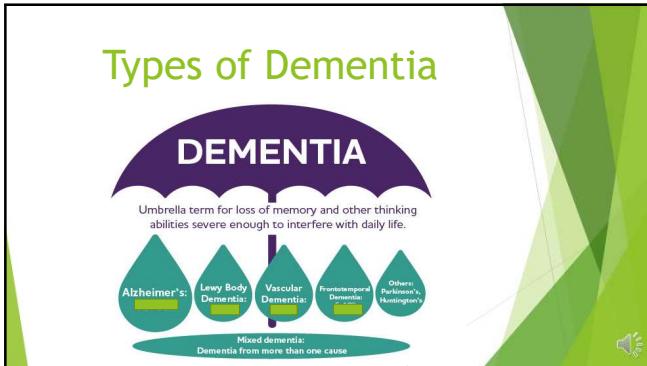
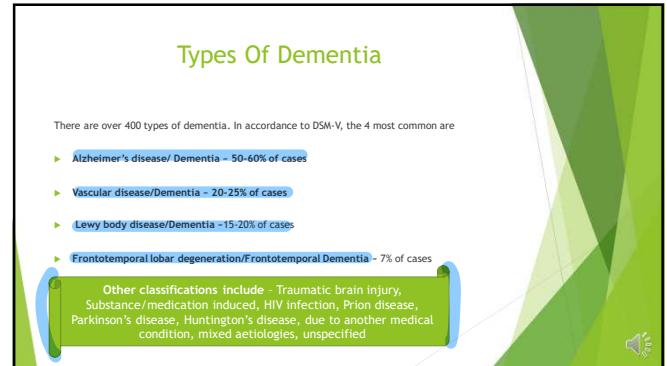


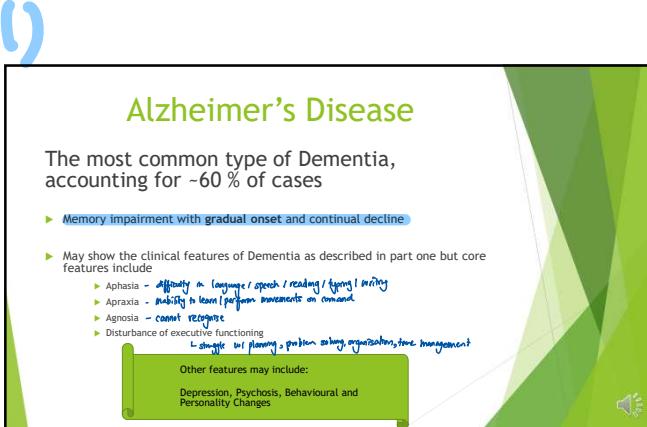
L9



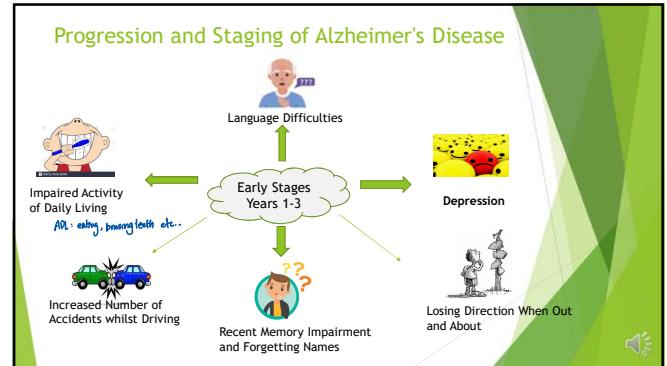
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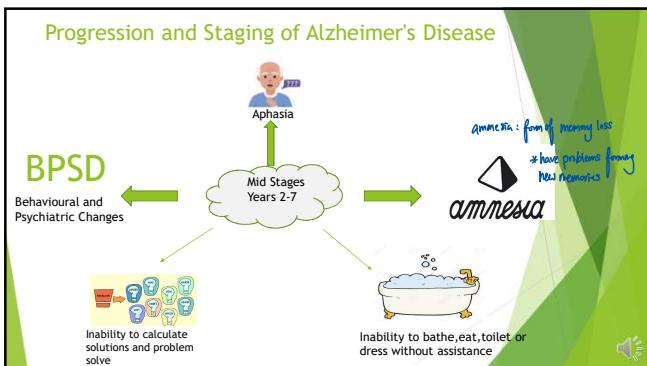
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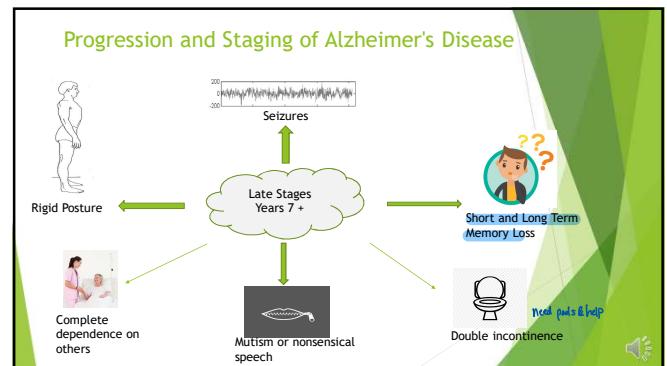
3



4



5



6

**Aetiology Of Alzheimer's Disease**

- Demographic Factors**
  - Increasing Age
  - Family History
  - Down Syndrome
- Genetic Factors**
  - Down Syndrome
  - ApoE4
- Environmental and Medical Risk Factors**
  - Low IQ
  - Previous Head Injury
  - Cerebrovascular disease
  - Depression
  - Diabetes Mellitus
  - Obesity

7

2)

**Vascular Dementia (VaD)**

- Sudden onset followed by a step wise progressive decline
- Onset is usually around late 60's-70's
- Caused by an **infarct**, generally there is a history of **hypertension, stroke and TIA**
  - ↳ Area of necrosis in tissue / organ
  - ↳ Ischaemic / haemorrhagic attack
- Approx 10% of people develop Dementia after a first stroke and more than a 1/3 after recurrent strokes
- prevention is the best treatment (good management of blood pressure, diabetes, heart disease, cholesterol, smoking)

8

**Vascular Dementia (VaD)**

Clinical features include:

- Emergent of Emotional and Personality changes ( inc Depression), followed by memory impairment
- Apraxia
- Agnosia
- Dysarthria → muscle used for speech is weakened
- Dizziness

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**Vascular Dementia (VaD)**

\***These are not in Alzheimer disease**

Often Focal neurological signs ( which are not present in AD)

- Gait disturbance - In Late VaD there is a **shuffling gait** which differentiates from Parkinson's by it's **broad base** and **preserved arm swing**
  - J deviation from normal walking
- Weakness of extremities → limbs
- Extensor plantar response → when a sharp object is inserted up the patient's foot, the big toe will bend backwards
- Pseudobulbar palsy → **inhibiting emotional expression disorder** (due to **facial muscle**) but in healthy adults toes will bend forward
- Exaggeration of deep tension reflexes

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**Aetiology Of Vascular Dementia**

- Family history
- Male sex
- Hypertension
- History of **stroke** or **transient ischaemic attacks (TIAs)**
- Diabetes mellitus (DM)
- Smoking
- Atrial fibrillation (AF)
- Recent studies have shown **similar risk factors as for AD**

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3)

**Lewy Body Dementia**

↳ has similar features to parkinsons

Key Features Include

- Progressive cognitive decline, especially in **attention and visuospatial ability**
- A variant of **Klebsler's disease**, more common in men
- Persistent and well-formed visual hallucinations, sometimes auditory
- Early gait disturbances
- Parkinson's type features
- Other psychotic features

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### Lewy Body Dementia

- ▶ Other supportive features include
  - ▶ Repeated falls
  - ▶ Syncope → fainting
  - ▶ Transient loss of consciousness
  - ▶ Systemised delusions
  - ▶ Non-visual hallucinations
  - ▶ REM sleep behaviour disorder
  - ▶ Depression
- ◀ **Extremely sensitive to the side-effects of antipsychotics**



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### Aetiology Of Lewy Body Dementia

- ▶ Closely related to Parkinson's disease and both characterised as **synucleinopathies**
- ▶ Family History
- ▶ No known environmental risk factors
- ◀ **disease group neurodegenerative disorder**  
→ common pathology lesion composed of aggregates of insoluble  $\alpha$ -synuclein protein in selectively vulnerable populations of neurons and glia.



14

4)

### Frontotemporal Dementia

- ▶ Most common form of presenile Dementia
- ▶ Onset between 45-70 years of age
- ▶ **Frontal lobe** pathology responsible for **behavioural and personality changes**
- ▶ **Temporal lobe** pathology responsible for **language disorder**




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### Frontotemporal Dementia

- ▶ Insidious onset, slow progression
- ▶ Early loss of insight
- ▶ Early signs of disinhibition
- ▶ Distractibility and impulsivity



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### Frontotemporal Dementia

- Language Features**
  - ▶ Progressive decrease in speech output
  - ▶ Echolalia → repeat words / phrases someone has said to them
  - ▶ Perseveration → repeat same words over and over again
- Affective Features**
  - ▶ Depression
  - ▶ Apathy
  - ▶ Emotional blunting



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### Aetiology of Frontotemporal Dementia

- ▶ Primarily Unknown → **but search have strong genetic link**
- ▶ Mutations in progranulin (GRN)
- ▶ TAU- linked to Chromosome 17
- ▶ TDP-43 and C9orf72 genes
- ◀ **covered in Dr Shafizadeh's lectures**



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5)

## Clinical Diagnosis

### The Importance Of Early Diagnosis

- Reversible/treatable conditions such as pseudo-dementia are detected and excluded
- Patient and family have time to plan for the future
- Personal affairs may be put in order while the individual still has insight.
- Able to discuss discussions their future care while they still have insight and agree Advanced Directives for example.
- Early access by the person with dementia and their family, to support groups, e.g. Alzheimer's disease Society
- Treatment that may slow progression of the disease can be more effectively targeted to the right stage of the disease.

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## Clinical Diagnosis

- Complete history, including medical, physical and mental state examinations
- Review any medicines being taken as those with anticholinergic and sedative side effects can impact adversely on cognition
- Diagnostic criteria from either DSM or ICD have been met
- Psychometric tests have been performed
- Neuroimaging has been performed if possible e.g. MRI and CAT scans

*↳ help which type of dementia they have and disease progression*

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 will be discussed in workshops

## Investigations For Establishing The Cause Of Dementia and Potential Differential Diagnosis

- Primary Care**
- FBC - full blood count
  - U and E's - urea and electrolyte
  - LFT's - liver function test
  - CRP - C-reactive protein
  - Calcium and Phosphate - electrolyte check
  - Thyroid Function
  - Vitamin B12 and Folate
  - Urine dipstick
  - Blood Glucose
  - Temperature

- In Secondary Care**
- MRI and CT scan
  - Urinalysis
  - HIV status
  - Neuropsychological assessment
  - EEG

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*choice dependent on where they are  
GP or specialist...*

## Clinical Diagnosis

### Clinical Screening Tools

- Mini-Mental State Examination- MMSE → most commonly used & advocated by NICE
- Abbreviated Mental Test Score-AMTS → help determine the extent of cognitive decline and assess cognitive function (scale to perform 10 items), score range 0-10 (7 or less indicating impairment)
- Alzheimer's Disease Assessment Scale- cognitive subscale- ADAS-cog → for alzheimer disease
- Addenbrooke's Cognitive Examination 3 -ACE3 or mini ACE → easier and more readily available and no payment needed unlike MMSE you get to pay

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## Mini-Mental State Examination- MMSE

- MMSE to assess cognitive function and decline
- MMSE tests memory, attention, calculation, orientation, language, ability to follow command and praxis → ability to name common objects
- Primarily used to aid diagnosis of Alzheimer's and recommended by NICE to assess the severity of AD and response to pharmacological treatment
- Takes less than 10-15 minutes to perform
- 8 Questions
- Score 0-30
- Has limitations
  - \* less sensitive in early stages of dementia
  - \* late stages - difficult to do assessment
  - \* Some ppl may perform less well educated or have learning disabilities
  - \* from different cultural background with different language

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Mini Mental State Examination (adapted from Folstein et al.)

| Patient Name | Date of Birth | Section                      | Questions:   | Max points | Patient Score |
|--------------|---------------|------------------------------|--|------------|---------------|
|              |               | 1. Orientation               | a) Can you tell me today's date/month/year?<br>b) What day of the week is it today?<br>c) What month is it? What year?<br>d) What is your name?<br>e) What is the name of the building/floor?  | 5          |               |
|              |               | 2. Registration              | I should like to test your memory.<br>(name 3 common objects: e.g. "Ball, car, man")<br>C. Please repeat the words I said to you.<br>(repeat up to 5 trials until all three are remembered)<br>(record number of trials needed here) | 3          |               |
|              |               | 3. Attention & Calculation   | a) From 100 subtracting 7 and give watch answer:<br>stop after 5 trials<br>b) Spell the word "WORLD" backwards. (D-L-R-O-W).   | 5          |               |
|              |               | 4. Recall                    | What were the three words I asked you to say earlier?<br>(check off each word if objects were not remembered during registration test)   | 3          |               |
|              |               | 5. Language Naming/Repeating | Name these objects (show a watch) (show a pencil)  | 2          |               |
|              |               | 6. Reading:                  | (show card or write "CLOSE YOUR EYES")   | 1          |               |
|              |               | Writing:                     | Now can you write a short sentence for me?   | 1          |               |
|              |               | 7. Two-Stage Command:        | Take this paper in your left (or right) hand,<br>fold it in half and put it on the floor.  | 3          |               |
|              |               | 8. Construction              | Will you copy this drawing please?   | 1          |               |
| Total Score  |               |                              |  | 30         |               |
| Examiner     |               |                              |  |            | Notes         |

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| Mini-Mental State Examination- MMSE                         |   |
|---|---|
| <b>Table 2.5: Interpreting MMSE scores (reference NICE)</b> |   |
| <b>MMSE Score</b>   | <b>Cognition function/degree of dementia</b>                                    |
| 27-30   | Normal  |
| 25-27   | Mild Cognitive Impairment   |
| 21-26   | Mild AD<br>(55.5% of all cases are classified as mild)                          |
| 10-20   | Moderate AD<br>(32.1% of all cases are classified as moderate)                  |
| 10-14   | Moderately severe AD  |
| <10   | Severe AD<br>(12.5% of all cases are classified as moderately severe to severe) |

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L14

## Medication Used In Dementia and Medicine Optimisation

Joanne Headspeath  
NSFT

1

## Stages Of Medication

- ▶ To prevent dementia
- ▶ At the onset of dementia
- ▶ During the later stages of dementia

2

## Types Of Medication

can help prevent dementia

- ▶ Acetylcholinesterase inhibitors (AChEIs), e.g. Donepezil, Rivastigmine, Galantamine
- ▶ NMDA antagonists, e.g. Memantine
- ▶ Antioxidants, e.g. Ginkgo
- ▶ Anti-inflammatories, e.g. Ibuprofen
- ▶ Neurotrophic factors, e.g. Oestrogen
- ▶ Antiamyloid agents, e.g. Tramiprosate

3

## Possible Agents To Prevent Dementia

|  | Useful?  |
|--|--|
| Taking AChEIs before a diagnosis of dementia | ✗  |
| NSAIDs (started early)                       | (✗)  |
| Antihypertensives                            | ✓  |
| Beer   | ✓ → small consumption due to beer containing SSRin which may decrease bioavailability of aluminium |
| Oestrogen                                    | ✓ → potent chemical factor that prevents vascular disease & improve blood flow in cerebral vessels |
| Oestrogen-based HRT                          | ✗  |
| Fish   | ✓ for risk ↓ in developing dementia  |
| Omega-3                                      | ✗  |
| Lithium                                      | (✓) → bipolar patients - associated w/↑ in dementia, but other studies show differently            |
| Statins                                      | (✓)  |
| Vitamins (B, C, E, folic)                    | (✓) [ further studies required ]   |

Caution: before making any changes to your medication please discuss with your doctor first.

vit B may lower homocysteine and may slower the rate of atrophy in older ppl w/ mild cognitive impairment

4

## Agents At The Onset Of Dementia

|                              | Useful?                                      |
|------------------------------|--|
| Ginkgo                       | ✗  |
| Ginseng                      | ✓ → may help increased cognitive improvement |
| Vitamin E                    | ✗  |
| Folic acid                   | (✓) → no consistent evidence                 |
| Multivitamins and folic acid | ✗  |
| Omega 3                      | (✓)  |
| Antiamyloid                  | ✗ (may help at start of dementia)            |

Caution: before making any changes to your medication please discuss with your doctor first.

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## IS PREVENTION BETTER THAN CURE?

Recent research

### ALZ-801/tramiprosate\* development history

- 2009 Alzheon develops ALZ-801, improved pro-drug of tramiprosate, based on overall population >35% modest gains seen in prevention trial success
- 2013 Alzheon analysis shows robust clinical signal in APOE4+ patients who are known to have amyloid-positive AD
- 2015 Alzheon discovery of J-35PA natural anti-oligomer program
- 2017 ALZ-801 receives FDA Fast Track designation
- 2018 ALZ-801 mechanism of action defined by Alzheon & optimal clinical dose determined
- 2020 Alzheon awarded \$177M by NIA to fund Phase 3 in FTD-AD
- 2020 ALZ-801 Phase 2 AD biomarker study initiated
- 2021 ALZ-801 Phase 3 (H2021 starts)

\*Active metabolite of ALZ-801, licensed by Alzheon from Bellus Health/Neurochem in 2013

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## IS PREVENTION BETTER THAN CURE?

### Aducanumab- Anti-amyloid antibody

- designed to target amyloid plaques in early stages of Alzheimer's
- The Phase III trials aimed to evaluate the safety of Aducanumab and the effect it had on memory, thinking and day-to-day activities in people with a confirmed diagnosis of mild cognitive impairment (MCI) or mild Alzheimer's disease.
- Phase III clinical trials of Aducanumab in 2019 were halted as early indications suggested they would not benefit people in the early stages of Alzheimer's
- In 2020, following greater data availability and higher doses used, Market approval was filed to the FDA, which is still pending.

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## IS PREVENTION BETTER THAN CURE?

- Disease modifying treatment will only work if taken early enough, maybe decades before diagnosis of dementia.
- Disease modifying treatment is expected to yield more dramatic benefits than treatment of established dementia.

