsychiatric side-effects

Gabapentin • MOA of Gabapentin and Pregabalin? Inhibits voltage gated Ca channels as a GABA analog • used for add-on therapy in partial or generalised seizures. • does not induce cytochrome P450 unlike other anticonvulsants such as phenytoin and phenobarbitone. • Requires dose adjustment in renal disease
a patient with epilepsy and hepatic impairment Topiramate
Vigabatrin Visual field defects

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Levetiracetam (Keppra)
• Action unknown. • it does not affect hepatic enzymes, but dose reduction is required in renal failure. • Usage: Is an adjunctive treatment for partial seizures with or without secondary generalisation. • Advantages: The drug appears to be well tolerated with few side effects. has least interactions and is safe with warfarin .

Procyclidine • Action antimuscarinic • Indication used to treat the Parkinsonian side effects of neuroleptics; • Signs of procyclidine overdose include: Agitation Confusion Sleeplessness lasting up to 24 hours or more Pupils are dilated and unreactive to light. Visual and auditory hallucinations and tachycardia have also been reported.

Barbiturates • Examples phenobarbital, pentobarbital, thiopental, and secobarbital • Mechanism increases GABAA action by ↑ duration of Cl- channel opening resulting in ↓ neuron firing barbitDURATE • Clinical use CNS depressant for anxiety and seizures induction of anesthesia (thiopental) • kinetics induction of P450 tolerance/dependence • Phenobarbitone suppress the central nervous system causing: Hypoventilation (and therefore a respiratory acidosis) Hypotension, and Hypothermia.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 13

Pharmacology

Anticholinergic syndrome Common causes Signs and symptoms Management • tricyclic antidepressants • atropine • H-1-antihistamines • hot, dry skin • hypertension • tachycardia • urinary retention
• dilated pupils (mydriasis) • Agitated delirium can also occur supportive • Although physostigmine, a reversible inhibitor of acteylcholinesterase, is effective in treating symptoms, there is a significant risk of cardiac toxicity (bradycardia, AV conduction defects and asystole).
• Treatment therefore consists of withdrawal of the precipitating drug and supportive care.

Serotonin syndrome Causes • monoamine oxidase inhibitors • SSRIs • ecstasy • amphetamines • The serotonin syndrome occurs primarily because of interactions between monoamineoxidase inhibitors (MAOI) and drugs that enhance serotonin function (eg selective serotonin-reuptake inhibitors (SSRIs)) Features • neuromuscular excitation (e.g. hyperreflexia, myoclonus, Tremor, rigidity) • autonomic nervous system excitation (e.g. hyperthermia) • altered mental state • sweating • tachycardia Management (Cyproheptadine may be useful in treatment) • stopping the precipitating drugs • instituting generalised cooling measures and diazepam to reduce agitation • Studies have suggested that drugs possessing serotonin-antagonist activity (eg cyproheptadine, methysergide) may provide some benefit in the management of patients with the serotonin syndrome

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Oculogyric crisis An oculogyric crisis is a dystonic reaction to certain drugs or medical conditions Features • restlessness, agitation • involuntary upward deviation of the eyes Causes • phenothiazines • haloperidol Usually a consequence of typical neuroleptic drugs such as haloperidol or chlorpromazine, but is unusual with newer agents such as olanzapine or clozapine. • metoclopramide • postencephalitic Parkinson's disease

The condition is often precipitated by re-introduction of the agent. Management • procyclidine (usually IV or IM)
• Benztropine

St John's Wort Overview • shown to be as effective as tricyclic antidepressants in the treatment of mild-moderate depression • mechanism: thought to be similar to SSRIs (although noradrenaline uptake inhibition has also been demonstrated) • NICE advise 'may be of benefit in mild or moderate depression, but its use should not be prescribed or advised because of uncertainty about appropriate doses, variation in the nature of preparations, and potential serious interactions with other drugs' Adverse effects
• profile in trials similar to placebo • can cause serotonin syndrome • inducer of P450 system, therefore decreased levels of drugs such as warfarin, ciclosporin. The effectiveness of the combined oral contraceptive pill may also be reduced.

