Dementia

Dementia occurs in a cluster of diseases (mental decline)

It is a prominent part of Alzheimer's disease.

Symptoms: forgetfullness, memory loss, reduced reasoning, trouble paying attention, impaired judgement and problem solving, visual perception issues that aren't related to normal age-related changes, changes in personality and behavior, any other changes that interfere with a person's normal daily functions.

Dementia gets progressively worse.

Pathphysiology of Alzheimer's Disease

Medications to Treat Dementia Behaviors

Antidepressants

Antipsychotics

Benzodiazepines

Buspirone

Dextromethorphan/Quinidine

Image Explained

There is an enlarged left ventricle, a thinner cortex, an atrophied hippocampus, and atrophy all over.

The hippocampus is responsible for spacial and recent memory. This is where Alzheimer's starts.

Cholinesterase Inhibitors

MOA: Prevents the breakdown of ACh, leading to increased ACh and increase in cholinergic activity in the CNS.

Indications: better for mild cognitive impairment, you must have cholinergic neurons left. **NO disease modifying effects seen**

Side Effects: **mainly GI related** (N/V/D/Anorexia, advise taking with food to help), could cause bradycardia (risk of syncope, increased fall risk)

Contraindications: Pregnancy, liver disease, peptic ulcer

Considerations: should be tapered off, otherwise can cause discontinuation syndrome: difficulty concentrating, altered consciousness, delirium, hallucinations, insomnia, agitation, anxiety, labile mood

Rule of Thirds: 1/3 of patients will improve on these, 1/3 of patients will stabilize (slow progression temporarily), 1/3 of patients will experience no improvement.

Donepezil (Aricept): Oral tablet (Aricept), ODT (Aricept RDT), patch (Adlarity), ER caps combo with memantime for more severe cases (Namzaric). Well tolerated and is NOT hepatotoxic T1/2 ~70 hours. Also approved for severe cognitive impairment. Has less GI effects compared to other agents (Rivastigmine)

Galantamine (Razadyne): Tablet (Razadyne), ER capsule (Razadyne ER), oral soultion

Rivastigmine (Exelon): Capsule (Exelon) patch

Lewy Body vs Alzheimer's

Alzheimer's Disease
vs
Dementia with Lewy Bodies

Characteristics	Alzheimer's Disease	Dementia with Lewy Bodies
Prevalence	most common; 60% to 80% of dementia cases	third most common; 5% to 10% of cases
Median Survival Time	84.6 years old	78 years old
Antipsychotic Medication Sensitivity	Less prone to side effects	More prone to side effects
Physical Abilities	Tend to be affected during the later stages	Tend to be affected during the earlier stages
Visual Hallucinations	Less prevalent and occur later	More prevalent and occur earlier

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Benzodiazepines

Used only for severe anxiety.

Buspirone

MOA: antagonist of 5HT1A receptor

Indications: used for anxiety and mild/moderate agitation

Anxiolytic drug.

Well tolerated.

Limited data in dementia patients.

Has addictive potential.

Five Pathological Types of Dementia

Alzheimer's disease- the most common cause of dementia

Vascular dementia- this type of dementia is caused by damage to the vessels that supply blood to you brain. Is caused by atherosclerosis in the carotid arteries, and other arteries serving the brain.

Lewy body dementia- on its own or in Parkinson's dementia

Five Pathological Types of Dementia (cont)

Frontotemporal dementia- atrophy of neurons that die off in the frontotemporal region.

Mixed dementia.

Pathophysiology of Alzheimer's Disease

It is a progressive memory impairment, dementia, and cognitive dysfunction.

It occurs in up to 20% of patients over 85 (5th leading cause of death 65+)

It is a progressive loss of neurons, especially cholinergic neurons.

There is also an inflammatory process.

There is increased amyloid beta peptide deposits in the cerebral cortex (they are insoluble so they stick together) this leads to plaque formation, lesion, and neuronal fibrillary tangles (Tau proteins)

The alpha and beta tubulin dimers are wrapped around in a spiral to hold the microtubule together. Normally the tau protein holds microtubules together. But the **hyperphosphorylation** of tau causes a disassociation of the microtubules, forming a "clump" that tangles.

Mitochondrial dysfunction.

Increased glutamate activity may also play a role (NMDA receptor)

The bottom line is there is an **increase** in amyloid beta and a **decrease** in amyloid beta breakdown.

This typically starts out in the hippocampus, it spreads out from there.

Found in 20% of patients over 85.

Alzheimer's Pharmacology

Cholinomimetic drugs are a main focus of Alzheimer's therapy because there is evidence of loss of cholinergic neurons in this disease.

Decreasing glutamate is another focus of therapy due to excess glutamate excitation being present in this disease.

NMDA Receptor Blockers

Drug: Memantine **(Namenda)**

MOA: by blocking NMDA receptor, decreases the activity of glutamate

Place in Therapy: used in patients with more moderate cognitive impairment

Formulation: comes in a titration pak until goal dose achieved

Side Effects: overall well tolerated, more common ADRs are dizziness, confusion, HA, constipation.

Contraindications: Gastric ulcers, lung disease, heart disease, kidney disease.

Considerations: Patients should taper off of memantine, Abrupt discontinuation could lead to withdrawal effects like insomnia, aggression, delusions, and disinhibition. Treatment should be stopped after 6 months if no improvement is seen.