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## Medication At The Onset Of Dementia THE AChE's → not cures but can slow down the symptom progression

### Donepezil Aricept® 5 – 10 mg OD ON (orodisp. available)

*not cure, slowing patient down, some patients stop taking patient after 1-2 days*

Selective reversible AChE inh.  
License: mild-moderate dementia in AD  
 $T_{1/2}$ : 70 hours  
Protein binding: 96 %  
↓4 week interval before dose increase

### Galantamine Reminyl® Galantena® 4 – 12 mg BD (Liq. & MR available)

*not cure, enhances response of nAChR to ACh*

Selective reversible AChE inh.  
License: mild-moderate dementia in AD  
 $T_{1/2}$ : 7-8 hours  
Protein binding: 18%  
↓ animal: 4 weeks interval before dose increase

### Rivastigmine Exelon® 1.5 – 6 mg BD (Liq. & patch available)

*not cure, patch: 12 mg BD, 22 mg OP*

Non-selective reversible AChE inh (non-competitive)  
License: mild-moderate dementia in AD or PD  
 $T_{1/2}$ : 1 hour  
Protein binding: 40%  
↓ animal: 4 weeks interval before dose increase

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tablet  
disposable tablet  
capsules  
patch  
liquid

} formulation to meet most ppl's needs (later in dementia straitening mechanism deteriorate, so useful)

## General Overview of AChEI's

### DOES IT WORK?

The three possible outcomes of AChEIs :

- Improvement → 1/3 improve in memory / daily function on first treatment  
↓ effects lasting 6-12months, some cases upto 2years
  - Non-decline → 6-12months
  - No response → if treatment switched it may get better
- Each of these in equal proportions in the population

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## General Overview of AChEI's

### IF IT WORKS

- The progressive decline in functioning that would otherwise have occurred can be delayed for several months or years
- This reduces carer burden
- This delays the need for transfer to a dementia-care home or hospital

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## General Overview of AChEI's

### IF IT DOESN'T WORK

- Failure to benefit from one AChEI does not necessarily mean that someone will not respond to another.
- Also, poor tolerance to one AChEI does not rule out good tolerance to another.

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## Tolerability

- ▶ Slow titration is recommended
- ▶ **Rivastigmine patches are better tolerated than capsules**
- ▶ Rivastigmine is best choice for patients taking multiple medications, and also licensed in Parkinson's disease

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## NICE technology appraisal 217- last update June 2018

→ information on 3 AChEi and memantine

- Use the least expensive one first - **donepezil** used in 70-80% of patients (good tolerance)
  - in some GPs it can be prescribed w/o referral to specialist
  - diagnosis and commencement should be done by specialist (Specialist psychiatric nurses)
- alternative AChE inhibitor could be prescribed if it is considered appropriate when taking into account **adverse event profile, expectations about adherence, medical comorbidity, possibility of drug interactions and dosing profiles**
- Rivastigmine can be used in dementia associated with Parkinson's disease

↳ hallucination is very common and this type of dementia is very similar to Lewy body dementia

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## TASK 1

Can you predict the following from your knowledge of the **pharmacology and pharmacokinetics of these drugs**?

- ▶ Peripheral cholinergic effects
- ▶ Cautions
- ▶ Contra-indications
- ▶ Drug interactions

Please read appropriate BNF entry for AChEi's to refresh your knowledge

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## Adverse Effects

When they start to work, the AChEis cause cholinergic stimulation of the body too:

- ▶ Common side-effects: Nausea, Vomiting, Diarrhoea, Loss of appetite, Sleep disturbance, Abnormal dreams, Headache, Incontinence, Fatigue, Agitation
- ▶ **bradycardia** (dangerous in certain heart diseases, or if taking heart-slowing drugs, e.g. Digoxin, beta-blockers, calcium-channel blockers)

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## Medicines That May Cause Cognitive Impairment

↳ no co-prescription is essential?

- ▶ Some commonly prescribed medicines are associated with increased anticholinergic burden, and therefore cognitive impairment
- ▶ There are validated tools for assessing anticholinergic burden- e.g. the **Anticholinergic Cognitive Burden Scale**
- ▶ **These are examples that may cause cognitive impairment**
- ▶ EXAMPLES (List not Exhaustive)
  - ▶ Antihistamines e.g Diphenhydramine
  - ▶ **Tricyclic Antidepressants**
  - ▶ Antipsychotics e.g Quetiapine
  - ▶ Drugs used in Urinary Incontinence- e.g. Solifenacin
  - ▶ **Hycosine**
  - ▶ Pain Killers- e.g. Morphine
  - ▶ Some Asthma and COPD meds

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## Medicine Optimisation

→ these meds take time to work  
→ aim is to try and limit need of functioning for as long as possible and delay decline  
→ improvement only seen in 1/3 of patients

- Donepezil can cause sleep disturbance and nightmares - **give dose in the morning**. (longer half-life at upper ages)
- Rivastigmine patches can cause a rash. If mild, an **emollient cream** can be used to soothe it. If severe then prescriber should be informed. **Rotation of the application site helps.**
- Nausea is a common side-effect. This may be minimised by **taking doses after food**. (longer a transient side effect of AChEi, but if last longer than 3 weeks → doctor may prescribe alternative AChEi or memantine)
- Bradycardia may occur. Check pulse every few months and **seek advice if less than 50 bpm**.

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## Medication During Later Stages of Dementia

### MEMANTINE (Ebixa®)



- Licensed for moderate to severe dementia in Alzheimer's Disease
- Monotherapy is recommended for managing moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors or severe Alzheimer's disease
- NMDA receptor antagonist that may be neuroprotective and thus disease modifying
- Usually started at 5 mg daily for one week and then increased by 5 mg per week, until 20 mg daily is reached. Some practitioners do titrate faster than this in some cases.
- All tablets for memory are now available in generic form  
→ this can cause confusion for some patients w/ dementia as they may reflect to take different looking meds
- Common side-effects: Headache, Constipation, Dizziness, Hypertension, Dyspnoea

Please read appropriate BNF entry for Memantine to refresh your knowledge on side effects, interactions, cautions and contra-indications

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*gives a shorter route to help patients start memantine during the titration period & also in liquid formulation available*

## What About Treatment For Patients That Have Dementia Other Than Alzheimer's?

All treatment only licensed for Alzheimer's disease  
some are supported by NICE

### UNLICENCED USE

- Offer donepezil or rivastigmine to people with mild to moderate dementia with Lewy bodies if donepezil and rivastigmine are not tolerated.
- Only consider galantamine for people with mild to moderate dementia with Lewy bodies if donepezil and rivastigmine are not tolerated.
- Consider donepezil or rivastigmine for people with severe dementia with Lewy bodies.
- Only consider AChE inhibitors or memantine for people with vascular dementia if they have suspected comorbid Alzheimer's disease, Parkinson's disease dementia or dementia with Lewy bodies.
- Do not offer AChE inhibitors or memantine to people with frontotemporal dementia.  
↳ no evidence at all right now

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## Evidence for AChE inhibitors and memantine

- NICE technology appraisal 217 (2011, last update June 2018)
- 17 new RCTs and four systematic reviews
- Increase in evidence for clinical effectiveness of AChE inhibitors and memantine
- New studies strengthened evidence for cognitive outcomes
- Memantine improved cognition at 12 weeks and function at 24 weeks (pooled data of new and previous evidence)



## Evidence for AChE inhibitors and memantine

- Quality of RCTs submitted to NICE was 'disappointing' because:
  - observed cases instead of intention to treat analysis
  - inadequate reporting of randomisation and allocation
  - small study size (donepezil in particular).

22



23

## Evidence outcomes from key trials

- Reduced carer burden with galantamine
- Adverse drug reactions more frequent with rivastigmine
- No significant difference in cognitive function between AChE inhibitors
- Significant delay in worsening symptoms with memantine (compared with placebo)
- NICE (co-led at use of memantine and bnd with AChE in the appraisal concluded that no extra benefit when using them in combination  
↳ Practitioners see importance in combined therapy in everyday practice



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## Policy, guidelines and background documents

- NICE. Clinical guideline NG97: Dementia: assessment, management and support for people living with dementia and their carers. 2018.
- Department of Health. Living well with dementia: a national dementia strategy. Department of Health. 2020.
- NICE. Quality standard [QS184]: Dementia. 2019.
- NICE. Technology appraisal 217: Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. 2011.
- Alzheimer's Society documents



L15

Management of Behavioural and Psychological Symptoms of Dementia

Joanne Headspeath, NSFT

1

Behavioural symptoms  
From observation:

- Physical Aggression
- Screaming
- Wandering
- Culturally inappropriate behaviour
- Sexual Disinhibition
- Swearing

2

Psychological symptoms

From interviews:

- Anxiety
- Depression
- Hallucinations
- Delusions

3

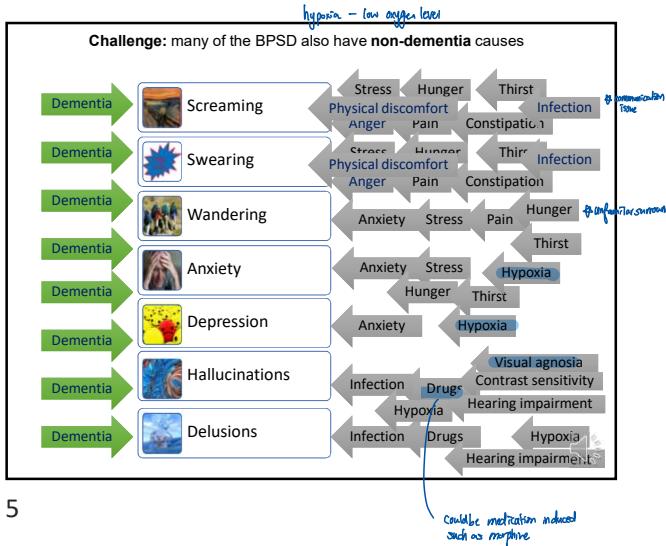
BPSD progression with stages of dementia

Mild: anxiety and depression, patient still aware

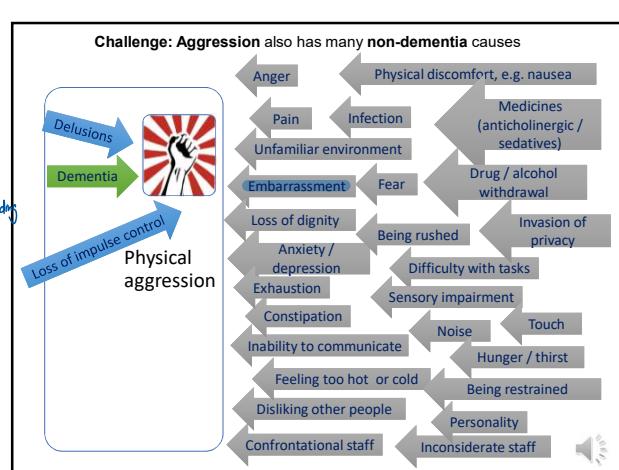
Moderate: anxiety, wandering, physical aggression, pain, they cannot remember what they were angry about, bed bound

Severe: anxiety, wandering, physical aggression, pain, they cannot remember what they were angry about, bed bound

4



5



6

### Non-drug intervention

**Modification** of behaviour of the **carer** may:

- reduce the occurrence of BPSD
- remove the need to **treat** the BPSD

Symptoms of BPSD can resolve **itself after 4-6 weeks**

- music therapy
- massage
- reminiscence therapy

Alzheimer's Society  
Leading the fight against dementia

**Optimising treatment and care**  
for people with behavioural and psychological symptoms of dementia

A best practice guide for health and social care professionals

7

### Non-drug treatment principles



Identify what symptom(s) cause most concern



Describe each symptom in detail



The ABC approach

To positive behaviour support plan

Antecedent (A) → what happens before behavior (B) → what was the behavior Consequence (C) → what happens afterwards

8

### Pain in dementia

Under-reported by patient in both frequency and intensity, but they are still in pain



**Best practice:**  
Abbey Pain scale



How is your Pain Today?

point-to-face expression

| Abbey Pain Scale   |      |  |  |
|--|------|--|--|
| For measurement of pain in people with dementia who cannot verbalise their experience of pain  |      |  |  |
| Instructions to carer: Please answer the following questions for the person you are caring for.  |      |  |  |
| Name of person completing the scale  |      |  |  |
| Date   | Time |  |  |
| Last time rated score  |      |  |  |
| Q1 Movement  |      |  |  |
| (eg walking, getting up)   |      |  |  |
| Score 0 = None 1 = Slight 2 = Moderate 3 = Severe  |      |  |  |
| <input type="checkbox"/>   |      |  |  |
| Q2 Facial expression   |      |  |  |
| (eg smiling, grimacing, frowning, looking frightened)  |      |  |  |
| Score 0 = Mild 1 = Moderate 2 = Severe 3   |      |  |  |
| <input type="checkbox"/>   |      |  |  |
| Q3 Change in body language   |      |  |  |
| (eg increased or decreased activity, change in body posture, increased or decreased confusion, difficulty in eat, abdomen in usual pattern)  |      |  |  |
| Score 0 = Mild 1 = Moderate 2 = Severe 3   |      |  |  |
| <input type="checkbox"/>   |      |  |  |
| Q4 Bedridden   |      |  |  |
| (eg unable to sit, stand, walk, unable to move about)  |      |  |  |
| Score 0 = None 1 = Moderate 2 = Severe 3   |      |  |  |
| <input type="checkbox"/>   |      |  |  |
| Q5 Physical changes  |      |  |  |
| (eg increased sweating, shivering, temperature, increased pulse, perspiration)   |      |  |  |
| Score 0 = None 1 = Moderate 2 = Severe 3   |      |  |  |
| <input type="checkbox"/>   |      |  |  |
| Q6 Environmental   |      |  |  |
| (eg increased confusion, difficulty in eat, abdomen in usual pattern)  |      |  |  |
| Score 0 = None 1 = Moderate 2 = Severe 3   |      |  |  |
| <input type="checkbox"/>   |      |  |  |
| Add scores for Q1, 2 and record total  |      |  |  |
| Total pain score: <input type="text"/>   |      |  |  |
| How has this been treated so far today?  |      |  |  |
| Please tick the box that matches the treatment given.  |      |  |  |
| Finally, tick the box that matches the type of drug given.   |      |  |  |
| <input type="checkbox"/> Opioids <input type="checkbox"/> Benzodiazepines <input type="checkbox"/> Antidepressants <input type="checkbox"/> Antipsychotics<br><input type="checkbox"/> Analgesics <input type="checkbox"/> Anticholinergics <input type="checkbox"/> Anticonvulsants <input type="checkbox"/> Antihistamines |      |  |  |

if pain manage it will change patient BPSD symptoms

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### Principles of psychiatric drug treatment for BPSD

Discuss risks and benefits of treatment  
Check that symptoms have:



e.g.) infection  
no physical cause



e.g.) symptoms induced by their treatment  
- medication  
no iatrogenic cause

no environmental cause



e.g.) bedroom being too hot or cold



no response to  
(or not treatable by)  
non-drug interventions

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### Introducing psychiatric medicines

- Prescribing must involve an assessment of:



patient capacity



informed consent



judicious dosages  
(good judgment and sensible)



Slow and cautious dose titration

→ to balanced unwanted effects

### Monitoring psychiatric medicines

every 3 months antipsychotics - every 6 weeks



Time-limit  
prescription when  
possible



Review  
symptoms and  
behaviour



Review side  
effects



Reduce drug  
dosages



Discontinue  
when  
possible



Review all psychotropics at  
least every 3 months

Review all antipsychotics  
at least every 6 weeks

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12

### Combinations

- use medicines that address several different symptoms to avoid unnecessary polyprescribing
- e.g.

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### Management with psychiatric medicines

Anxiety Antidepressant

16% of dementia patients - 4% non-dementia

Mild Moderate Severe

Challenge:

- many patients develop completely new anxieties
- original coping-skills fail

*night causes anxiety also Vascular dementia*

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### Management with psychiatric medicines

Depression 50% of patients Antidepressant

Challenge: many patients already have the key diagnostic symptoms of depression

Apathy (lack of interest or concern) Weight loss Sleep disturbance Agitation

Apathy 50% of patients Anticholinesterase → until control use for apathy

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### Non-antipsychotics for BPSD

These have limited evidence but may be worth a trial

Memantine NMDA antagonist

Ebixa 10 mg Memantine hydrochloride

Anticholinesterase inhibitors

Aricept 10mg Donepezil Once-daily EXELON PATCH (rivastigmine)

Reminyl XL 24mg Pramipexole Hydrochloride

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### Management with antipsychotics

| Appropriate                             | Inappropriate  |
|---|--|
| When all are true:                      |  |
| Persistent aggression                   | Anger, Physical discomfort, e.g. nausea, Medicines (anticholinergic/ sedatives)  |
| Moderate to severe Alzheimer's dementia | Pain, Infection, Unfamiliar environment, Fear, Drug/alcohol withdrawal   |
| Unresponsive to non-drug approaches     | Embarrassment, Being rushed, Invasion of privacy   |
| Risk of harm to self or others          | Loss of dignity, Anxiety, Difficulty with tasks, Sensory impairment, Noise, Touch, Hunger/thirst, Being restrained, Personality, Personal care, Confrontational staff, Inconsiderate staff |

*if cause is:*

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### Management with antipsychotics

Hallucinations Antipsychotics

50% of patients

Mild Moderate Severe

Challenge:

- Visual misperceptions are not hallucinations

Visual agnosia (difficulty recognising faces or objects)

ZSHC HSKRN CHORD HONDRS LUDPHEZ LUDPHEZ LUDPHEZ LUDPHEZ LUDPHEZ

Essential to examine both: auditory function and visual function

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### 5 Typical Delusions



People are stealing things



Spouse or other caregiver is an imposter



Abandonment



Misidentification  
e.g. when lost in mirror



Infidelity  
convinced their spouse is unfaithful



### Delusion: Misidentifications

Misperceptions with associated belief that is held with **delusional intensity**.

