PHARMACOLOGICAL MANAGEMENT OF DEMENTIA

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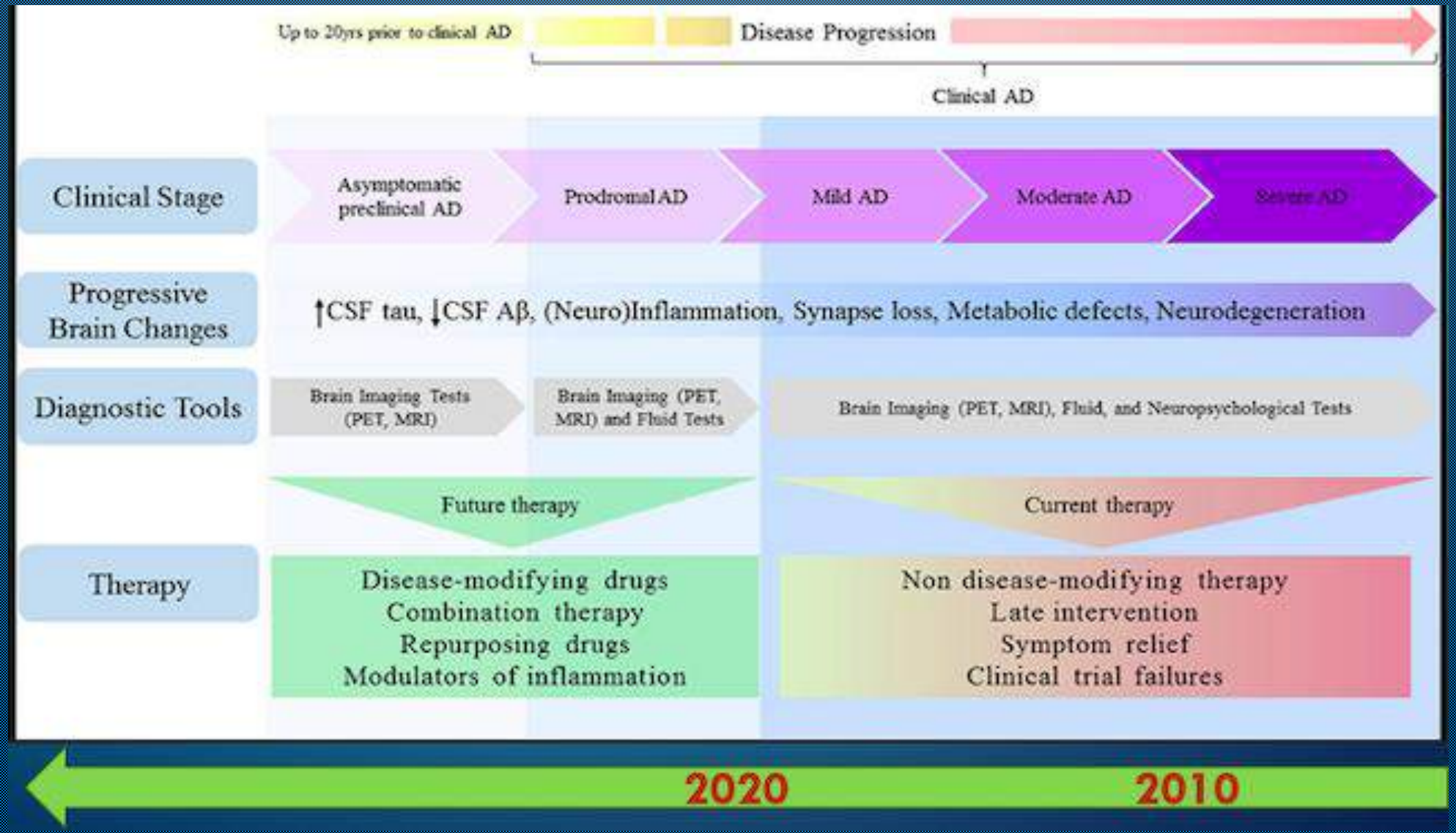
OUTLINES

- INTRODUCTION
- DISEASE SPECIFIC TREATMENT
- MANAGEMENT OF NEUROPSYCHIATRIC SYMPTOMS
- VASCULAR RISK FACTORS CONTROL
- MANAGEMENT OF MEDICAL COMORBIDITIES
- AVOIDING ADVERSE DRUG EFFECTS

INTRODUCTION

- Management is complex in patients with dementia
- Patients have decreased ability to make decision, adhere to treatment plans and report adverse effects of therapy
- No cure for dementia
- Early diagnosis can help to consider medications and therapies which can help slow down the progression of disease and ease some symptoms