Dopamine receptor agonists Overview • e.g. bromocriptine, cabergoline , ropinirole, apomorphine • ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide*) have been associated with pulmonary, retroperitoneal and cardiac fibrosis.
 The Committee on Safety of Medicines advice that an ESR, creatinine and chest xray should be obtained prior to treatment and patients should be closely monitored *pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction Action • L-DOPA is a precursor of dopamine. Dopamine itself does not cross the blood-brain barrier and so is no effective as a drug. • Levodopa exerts its therapeutic action after being converted by dopa decarboxylase to dopamine in the brain (in the striatum).
• It is also converted to dopamine in the periphery, causing nausea and vomiting through action at the area postrema, which lies outside the blood-brain barrier in the brain stem. Indications • Parkinson's disease Currently treatment is delayed until the onset of disabling symptoms
 If the patient is elderly, L-dopa is sometimes used as an initial treatment • prolactinoma/ galactorrhoea • cyclical breast disease • acromegaly Adverse effects • nausea/vomiting • postural hypotension • hallucinations • daytime somnolence

Chapter 13

Pharmacology

Bromocriptine
Action • Bromocriptine is an ergotamine dopamine agonist that leads to activate central and peripheral D2 receptors Indications • used to inhibit prolactin release from the anterior pituitary • preferred in women who are looking to get pregnant (less teratogenicity than cabergoline). Side effects • Common: nausea, nasal congestion, constipation,
• Uncommon: dizziness (orthostatic hypotension) • Rare
 Tinnitus Excessive sleepiness (it is seen more commonly with modern agents such as ropinirole). Pulmonary fibrosis Vasospasm in the peripheral circulation: Higher doses may

cause cold-induced peripheral digital vasospasm (Raynaud's phenomenon). Hallucinations and psychosis : exacerbation or unmasking of depression and psychosis (only at very high doses)

Dopa-decarboxylase inhibitors
• Reduce the extracerebral complications of L-dopa therapy. These include nausea, vomiting, postural hypotension and cardiac arrhythmias. • When given in combination with dopamine agonists dyskinetic movements are more likely. • Carbidopa is an inhibitor of dopa decarboxylase that does not cross the blood-brain barrier, so it reduces peripheral, but not central, metabolism of levodopa to dopamine, thereby reducing the unwanted side effect but not the therapeutic action. • Benserazide is another peripheral dopa decarboxylase inhibitor that is commonly used in combination with levodopa (as co-beneldopa (Madopar)).

Amitriptyline (tricyclic antidepressants) Adverse effects Antimuscarinic effects: relatively common and occur before an antidepressant effect is obtained. • Dry mouth • Constipation paralytic ileus • Urinary retention • Tolerance is often achieved if treatment is continued • adverse effects may be less troublesome if treatment is begun with small doses and then increased gradually, although this may delay the clinical response.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• Blurred vision and disturbances in accommodation • Increased intraocular pressure, and • Hyperthermia.

Neurological adverse effects: • Drowsiness • Headache • Peripheral neuropathy • Tremor • Ataxia • Epileptiform seizures • Tinnitus Gastrointestinal complaints include: • Sour or metallic taste • Stomatitis, and • Gastric irritation with nausea and vomiting. • rarely, cholestatic jaundice cardiovascular • Orthostatic hypotension and tachycardia can occur in patients without a history of cardiovascular disease, and may be particularly troublesome in the elderly. blood disorders: • Eosinophilia • Bone marrow depression • Thrombocytopenia • Leucopenia, and • Agranulocytosis. Endocrine effects • testicular enlargement • gynaecomastia and breast enlargement, and galactorrhoea. • Sexual dysfunction. • Changes in blood sugar concentrations • hyponatraemia associated with inappropriate secretion of antidiuretic hormone. • increased appetite with weight gain (or occasionally anorexia with weight loss). • Sweating may be a problem. Others • Hypersensitivity reactions, such as urticaria and angioedema, and photosensitisation have been reported Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• extrapyramidal symptoms including speech difficulties (dysarthria).Confusion, hallucinations, or delirium may occur, particularly in the elderly, and mania or hypomania, and behavioural disturbances (particularly in children) have been reported.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 13