4 main types:



presence of persons in the patient's own house (the 'phantom boarder' syndrome)



cannot identify own self in mirror



cannot identify others



Television / photographs are seen as "real"



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### Antipsychotics and Dementia

↳ double the risk of death

- 180,000 people with dementia in UK (25%) are prescribed antipsychotics



Multiple Side effects from antipsychotic



✗ 1800 strokes



✗ 1600 deaths

Antipsychotics double the risk of death



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↳ covered in schizophrenia module

### Major adverse outcomes with antipsychotics



Over-sedation  
and Dehydration



\* infection and stroke 3 times more likely



Stroke

- Risperidone and olanzapine – noted 2004.  
Warning extended to all antipsychotics by 2008.



Falls



Fractures



\* increase risk of falls by double



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### Major adverse side-effects

Antipsychotic drugs also lead to:



Sedation



Parkinsonism



Gait Disturbance



Dehydration



Falls



Chest infections



Confusion



Movement problems: tremor, rigidity



Agitation, restlessness, akathisia



Dry mouth, blurred vision, constipation



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### Risperidone for BPSD



Superior to placebo for aggression and psychosis in dementia



restart treatment for up to 6 weeks  
→ reduces to once daily or dementia  
→ not licensed for any other dementia

- Others are ineffective or have harmful side-effects

Greater cognitive decline  
with quetiapine when compared to placebo

↳ possible reason could be that quetiapine has anti-cholinergic effect



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**Risperidone**

Appropriate

when all are true:

Persistent aggression

Moderate to severe Alzheimer's dementia

Unresponsive to non-drug approaches

Risk of harm to self or others

Starting dose 0.25 mg twice daily

Adjust by increments of 0.25 mg twice daily, not more frequently than every other day, if needed

Optimum dose is 0.5 mg twice daily for most patients

Some patients need 1 mg twice daily

Maximum 6 weeks

Evaluate frequently and regularly

Reassess the need for continuing treatment reassessed

**Discontinuation of antipsychotics**

- Many patients can stop antipsychotics for BPSD safely without worsening of symptoms



Continue antipsychotic if patient relapses



Do not stop antipsychotic treatment if it is for schizophrenia



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**Don't use benzodiazepines instead**

Antipsychotics



Benzodiazepines

\*benzodiazepine increases risk of falls by 8 times

**Summary of best practice****First line:**

Non-drug psychosocial interventions



Most BPSD resolve after 4 - 6 weeks



Assessment and appropriate treatment of medical conditions, e.g. pain, infection, depression

**In severe aggression:**

Risperidone



Avoid Haloperidol and Quetiapine



\*others : risks are greater than benefits



\*others : risks are greater than benefits

only licensed antipsychotic

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**END OF**  
**WEEK 4 //** 5

L08

## Epilepsy

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SCREENCAST 2

1

### Learning objectives

- To understand the long term management of epilepsy using anti-epileptic therapy
- To describe the drugs available to treat different types of epilepsy and associated notable pharmacokinetic features.
- To discuss the role of therapeutic drug monitoring in antiepileptics and when it is appropriate to use.



2

### Management of Epilepsy<sup>(1)</sup>

*is based on the epileptic syndrome or seizure type  
is taking into account other co-morbidities and gender, including patient/carer preferences*

- Anti-epileptic treatment is individualised to the patient
  - Every patient should be given a care plan that is agreed with between the patient and/or family/carers as well as primary and secondary care teams.
- Epilepsy specialist nurses are also involved in the care of patients providing support and advice to the patient as well as supporting primary and secondary care practitioners(1).
- Aim for monotherapy as this reduces the likelihood of interactions and adverse side effects. Usually doses are started low and then titrated up gradually until control is achieved(2).
- If the 1<sup>st</sup> AED fails, treatment is switched to another (1) *second epileptic susceptibility and due to switch to second AED before the first has been fully effective. You are not alone*
- If the 2<sup>nd</sup> AED fails, then combination therapy is considered – but this is only considered when monotherapy has been tried and not resulted in seizure freedom(1).

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### Therapeutic Drug Monitoring<sup>(1)</sup>

- This is relevant in managing epilepsy in certain circumstances and with certain medications (but not all AEDs).
- Regular blood tests are not generally recommended and should only be undertaken if it is clinically needed and recommended by the specialist.
- Generally, the main reasons for doing a blood test would be<sup>(1)</sup>:
  - To identify non-adherence
  - Investigate suspected toxicity
  - Adjustment of phenytoin doses
  - Managing interactions with other medication
  - For specific clinical conditions – e.g. organ failure, pregnancy



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### Other points to be aware of with AEDs

- AEDs and suicidal behaviours - MHRA/CHM advice that if patients experience any changes in mood, distressing thoughts, self-harm etc, medical advice should be sought as soon as possible to assess whether a change to their medication is necessary(2).
- Antiepileptic hypersensitivity syndrome though very rare is associated with some AEDs and can be fatal and the drug should be stopped immediately if symptoms occur.(2)
- Many of the AEDs in the BNF mention patients may need vitamin D supplementation if they are immobile for long periods of time, or have inadequate sun exposure or dietary intake. *vitamin D is important for bone health*

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### Antiepileptic drugs

- Sodium Valproate
- Carbamazepine
- Ethosuximide
- Lamotrigine
- Levetiracetam
- Phenobarbital
- Phenytoin
- Summary of other AEDs

NOTE – the pharmacology of these drugs will not be discussed in these screencasts as you will have a separate screencast on this in detail.



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## Sodium Valproate - CHM safety advice

- Any use of sodium valproate in women of child-bearing potential who cannot be treated with other medicines is in accordance with a pregnancy prevention programme.

- Before initiating sodium valproate in patients younger than 55 years old - 2 specialists should independently consider and document that there is no other effective or tolerated treatment for patients aged under 55 years old.

- Patients currently on sodium valproate treatment are advised not to stop taking it unless they are advised to by their specialist.

- Pregnancy prevention programme
  - Exclusion of pregnancy
  - Risk acknowledgement form
  - Highly effective contraception
- Changes to the medicine packaging have also been done to emphasise the warnings – using smaller box sizes; warnings on the outside of the box and alert cards are given to every patient(3).
- For further information go to: <https://www.gov.uk/guidance/valproate-use-in-women-and-girls>

both signed by patient & prescriber  
→ renewed annually

- All products containing sodium valproate or valproic acid should not be started and prescribed to patients under 55 years old (male or female) unless 2 specialists independently consider and document that there is no other effective or tolerated treatment and unless there is compelling reasons that reproductive risks do not apply.
- Any use of sodium valproate in girls and women of child-bearing potential who cannot be treated with other medicines has to be in accordance with a pregnancy prevention programme.
  - Women of child-bearing potential and girls currently on sodium valproate treatment are advised not to stop taking it unless they are advised to by their specialist. It has been advised that their treatment to be continued until a second opinion signature is required.
  - If the treatment is to continue, a second opinion signature is required.
  - This process is also to be initiated for male patients as well.

L male be fertility of men can be affected as well

## Sodium Valproate – Safety update

- MHRA safety advice on Sodium Valproate and its use in women of childbearing potential due to Sodium Valproate's association with the risk of birth defects and developmental disorders.
- In women who take sodium valproate while pregnant, around 1 in 10 babies will be at risk of a birth defect, and 4 in 10 will be at risk of a developmental disorder. Therefore current advice dictates that women of childbearing potential should not be prescribed Sodium Valproate unless on a Pregnancy Prevention programme(3).
- Changes to the medicine packaging have also been done to emphasise the warnings – using smaller box sizes; warnings on the outside of the box and alert cards are given to every patient(3).
- For further information go to: <https://www.gov.uk/guidance/valproate-use-in-women-and-girls>

facial skull malformations  
- malformation of eyes

↳ (a) 3a

② guide to which contraindications are valid

- 7 \* Before initiating sodium valproate in patients younger than 55 years old  
→ 2 specialists should independently consider and document that there is no other effective or tolerated treatment for this patient

## Sodium Valproate

Patients with child bearing potential [ + actively treat other side effects ] or women who can't have children [ have children ]

- Primary Indication<sup>(1,4)</sup>**  
(If patients are not of childbearing potential or on a PPP programme):
- 1<sup>st</sup> Line – Generalised tonic-clonic seizures, Absence Seizures, Myoclonic seizures, Tonic or Atonic seizures, ~~Neuroleptic-induced dyskinesia~~
  - Can be used as a ~~2<sup>nd</sup> line agent~~ in focal seizures if other AEDs are not suitable or not tolerated
  - Potential 1<sup>st</sup> line agent for Dravet's syndrome, Lennox-Gastaut syndrome
  - Adjunctive to other AEDs in certain epilepsies.

↳ 2<sup>nd</sup> line for absence seizures  
if other AED not suitable

## Other Indications

- Migraine prophylaxis (unlicensed)
- Mania in Bipolar disorder (either as sodium valproate or as semi-sodium valproate)

## Adverse Side effects

- Nausea, weight gain → important to monitor for psychiatric adverse events (PSE)
- Transient elevation of LFTs, blood dyscrasias alopecia (hair loss), Liver toxicity and pancreatitis (rare).

changes in blood levels  
→ anaemia, thrombopenia

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## Sodium Valproate

## Notable Pharmacokinetics

- Crosses into through the placenta (therefore causing birth defects or developmental disorders)
- Half-life ranges between 8-20 hours (Usually shorter in children)
- Metabolised through the liver mainly via glucuronidation(5)
- Enzyme inhibitor of a few CYP enzymes (6)

450 and 229

## Monitoring:

- ✓ Liver function tests are conducted before starting Sodium valproate, and within 6 months of starting treatment.
- Full blood count done as well before starting treatment to ensure no potential for bleeding.
- Blood dyscrasias → bone marrow, mouth ulcers, fever ) nausea (or) lethargy (or) convulsions
- Liver disorders → jaundice and other non-specific symptoms that could be sudden in onset – general tiredness/lethargy/drowsiness/loss of strength, anorexia, swelling (sometimes associated with repeated vomiting and abdominal pain)
- Pancreatitis<sup>(5)</sup>

abdominal pain

Nausea, acute abdominal pain

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## Carbamazepine

## Primary Indication

- 1<sup>st</sup> line** → focal seizures, other types of epilepsy that include benign epilepsy with centrotemporal spikes, ~~benign partial seizures or late onset childhood-onset epilepsy (Lennox type)~~

Can be considered for generalised tonic clonic seizures (but be aware it can exacerbate myoclonic and partial seizures – if these are present this is not suitable)

Adjunctive in focal seizures → add on therapy as above

- Prophylaxis in Bipolar disorder unresponsive to lithium
- Trigeminal neuralgia → ↓ pain part or face (difficult to beat + painful)
- Adjunct to acute alcohol withdrawal (unlicensed)
- Diabetic neuropathy (unlicensed)

## Other Indications

- Drowsiness, dry mouth, nausea, vision disorders
- Blood disorders – leucopenia, eosinophilia, thrombocytopenia
- Hyponatraemia – can lower seizure threshold
- Skin disorders

10

## Carbamazepine

## Notable Pharmacokinetics

- Enzyme inducer – induces multiple CYP enzymes in the liver.
- Has multiple formulations (immediate release tablets, MR release, liquid). However different preparations are NOT bioequivalent(7)
- It is metabolised in the liver and its clearance can be affected not only by other drugs causing enzyme induction/inhibition but also by autoinduction of its own metabolism – thus altering the half-life of the drug after continued administration(7,8).
- Interacts with other AEDs

Monitoring<sup>(9)</sup>

- Pre-treatment screening is necessary in patients of Han Chinese or Thai origin for the allele HLA-B\*1502 → ~~carbamazepine reaction~~ drug induced hepatitis
- Manufacturer recommends blood counts, liver and renal function tests – however the actual value of these tests is not known<sup>(9)</sup>
- Monitor for any blood dyscrasias, liver or skin disorders

patient & carers advised to recognise signs and seek medical help if needed  
– fever, mouth ulcers, hearing, bleeding

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## Oxcarbazepine

- Analogue of carbamazepine. It is a prodrug that is converted in the liver into its active metabolite.
- Is a weak enzyme inducer of CYP enzymes (CYP3A4 and 3A5); also enzyme inhibitor of CYP2C19
- Patients that are allergic hypersensitivity to carbamazepine have a 25-30% chance of experiencing a similar reaction to oxcarbazepine.
- Has more linear pharmacokinetics – no self-induction of metabolism(10) → makes it more predictable

## Eskarcarbazine

- Like that of Oxcarbazepine – weak inhibitor and inducer of certain CYP enzymes
- Does not affect its own metabolism or clearance
- Long half-life therefore once daily dosing(11) → carbamazepine, its several times a day
- Risk of hypersensitivity reactions
- Similar side effects to oxcarbazepine – but can also prolong the PR interval and therefore caution should be used in associated medical conditions(12)

12

80%

3)

### Ethosuximide

*Add on*

|                                 |   |
|---------------------------------|---|
| <b>Primary indication</b>       | - 1 <sup>st</sup> line for absence seizures, childhood absence epilepsy, and other absence epilepsy syndromes (1).<br>- Additive for absence seizures and other absence epilepsy syndromes<br>- It is also licensed for myoclonic seizures (2) → NICE guidance X → only SPC   |
| <b>Other indications</b>        | - None X  |
| <b>Adverse side effects</b>     | - GI discomfort (nausea, vomiting, diarrhoea, constipation), anxiety, sleep disturbances, behavioural disorders, ataxia (incoordinated movements and balance), drowsiness.<br>- Blood disorders, rash (Steven-Johnson syndrome)   |
| <b>Notable pharmacokinetics</b> | - Absorbed well orally, excreted mainly in the liver (13).<br>- Available in oral capsule and oral form.<br>- Generally, there are no notable interactions with other AEDs (14, 15). → some plasma concentration changes when given with certain other drugs - carboxen + phenytoin   |
| <b>Monitoring</b>               | - Monitor for any blood dyscrasias:<br>o Patients/carers should be told how to recognise the signs - to seek medical attention if they experience a fever, rash, mouth ulcers, bruising or bleeding (16)<br>- Monitor for suicidal thoughts.<br>- Patients/carers should report any signs or symptoms of suicidal thoughts or behaviour. (13) |

13

4)

## Lamotrigine

14

5)

### Levetiracetam

*Add on for certain epilepsy syndromes*

|                                 |   |
|---------------------------------|---|
| <b>Primary Indication</b>       | - 1 <sup>st</sup> line focal seizures (after carbamazepine and Lamotrigine), myoclonic seizures, focal seizures<br>- Additive in focal seizures, generalised tonic-clonic seizures, myoclonic seizures<br>- 2 <sup>nd</sup> line - absence seizures, asymptomatic seizures, idiopathic generalised seizures, epilepsy syndromes   |
| <b>Other indications</b>        | - None X - monitoring for certain epilepsy syndromes  |
| <b>Adverse side effects</b>     | - Drowsiness, dizziness, anxiety, GI discomfort (feeling full of energy), insomnia, behavioural abnormalities (drowsiness, irritability, restlessness, aggression, hyperactivity, depression, suicidal behaviours, thrombocytopenia, leukopenia (18))<br>- Uncommon/fare - suicidal behaviours, thrombocytopenia, leukopenia (18)   |
| <b>Notable pharmacokinetics</b> | - Oral bioavailability is almost 100% with large interindividual profile, allowing plasma levels to be more predictable, therefore plain levetiracetam is not needed.<br>- It is not extensively metabolised by the body, and a large proportion is excreted through the kidney unchanged. Some of the drug is metabolised through hydrolysis and does not involve the CYP450 hepatic isoenzymes (19) |
| <b>Monitoring</b>               | - None except for general counselling of AEDs.  |

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6)

## Phenobarbital

16

7)

### Phenytoin

*Add on 3<sup>rd</sup> line for focal seizures*

|                             |  |
|-----------------------------|--|
| <b>Primary Indication</b>   | - old drug   |
| <b>Other Indications</b>    | - Additive in refractory focal seizures in tertiary care settings; also additive in tertiary care settings to treat benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type) (22)  |
| <b>Adverse Side effects</b> | - Trigeminal neuralgia (usually as 2 <sup>nd</sup> or 3 <sup>rd</sup> line and often under a specialist)<br>- Liver pain or fever<br>- Drowsiness, confusion, hirsutism, gingival hyperplasia (overgrown gums), cerebellar dysfunction, bone and bone marrow disorders (can affect the hematopoietic system - formation of different blood types of cells resulting in megaloblastic anaemia, granulocytopenia, etc.) (23)<br>- Symptoms of Phenytoin toxicity - nystagmus, diplopia, slurred speech, ataxia, confusion and hyperglycaemia (23). |

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## Phenytoin

18

8)

## Other AEDs

| Antiepileptic | Indication <sup>(1)</sup>   | Other information  |
|---------------|---|--|
| Carbamazepine | Adjunctive for refractory focal seizures, generalised tonic-clonic seizures, absence and myoclonic seizures in tertiary care setting, and a few other epilepsy syndromes.   | Other indications – short-term anxiety<br>Not licensed for monotherapy<br>It is not prescribable on the NHS in primary care except for epilepsy and must have the 'SLS' written on the script.<br>Plasma drug concentrations sometimes taken in certain circumstances (e.g. when given in children, status epilepticus, etc)(24).<br>Few pharmacokinetic interactions with other AEDs.<br>S/E – similar to other benzodiazepines, suicidal behaviours, muscle weakness, skin reactions(25).<br>S/E – Dizziness, suicidal ideation, prolongation of PR interval. Hypersensitivity syndrome<br>Few pharmacokinetic interactions with other AEDs(26). |
| Ezogabine     | 2 <sup>nd</sup> line for refractory focal seizures in tertiary care. NICE mentions its use in other types of epilepsy but again under specialist care.  |  |
| Gabapentin    | Adjunctive treatment in refractory focal seizures. NICE mentions it as an adjunctive to a few other epilepsy types/syndromes however it is not recommended with some seizure types due to it worsening symptoms.                | Other licensed uses: peripheral neuropathic pain, Unlicensed uses: menopausal symptoms (flushing) in women with breast cancer, Oculargia in Multiple Sclerosis (MS), Raynaud's syndrome, and trigeminal neuralgia. S/E – respiratory depression (MRHA warning), suicidal ideation, increased seizures, drowsiness, dizziness (27, 28).<br>Few pharmacokinetic interactions with other AEDs. Caution with Gabapentin given with opioids (esp in elderly)(28). New Schedule 3 – risk of abuse.   |
| Pregabalin    | Adjunctive for refractory seizures (ideally under tertiary care). NICE mentions it as an adjunctive to a few other epilepsy types/syndromes however it is not recommended with some seizure types due to it worsening symptoms. | S/E – hypersensitivity reactions (angioedema), dizziness, drowsiness, weight gain, blurred vision(29, 30).<br>No significant pharmacokinetic interactions with other AEDs(30).<br>New Schedule 3 – risk of abuse.  |