Other notes: has a long half life 60-80 hours, 100% absorbed orally. **Memantine in combination therapy with a cholinesterase inhibitor is recommended in moderate to severe disease (efficacy not shown in mild disease)** Memantine comes in combo with Donepezil (Namzaric)**

Antidepressants

Agitation:	**Citalopram (has the most data)**, escitalopram, sertraline, mirtazapine, trazodone
Depressions:	citalopram, sertraline
Psychosis:	citalopram
Insomnia/-Sleep problems:	trazodone
Anxiety:	trazodone *antidepressants haven't been studied for anxiety in dementia
Neuropathy:	Duloxetine, desvenlafaxine
Notes:	citalopram/escitalopram: QT prolongation, limit dosing
	trazodone: sedation and orthostatic hypotension risk
	Avoid TCA due to anticholinergic effects (already low on ACh)

Dextromethorphan/Quinidine

MOA: blocks the NMDA receptor, reduces agitation, reduced excitotoxicity in cholinergic nerves, inhibits the breakdown of dextro

Indications: Used for agitation in Alzheimer's disease, FDA approved for pseudobulbar effects (uncontrolled laughing/crying due to neurological condition)

Formulation: oral every expensive

Characteristics of Alzheimer's Disease

Memory Decline

They start having: learning problems, trouble with problem solving, poor judgement making, trouble communicating, depression and mood swings

Sundowners syndrome- in the later afternoon/early evening they experience additional confusion, irritablity, agitation, prancing, and wandering.

Finally there is a loss of self care.

Parkinson's Disease with Lewy Body

Lewy body dementia are dementia with Lewy bodies and Parkinson's disease dementia.

Lewy bodies are made up of brain proteins that are misfolded and forms aggregates. The protein aggregates causes cell death.

This type of dementia is the 3rd most common type of dementia.

Quetiapine and Clozapine are used off-label. Can also use Achase inhibitors.

It is important to determine Lewy body vs. Alzheimer's because the pharmacotherapy is different.

Lewy Body vs. Alzheimer's: lewy body has reduces DA uptake vs Alzheimer's. Lewy body has less temporal lobe atrophy it can be confirmed on MRI. Lewy body has less occipital lobe glucose metabolism per PET scan. (this may be the reason for increased visual hallucinations in Lewy body because of occipital lobe hypometabolism)

Alzheimer's Disease and Acetylcholine

Acetylcholine (ACh) is released by neurons in the CNS.

It is involved in memory, motivation, arousal, and attention.

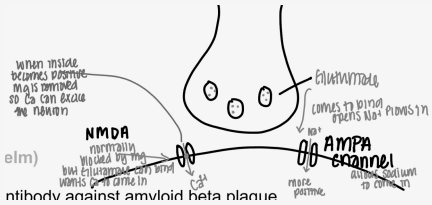
ACh is broken down by acetylcholinesterase.

In Alzheimer's disease, there is a decreased synthesis of ACh, which leads to impaired cholinergic function.

It begins in the hippocampus and spreads out to all areas of the cerebrum.

1/3 of cases are inherited.

Monoclonal Antibody: Amyloid Beta



Monoclonal Antibody: Amyloid Beta

Aducanumab (Aduhelm)

MOA: a monoclonal antibody against amyloid beta plaque

Place in therapy: FDA approved for MILD cognitive impairment, approved with the accelerated approval pathway (saw a plaque reduction but plaque reduction hasn't been associated with clinical improvements) cost is high, efficacy data is lacking, insurance doesn't like to cover it.

Formulation: given as a 1 hour infusion every 4 weeks

Side Effects: edema, cerebral microhemorrhage -> patients must have MRI at start and continually to monitor any changes.

Monoclonal Antibody: Amyloid Beta (cont)

Considerations: $56,000, serious side effects, benefits unknown. Has been shown to reduce plaques.

Antipsychotics

Psychosis: delusions, hallucinations, and paranoia

Only used in patients with severe agitation or psychosis that are distressing to the patients or makes them act in a way that they are dangerous to themselves or others. This is a last resort.

They are not to be used as a chemical restraint

There are not a lot of benefit seen in these drugs in the populations, LOTS of side effects. Most evidence with aripiprazole, olanzapine, risperidone. Haloperidol is reserved for emergency use.

Caution: CV events, metabolic effects of antipsychotics (weight gain, DM, dyslipidemia), **sedation**, QT prolongation

Labeled waring for antipsychotic use in patients with dementia- increased risk of death and cerebrovascular events

Cognitive impairment

Cholinesterase inhibitors will help attention, executive function (emotions, memory, impulse control, tasks, organization) and visuospatial deficits (spatial judgement, visual analysis)

Donepezil or Rivastigmine recommended as first line options.

Memantine NOT shown to work in this population.

Psychosis/Behavioral Symptoms

Cholinesterase Inhibitors are shown to help with behavioral symptoms, there is limited evidence that they help with hallucinations and delusions. They can help with negative symptoms (things missing from personality--emotion, speech, motivation, and anhedonia)

Last line: antipsychotics- unlikely effective and may worsen motor symptoms

Quetiapine or Clozapine may be tried at low doses, doesn't affect motor symptoms

Nuplazid (pimavanserin): FDA approved for hallucinations/delusions associated with Parkinson's disease (positive diseases)

Positive symptoms are things that are there: hallucinations, delusions

It blocks the 5HT2A and C receptors, NOT DA receptors so less effects on motor symptoms. High risk of side effects or death (almost 10%). QT prolongation. Also helps with anxiety.