Tricyclic overdose

• Overdose of tricyclic antidepressants is a common presentation to emergency departments. Amitriptyline and dosulepin (dothiepin) are particularly dangerous in overdose. • Other tricyclic antidepressants includes imipramine • Early features relate to anticholinergic properties: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include: • Hypertension
 results from the blockade of norepinephrine reuptake is an early and transient finding.
 Catecholamines are eventually depleted and in most patients hypertension is mild and self-limiting and is best left untreated. • Orthostasis and hypotension
 are the result of direct myocardial depression, catecholamine depletion, alphaadrenergic blockade, and arrhythmias.
 The combination of decreased contractility and vasodilation produce decreased preload and can result in severe and refractory hypotension.
• Arrhythmias secondary to blockage or slowing of fast sodium channels (causing a quinidine-like effect)
 the most serious consequence of TCA overdose. Mild overdoses produce sinus tachycardia, mostly as a result of anticholinergic effects. More severe overdoses result in prolonged QRS and QTc intervals, followed by a prolonged PR interval, and, finally, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation. • seizures • metabolic acidosis • coma ECG changes include: (ECG is the most appropriate initial action) • sinus tachycardia • widening of QRS • prolongation of QT interval

Widening of QRS > 100ms is associated with an increased risk of seizures whilst QRS > 160ms is associated with ventricular arrhythmias Management • Check U&Es, looking specifically for hypokalaemia, and ABG looking for acidosis. Hypokalaemia should be corrected. ECG should be done to assess the QRS interval. • Gastric lavage should only be considered if it is within one hour a potentially fatal overdose. 50 g of charcoal can be given if it is within one hour of ingestion. • 50 ml of 8.4% sodium bicarbonate should be given if the pH is less than 7.1, QRS interval is more than 0.16 s, or there are cardiac arrhythmias or hypotension.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

 Indication for sodium bicarbonate in tricyclic poisoning includes wide QRS complex. Intravenous sodium bicarbonate is the standard initial therapy for patients who develop cardiotoxicity (usually a QRS > 100ms or a ventricular arrhythmia) as a result of tricyclic antidepressant (TCA) overdose. Mechanism of Sodium bicarbonate action: alkalinisation of blood to a pH of 7.45-7.55 uncouples TCA from myocardial sodium channels;
 also, additional sodium increases extracellular sodium concentration, thereby improving the gradient across the channel. Intravenous magnesium sulphate can be used as a second-line agent in refractory arrhythmias. IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity • arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g.

Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias • intravenous lipid emulsion is increasingly used to bind free drug and reduce toxicity • dialysis is ineffective in removing tricyclics • Patients who display signs of toxicity should be monitored for a minimum of 12 hours. Tricyclic Withdrawal symptoms rare and include: • cholinergic effects such as: abdominal cramps, diarrhoea, vomiting and dehydration • extrapyramidal symptoms such as: anxiety, psychosis, delirium and mania

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Monoamine oxidase (MAO) inhibitors
Overview • serotonin and noradrenaline are metabolised by monoamine oxidase in the presynaptic cell Non-selective monoamine oxidase inhibitors • e.g. tranylcypromine, phenelzine • used in the treatment of atypical depression (e.g. hyperphagia) and other psychiatric disorder • not used frequently due to side-effects • Abrupt withdrawal of phenelzine leads to panic, shaking, sweats and nausea Adverse effects of non-selective monoamine oxidase inhibitors • hypertensive reactions with tyramine containing foods e.g. cheese, pickled herring, Bovril, Oxo, Marmite, broad beans • anticholinergic effects

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Selective serotonin reuptake inhibitors (SSRIs) Selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for the majority of patients with depression.
• citalopram and fluoxetine are currently the preferred SSRIs • sertraline is useful post myocardial infarction as there is more evidence for its safe use in this situation than other antidepressants • SSRIs should be used with caution in children and adolescents. Fluoxetine is the drug of choice when an antidepressant is indicated Adverse effects • gastrointestinal symptoms are the most common side-effect