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## Other AEDs

| Antiepileptic | Indication <sup>(1)</sup>  | Other information   |
|---------------|--|---|
| Rufinamide    | Adjunctive treatment in Lennox Gastaut syndrome  | S/E – hypersensitivity syndrome<br>Child-bearing women should be on oral contraceptives whilst in this Dosage of Rufinamide is altered when given with Sodium valproate(31).  |
| Vigabatrin    | Adjunctive for refractory focal seizures in tertiary care. Potential 1 <sup>st</sup> line agent for infantile spasms   | Serious S/E – can cause visual field defects. Pts advised to have visual field testing before starting and end of treatment. Also neuroleptic synergies (drowsiness, stupor, confusion)(32). Other side effects – suicidal thoughts, headache, GI disturbances, joint pain. Not much is metabolised in the body and is mainly eliminated via the kidneys. A few pharmacokinetic interactions with other AEDs(33). |
| Tigagabine    | Adjunctive for refractory focal seizures. NICE mentions it as an adjunctive to a few other epilepsy types/syndromes however it is not recommended with some seizure types due to it worsening symptoms.  | S/E – suicidal behaviours, visual field disorders, depression, drowsiness, increased seizures.<br>Does have some pharmacokinetic interactions with other AEDs(34).  |
| Topiramate    | Adjunctive in refractory focal seizures, generalised tonic-clonic seizures. NICE mentions it as an adjunctive to a few other epilepsy types/syndromes. BNf and license for the drug also mention monotherapy use in focal seizures and generalised tonic-clonic(35). | Other indications – migraine prophylaxis<br>S/E – drowsiness, dizziness, confusion, decreased sweating, hyperthermia, suicidal behaviours, mood disturbances, vision disorders, weight changes.(36)<br>Women of childbearing potential should be on highly effective contraception.(35)   |

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## Other AEDs

| Antiepileptic | Indication <sup>(1)</sup>  | Other information  |
|---------------|--|--|
| Zonisamide    | Adjunctive in refractory focal seizures. NICE mentions it as an adjunctive to a few other epilepsy types/syndromes/seizures. BNf and license of the drug also mention monotherapy use in focal seizures. | S/E – heat stroke (decreased sweating, kidney stones, suicidal ideation, metabolic acidosis, weight loss, Blood disorders, hypersensitivity reactions.(37)<br>CaT – in sulfonamide hypersensitivity<br>General advice is to ensure adequate hydration, counselling on how to avoid over-heating(38).<br>Women of childbearing potential should be on highly effective contraception(38).<br>No significant pharmacokinetic interactions with other AEDs. |
| Perampanel    | Adjunctive for focal seizures, and generalised tonic-clonic seizures(39). Not included in NICE guidance on the management of epilepsy.   | S/E – suicidal behaviours, severe cutaneous skin reactions, dizziness, drowsiness, aggressive behaviour, weight gain.(40)<br>Does have some pharmacokinetic interactions with other AEDs.  |
| Briavacetam   | Adjunctive for focal seizures, Not included in NICE guidance on the management of epilepsy.  | New AED – not much use in practice (so far)<br>S/E – suicidal ideation, decreased appetite, drowsiness, dizziness, fatigue(41).  |

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## MHRA Guide

| AED involved                        | Category 1  | Category 2  | Category 3   |
|-------------------------------------|---|---|--|
|                                     | Carbamazepine, phenytoin and primidone                              | Clobazam, clonazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, topiramate, zonisamide  | Brivaracetam, ethosuximide, gabapentin, lamotrigine, levetiracetam, topiramate, zonisamide   |
| Advice for healthcare professionals | Patient's should be maintained on a specific manufacturer's product | The need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with patient/carer taking into account various clinical and non-clinical factors. | Patient's should be maintained on a specific manufacturer's product should be based on clinical judgement and consultation with patient/carer taking into account various clinical and non-clinical factors. |

consider before any drugs made  
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23

## Ketogenic diet (Non-pharmacological) → treatment

|  |
|--|
| This is a high fat, low protein, low carbohydrate diet and is mainly used with patients difficult to treat epilepsy.   |
| We recommend it should only be used under a tertiary care epilepsy specialist.   |
| The theory behind how it works is that it mimics a state of starvation for the brain, forcing the body to break down fat instead of carbohydrate to produce energy.  |
| There are 3 different types of ketogenic diet:   |
| Very low carb, high fat diet   |
| Medium carb, high fat diet   |
| Very low carb, medium fat diet   |
| Very low carb, high fat diet   |
| Very low carb, medium fat diet   |
| Very low carb, very low fat diet   |
| For more information please see:   |
| An overview of the ketogenic diet - information for children, young people and families. Great Ormond Street Hospital for Children NHS Trust. [available at: <a href="https://www.gosh.nhs.uk/childrens-health-information/conditions-disorders/epilepsy/epilepsy-treatment/epilepsy-diet-overview">www.gosh.nhs.uk/childrens-health-information/conditions-disorders/epilepsy/epilepsy-treatment/epilepsy-diet-overview</a> ] (Accessed 05/01/2021) |

## tension epilepsy syndromes

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L19

## Epilepsy

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SCREENCAST 3

1

### Learning Objectives

- To describe how drugs can exacerbate epileptic seizures
- To discuss the duration and withdrawal of therapy in patients with epilepsy
- To describe the management of women with epilepsy in relation to contraceptive needs and pregnancy
- To explain the importance of bone health in patients with epilepsy

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### Drugs that exacerbate epileptic seizures

- Prescription and illicit drugs can precipitate a seizure – also includes alcohol
- Ways in which drugs can trigger seizures include:
  - Induction or inhibition of hepatic enzymes by other drugs can alter the **pharmacokinetics** of AEDs and **affect plasma concentration**.
  - Some AEDs can themselves worsen and/or precipitate some types of seizures(1)
  - Secondary effects of other drugs used for other medical reasons can precipitate seizures – **hyponatraemia, serotonin syndrome**(2).
  - Other factors that can affect dose/plasma concentration of AEDs – e.g. renal or hepatic impairment. Or co-administered with interacting drugs or drugs that are cautioned in epilepsy e.g. ciprofloxacin, theophylline(3) *not only drug to drug interaction but also drug enzyme interaction*
- All healthcare professionals should be vigilant for POMs that can potentially exacerbate seizures in patients with epilepsy.

reduction in seizures

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e.g.) ciprofloxacin (antibiotic)  
theophylline (COPD)

### Duration of AEDs and withdrawal

- A main aim of AED treatment in all patients is to become **seizure free**, and some patients do achieve this. However, many experience adverse side effects which can affect their **quality of life**, so **withdrawal of treatment is desirable** though not always achievable due to fear of seizure recurrence(4).
- AED treatment can be discontinued in patients that have been seizure free for at least 2 years(1).
  - The AED would slowly be withdrawn – over 2-3 months but sometimes longer
  - Patients who are on **barbiturates** and **benzodiazepines** – their withdrawal must be much **slower** (over 6 months) due to withdrawal symptoms and potential seizure recurrence.
  - If patients are on **multiple AEDs** – **one drug must be withdrawn at a time**.

Withdrawal from AEDs should be under the supervision of a specialist, and a plan in place that has been agreed with the patient as to what to do if they start to have seizures again(1).

*risk and benefits should be fully understood and other factors taken into account*  
*e.g.) risk of seizure recurrence (remain or after withdrawal)*  
*if they take x medication, difficult to predict*  
*seizure type/syndrome may depend on off if next epilepsy occurred*  
*if epilepsy surgery? MRI abnormalities?*

### Management of women and girls with epilepsy

- Women and girls with epilepsy need to be thoroughly counselled and informed about topics such as **contraception, pregnancy, breastfeeding** and **menopause** to ensure treatment can be personalised to fit individual needs and (if appropriate) involve carers and close family members(1). *Self study this*
- Things discussed may include:
  - Risk of AEDs in general causing **malformations** and other **developmental disorders** in unborn children. Also highlighting the lack of information regarding this with **newer AEDs**
  - Risks and benefits of individual AEDs – most especially the risks associated with **sodium valproate** if relevant to the patient.

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### Management of women and girls with epilepsy - Contraception

- Patients need to be counselled on the **potential interactions** AEDs have with **oral contraceptives**, and assessment needs to be carried to balance the risks and benefits of treatment<sup>(1)</sup>. This would be dependent on:
  - Individual AED treatment regimen
  - Risks and benefits of different contraception methods
- AEDs can be divided into two categories<sup>(1)</sup>:
  - Enzyme-inducers
  - Non-enzyme inducers

*[important bc influence choice on which anti-epileptic drug to take & choice of contraception]*

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## Enzyme Inducing Drug

### Management of women and girls with epilepsy - Contraception

| Enzyme inducers               | Non-enzyme inducers |
|-------------------------------|---------------------|
| Carbamazepine                 | Acetazolamide       |
| Eskarbazepine                 | Clobazam            |
| Oxcarbazepine                 | Clonazepam          |
| Phenobarital                  | Ethosuximide        |
| Phenytoin                     | Gabapentin          |
| Primidone                     | Lacosamide          |
| Rufinamide                    | Levetiracetam       |
| Topiramate (doses over 200mg) | Pregabalin          |
|                               | Sodium valproate    |
|                               | Tigabine            |
|                               | Vigabatrin          |
|                               | Zonisamide          |

Adapted from NICE guidance: CG137 Epilepsy: Diagnosis and management. <https://www.nice.org.uk/guidelines/cg137> (Accessed 05/01/2021) [1]

\*\* Lamotrigine – combined oral contraceptives affect the metabolism of lamotrigine

7 \* certain drugs are enzyme inducers over a certain dose

### Management of women and girls with epilepsy - Contraception

Patients on **enzyme-inducing AEDs** are able use(1, 5): *anti-epileptic drug → may affect the metabolism of contraceptive and make it less effective*

- Progestrone only depot injections

• Levonorgestrel intrauterine device

• Copper-intrauterine device (non-hormonal)

• Combined oral contraceptive – reference to guidance in individual SPCs should be looked at. The BNF states only if the ethinylestradiol dose is 50mcg or more daily and use of an extended or tricyclic regimen followed by a shortened break (4 days) before restarting (unlicensed).

Contraceptives that are NOT appropriate(5)

- Oral progestrone only pills

• Progestrone only implants

• Combined oral contraceptives with less than 50mcg of ethinylestradiol.

**NOTE – if the enzyme inducing AED is withdrawn – the enzyme induction persists for 4 weeks after and therefore contraception methods must be continued during this time.**

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## Summary

### Management of women and girls with epilepsy - Contraception

In the case of **emergency hormonal contraception** with enzyme-inducing AEDs(6):

- **Copper IUD** (most effective form of emergency contraception)
- **Levonorgestrel 1.5mg tablets – double dose** should be taken to provide cover if Cooper IUD is not suitable or acceptable to patient
- **Ulipristal Acetate 30mg tablet – NOT appropriate to give!**
  - “EllaOne”
  - ↳ effectiveness not known

Primary option

### Management of women and girls with epilepsy - Contraception

Adapted from the Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists CPG guidance: Drug interactions with Hormonal contraception. Published in January 2017, Last reviewed Jan 2019. <https://www.fshn.org.uk/standards-and-guidance/documents/cpg-clinical-guidance/drug-interactions-with-hormonal/> (Accessed 06/01/2021) [8]

| Drug type<br>(Enzyme-Inducers<br>(during use and for 4 weeks<br>afterwards)) | CHC | POP | IMP | DMPA | LNG-IUS | Cu-IUD (EC) | LNG-EC | UPA-EC |
|--|-----|-----|-----|------|---------|-------------|--------|--------|
| Known clinical interaction: avoid use & advise alternative method            |     |     |     |      |         |             |        |        |
| Potential interaction: caution required                                      |     |     |     |      |         |             |        |        |
| No clinical interaction: method suitable                                     |     |     |     |      |         |             |        |        |

Contraceptive methods: CHC: combined hormonal contraception; Cu-IUD: copper intrauterine device; DMPA: progestogen-only injectable; depo medroxyprogesterone acetate; EC: emergency contraception; IMP: implant; LNG-IUS: levonorgestrel-releasing intrauterine system; POP: progestogen-only pill; UPA: ulipristal acetate

Non-hormonal contraceptive (NET-EN) is rarely used in UK practice but should be considered as for DMPA.

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## Non-enzyme Inducers → normal contraceptives can be used

### Management of women and girls with epilepsy - Contraception

- With AEDs that are non-enzyme inducers – **normal contraceptive methods can be used as if they were not on an AED.**
- The main exception is **lamotrigine** as the combined oral contraceptive reduces the efficacy of lamotrigine(6).
  - Increase the risk of seizures for the patient during days 1-21 of their cycle, and then during the pill free period there is the **risk of toxicity** as there is increased exposure to the lamotrigine(6).
  - A **progesterone-only contraceptive Desogestrel** is also thought to potentially increase the exposure of Lamotrigine and therefore **careful monitoring would be needed(6).**

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one method: continuous combined hormonal contraception regimen  
→ no pill free period to avoid change in lamotrigine levels

### Management of women and girls with epilepsy - Contraception

Summary of guidance given for patients on lamotrigine requiring contraception from the FSRH(6):

| Method      | Clinical recommendation  |
|-------------|--|
| CHC         | Potential risk of reduced seizure control while taking CHC, and potential for toxicity in the first few days of taking CHC may outweigh the benefits and alternative methods should be considered. |
| POP         | May increase lamotrigine levels. Monitor for side effects.   |
| IMP         | No need for extra precaution.  |
| DMPA        | No need for extra precautions.   |
| LNG-IUS     | No interaction.  |
| Cu-IUD (EC) | No interaction.<br>→ Most effective method of EC.  |
| LNG-EC      | No interaction.  |
| UPA-EC      | No interaction.  |

Adapted from the Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists CPG guidance: Drug interactions with Hormonal contraception. Published in January 2017, Last reviewed Jan 2019. <https://www.fshn.org.uk/standards-and-guidance/documents/cpg-clinical-guidance/drug-interactions-with-hormonal/> (Accessed 06/01/2021) [8]

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Contraceptive methods: CHC: combined hormonal contraception; Cu-IUD: copper intrauterine device; DMPA: progestogen-only injectable; depo medroxyprogesterone acetate; EC: emergency contraception; IMP: implant; LNG-IUS: levonorgestrel-releasing intrauterine system; POP: progestogen-only pill; UPA: ulipristal acetate

Non-hormonal contraceptive (NET-EN) is rarely used in UK practice but should be considered as for DMPA.

2

## Preconception

### Management of women and girls with epilepsy - Pregnancy

#### Preconception

- Discuss it with their doctor for the pregnancy to be planned.
  - regularly reviewed at routine consultations when talking to patients who are of child-bearing potential.
- Counselling about the importance of taking AEDs (if appropriate), discussion of the potential risks of AEDs on a developing foetus vs the increased risk of seizures to mother and foetus; also, the possibility of status epilepticus and SUDEP in patients who plan to stop AED therapy(7).
  - The risk of foetal malformations is related to the type, number and dose of AED
  - Risk of malformations of the foetus is higher in patients on AEDs.
  - Women with epilepsy who are pregnant are also at increased risk of SUDEP during pregnancy and just after birth(8, 9).

*lowest possible dose of AED and usual polytherapy*

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#### Management of women and girls with epilepsy - Pregnancy

Preconception (continued)

- NICE recommends monitoring anti-epileptic medication levels in women/girls with epilepsy who are planning pregnancy and are considered at risk of their seizures worsening.
- Obtain baseline concentrations
- NICE recommends patients on certain AEDs to be monitored and doses adjusted as per safety review!
- Monitoring of AED levels during pregnancy and through a dental care informed choices
- Doses return to pre-conception doses

*carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarital, phenytoin*

*dependent on patient + clinical need*

## Pregnancy

### Management of women and girls with epilepsy - Pregnancy

#### Pregnancy

- Notify the UK Epilepsy and Pregnancy register → gather info on malformation.
- Care of women with epilepsy when pregnant should be shared with the epilepsy specialist and obstetrician/midwife(1). Good communication between them should continue throughout the pregnancy to allow follow up and planning of delivery with the patient(1).
- NICE guidance states "Women should be informed that they are likely to have healthy pregnancies but should be aware of the risk of complications during pregnancy and labour are higher in patients with epilepsy" (1) than those without.
- Women with epilepsy while pregnant who are taking AEDs should be offered high resolution ultrasound scans to screen for structural anomalies at around 18-20 weeks(1)
- Routine drug monitoring of AEDs is not recommended during pregnancy except in clinically appropriate circumstances (e.g. increased frequency of seizures) (1)
- Genetic counselling should also be considered if there are known risk factors or fear of inheritance of epilepsy – especially with idiopathic epilepsy and positive family history (1,11)

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*factors that trigger seizures should be monitored*

- sleep deprivation
- absence + complex
- seizure type + frequency

*→ some require more frequent review if t/t, learning disability, or active epilepsy, bilateral tonic-clonic seizures or have multiple risk factors*

*↓ seizure w/t  
last 12 months*

## After Birth

### Management of women and girls with epilepsy - Pregnancy

#### After Birth

- Babies born to mothers who are on enzyme inducing AEDs are given a 1mg Vitamin K parentally at delivery(1)
- Patients are encouraged to breastfeed as it is generally safe whilst on AEDs – there are exceptions of course and patients also need to be supported in their choice of feeding that suits the patient(1).
  - Individual SPCs of AEDs should always be consulted
  - Risk and benefits of breastfeeding whilst on AEDs also should be discussed between the clinician and patient
- Also certain safety precautions should be discussed and taken with the patient and/or carer to help reduce accidents and harm to the infant and mother(1, 9):
  - Bathing → don't bathe, shower to reduce risk of drowning
  - Feeding → sit on floor, reduce risk of choking
  - Changing nappies → on the floor
  - Going outside → avoid falls to motor.