PARADIGM SHIFTS IN MANAGEMENT OF ALZHEIMER'S



DISEASE SPECIFIC TREATMENT

AIzheimer's Disease

- Neurodegenerative disorder of uncertain cause and pathogenesis and most common cause of dementia
- While treatments are available that can ameliorate some symptoms of illness, there is no cure currently available

Two types of medications

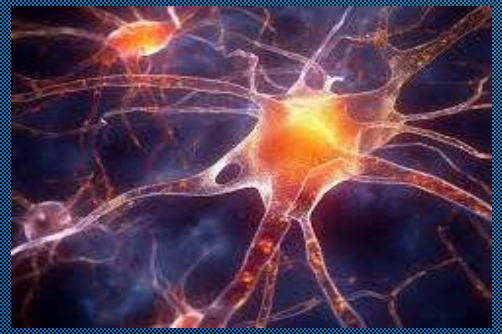
1. Acetylcholinesterase inhibitors (Cholinesterase inhibitors)
2. NMDA receptor antagonist

CHOLINESTERASE INHIBITORS

Normal Brain

Adequate levels of Acetylcholine

Send messages between nerve cells

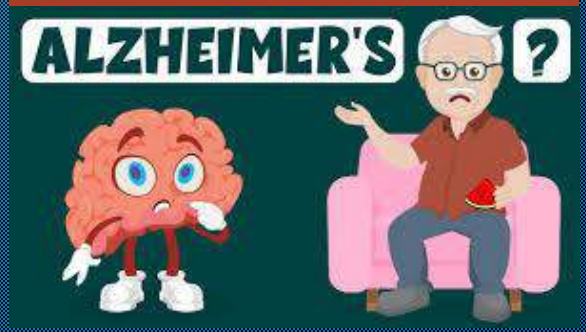


Cholinesterase inhibitors

Alzheimer's Brain

- Lower levels of Acetylcholine
- Loss of nerve cells which respond to Ach

Worsening of symptoms



CHOLINESTERASE INHIBITORS

- Patients with AD have reduced cerebral content of choline acetyltransferase, which leads to decrease in acetylcholine synthesis and impaired cortical cholinergic function
- Patients with newly diagnosed AD dementia, suggest a trial of Cholinesterase inhibitors (Grade 2A)
- Patients with mild to moderate severity of dementia (MMSE-10 to 26) most likely to derive clinical benefit
- Decision should be individualized in patients with very advanced dementia (MMSE<5) at the time of diagnosis

CHOLINESTERASE INHIBITOR MEDICATIONS

Donepezil

- Initiate 5mg HS, increase 10mg/D after 4-6 weeks and maximum 23mg/D after 3 months if warranted
- Original – Aricept
- Generic – Servonex, Gersia, Dopizil, Donzeral

Galantamine

- 4mg BD, titrate to 8-12mg BD, caution in hepatic impairment
- Original - Reminyl

Rivastigmine

- Oral
  - Initiate 1.5mg BD, increase 1.5mg/dose every 2 weeks.
  - Not to exceed 6mg BD.
- Transdermal
  - Initiate 4.6mg/D, increase 9.5mg/D after minimum 4 weeks.
  - Effective dose range 9.5-13.3mg/D.
- Original - Exelon
- Generic - Rivamer

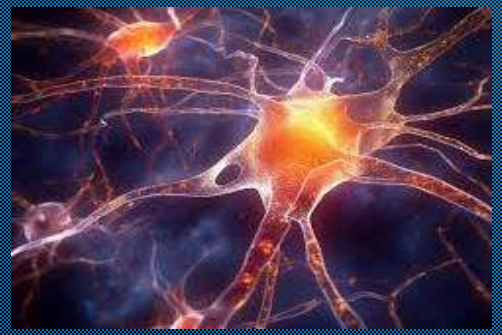
- Prescribed for mild to modorate Alzheimer disease
- Symptoms improving temporarily for 6-12 months
- Impact - reduced anxiety, improvement in memory and concentration daily activities, personal care, dressing and shopping
- Unfortunately, impact of these medicatuns gradually reduced with symptoms then gradually worsening
- S.E
  - LOA, Nausea, Vomiting, Diarrhoea, Muscle cramps, Headche, Dizzness, Fatigue, Insomnia