• there is an increased risk of gastrointestinal bleeding in patients taking SSRIs. A proton pump inhibitor should be prescribed if a patient is also taking a NSAID • patients should be counselled to be vigilant (رذح) for increased anxiety and agitation after starting a SSRI • fluoxetine and paroxetine have a higher propensity for drug interactions • The Committee on Safety of Medicines (CSM) have reported that hyponatraemia is associated with all types of antidepressants; however it has been reported more frequently with selective serotonin reuptake inhibitors (SSRIs) than with other antidepressants. • Hyponatraemia should be considered in all patients who develop drowsiness, confusion or convulsions whilst taking an antidepressant.
Citalopram and the QT interval • citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with:
 congenital long QT syndrome; known pre-existing QT interval prolongation;
 or in combination with other medicines that prolong the QT interval • the maximum daily dose is now 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment Interactions • NSAIDs: NICE guidelines advise 'do not normally offer SSRIs', but if given

co-prescribe a proton pump inhibitor • warfarin / heparin: NICE guidelines recommend avoiding SSRIs and considering mirtazapine • aspirin: see above • triptans: avoid SSRIs • monoamine oxidase inhibitor (MAOI) serotonin syndrome follow up • Following the initiation of antidepressant therapy patients should normally be reviewed by a doctor after 2 weeks.
• For patients under the age of 30 years or at increased risk of suicide they should be reviewed after 1 week.
• If a patient makes a good response to antidepressant therapy they should continue on treatment for at least 6 months after remission as this reduces the risk of relapse.
Discontinuation symptoms • When stopping a SSRI the dose should be gradually reduced over a 4 week period (this is not necessary with fluoxetine).
• Paroxetine has a higher incidence of discontinuation symptoms Withdrawal of paroxetine can lead to deterioration in mood and cognition and orofacial dystonias • Symptoms: increased mood change restlessness difficulty sleeping unsteadiness sweating gastrointestinal symptoms: pain, cramping, diarrhoea, vomiting paraesthesia

Notes & Notes for MRCP
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Lithium

• Lithium is mood stabilising drug used most commonly prophylactically in bipolar disorder but also as an adjunct in refractory depression.
• It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys. Mechanism of action - not fully understood, two theories: • interferes with inositol triphosphate formation • interferes with cAMP formation Adverse effects

• nausea/vomiting, diarrhoea • fine tremor • polyuria (secondary to nephrogenic diabetes insipidus) • thyroid enlargement, may lead to hypothyroidism • ECG: T wave flattening/inversion • weight gain • Hypercalcaemia and primary hyperparathyroidism.
 It has been suggested that lithium alters the sensitivity of the parathyroid cells to calcium hyperplasia.
 Other studies have however failed to confirm an excess of parathyroid hyperplasia in this population, suggesting instead that lithium selectively stimulates growth of parathyroid adenomas in susceptible patients, who are best treated therefore with adenoma excision rather than total parathyroidectomy. Pregnancy
• Exposure to lithium in utero is associated with Ebstein's anomaly. • Lithium is contraindicated during the first trimester and when breast-feeding. • In the first trimester lithium can cause atrialisation of the right ventricle. • During the second and third trimesters lithium can be used, but dose requirements are increased. • Immediately after delivery lithium dose requirements return to normal abruptly. Lithium levels can rise dangerously if a high dose is continued.
• Long-term treatment with lithium can produce frank hypothyroidism Lithium is concentrated by the thyroid and inhibits thyroidal iodine uptake. It also inhibits iodotyrosine coupling, alters thyroglobulin structure, and inhibits thyroid hormone secretion.
 The best management in this case would be to discontinue the lithium therapy and replace it with another agent (after consulting the patient’s psychiatrist) – carbamazepine, sodium valproate

or lamotrigine could all be alternative agents for mood stabilisation. Lamotrigine is the preferred option, assuming pregnancy is

Pharmacology desired. • Lithium is excreted in breast milk and if the infant becomes dehydrated, then toxic lithium levels develop rapidly. Monitoring of patients on lithium therapy • NICE and the National Patient Safety Agency (NPSA) recommends:

1. lithium blood level should 'normally' be checked every 3 months. Levels should be taken 12 hours post-dose
2. thyroid and renal function should be checked before starting treatment and then every 6 months
3. patients should be issued with an information booklet, alert card and record book
4. monitor serum lithium levels 1 week after treatment starts and every dose change, and then every 3 months.