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### Management of women and girls with epilepsy - Pregnancy

#### Preconception

- Discussion of the risks and benefits of potential changes to the dose of the AED and/or the choice of AED (7).
  - The aim is to be on the lowest effective dose to obtain seizure control before and during pregnancy(1).
  - Avoid use of polytherapy where possible(1)
- Taking a supplement containing folic acid before becoming pregnant
  - To help prevent neural tube defects – one of the most common congenital malformations associated with women on AEDs(10) – especially carbamazepine
  - 1mg of folic acid is recommended in women with epilepsy taking AEDs for at least the first trimester

If a woman with epilepsy has an unplanned pregnancy, all the above will still need to apply → often longer

**NOTE - Important for the patient not to stop their AED therapy or change it until they have had a discussion with their doctor and/or specialist.**

#### AEDs in pregnancy - safety review

*taking care & birth abnormalities*

| Risk of birth anomalies   |  |
|---|--|
| • Lennox-Gastaut syndrome   | and carbamazepine are safer to use in pregnancy than other anti-epileptics(11)   |
| • Carbamazepine, phenobarital, Phenyltoin or primidone are associated with an increased risk of physical birth anomalies compared to the general population(11) |  |
| • Valproate   | is associated with an increased risk of birth anomalies taken during pregnancy which can increase the risk the child may have difficulty with learning and thinking ability (neurodevelopmental effects)(11) |
| • General population  | 1 in 3 out of 100 babies   |
| Carbamazepine   | 4 in 5 out of 100 babies   |
| Phenobarital  | 4 in 7 out of 100 babies   |
| Phenytoin   | 1 in 2 out of 100 babies   |
| Primidone   | 4 in 7 out of 100 babies   |
| Valproate   | about 15 out of 100 babies   |

*④ Phenytoin, topiramate or zonisamide*  
*→ during pregnancy increase risk of baby born smaller than expected compared to general population*

### Management of women and girls with epilepsy - Pregnancy

#### Pregnancy

##### Risk of seizures during pregnancy

- NICE guidance states that generally, women with epilepsy are unlikely to experience an increase in seizure frequency while pregnant or during first few months after birth(1).
  - HOWEVER – patients that have generalised tonic-clonic seizures should be informed that the fetus may be at relative higher risk of harm during a seizure and may depend on seizure frequency(1).
  - With focal, absence and myoclonic seizures there is no evidence of adverse effects to the fetus unless the mother falls or sustains an injury as a result of the seizure(1).
- Risk of seizures during labour is also low however it is currently recommended patients give birth in hospital where there are the facilities for resuscitation and treatment of seizures(10).
  - Patients would be kept under close observation in hospital, in an open bay (not in a room alone). This is again because of risk of SUDEP.

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#### Epilepsy and bone health

*related to metabolism of vit D, by CYP450 enzyme, due to AEDs (not understood)*

- It has long been thought that long term use of AEDs (both enzyme inducing and non-enzyme inducing) increases the likelihood of bone loss, reduced bone density, risk of osteoporosis and fractures at least in part as a result of seizures(12).
  - Enzyme inducers – carbamazepine, phenytoin, primidone, and non-enzyme inducer Sodium Valproate. There have not been enough studies to comment on the effect of newer AEDs and their effect on bone health in patients.
  - Risk to bone health increased if on multiple AEDs(13) or for long periods of time.
- NICE guidance recommends monitoring of vit D levels of patients on enzyme inducing AEDs every 2-5 years.(1)
  - x supplement*
- Other tools that could be used are DXA scans and the FRAX tool(14).
  - fracture risk assessment tool*
- Counselling patients about bone health is important (15)

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*adequate amount of vit D to calcium ↑ sun exposure, suitable exercise, + reduce alcohol intake*

## Epilepsy and Driving

- It is important that patients inform the DVA if they have an epileptic seizure or blackouts AND stop driving immediately (16).
  - People who fail to inform the DVA could be fined up to £1000 and be prosecuted if it results in an accident.
  - Informing the DVA can be done online or by filling in a FEP1 form
- For more information visit: <https://www.gov.uk/epilepsy-and-driving>
- There are a slightly different set of rules for people who have bus, coach and lorry driver licences.

② lorry or bus drivers  
different  
→ tough to manage  
for medical

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L25

# Parkinson's Disease

## Introduction

1

## Learning Outcomes

By the end of this screencast you will be able to...

- Define Parkinson's Disease and Parkinsonism
- Describe the clinical presentation of the Parkinson's patient including motor and non-motor symptoms
- List the risk factors for developing Parkinson's Disease
- Explain how Parkinson's Disease is diagnosed

2

## Definition

Parkinson's disease is a chronic, progressive neurodegenerative condition resulting from the loss of the dopamine-containing cells of the substantia nigra. The resulting dopamine deficiency within the basal ganglia leads to movement disorders.

<https://cks.nice.org.uk/topics/parkinsons-disease/background-information/definition/>

3

## Prevalence

- PD is the 2nd most common neurodegenerative disease
- Around 137,000 people with Parkinson's Disease in the UK
- Lifetime risk of being diagnosed with PD is 2.7% (1 in every 37 people)
- Increasing prevalence with age
- More common in men than women
- Early onset variant
  - 1 in 20 patients diagnosed before 40 yrs

<https://cks.nice.org.uk/topics/parkinsons-disease/background-information/prevalence/>

4

## Clinical Presentation

|   |  |
|---|--|
| • Motor Symptoms  | • Non-motor Symptoms   |
| <ul style="list-style-type: none"> <li>• Bradykinesia</li> <li>• Muscle Rigidity</li> <li>• Tremor</li> </ul> | <ul style="list-style-type: none"> <li>• Depression/anxiety</li> <li>• Fatigue</li> <li>• Cognitive impairment/dementia</li> <li>• Sleep disturbance</li> <li>• Constipation</li> <li>• Hyposmia (reduced sense of smell)</li> <li>• Sialorrhoea (drooling/excessive salivation)</li> <li>• Excessive sweating</li> <li>• Urinary/bladder problems</li> <li>• Pain</li> <li>• Hypotension</li> </ul> |

*Parkinsonian  
→ 3 of the main symptom presenting patient*

*+ Stroke (e.g. infarct) can be caused*

*Impact on QOL*

5

*Lack of dopaminergic neurons causes dysregulation  
→ produce symptom*

## Dopaminergic Pathways

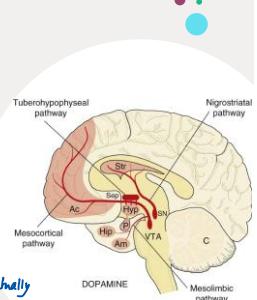
• Functions of dopaminergic pathways divide broadly into:

• Motor control (nigrostriatal system)

• Behavioural effects (mesolimbic and mesocortical systems)

• Endocrine control (tuberohypophyseal system)

*Substantia nigra first part of the brain to actually experience cell loss*



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## Motor Symptoms - Bradykinesia

- 'Slowness of voluntary movement'
- This can be **asymmetrical and unpredictable**
  - Mask-like face/limited expressions; limited blinking
  - Hypophonia (soft voice) and/or monotonous voice
  - Micrographia** (small handwriting)
  - Difficulty performing fine motor actions (e.g. fastening button)
  - Shuffling gait

↳ smaller steps

**Bradykinesia**

*Brady = slowness      Kinesis = movement  
of voluntary movement*

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## Motor Symptoms - Rigidity

- any muscles that decrease the angle:
- Increased muscle tension
- Flexor muscles of trunk and limbs mainly affected
- Characteristic stooping posture
- Rigidity affects balance → increased risk of falls
- + slow reaction → more bradykinesia
- Associated muscle pain common

[Fig 2 Caring for patients with Parkinson's disease in general hospital settings.  
Available at: <https://journals.rnii.com/doi/aop-pdf/10.7748/nop.2017.e861>]

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## Motor Symptoms - Tremor

- Not all Parkinson's patients will have tremor.
- It presents as:
  - Rest tremor (normally in one or both hands)
  - Patient finger have a rolling "pill-rolling" movement
  - May affect chin, lips, face, and legs
  - May appear unilaterally
- other reasons for tremor:
  - Medication side effect, alcohol, hyperthyroidism or another neurological condition

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## Motor Symptoms - Tremor

Parkinson's Disease may present with RESTING TREMOR

Not to be confused with ESSENTIAL TREMOR (ET):

- Unknown cause
- Associated with movement
- Mild and stable
- Both hands and arms
- May affect head and voice

Other types of tremor:

- Postural tremor (occurs when the person maintains a position)
- Kinetic tremor (associated with voluntary movement)

ET is the most common cause of postural & kinetic tremors.

ET is normally treated with beta-blockers. This would normally be propranolol, started at a low dose and titrated as required.

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## Motor Symptoms - Tremor

| Action or postural tremor             | Intention tremor  | Resting tremor                 |
|---------------------------------------|---|--------------------------------|
| Anticholinergics                      | Amitriptyline, mepartoline, procainamide                        | -                              |
| Antibiotics, antivirals, and antimyco | -   | Vidarabine                     |
| Antihistamines and mood stabilizers   | Amitriptyline, lithium, SSRIs                                   | Co-trimoxazole, amphotericin B |
| Antiseptics                           | -   | Lithium                        |
| Bronchodilators                       | Valproic acid   | SSRIs, lithium                 |
| Cancer treatments                     | Salsalate, salmeterol   | Valproic acid                  |
| Chemotherapeutics                     | Tamoxifen, cytarabine, ifosfamide                               | -                              |
| Drug of misuse                        | Cocaine, ethanol, MDMA, nicotine                                | Cytarabine, ifosfamide         |
| Gastrointestinal drugs                | -   | Ethanol                        |
| Hormones                              | Metoclopramide, cimetidine                                      | -                              |
| Immunosuppressants                    | Thyroxine, calcium, medroxyprogesterone                         | Thalidomide                    |
| Methylxanthines                       | Adenosine receptor antagonists                                  | Cocaine, ethanol, MDMA, MPTP   |
| Neuroleptic and dopamine depleters    | Theophylline, caffeine  | -                              |
| Nutritional factors                   | Haloperidol, thioridazine, cimazoline, reserpine, tetrabenazine | Metoclopramide                 |
| Other substances                      | -   | Medroxyprogesterone            |

Additional data from Deuschl et al.: MDMA=3,4-methylenedioxymethamphetamine (ecstasy); MPTP=1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; SSRIs=selective serotonin reuptake inhibitors.

Table: Main drugs known to cause postural, intention, and resting tremors

(1) \* tremor from antipsychotic start w/ 10 weeks of first starting the drug.  
→ more common in first generation antipsychotic  
e.g.) Haloperidol or chlorpromazine  
less common w/ 2nd generation  
e.g.) clozapine, olanzapine, risperidone, quetiapine

(2) \* Beta agonist used for asthma or COPD  
→ Salbutamol, salmeterol

(3) \* Anticholinergics such as propantheline, metoclopramide

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## Aetiology

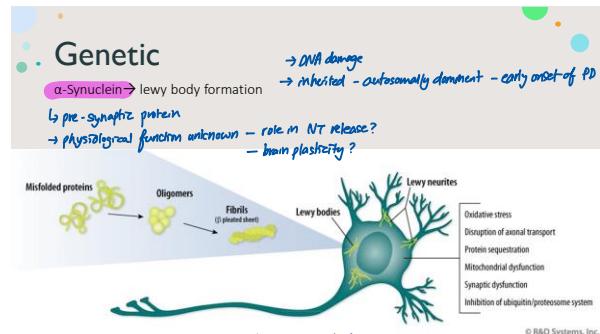
| Extrinsic   | Intrinsic  |
|---|--|
| Environmental   | Physical   |
| <ul style="list-style-type: none"> <li>Prescription drugs           <ul style="list-style-type: none"> <li>Antipsychotics</li> <li>Antiemetics</li> <li>Reserpine &amp; tetrabenazine</li> <li>Recreational Drugs</li> <li>Free radicals</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>Cerebral ischaemia</li> <li>Viral encephalitis</li> <li>Brainstem injury</li> <li>Dementia pugilistica</li> <li>(Parkin gene) mutation (early onset)</li> </ul> |
| Physical  | Genetic  |
|   | <ul style="list-style-type: none"> <li>&gt; age &gt; prevalence</li> <li><b>Biggest risk factor</b></li> </ul>   |

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2

| Environmental            |   |
|--------------------------|---|
| Antipsychotics           | Typical antipsychotics<br>Extra-pyramidal side effects: $\rightarrow$ drug induced movement disorders (involuntary or uncontrolled movements)                 |
| Antiemetics              | Metoclopramide, Prochlorperazine<br>Extra-pyramidal side effects  |
| Reserpine, tetrabenazine | Depletes monoamines from pre-synaptic storage, reducing Dopamine release $\rightarrow$ treatment of involuntary movement disorders                            |
| Recreational drugs       | MPTP (contaminant found in MPPP 'synthetic heroin') – metabolite kills dopaminergic neurones in substantia nigra<br>$\downarrow$ due to loss of these neurons |

13

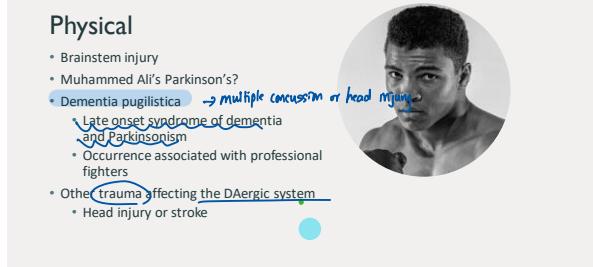
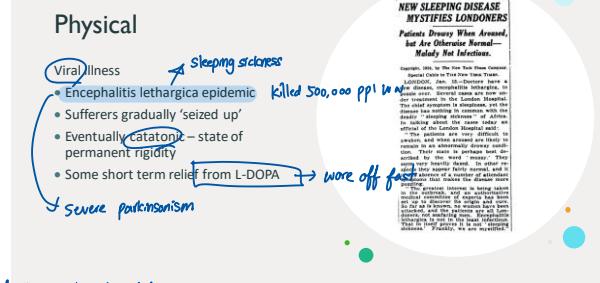


14  $\downarrow$  mutated  $\alpha$ -synuclein  $\rightarrow$  misfolded protein production  
 $\rightarrow$  aggregate w/i neuron  
 $\rightarrow$  cause damage to cellular components  
 $\rightarrow$  accumulate in large masses – called Lewy bodies  
 $\downarrow$  cause neuronal dysfunction and cell death

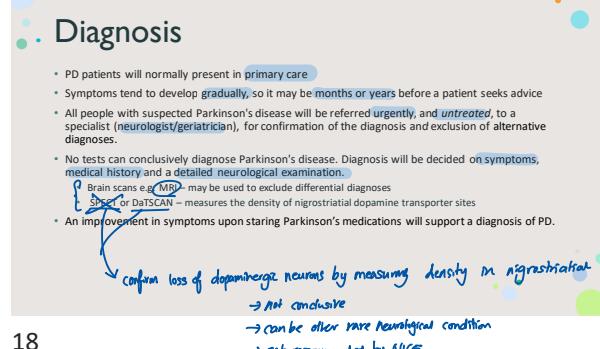
cause? Symptom? Unnamed



15 enzymatic protein: critical role in maintaining mitochondrial quality control  
 $\rightarrow$  encoded by PARK2 gene  
 $\downarrow$   
 loss of protective function  
 $\downarrow$   
 ↑ cell damage/death



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L30



## Learning Outcomes

By the end of this screencast you will be able to...

- Describe the benefits and harms of pharmacological treatments available for motor symptoms
- Explain how to support patients with treatment decision-making
- Understanding the importance of correct and consistent timing of administration of Parkinson's medication

## Treatment of Motor Symptoms

### First Line Therapy:

- Offer levodopa to people with early Parkinson's disease whose motor symptoms affect their quality of life
- Consider a choice of dopamine agonists, levodopa, or monoamine oxidase B inhibitors for people with early Parkinson's disease whose motor symptoms do not affect their quality of life

(Parkinson's disease in adults. NICE guideline [NG71] Published 19 July 2017)

## Treatment of Motor Symptoms

*first line therapy should be optimised*

### Adjunctive Therapy:

#### When?

*uncontrolled shakers and fits*

#### What?

- When dyskinesia or motor fluctuations develop (including "wearing off" episodes)  
*→ when effective meds start to wear off*
- Offer a choice of dopamine agonists, monoamine oxidase B inhibitors, or catechol-O-methyltransferase inhibitors as an adjunct to levodopa
- If dyskinesia is not adequately managed by modifying existing therapy, consider amantadine

(Parkinson's disease in adults. NICE guideline [NG71] Published 19 July 2017)

LEVODOPA

## Treatment of Motor Symptoms Levodopa

- First line agent
- Dramatically improves motor function *- 80% of patients show improvement*
- Palliative treatment – no effect on disease progression
- Effectiveness decreases with time, must escalate dose
  - receptor down-regulation *- compensating mechanism*
  - disease progression
- When do we start treatment?
  - Boys old want to start as soon as possible to improve symptoms*
  - Younger - wants to delay as much as they can*
  - make most of their life now*
  - decision personal to patient*

## Treatment of Motor Symptoms Levodopa

### Unwanted Effects:

1. Dyskinesia (involuntary movements)
  - from 2 years (50% of patients by year 5) *→ appear time of peak therapeutic effect*
  - face and limbs *- not painful*
2. Fluctuations in Clinical State
  - "on-off" phenomena *bradykinesia and rigidity → suddenly worsen and improve*
  - wearing off effect (end of dose deterioration) *→ patients who has been taking Levodopa long term*  
*→ e.g.) morning after taking it at night:*
  - freezing
  - Entacapone (COMT inhibitor) may help
3. Acute Side Effects
  - Nausea and anorexia
  - Hypotension
  - Sleep disturbances including sudden onset of sleep – implications for driving
4. Psychological Effects
  - *Psychological effects*
    - impulsive, compulsive
    - schizophrenia like symptoms
    - 20% patient experience confusion, insomnia

# LEVODOPA + INHIBITORS

## Treatment of Motor Symptoms Inhibiting metabolism of Levodopa

Dopadecarboxylase Inhibitors:

- Carbidopa
  - Benserazide
- help reduce peripheral metabolism of Levodopa  
→ reduce peripheral side effect and don't cross BBB

- Levodopa is given as a combination product with either carbidopa or benserazide
- These reduce peripheral metabolism of levodopa and improve absorption of levodopa
- Reduce peripheral side effects
- They do not cross the BBB

Carbidopa + Levodopa = Co-careldopa (e.g. Sinemet®)  
Benserazide + Levodopa = Co-beneldopa (e.g. Madopar®)

## ① COMT

## Treatment of Motor Symptoms Inhibiting metabolism of Levodopa

COMT Inhibitors:

- Entacapone → add on therapy to co-careldopa or co-beneldopa
  - Tolcapone
- ↳ rarely used due to risk of liver toxicity
- Entacapone is given as an adjuvant to co-careldopa/co-beneldopa or as a combination product with co-careldopa
  - Potentiates the effects of levodopa
  - Helps counteract fluctuations in plasma concentration of levodopa
  - Add on therapy – not useful alone

Co-careldopa + Entacapone = Stalek®, Stalevo®, Sastravi®

bright yellow reddish orange colour that's harmless  
commonly cause diarrhoea – settle w/ prolonged use  
increase effects of Levodopa – may worsen side effects of Levodopa such as  
→ dyskinesia, nausea, psychosis

## 2

## Treatment of Motor Symptoms

## Dopamine Receptor Agonists

first to delay introduction of L-DOPA

- Monotherapy (vs L-DOPA)

- reduced (+ increase time to) motor complications (less dyskinesias)
- slightly poorer improvement in motor function
- possibly greater neuro-psychiatric side effects

or

add on therapy

- Prolonged action – up to 3 hours

- Modified release Tablet/Capsule
- Slow onset
- Sustained action 4-5 hours

↳ used for overnight

↳ Intestinal gel for infusion (Duodopa® - co-careldopa)

↳ Administration via enteral tube

mimic effect of dopamine

better tolerated

Non-ergot derived:

Ropinirole  
Rotigotine  
Pramipexole

↳ only used if adequate from non-ergot derived

Ergot derived:

Bromocriptine  
Cabergoline  
Lisuride  
Pergolide

older effective in controlling PD symptoms, but limited by side effects such as nausea, vomiting, fibrotic reactions of the lung/heart  
→ very dangerous

Agonist

- short plasma half-life 6-8H
- 3 times daily dosing required
- slow release formulations available.