NMDA RECEPTOR ANTAGONISTS

Normal Brain

Normal levels of Glutamate

Send messages between nerve cells

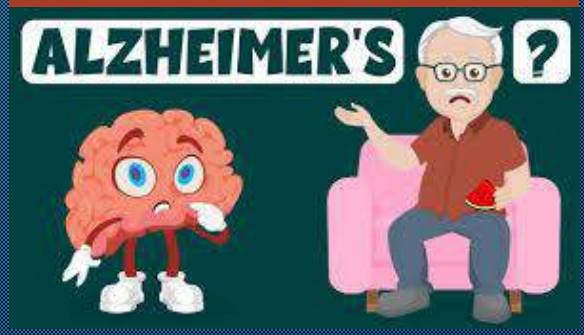


NMDA receptor antagonist

Alzheimer's Brain

- Excess amount of Glutamate
- Damage nerve cells in brain

Worsening of symptoms



NMDA RECEPTOR ANTAGONISTS

Memantine

- Patients with moderate to advanced Dementia (MMSE ≤18)
- Suggest adding memantine 10 Mg BD to a ChEI or alone in people with severe Alzheimer who do not tolerate or benefit from a cholinesterase inhibitors (Grade 2B)
- Initiate 5mg OD, increase by increment 5mg/D each week
- Maintenance 10mg BD after 5 weeks
- Benefit – slow the progression of symptons such as disinbition, difficulties with daily activities. (washing, dressing and shopping)

NMDA RECEPTOR ANTAGONISTS

- S.E – Less common and less severe then cholinesterse inhibitors
- Dizziness, headches, tiredness, increased B.P and constipation
- MMSE <10 – Continue Memantine (Grade 2C)
- Available Memantine in Myanmar – Admenta, Memantine, Denigma
- In some patient with advanced dementia, may make sense to discontinue administration of medications to maximize quality of life and patient's comfort.

DISEASE MODIFYING THERAPY

Aducanumab

- Recombinant monoclonal antibody directed against amyloid beta
- Given in monthly IV infusion, ideal treatment duation is unknown
- Approved by US FDA in June 2021 for treatment of mild AD who are still indepent in basic daily functioning
- Highly effective in reducing brain Amyloid Levels
- Phase Ib trial
  - 165 patients of mild AD shows substantial reduction of amyloid plaques on PET imaging. (dose and time dependent)
  - Only small and inconststent clicinal effects

- **Risks –** ARZA (Amyloid Related Imaging Abnormalities) especially in *APOE* e4 and carriers
- **Use of Adunacumab should be limited to;**
  - ✓ Mild cognitive impairment or mild dementia
  - ✓ Documented amyloid pathology in PET scan or CSF
  - ✓ No contraindications
    - Non AD pathologies (LBD, VaD) Down syndrome
    - Patients with high risk of hemorrhagic side effects
    - Anticoagulants or antiplatelet use (other than Aspirin 81 mg/day)
    - Bleeding disorders or other conditions leading to increased risk of CNS hemorrhage

What you should know about aducanumab (brand name Aduhelm)

FDA approval of aducanumab for mild Alzheimer disease is controversial. Although the drug reduces plaque in the brain, experts are uncertain whether this is linked to improved patient symptoms and quality of life.

The bottom line on FDA approval

In clinical trials, aducanumab reduced visible plaque in the brain, which is considered a **surrogate outcome** (a test result with no direct patient benefit).

Aducanumab did NOT have a noticeable effect on **patient outcomes** (something directly felt or experienced by the patient such as improvement in symptoms or quality of life).

Surrogate and patient outcomes for aducanumab treatment

OUTCOME CLASSIFICATION	OUTCOME IMPORTANCE	EFFECT OF ADUCANUMAB
Surrogate outcome *Change in a test result*	Less important *No direct patient benefit*	***Reduced visible plaques in the brain***
Patient outcomes *Improved symptoms and increased quality of life*	More important *Can be directly felt or experienced by patient*	***Not shown to noticeably improve symptoms of dementia or quality of life***

Serious adverse effects are common

Edema (swelling) and hemorrhage (bleeding) in the brain can cause confusion, dizziness, headache, and nausea, sometimes leading to hospitalization and long-term impairment.

THERAPY WITH UNPROVEN BENEFIT

- Antioxidants
  - Vitamin E – Resonable to offer 1000 IU BD in patients with mild to moderate AD May provide a benefit in slowing progression of disease but benefit is likely to be small
- Estrogen replcement
- Anti inflammatory drugs – NSAIDs
- Ginkgo biloba
- Vitamin B
- Omega 3 fatty acids

Vascular Dementia (VaD)

- Second most common cause of Dementia
- Heterogenous condition including single large infarcts, multiple small infarcts caused by emboli, strategically located lesions and diffuse white matter changes essociated with chronic hypoperfusion
- No specific licensed treatment for VaD
- Important to reduce underlying CVD risk factors and associated symptoms
- Only consider ChEIs or Memantine if they have suspected comorbid AD, PD dementia or Dementia with LB