Lithium monitoring (NICE 2017): thyroid and renal function serum lithium levels ECG before treatment 1 week after treatment starts For people at high risk of cardiovascular disease every 6 months every dose change

every 3 months

Sodium valproate is the second line therapy for bipolar disorder in patients who don’t tolerate lithium or where it’s contraindicated. Interaction: • Acetazolamide leads to decreased lithium concentration Osmotic diuretics and carbonic anhydrase inhibitors such as acetazolamide lead to decreased lithium concentration because of increased excretion • Calcium channel blockers combined with lithium may cause a syndrome of ataxia, confusion and sleepiness, which is reversible on stopping the drug. • ACE inhibitors lead to increased lithium concentration because of decreased excretion. • thiazide diuretics increased lithium reabsorption and may cause lithium intoxication. • Methyldopa also leads to increased risk of neurotoxicity.

Lithium toxicity Toxicity may be precipitated by dehydration, renal failure, diuretics (Especially bendroflumethiazide) or ACE inhibitors and ARBs • Lithium has a very narrow therapeutic range (0.4-1.0 mmol/L)
• long plasma half-life (20 h)
• excreted primarily by the kidneys.
• Lithium toxicity generally occurs following concentrations > 1.5 mmol/L.
• Toxicity may be precipitated by dehydration, electrolyte imbalance, renal failure, , and drugs
Drugs that may precipitate lithium toxicity include: • diuretics (especially bendroflumethiazide), • ACE inhibitors & ARB • NSAIDs • Metronidazole • Tetracycline

• Phenytoin • Ciclosporin • Methyldopa Features of toxicity • coarse tremor (a fine tremor is seen in therapeutic levels) • hyperreflexia • acute confusion • dysarthria • ataxia • seizure • coma Mild to moderate toxicity
(levels less than 2 mmol/L) severe toxicity (levels more than 2 mmol/L) • anorexia • vomiting • ataxia • dysarthria • blurring of vision • coarse tremor • diarrhoea • drowsiness, and • muscle weakness. • circulatory failure • coma • convulsions • hyper-reflexia • oliguria • psychosis, and • death (in severe cases).

Management • The management of lithium toxicity is largely supportive.
• The first step is to establish renal function and correct serum electrolytes. • Which investigation will help you in the immediate setting? Serum electrolytes and renal function
 Renal function will determine the patient's ability to excrete lithium. Lithium levels should be taken but may be of limited value in the acute setting (rapid result may not be available; levels not always reliable especially with sustained release preparations). • mild-moderate toxicity may respond to volume resuscitation with normal saline.
 In case of significant hypernatraemia , 5% dextrose is an initial option for fluid replacement • haemodialysis may be needed in severe toxicity indication of Haemodialysis: if serum lithium levels > 4 mmol/l or serum lithium levels > 2.5 mmol/l with signs of significant lithium toxicity (e.g. seizures, depressed mental status) or inability to excrete lithium (e.g. renal disease, decompensated heart failure). • sodium bicarbonate is sometimes used but there is limited evidence to support this.
 By increasing the alkalinity of the urine, it promotes lithium excretion • Activated charcoal does not bind lithium effectively and is therefore ineffective except where co-ingestion of other poisons is suspected. • Whole bowel irrigation should be considered in adults who have ingested a slow release preparation of lithium of greater than 4 g. Prognosis • 10% of patients who survive severe lithium toxicity will be left with a neurological deficit.