↳ Rotigotine → near agent

→ delivered as transdermal patch

→ useful for patient that can't take oral PP meds

## 3

## Treatment of Motor Symptoms

## Inhabiting Metabolism of Dopamine

→ increases dopamine concentration in CNS.

• Monoamine oxidase B inhibitors:

↳ Selegiline

↳ Rasagiline

↳ Alone or as adjunct

- Enhances levodopa action/overcome 'end of dose' effect

- MAO-B metabolises dopamine inhibition increases dopamine concentration

- Selectivity for B type receptors so do not interact with tyramine (cheese)

• Side effects:

- nausea,
- postural hypotension,

- dyskinesia,

- confusion (elderly)

→ wine, dried meat

↳ metabolised to amphetamine – causes excitement, anxiety and insomnia

↳ similar drug but ↗ doesn't have this unwanted effect.

→ may partially slow disease progression

+ tachycardia symptoms

## Impulse Control Disorders

→ related to reward function of the brain.

2.6% - 13.8% revised. 58.3%  
with younger ppl w/ PD.

- Compulsive gambling
- Hypersexuality
- Binge eating
- Obsessive shopping

Can cause distress for patients and carers, financial difficulties, and even criminal convictions

• Action:

- Gradually reduce any dopamine agonist Monitor whether the impulse control disorder improves and whether the person has any symptoms of dopamine receptor agonist withdrawal
- Offer specialist cognitive behavioural therapy targeted at ICD behaviours if modification of dopaminergic therapy is not effective

# 4

## Treatment of Motor Symptoms

### Amantadine

- MOA not fully understood
- Increases dopamine levels (possibly by increasing dopamine release)
- Mild benefit to symptoms
- Only used as an adjuvant → add on therapy
- Efficacy diminishes within a few months of continuous treatment - slowly withdrawing and reintroducing the drug may prolong effectiveness
- Side effects:
  - Psychological – hallucinations, delusions, paranoia, anxiety, impulse control disorders
  - Sleep disturbances
  - ~~Gastric~~ vomiting, anorexia, weight loss, dry mouth
  - Hypotension
  - Palpitations

## Initiating Treatment (NICE)

Potential benefits and harms of dopamine agonists, levodopa and MAO-B inhibitors.  
(Parkinson's disease in adults. NICE guideline [NG71] Published 19 July 2017)

|  | Levodopa                           | Dopamine Receptor Agonists         | MAO-B Inhibitors                   |
|--|------------------------------------|------------------------------------|------------------------------------|
| Motor Symptoms   | More improvement in motor symptoms | Less improvement in motor symptoms | Less improvement in motor symptoms |
| Activities of daily living (ADL)                                 | More improvement in ADL            | Less improvement in ADL            | Less improvement in ADL            |
| Motor Complications  | More motor complications           | Fewer motor complications          | Fewer motor complications          |
| Adverse Events (excessive sleepiness, hallucinations, ICD, etc.) | Fewer specified adverse events     | More specified adverse events      | Fewer specified adverse events     |

*first line options*

## Adjuvant Therapies (NICE)

Potential benefits and harms of dopamine agonists, MAO-B inhibitors, COMT inhibitors and amantadine  
(Parkinson's disease in adults. NICE guideline [NG71] Published 19 July 2017)

|                                  | Dopamine Receptor Agonists          | MAO-B Inhibitors                          | COMT Inhibitors                           | Amantadine   |
|----------------------------------|-------------------------------------|---|---|--|
| Motor Symptoms                   | Improvement in motor symptoms       | Improvement in motor symptoms             | Improvement in motor symptoms             | No evidence of improvement in motor symptoms             |
| Activities of Daily Living (ADL) | Improvement in ADL                  | Improvement in activities of daily living | Improvement in activities of daily living | No evidence of improvement in activities of daily living |
| Off Time                         | More off-time reduction             | Off-time reduction                        | Off-time reduction                        | No studies reporting this outcome                        |
| Adverse Events                   | Intermediate risk of adverse events | Fewer adverse events                      | More adverse events                       | No studies reporting this outcome                        |
| Hallucinations                   | More risk of hallucinations         | Lower risk of hallucinations              | Lower risk of hallucinations              | No studies reporting this outcome                        |

## Significance of missing a dose

- Acute akinesia (the inability to initiate movement)
- Unable to communicate and become more physically dependant on others
- Loss of the ability to swallow, which increases the risk of aspiration
- Increased risk of falls, and a higher risk of fractures
- Neuroleptic-like malignant syndrome (very rare):**
  - marked rigidity (including respiratory causing hypoventilation), altered consciousness, leukocytosis and elevated creatine kinase
  - It is caused by a sudden, marked reduction in dopamine activity, either from withdrawal of dopaminergic agents or from blockade of dopamine receptors
  - More common in those with more severe PD symptoms or on high doses of levodopa

## Get it on Time



L31

# Parkinson's Disease

## Holistic Treatment of the Parkinson's Patient

### PART 2

1

## Learning Outcomes

By the end of this screencast you will be able to...

- Describe appropriate treatment of non-motor symptoms of Parkinson's disease
- Optimise medicines use for Parkinson's patients
- Recognise the multi-disciplinary contributions required in care of Parkinson's patients

2

## Treatment of Non-Motor Symptoms

- Mental Health:
  - Depression, anxiety, and apathy
  - Dementia and cognitive impairment
  - Impulse control and psychotic symptoms
- Autonomic dysfunction:
  - Constipation
  - Orthostatic (postural) hypotension
  - Dysphagia → weight loss, aspiration pneumonia
  - Excessive salivation and sweating → could be better than constipation
  - Bladder and sexual dysfunction
- Nausea and vomiting
- Pain
- Sleep disturbance and daytime sleepiness
- Pressure sores

**May be symptoms of Parkinson's Complications, or adverse effects of anti-Parkinsonian medication**

**#Symptom      #Side effect      ] both ]**

3

## Treatment of Non-motor Symptoms

### Mental Health

- Depression → SSRI → common in patients w/ chronic health conditions → psychological therapy
- Dementia - consider Rivastigmine (licensed) or off-label use of donepezil, galantamine
- Confusion and hallucinations - quetiapine (1<sup>st</sup> line) or clozapine (2<sup>nd</sup> line)
- Impulse control and psychotic symptoms - optimise drug therapy

*only if severe and problematic*

*already discontinued*

*high risk drug - need monitoring*

*- all de-prescribing drugs may cause impulse control disorder but dopamine drugs at highest risk*

*\* carefully avoid anticholinergics in PD because anticholinergic side effects may worsen disease*

*→ common W/ clozapine :: extreme caution needed*

4

## Treatment of Non-motor Symptoms

### Autonomic Dysfunction

- Constipation - stimulant + softener → if regular - stool softener on repeat
- Postural hypotension - midodrine/fludrocortisone
- Dysphagia - medicines optimisation + different formulations e.g. tablets → if cause suggests he is unable to eat → refer to dietitian for supplementing feeds or fluid thickener to swallow fluids
- Salivation/drooling - glycopyrronium → if ineffective
- Bladder dysfunction - antimuscarinics
- Sexual dysfunction - PDE5 inhibitor (Sildenafil etc.) → more options available to them on NICE

*patient can be referred for botulinum toxin treatment (below)*

*or consider other anticholinergics e.g. Xylazine, but need to be cognisant of anticholinergics burden*

*→ consider associated risk of cognitive impairment*

*Some caution applies*

5

## Treatment of Non-motor Symptoms

### Nausea and Vomiting

- Comperidone → first line treatment in PD
- Consider cyclizine or ondansetron → BUT NEVER ~~✓~~ metoclopramide or prochlorperazine
- Protein-free snacks with Levodopa doses to reduce side effects

### Pain

- Follow pain ladder
- Consider side effects of cognitive effects of analgesic agents - worsen dementia and confusion
- Physiotherapy
- NSAIDs - need GE protection

*beneficial to patients to have appropriate exercise to keep mobile - reduce aches and pains*

6

- Treatment of Non-motor Symptoms
- Sleep disturbances & Daytime sleepiness
  - Sedatives → can cause cognitive side effects - increase falls risk (good for short term occasional use)
  - Daytime sleepiness **modafinil**
    - specialist use only (not OTC)
- Pressure Sores
  - Barrier creams →
  - Change position every 2 hours ✓
  - Pressure relieving mattresses and cushions ✗
    - ) carers may need to know this  
∴ consulting

7

Table 1: Drugs to avoid (and use) when treating hallucinations and nausea in patients with Parkinson's disease

| Drug               | Treatment of hallucinations/ confusion | Treatment of nausea/vomiting | Vigilance required |
|--------------------|--|------------------------------|--------------------|
| Chlorpromazine     | X                                      |                              |                    |
| Fluphenazine       | X                                      |                              |                    |
| Perphenazine       | X                                      |                              |                    |
| Trifluoperazine    | X                                      |                              |                    |
| Flupenthixol       | X                                      |                              |                    |
| Haloperidol        | X                                      |                              |                    |
| <b>Quetiapine</b>  | Y                                      |                              |                    |
| <b>Chlorpine</b>   | Y                                      |                              |                    |
| Metoclopramide     |  | X                            |                    |
| Prochlorperazine   |  | X                            |                    |
| <b>Dopiperidol</b> |  | Y                            |                    |
| Cyclizine          |  | Y                            |                    |
| Ondansetron        |  | Y                            |                    |
| Antihistamines     |  |                              | Y*                 |
| Antidepressants    |  |                              | Y*                 |
| Antipsychotics     |  |                              | Y*                 |

Clinical Pharmacist, August 2018, Vol 10, No 8, online | DOI: 10.1211/CP.2018.20205260

8

BMJ article

**Box 2: Recommended pharmacological management of non-motor symptoms of Parkinson's disease**

- When modifiable cause and non-pharmacological treatments have been ruled out:

  - Excessive daytime sleepiness - Consider modafinil [Based on low quality evidence from 4 RCTs]
  - Rapid eye movement sleep behavior disorder - Consider clonazepam [Based on low quality evidence from 1 RCT]
    - If neither is effective, consider clonazepam [Based on high quality evidence from 1 RCT]
  - Orthostatic hypotension - Consider midodrine (taking into account the contraindications and monitoring requirements) [Based on low quality evidence from 2 RCTs]
    - Midodrine is contraindicated, not tolerated, or ineffective, consider fludrocortisone\* (taking into account its safety profile and potential interactions with other medications) [Based on very low quality evidence from 1 RCT and the experience and opinion of the GDG]
  - Dementia - Identify and manage in accordance with NICE guidance on depression in adults with a chronic physical health problem<sup>2</sup>
  - Headaches and delusions - Do not treat if well tolerated [Based on experience and opinion of the GDG]
  - Confusion and memory impairment - Consider donepezil [Based on moderate quality evidence from network meta-analysis of 3 RCTs]
  - Standard treatment is not effective, offer clozapine in people without cognitive impairment [Based on a patient monitoring service is needed] [Based on no to moderate quality evidence from network meta-analysis of 3 RCTs]
  - Lower doses of quetiapine and clozapine are required for people with Parkinson's disease than in other indications [Based on experience and opinion of the GDG]
  - Do not offer olanzapine [Based on no to moderate quality evidence from network meta-analysis of 3 RCTs]
  - Demerol - Offer a cholinesterase inhibitor for mild to moderate dementia (donepezil, donepezil\*, or galantamine\* capsules or investigational patches\*) [Based on high quality evidence from network meta-analysis of 7 RCTs]
  - Consider memantine\* if cholinesterase inhibitors are not tolerated or contraindicated [Based on no to moderate quality evidence from 3 RCTs]
  - Donepezil - Consider glycopyrronium bromide\* [Based on very low to moderate quality evidence from 3 RCTs]
    - If glycopyrronium bromide is not effective, not tolerated or contraindicated, consider refer to a specialist service for botulinum toxin A\* [Based on very low to moderate quality evidence from 1 RCT]
  - Consider anticholinergic medications on glycopyrronium bromide only if the person's risk of cognitive adverse effects is thought to be minimal [Based on experience and opinion of the GDG]

\*Off-line

9

## Medicines Management

- Review of all aspects of their care every 6-12 months → done by specialist + consultant
  - Normally only start or alter anti-parkinsonian medications on the advice of a specialist → get instruction on target dose and we have to manage the titration to optimise treatment
  - Drugs may need to be titrated to optimise
  - Drug changes need to be actioned promptly
  - Prioritise medicines reconciliation for Parkinson's patients → be quick decline
  - Sudden drug cessation may precipitate acute akinesia or neuroleptic malignant syndrome ↓ sensitivity to move

bc affect patients QoL

10

## Medicines Management

- Small doses of Levodopa at increased frequencies to reduce 'peaks and troughs' and dyskinesia
  - Proteins inhibit absorption. Wait 30-60 minutes after medication before eating
  - Brand specific prescribing - active component may be different
  - Print medication timings on pharmacy labels
  - Manage underlying issues which may affect absorption e.g. constipation, drug interactions
  - Avoid medications which worsen symptoms
    - OTC avoid sympathomimetics (e.g. pseudoephedrine) with MAO-B inhibitors
    - OTC antihistamines
    - Calcium channel blockers - occasional EPS, frequency unknown

encourage swallowing in upright position (aid dysphagia)

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#### Multidisciplinary Care

- SALT, physio, OT, dietetics, social care, community nursing, continence, psychology, mental health services, specialist nurses, consultants

### Other Considerations:

- DVLA must be informed
  - Awareness of communication difficulties – quiet voice, slurred speech, reduced facial expressions and body language → difficult non-verbal cues
  - Encourage self-administration and independence
  - Recommend colecalciferol  
↓  
vitamin D supplements

12

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# Nausea and Vomiting - Aetiology & Referral

Catherine Heywood  
(NNUH/UEA)  
(with thanks to Gemma May)

1

**Learning Outcomes**

By the end of this screencast, with respect to nausea and vomiting you will be able to:

- ▶ Outline the common causes of N&V
- ▶ Know when appropriate to refer patients with N&V for further investigations

2

## Causes of vomiting

- ▶ GI causes
  - ▶ Gastro-enteritis
  - ▶ Peptic ulceration
  - ▶ Appendicitis
  - ▶ Gastric carcinoma
  - ▶ Infection (relatively common)
- ▶ Organic disease
  - ▶ Renal failure (uraemia) - *high levels of urea can cause patients to be unwell*
  - ▶ Diabetic ketoacidosis - *vomiting*
  - ▶ Myocardial infarction - *pain (N&V)*  
- *MI in the inferior wall more likely to cause vomit*

3

- ▶ Central nervous system causes
  - ▶ Migraine
  - ▶ Meningitis
  - ▶ Vestibular disease (Meniere's)
- ▶ Post-op nausea & vomiting (PONV)
  - ▶ Complex & multifactorial (e.g. pain, surgery, anaesthesia) → outcome into consideration  
*- challenging to treat*
- ▶ Motion sickness
  - ▶ Conflicting information between eyes and body - car, sea, reading while travel
  - ▶ Children <1 labyrinth not functional
  - ▶ Children 3-12 most vulnerable

4

## Drugs causing N & V

- ▶ Opiates - *pain*
- ▶ Antibiotics (doxycycline)
- ▶ Digoxin
- ▶ Levodopa - *PP*
- ▶ Aminophylline / theophylline
- ▶ Chemotherapy *cytotoxic*
- ▶ Lots of others!