Therapeutic drug monitoring Lithium • range = 0.4 - 1.0 mmol/l • take 12 hrs post-dose Digoxin • at least 6 hrs post-dose Ciclosporin • trough levels immediately before dose Phenytoin • trough levels immediately before dose

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Baclofen • gamma-aminobutyric acid-B receptor agonist • The primary site of action is the spinal cord by depressing monosynaptic and polysynaptic transmission. • It can hyperpolarise cells by increasing K+ conductance and inhibit Ca2+ channels in others. • Avoid abrupt withdrawal as it can cause serious side-effects including: Autonomic dysreflexia. hallucinations Baclofen toxicity • Onset of toxicity is rapid and its effect can last up to 35-40 hours post ingestion. • Features include: Drowsiness Coma Respiratory depression CO_2 retention is likely to be due to central nervous system depression and reduction in diaphragmatic contraction secondary to baclofen toxicity. Hyporeflexia Hypotonia Hypothermia, and Hypotension. Bradycardia with first degree heart block and prolongation of Q-T interval can occur. • Treatment is usually

supportive and often requires intensive care. Intubation and mechanical ventilation • Patients with a high risk of aspiration pneumonia (↓ glasgow coma scale (GCS)) are a contraindication to non-invasive ventilation.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Endocrinology drugs

For all diabetic drugs See endocrinology

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lipid-lowering agents See endocrinology (Hyperlipidaemia: management)

Octreotide Octreotide Stimulation of the somatostatin (SMS) receptor

Overview • long-acting analogue of somatostatin • somatostatin is released from D cells of pancreas and inhibits the release of growth hormone, glucagon and insulin Uses • acute treatment of variceal haemorrhage • acromegaly • gastrinomas • carcinoid syndrome • prevent complications following pancreatic surgery • VIPomas • refractory diarrhoea Adverse effects • gallstones (secondary to biliary stasis)

Orlistat Reduces fat absorption from the intestine • Orlistat promotes weight loss and improves co-morbidities in obese patients • Orlistat operates by preventing the absorption of fat molecules in the intestinal tract • Approximately 30% of fat that would otherwise have been absorbed passes straight through the bowel and is excreted in the faeces • As a result it can cause 'fatty stools', urgency and increased frequency of defaecation often with anal leakage or oily spotting • these effects encourage people taking the drug to limit fat intake • Orlistat itself is not absorbed, except in very small quantities and thus its side-effects are restricted to the gastrointestinal tract • Patients taking orlistat may require concomitant vitamin supplements because of malabsorption of fat-soluble vitamins such as vitamins A, D, K and E • Orlistat is shown to be clinically efficacious in reducing a person's weight over a period of a year • Study results also showed significant improvement in reducing fasting glucose, total cholesterol, LDL-cholesterol and blood pressure

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 13

Pharmacology

Obs & Gyna drugs

Prescribing in pregnant patients Very few drugs are known to be completely safe in pregnancy. The list below largely comprises of those known to be harmful.

Drugs Antibiotics • ACE inhibitors, ARBs • Statins • Warfarin • Sulfonylureas • Retinoids (including topical) • Cytotoxic agents • Tetracyclines • Aminoglycosides • Sulphonamides • Trimethoprim • Quinolones: the BNF advises to avoid due to arthropathy in some animal studies • The majority of antiepileptics including valproate, carbamazepine and phenytoin are known to be potentially harmful. The decision to stop such treatments however is difficult as uncontrolled epilepsy is also a risk. • Verapamil is relatively safe in pregnancy and has been widely used to treat maternal and fetal supraventricular tachycardias.
• Amiodarone is associated with fetal hypothyroidism,
• lisinopril with oligohydramnios,
• lithium with Ebstein's anomaly,
• and warfarin with facial / CNS abnormalities.

Combined oral contraceptive pills Mechanisms of action
• Estrogen Hypothalamus: ↓ release of GnRH Pituitary: ↓ LH → inhibits ovulation, ↓ FSH → prevents ovarian folliculogenesis • Progestin → thickens the cervical mucus, preventing the entry of sperm.

Advantages

• Treatment of menopausal symptoms such as hot flashes. • Other beneficial effects of MHT include the decreased risk of colon cancer, diabetes mellitus type 2, and all-cause mortality for women ages 50-59 years.