5

Cause N&V by one of two methods:-

- ① Mimicking the action of neurotransmitters
  - E.g. opiates, levodopa or causing a change in levels of a transmitter
  - 5HT, re-uptake inhibitors
- ② Activation of the abdominal afferent system (peripheral)
  - Delaying gastric emptying
  - or direct activation of mucosal afferent system

6

\* N&V can be a major cause of morbidity

- 20% of patients who suffer from drug induced N&V
- refuse to have any further therapy w/ that drug
- gap between taking drug + onset of N&V
- last 3-6h
- anticipation vomiting : thought of taking the drug 10-40.
- + use antiemetics in advance crucial
- + use opiate analgesics for treating N&V pain

1

## Meniere's disease

- Disorder of inner ear → associated w/ dilation of endolymph system (system of fluids inside)
- Excess fluid in labyrinth canals (hydrops)
- No diff. in male or female
- 0.1% of population, common between 20 to 50 years old
- Incapacitating attacks characterised by
  - Giddiness, vertigo, N&V
  - Hearing loss
  - Tinnitus
- Sudden onset - last 20 minutes to several hours
- Migraine present in 30% of sufferers

no warning  
many attacks, quickly

7

7

## Vertigo → dizziness

- Sensation of rotation or spinning
  - Patient (objective) or their surroundings (subjective)
- Young people - labyrinthitis → inflammation of labyrinth
- Benign Paroxysmal Positional Vertigo (BPPV) in elderly
  - movement of naturally occurring calcium crystals by other debris known as otoliths → present in ear canal → becomes enlarged and move into ear canals → displacement of endolymph fluids → leading to loss of balance + associated symptoms
- Other causes:
  - Head injury, migraine, multiple sclerosis
  - Patients with vertigo and N&V should be referred → there could be other cause
- Some drugs are vestibular toxic → consequence cause vertigo
  - Aminoglycosides, anticonvulsants, furosemide (NSAIDs), quinine, antibiotics - gentamycin
  - L-V (Heart failure)
  - Nausea (long term)



elderly  
X2-3 more common in women.  
movement of naturally occurring calcium crystals  
by other debris known as otoliths → present in ear canal → becomes enlarged and move into ear canals → displacement of endolymph fluids → leading to loss of balance + associated symptoms  
short-lived can be managed w/ meds

max long lasting  
due to autoreflex

8

## Morning Sickness → anytime of day

- 50-90% of women experience nausea during first trimester → respect pregnancy
- Begins shortly after first missed period
- Peaks weeks 10-14
- Often disappears after 4th month
- Due to high levels of hCG
  - levels rise rapidly in early stages
- Hyperemesis Gravidarum
  - Severe, persistent N&V during pregnancy
  - Weight loss, dehydration, acidosis, ketosis
  - 1-3 per 1000 deliveries
  - Untreated can be fatal to mother, foetus or both



9

9

## Reasons for Treating N&V:

- Highly unpleasant for patient
- Dehydration
- Renal impairment
- Electrolyte abnormalities → K<sup>+</sup> Na<sup>+</sup> Mg<sup>2+</sup>
- Weight loss

X underlying cause need to be investigated.

10

## Symptoms requiring referral

if additional symptoms on top of N&V

- Severity of symptoms
  - Projectile vomiting - pyloric stenosis
  - Sour smelling vomiting - pyloric stenosis
  - Blood in vomit → underlying cause may be present
- Duration of symptoms
  - Dehydration → renal impairment + electrolyte abnormalities

> narrowing of outlet from stomach  
risking blockage

11

11

## Symptoms requiring referral

- Other symptoms
  - Severe diarrhoea/long duration
    - Gastro-enteritis, infection
  - Weight loss + N&V → malabsorption / malnutrition.
    - Requires referral
  - Abdominal pain
    - Appendicitis, biliary colic, renal colic, hernias
  - Dizziness → vertigo
    - Meningitis, head injury, Meniere's disease

12

12

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# Nausea and Vomiting - Drug Therapy & Management

Catherine Heywood  
(NNUH/UEA)  
(with thanks to Gemma May)

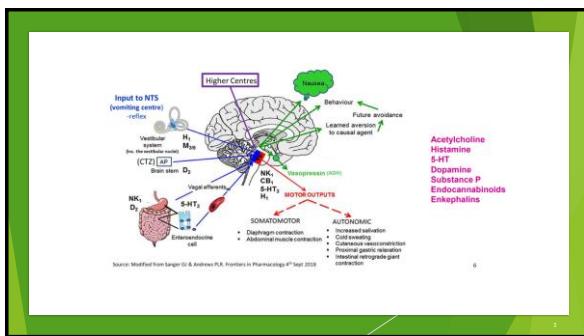
1

## Learning Outcomes

By the end of this screencast, with respect to nausea and vomiting you will be able to:

- ▶ Relate pharmacotherapy to pathophysiology
- ▶ Describe pharmaceutical management

2



3

## H<sub>1</sub> receptor antagonists: Antihistamines

**Stugeron 15**  
Film tablet  
Prevention of travel sickness

E.g. cinnarizine, promethazine, cyclizine.  
Available IV, used hospital settings.

Act within 2 hours  
Theobromine salts longer acting than hydrochloride

Side effects  
Drowsiness, dizziness, tinnitus

promethazine significant (take night before)

**Phenergan**  
Nausea and Vomiting Relief

4

↪ built in vestibular apparatus  
but for motion sickness.

②

## Anticholinergics (antimuscarinics)

E.g. hyoscine OTC tablet but patch preferred.

More effective for motion sickness.

- ▶ Act on muscarinic (M<sub>1</sub>) receptors centrally
- ▶ Also antispasmodic/gut action
- ▶ Side effects antimuscarinic side effects
  - ▶ Drowsiness, dry mouth, dry skin, decreased gut motility
  - ▶ Increase intra-ocular pressure & heart rate
  - ▶ Inhibit micturition
- ▶ Contraindicated in glaucoma, urinary retention

**Scopolene TTS**  
Permit for application to the skin

5

③

## D<sub>2</sub> Receptor Antagonists: Prochlorperazine (antipsychotic)

Inhibits D<sub>2</sub> receptors + some M<sub>1</sub>

Acts centrally + peripherally

Rapidly absorbed → comes in different formulations: injections, liquid, tablet, buccal tablet

Anti-dopaminergic

Parkinson's like Extra Pyramidal Symptoms - see next slide

Anti-cholinergic side effects
 

- ▶ Drowsiness
- ▶ Blurred vision
- ▶ Dry mouth

BTC
 

- ▶ Available as 10mg buccal formulation for migraine in patients over 18 and with previous diagnosis

Other Antipsychotics: Haloperidol and levomepromazine also inhibit D<sub>2</sub> receptors  
↳ reserved for positive care

**Stemetil**  
Injection 10 mg/ml

**Compro**  
Tablet 10 mg

**Buccastem M**  
Buccal tablet 10 mg

6

### D<sub>2</sub> Receptor Antagonists: Metoclopramide

- Blocks D<sub>2</sub> receptors (+ some 5HT<sub>3</sub>)
- Acts centrally & peripherally
- Antiemetic and pro-kinetic properties (stimulates gastric emptying - more effective in GI and biliary disease)
- Rapidly absorbed, peaks after 2 hours
- Max 30mg/day and for 5 days
- Side effects
  - 10% of patients experience transient side effects - drowsiness, dizziness, anxiety
  - Extra Pyramidal side effects (EPSE e.g. dystonia, cardiac dyskinesia, oculogyric crisis)** more common in 12-19 year olds and females (see CHMP advice)
- Warning from MHRA of SIE (warning from MHRA of SIE) X younger female affected
- max dose set at 30mg/d with max 5 day treatment

(e.g.) from theophylline (COPD)

available both oral/injectable

7

### D<sub>2</sub> Receptor Antagonists: Domperidone

- Blocks D<sub>2</sub> receptors
- Does not pass blood-brain barrier
  - Low incidence of central side effects
  - >2% patients dry mouth, headache, skin rash
- Useful in Parkinson's disease and under 30s (younger age group)
  - comes in tablet + suspending form
  - no injectable form
- reclassified to POM (Sept. 2014) - see MHRA warning on CV risk (ref)
  - Available for use in after-meal symptoms of fullness, nausea, epigastric bloating
  - Under 16 years not recommended OTC

8

### 5HT<sub>3</sub> Receptor Antagonists

- E.g. Ondansetron, granisetron and palonosetron
- 5HT<sub>3</sub> receptors located peripherally on vagal nerve endings and vomiting centre
- Selective act centrally and peripherally
- Generally well tolerated - less cardio/ CNS side effects

more widely used.

9

### NK<sub>1</sub> Receptor Antagonists

Newest class.

- E.g. Aprepitant, fosaprepitant
- Block neurokinin-1 receptors
- Newest class of antiemetics

For chemotherapy induced N&V

10

### Other treatments

- Chemotherapy induced nausea
  - Corticosteroids e.g. Dexamethasone → chemotherapy induced N&V
  - Cannabinoids e.g. Nabilone (resistant to others) → chemotherapy induced N&V
- Acupuncture → against sympathetic.
- Motion sickness
- Transcutaneous Electrical Nerve Stimulation (TENS)

11

### Anti-emetics

- Drugs which inhibit 5HT<sub>3</sub>, H<sub>1</sub>, D<sub>2</sub> and ACH receptors will inhibit vomiting

| Receptor Site    | Dopamine D <sub>2</sub> | Muscarinic | Histamine | 5HT <sub>3</sub> | NK <sub>1</sub> |
|------------------|-------------------------|------------|-----------|------------------|-----------------|
| Prochlorperazine | ++++                    | +          |           |                  |                 |
| Domperidone      | ++++                    |            |           |                  |                 |
| Metoclopramide   | +++                     | +          |           | ++               |                 |
| Promethazine     | ++                      |            | ++++      |                  |                 |
| Ondansetron      |                         |            |           | ++++             |                 |
| Aprepitant       |                         |            |           |                  | ++++            |

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| Anti-emetics                                 |   |
|--|---|
| Therapeutic group                            | Example drugs   |
| 5HT <sub>3</sub> antagonists                 | Ondansetron   |
| D <sub>2</sub> Antagonists                   | Phenothiazines (prochlorperazine, chlorpromazine)<br>Butyrophenones (haloperidol, droperidol)<br>Benzimidazoles (domperidone) |
| D <sub>2</sub> /5HT <sub>3</sub> antagonists | Metoclopramide  |
| Antihistamines                               | Cyclizine, promethazine, diphenhydramine  |
| Anticholinergics                             | Hyoscine, atropine  |
| Corticosteroids                              | Dexamethasone, methylprednisolone   |

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| ► Clinical Pharmacy and Therapeutics. Whittlesea C, Hodson K  |
| ► Physiology and pharmacology of nausea and vomiting Barbara J Pleuvry. Anaesthesia and Intensive Care Medicine 2012  |
| ► Domperidone: risk of cardiac side-effects<br><a href="https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects">https://www.gov.uk/drug-safety-update/domperidone-risks-of-cardiac-side-effects</a>  |
| ► Metoclopramide: risk of neurological adverse effects<br><a href="https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-changes-use-metoclopramide">https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-changes-use-metoclopramide</a> |
| ► Physiology of vomiting- YouTube video <a href="https://www.youtube.com/watch?v=LTIbp5xdwf4">https://www.youtube.com/watch?v=LTIbp5xdwf4</a>   |

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# OPIOIDS

## Opioids

- Opioids for mild/moderate pain – weak opioids – limited potency at mu receptor
  - Codeine
  - Dihydrocodeine
- Opioids for moderate/severe pain – strong opioids – high potency at mu receptor
  - Morphine
  - Diamorphine
  - Oxycodone
  - Fentanyl

## Considerations surrounding opioid analgesia

- Metabolism
    - Several opioids, including codeine, tramadol and oxycodone, are affected by variations in CYP2D6 metabolism → cause unpredictable variation in efficacy + toxicity
  - Side effects
    - Constipation ✓
    - Nausea/vomiting ✓
    - Drowsiness ✓
    - Sedation ✓
    - Respiratory depression ✓
  - Renal function → cleared by renal
  - Dependence/addiction
- breast feeding could be an issue  
→ opioid toxicity

# ADJUVANT THERAPY

## Adjuvant therapies

- Anti-epileptic drugs → analgesics : gabapentin, pregabalin, carbamazepine
- Antidepressants → Tricyclic Antidepressants, SSRI
- Other
  - Dexamehtasone for bone pain in palliative care
- Non pharmaceutical strategies
  - Physiotherapy
  - Exercise
  - Psychological therapy
  - Acupuncture

1)

## Chronic pain

- One of the most common reasons for GP consultation
- May be classified as per type
  - Musculoskeletal
  - Neuropathic
  - Non-specific persistent pain → chronic primary pain
  - Chronic headache syndrome

2)

## Musculoskeletal pain

### Mechanical pain

- Osteoarthritis
- Lower back pain
- Rheumatoid arthritis

3)

## Lower back pain/sciatica

- Low back pain that is not associated with serious or potentially serious causes
- Sciatica - leg pain secondary to lumbosacral nerve root pathology
- Worldwide lower back pain causes more disability than any other condition

## Low back pain/sciatica

- Treatment
  - Continue normal activities
  - Group exercise programs
  - Manual therapies **+ massage**
  - Psychological therapy
  - Oral NSAID **+ PPI** → **lowest possible for shortest time**
  - If NSAID contraindicated or not tolerated weak opioid +/- paracetamol for ACUTE pain only
  - Sciatica specific – **epidural injections (local anaesthetic + corticosteroid)**, spinal decompression surgery
  - Surgical treatments
    - Radiofrequency denervation
    - Spinal cord stimulation

## Case study

- Mr Bean, a fit and healthy 29 year old, enters your pharmacy, he was lifting some furniture at the weekend and hurt his back – he says he has been laying on the sofa since and this is the first time he has ventured further than the bathroom. He has been taking paracetamol but doesn't feel that it is doing much and wants something stronger – recommendations?

4)

## Osteoarthritis

- Most common form of **arthritis**
- Breakdown of the cartilage in the joints, most commonly **hips, knees, hands, lower back and neck**
- Symptoms
  - Joint pain **during and after activity**
  - Joint stiffness in the **morning or after rest**
  - Initial **limited range of motion**
  - Clicking or cracking in joints
  - Swelling around joints
  - Muscle weakness around the joint
  - Instability of the joint

## Osteoarthritis cont.

- Treatment
    - Exercise and manual therapy** → **mainly mobilisation, mobilisation or soft tissue techniques**
    - Weight loss if overweight/obese → **loss will help but not as much as 10%**
    - Paracetamol +/- topical NSAID
    - Topical capsaicin
    - If the above are ineffective or insufficient oral NSAID/COX-2 inhibitor may be considered
    - Intra-articular corticosteroid → **When other pharmacological treatments ineffective or unsuitable or to support therapeutic exercise**
    - Joint replacement**
- paracetamol and weak opioids may be considered – **Strong opioids X**  
→ **risk outweigh benefit**

5)

## Rheumatoid Arthritis

- Autoimmune disease **causing inflammation of the synovium**  
*Lining of the membrane covering joints*
- Can lead to erosion and deformation of the affected joints
- Other tissues may be affected in more advanced disease → **intestinal lung disease, inflammatory eye disorder**
- Symptoms
  - Symmetrical pain and swelling of the small joints in the hands and feet lasting >6 weeks**
  - Spread to the **larger joints**
  - Joints may be **warm and tender**
  - Stiffness on waking or following inactivity
  - Fatigue, fever and loss of appetite

## Musculoskeletal cont. treatment

- Corticosteroids or NSAIDs may be used for symptomatic control of an acute flare
- Physiotherapy
- Hand exercise program
- 'Treat to target strategy'
- Surgical treatment

6)

## Treat to target strategy

→ aim is to achieve remission or low disease activity

- Initial therapy
  - Monotherapy
    - Methotrexate/leflunomide/sulfasalazine
    - Hydroxychloroquine as alternative in those with mild or palindromic (periodic) disease
- Step Up Strategy
  - Additional DMARD (methotrexate/leflunomide/sulfasalazine/hydroxychloroquine) in combination where dose titration has not achieved remission/low disease activity
- Inadequate response to conventional DMARDs
  - Biological DMARDs
    - Upadacitinib/sarilumab/adalimumab/etanercept/infliximab....
- Inadequate response to biological DMARDs
  - Rituximab

DMARDs with multiple mechanisms  
of actions

## Neuropathic pain

- Definition - 'Central neuropathic pain is defined as 'pain caused by a lesion or disease of the central somatosensory nervous system', and peripheral neuropathic pain is defined as 'pain caused by a lesion or disease of the peripheral somatosensory nervous system'. IASP 2011

### Types

- Peripheral neuropathy → diabetic neuropathy, post hepatic neuralgia, trigeminal neuralgia, post surgical neuropathic pain, neuropathic cancer pain...
- Complex regional pain syndrome
- Central pain

↓  
causalgia

→ refer sympathetic dystrophy or sympathetically maintained pain

→ post stroke pain, spinal cord injury, MS pain

7)

## Neuropathic pain cont.

- Can be difficult to manage due to heterogeneity of its aetiologies, symptoms and underlying mechanisms
- Can be intermittent or constant, spontaneous or provoked pain
- Treatment
  - Amitriptyline/duloxetine/gabapentin (or pregabalin)
  - If initial drug ineffective try one of the others
  - Tramadol may be considered for acute rescue therapy
  - Consider capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments
  - Carbamazepine should be offered for management of trigeminal neuralgia

## Non-specific persistent pain → Chronic Primary Pain

- Includes conditions that may be recorded as
  - fibromyalgia →
  - complex regional pain syndrome →
  - myofascial pain → I have this ...
  - somatoform disorder
  - functional syndromes
  - chronic widespread pain →
  - pelvic pain of unknown origin

## Non-specific persistent pain cont.

- Treatment
  - Supervised group exercise program
  - Psychological therapy
  - Acupuncture✓
  - Antidepressants
    - Duloxetine/fluoxetine/paroxetine/citalopram/sertraline/amitriptyline
  - Several pharmacological therapies are not recommended for use in the treatment of persistent pain including paracetamol, opioids, NSAIDs, antiepileptic drugs, benzodiazepines....

## Case study

- Mrs Brown attends your clinic at the surgery, she has been suffering from fibromyalgia and when she saw you previously you arranged for some psychological therapy and a supervised group exercise programme. She has come back because the pain has not got any better, she's feeling really low and now she wants pills. Her friend takes gabapentin and this sounds like something she would like to try or at least some strong morphine.

8)

## Chronic headache

- Cluster-type (idiopathic, intermittent, unilateral eye, lasting less than 2 hours, occurring more than 3 days per week)
- Analgesic overuse (bilateral, constant, lasting 8 to 24 hours)
- Tension-type (primary headache, bilateral, constant, lasting 8 to 24 hours, 7 to 9 days per month)
- Post-trauma (bilateral, constant, lasting 8 to 24 hours, 7 to 9 days per month)
- Chronic migraine (primary headache, bilateral, lasting 1 to 4 hours)

9)

## Acute pain

- Sudden onset and result of something specific
- Usually <6 months duration
- Typically can be split into spontaneous insult/trauma and planned – surgery
- Spontaneous/trauma
  - Broken bones
  - Burns and cuts
  - Toothache
  - Headache
- Childbirth

10)

## Management

- Minor causes of acute pain
  - OTC analgesia
    - Paracetamol
    - NSAIDs – PO/topical
    - Low dose weak opioids
  - Non-pharmacological → e.g.) limb injury; protection, compression, elevation, rest
- More significant pain, where medical treatment is necessary, may necessitate higher levels of analgesia and additional therapies
- The WHO pain ladder can be used as a basis for acute pain management

## Palliative Care

- Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness (World Health Organisation [WHO])
- Recognised by the World Health Organisation as a priority are for standardisation of care
- Development of the WHO analgesic ladder
- Adequate analgesia combined with other symptomatic control to ensure patients are comfortable
- Palliative care ≠ end of life  
↳ antiemetics + analgesia

## Pain control in palliative care

- The WHO pain ladder should be adapted to the needs of individuals
- Basic principle of starting at the bottom may not be suitable for all
- Adjuvants should be considered at each step
- If pain control is not achieved move up a step
- Morphine is the most commonly used strong opioid analgesic, the availability of prolonged and immediate release preparations allows maintenance and breakthrough analgesia
- No maximum dose of morphine  
↳ but w/ increased dose, increased likelihood of toxicity

## Opioids: long-acting and breakthrough

- One long-acting opioid (prolonged release formulation) should be used with a short acting opioid (immediate release formulation) for breakthrough pain
- The breakthrough analgesia dose should be 1/10 to 1/6 of the daily long-acting dose
- Example
  - Zomorph 60mg BD
  - Total daily dose = 120mg
  - Breakthrough – oramorph 12 - 20mg 2 - 4 hourly
- Be aware of opioid equivalences when switching from one drug to another

## Syringe drivers

- If frequent doses of analgesics or other medications for symptom control are required a constant subcutaneous infusion can be administered via a syringe driver
- Drugs and diluent added to a syringe which is set to infuse over a defined time period, usually 24 hours
- Major concern is stability of the contents of the driver, multiple drugs are often combined and infused over a prolonged period of time → issue of precipitation or chemical incompatibility → deactivating the drugs
- Some resources to determine the compatibility of syringe driver contents and other information surrounding palliative care
  - [www.palliativedrugs.com](http://www.palliativedrugs.com)
  - Dickman et al 'The Syringe Driver : Continuous Subcutaneous Infusions in Palliative Care'
  - [www.pallcare.info](http://www.pallcare.info)

## Learning objectives

- Awareness of how pain is measured
- Apply the WHO pain ladder
- Define different types of pain and their management in accordance with National Guidance
- Describe management of pain in palliative care
- Apply principles of rational opioid prescribing
- Describe issues surrounding use of syringe drivers

## Guidelines and resources

- NICE
  - Guideline Chronic pain in over 16s: assessment and management Draft for consultation, August 2020
  - Osteoarthritis: care and management Clinical guideline [CG177] Published date: 12 February 2014 Last updated: 11 December 2020
  - Low back pain and sciatica in over 16s: assessment and management NICE guideline [NG59] Published date: 30 November 2016 Last updated: 11 December 2020
  - Rheumatoid arthritis in adults: management NICE guideline [NG100] Published date: 11 July 2018 Last updated: 12 October 2020
- SIGN
  - SIGN 136 - Management of chronic pain December 2013
- Palliative care
  - [www.palliativedrugs.com](http://www.palliativedrugs.com)
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  - [www.pallcare.info](http://www.pallcare.info)

Patient controlled analgesia (PCA) and other post-operative analgesia

Daren Whibourn  
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With thanks to Lindsay Morgan and Amy Bentham

## Learning objectives

- Describe the rationale for patient controlled analgesia (PCA)
- List the agents appropriate for PCA
- List the benefits and drawbacks of
- Design an adjunctive schedule to manage safety and side effects of PCA
- Describe the options for adjunctive post-operative analgesia

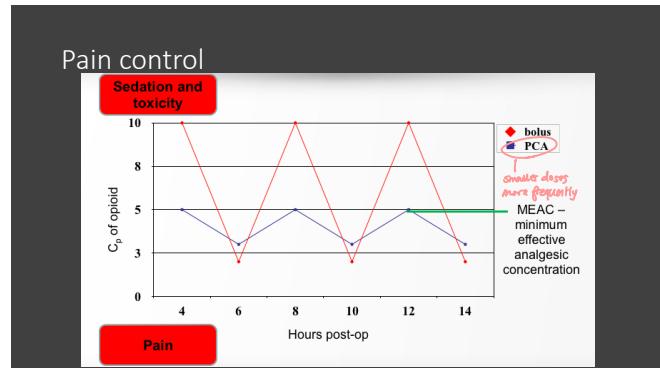
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Patient controlled analgesia (PCA)

- Process where patients can determine when and how much analgesic medication they receive
- IV PCA containing opiates/opioids most common
- Requires balance of safety, efficacy and tolerability
- Patient understanding is important
- Common post-operative analgesic option

## Drug delivery

- Loading dose (programmed by nurse)
  - Top ups thereafter (controlled by patient)
  - Lock out to prevent overdose
  - Adjuncts prescribed automatically for management of toxicity
- Monitoring**
- Pain scores
  - AVPU – alert, voice, pain, unresponsive



## Advantages and disadvantages of PCA

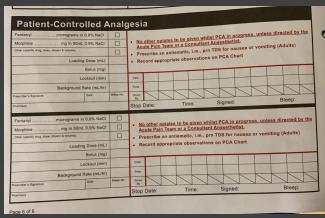
### Advantages

- Patient in control – can manage their own pain
- Predictable pain relief
- Active participants in their recovery
- Faster alleviation of pain *nowait*
- Patient doesn't have to wait for pain relief – reduced distress in waiting for pain relief
- Less time consuming for nurse
- Easy to titrate dose according to response or need of pain control

### Disadvantages

- Patient may not be responsive enough to use
- May be scared of self administration
- Poor dexterity
- Reduced mobility
- Potential to increase length of stay
- Liable to abuse
- Patients lack of understanding on how to use PCA
- SIDE EFFECTS

## Drugs used in PCA at NNUH



- Most commonly morphine or fentanyl, other options perphenazine and ketamine
- Loading dose – dose on initiation
- Bolus – the dose administered on triggering → *giving themselves 1mg*
- Lockout – minimum time between doses *5mins*
- Background rate – continuous infusion on top of which bolus doses are administered
- Other opiates?

## Monitoring during PCA use

- BP, pulse, respiratory rate, sedation, pain score, nausea
- Hourly for first 8 hours from initiation of PCA
- 2 hourly for subsequent 48 hours
- Then 4 hourly until discontinuation

## Managing side effects

- Nausea/vomiting
  - Cyclizine 50mg TDS *or ondansetron 4mg TDS*
- Pruritis *-itching*
  - Chlorphenamine 4mg TDS PO
- Respiratory depression (RR < 8)
  - O<sub>2</sub>
  - Turn off PCA
  - Monitor O<sub>2</sub> SATs *for very short half-life*
  - Consider naloxone 200-400mcg IV
- Excessive sedation
  - Remove PCA handset
  - Monitor O<sub>2</sub> SATs, pain and sedation scores
  - Ensure adequate non opioid analgesia is prescribed regularly

*Reverse opioid*

## Summary PCA

- PCA aims to put effective pain relief into the hands of the patient
- Side effects managed by predictive prescribing
- Lock out is important safety feature
- Variety of opioids suitable
- Increase rate of post-operative recovery
- Patient understanding and capability vital

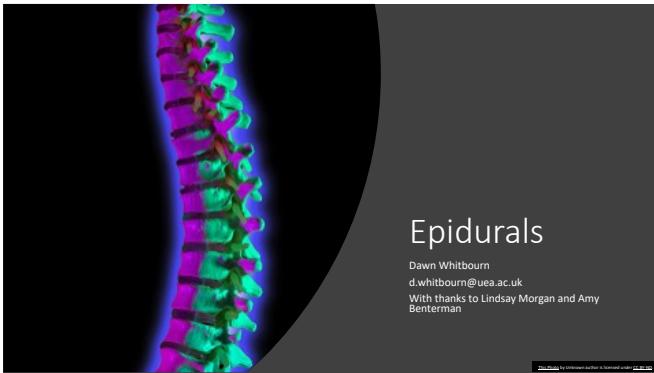
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## Other post-operative analgesia

- Multi-modal approach should be used offering analgesics with differing MOA
- Paracetamol should be offered post-operatively unless contraindicated
  - Weight >50kg – 1g QDS *less dose in light weight patients*
  - Weight <50kg – dose reduction
- Oral NSAID
  - Ibuprofen should be offered for immediate post-operative pain (except after surgery for fractured hip)
  - IV NSAIDs are not commonly used
  - Beware age and co-morbidities → renal impairment, asthma, etc.
- Oral opioid
  - If post-operative pain expected to be moderate to severe
  - Not with PCA or opiate containing epidural – can be given orally once PCA or epidural discontinued
  - Adjust the dose to help the person achieve functional recovery (such as coughing and mobilising) as soon as possible
- Gabapentin
  - If neuropathic post-operative pain expected
  - *If long term legating opiate – fentanyl patch, oxycodone or codeine wouldn't be given instead*
  - *Risk of drug interaction*

## Learning objectives

- Describe the rationale for patient-controlled analgesia (PCA)
- List the agents appropriate for PCA
- List the benefits and drawbacks of PCA
- Design an adjunctive schedule to manage safety and side effects of PCA
- Describe the options for adjunctive post-operative analgesia



## Learning outcomes

- Describe the anatomy of the epidural target
- Describe the properties of an ideal epidural analgesic formulation
- Lists the indications and contraindications for epidural anaesthesia
- List the benefits and drawbacks of epidural anaesthesia

## Post-operative pain

- 60% of patients report experiencing severe pain post operatively
- Poorly managed post operative pain can lead to complications and prolonged rehabilitation
- Well managed post operative analgesia **can also prevent acute pain progressing to chronic pain**

## Factors considered in choice of post-operative analgesia

- Patient factors including:
  - comorbidities
  - age
  - frailty
  - renal and liver function
  - allergies
  - current medicines
  - cognitive function
- Whether the surgery is immediate, urgent, expedited or elective
- Patient discussion to include:
  - likely impact of the procedure on the person's pain
  - person's preferences and expectations
  - pain history
  - potential benefits and risks, including long-term risks, of different types of pain relief
  - plans for discharge

## Epidural anaesthesia

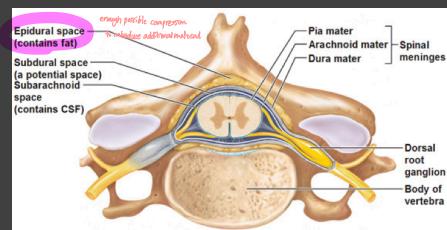
Epidural analgesia is the administration of analgesics (with or without adjuvants) into the epidural space. This technique enables analgesics to be injected close to the spinal cord and spinal nerves where they exert a powerful analgesic effect.

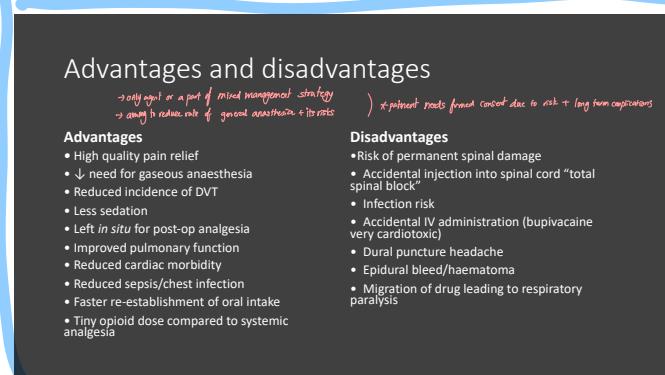
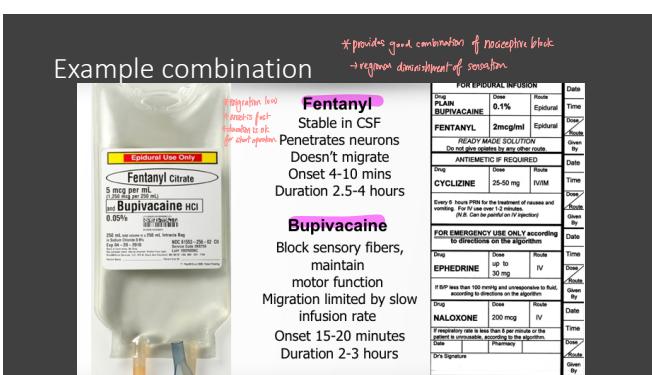
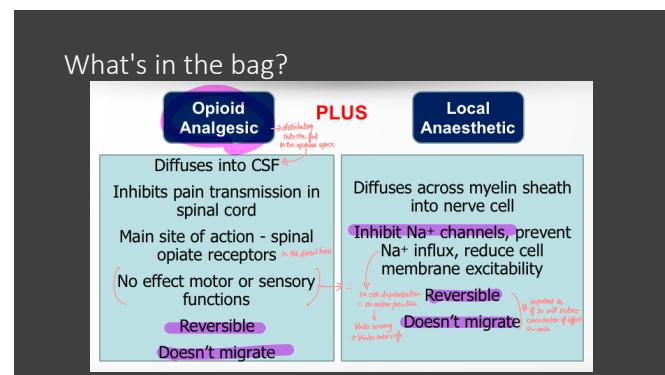
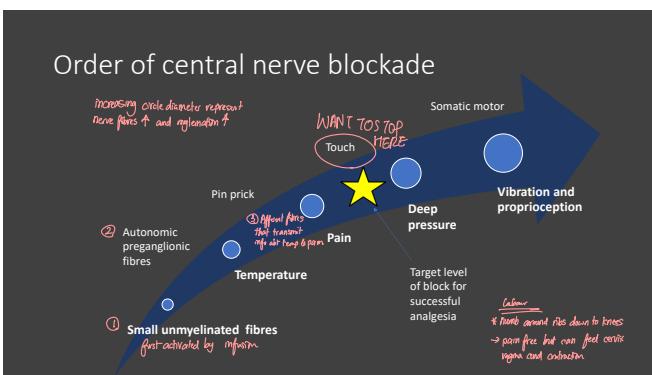
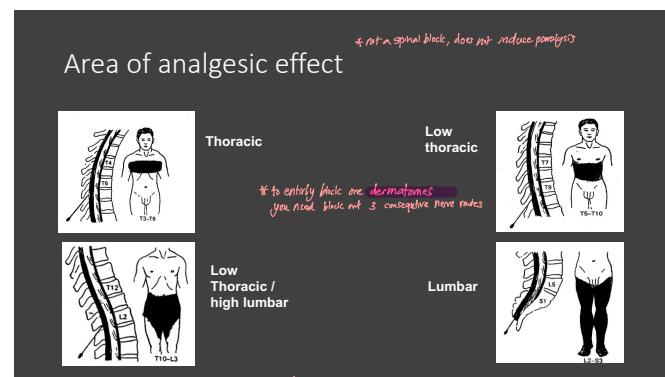
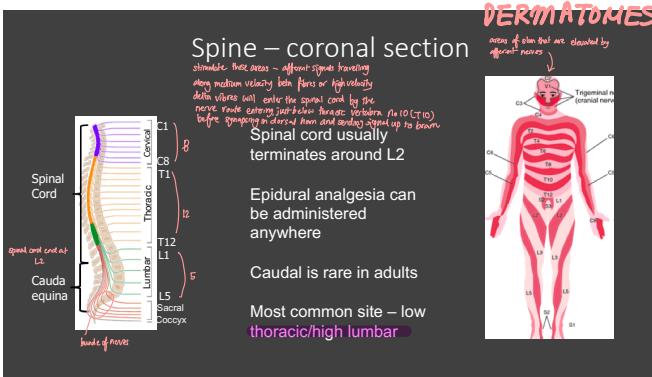
(Macintyre & Ready 2001, Wheatley 2001)

→ slight ↑ torque  
→ very low systemic side effects



## Transverse spine





## Side effects

*slightly less + technique related*

| Respiratory  | Cardiovascular   | Other   |
|--|--|---|
| <p><i>finest example of dangers</i></p> <p>Migration to C3-C5 blocks <b>phrenic nerves</b> → respiratory arrest<br/>Inability to cough<br/>Lack of awareness of breathing – panic<br/>Respiratory depression</p> | <p>Hypotension 2° to vasodilation<br/>T1-T4 – loss of chronotropic and inotropic drive - ↓ cardiac output<br/>Reflex tachycardia<br/>Depression of myocardial excitability (OD or accidental IV)</p> | <p>Vasodilation → heat loss<br/>→ hypothermia<br/>↓ hepatic/renal perfusion<br/>– impairment/failure<br/>Tinnitus<br/>Headache (late onset)<br/>Nausea and vomiting (opioid use and slowed peristalsis)<br/>Pruritus<br/>Sedation</p> |

## Rescue therapies

### Accidental IV admin of bupivacaine

- Intralipid® 20% shown to reverse LA-induced cardiac arrest in animal models
  - use reported in treatment of life-threatening toxicity without cardiac arrest
  - Recovery from LA-induced cardiac arrest may take one hour

*local anaesthetic*

### Opioid toxicity

- IV naloxone 100 - 400 micrograms
  - Short  $T_{1/2}$  hence repeated doses may be necessary

### Severe hypotension

- Ephedrine
- Dural puncture headache
- Blood patch

## Contraindications

- Patient refusal
- Infection at proposed site
- Clotting abnormalities
- Severe respiratory impairment
- Uncorrected hypovolaemia
- Raised intracranial pressure
- Neurological disease
- Difficult anatomy – spinal injury or deformity, extensive centripetal fat deposition
- Tattoos...? → area of epidural site? split opinions, inc bleeding?

## Summary

- Effective analgesia
- Increasingly common
- Usually mixture of opioid and local anaesthetic
- Improved post-operative outcomes
- Contraindications exist
- Short term side effects manageable with predictive prescribing
- Some long-term complications



## Learning outcomes

- Describe the anatomy of the epidural target
- Describe the properties of an ideal epidural analgesic formulation
- Lists the indications and contraindications for epidural anaesthesia
- List the benefits and drawbacks of epidural anaesthesia