Emergency contraception (after unprotected sexual intercourse) • Most effective when taken within 3 days of intercourse The rate of pregnancy is ≤ 3.0% if emergency contraception is taken within 72 hours. • Typically administered as a single dose or as two doses over one day • Significantly less effective in patients who are obese or overweight
• Action of emergency contraception: ↓ tubal motility and ciliary activity thereby preventing sperm from reaching the oocyte in the ampulla of the tube. • Example: levonorgestrel

Side effects
• Irregular periods (unscheduled bleeding): is the most common adverse effect • Breast tenderness • Headaches • ↑ incidence of functional ovarian cysts, hepatic adenomas • ↑relative risk of venous and arterial thrombotic events. • Erythema nodosum

Transdermal administration of estradiol is associated with a lower risk of stroke and venous thromboembolism than oral administration of estradiol and is unlikely to increase the risk of stroke and venous thrombosis above that of non-users.

Contraindications • People >35 years old who smoke tobacco (risk of cardiovascular events) • Migraine (especially with aura) • Breast cancer • Liver disease. • breast feeding < 6 weeks post-partum • Uncontrolled hypertension • History of thromboembolic disease (stroke or ischaemic heart disease) Progestogen only pills (POPs) • Examples: Norethindrone, drospirenone, and

desogestrel • Mechanism of contraception: Norethindrone → thickening cervical mucus thereby preventing sperm penetration; ovulation is not consistently suppressed.
 Drospirenone and desogestrel → suppression of ovulation.
• Advantages can be used whilst breast-feeding can be used in situations where the combined oral contraceptive pill is contraindicated (most women with medical comorbidities). • Failure rate = over 7 % (women choosing POPs are often subfertile as a result of breastfeeding or older reproductive age) • Hepatic enzyme-inducers (e.g. anticonvulsants phenytoin, carbamazepine, topiramate, and barbiturates and the antituberculosis drug rifampin) →↓efficacy of POPs.

Studies have shown that women taking estrogen- progestin combination OCPs before menopause have an increased risk of cervical carcinoma but a decreased risk of endometrial and ovarian carcinoma.

An entirely normal 16-year-old girl is very tall and would like to stop growing. What is the most appropriate treatment for her? Oral contraceptive pill The oral contraceptive pill used in this context would be associated with fusion of long-bone growth plates, and subsequent cessation of longitudinal growth.
 Although ideally she should be encouraged not to receive medical intervention at all, in this situation use of the OCP represents the lowest-risk option.

Chapter 13

Pharmacology

What is the action of emergency contraception in preventing conception following unprotected sexual intercourse.? Decreasing tubal motility and ciliary activity thereby preventing sperm from reaching the oocyte in the ampulla of the tube.

The rate of pregnancy is ≤ 3.0% if emergency contraception is taken within 72 hours after unprotected sexual intercourse. The earlier it is taken, the lower the likelihood of pregnancy!

Breast feeding: contraindications Breast feeding is acceptable with nearly all anti-epileptic drugs The major breastfeeding contraindications tested in exams relate to drugs (see below). Other contraindications of note include: • galactosaemia • viral infections - this is controversial with respect to HIV in the developing world. This is because there is such an increased infant mortality and morbidity associated with bottle feeding that some doctors think the benefits outweigh the risk of HIV transmission SAFE DANGEROUS • Antibiotics: penicillins, cephalosporins, trimethoprim • Endocrine: glucocorticoids (avoid high doses), levothyroxine* • Epilepsy: sodium valproate, carbamazepine • Asthma: salbutamol, theophyllines • Psychiatric drugs: tricyclic

antidepressants, antipsychotics** • Hypertension: β-blockers, hydralazine, methyldopa • Anticoagulants: warfarin, heparin • Digoxin *the BNF advises that the amount is too small to affect neonatal hypothyroidism screening **clozapine should be avoided

Notes & Notes for MRCP
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• Antibiotics: ciprofloxacin, tetracycline, chloramphenicol, sulphonamides • Psychiatric drugs: lithium, benzodiazepines, clozapine • Aspirin • Carbimazole • Sulphonylureas • Cytotoxic drugs • Amiodarone • vitamin A derivatives.

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