Parkinson's Disease Dementia

- Mild to moderate dementia
  - Offer ChEIs
  - Oral Rivastigmine is the only treatment for PDD
  - Off-label Use - Donepezil, Galantamine and Rivastigmine patches
- Severe dementia
  - Consider ChEIs
  - Mementine for people with PDD, only if ChEIs are not tolerated or are contraindicated

Dementia with Lewy Bodies

- Mild to moderate dementia
  - Donepezil or rivastigmine
  - If not tolerated to those drugs, consider Galantamine
- Severe dementia
  - Donepezil or rivastigmine
  - Memantine for people if AChEIs are not tolerated or are contraindicated

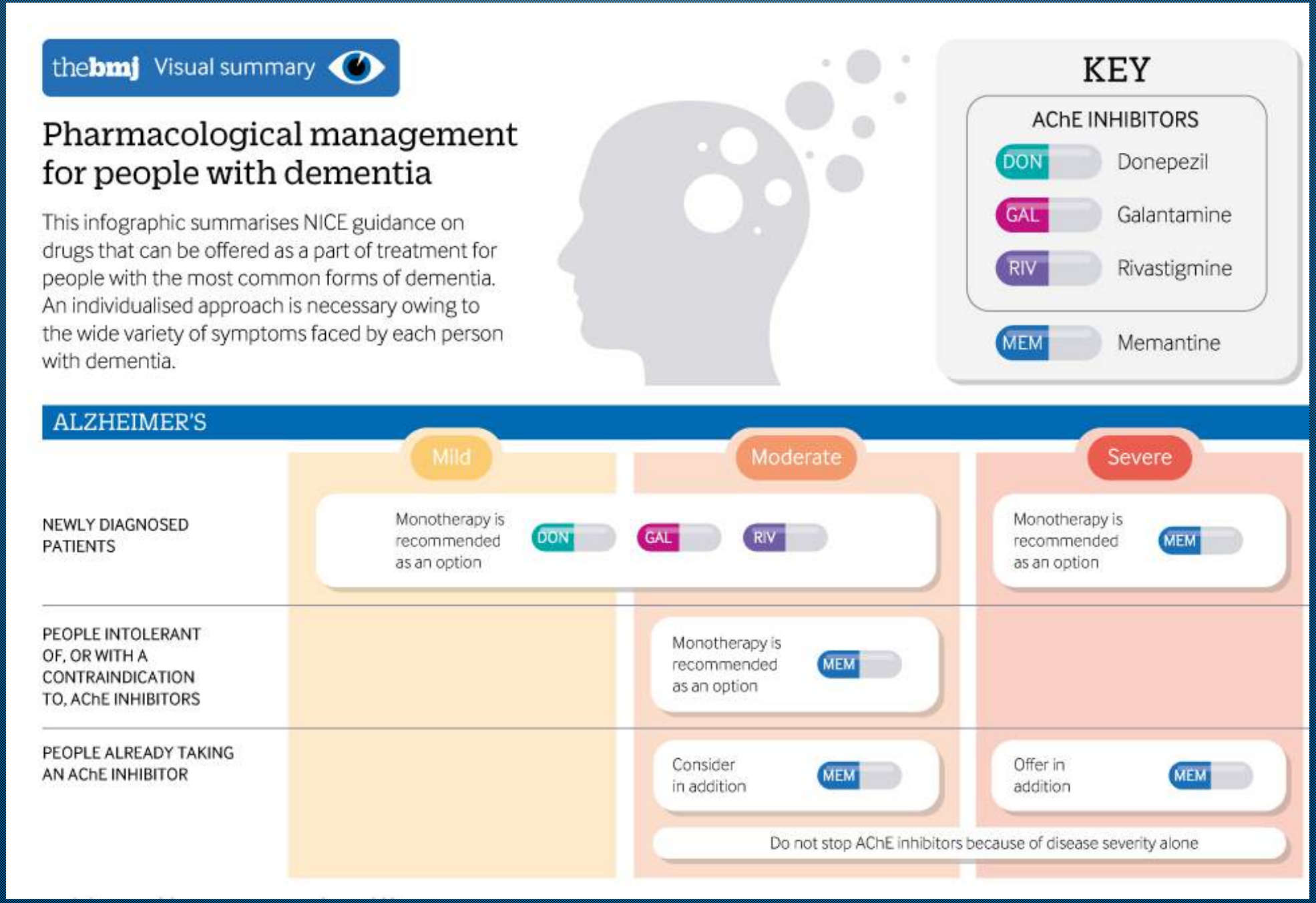
Fronto-Temporal Dementia

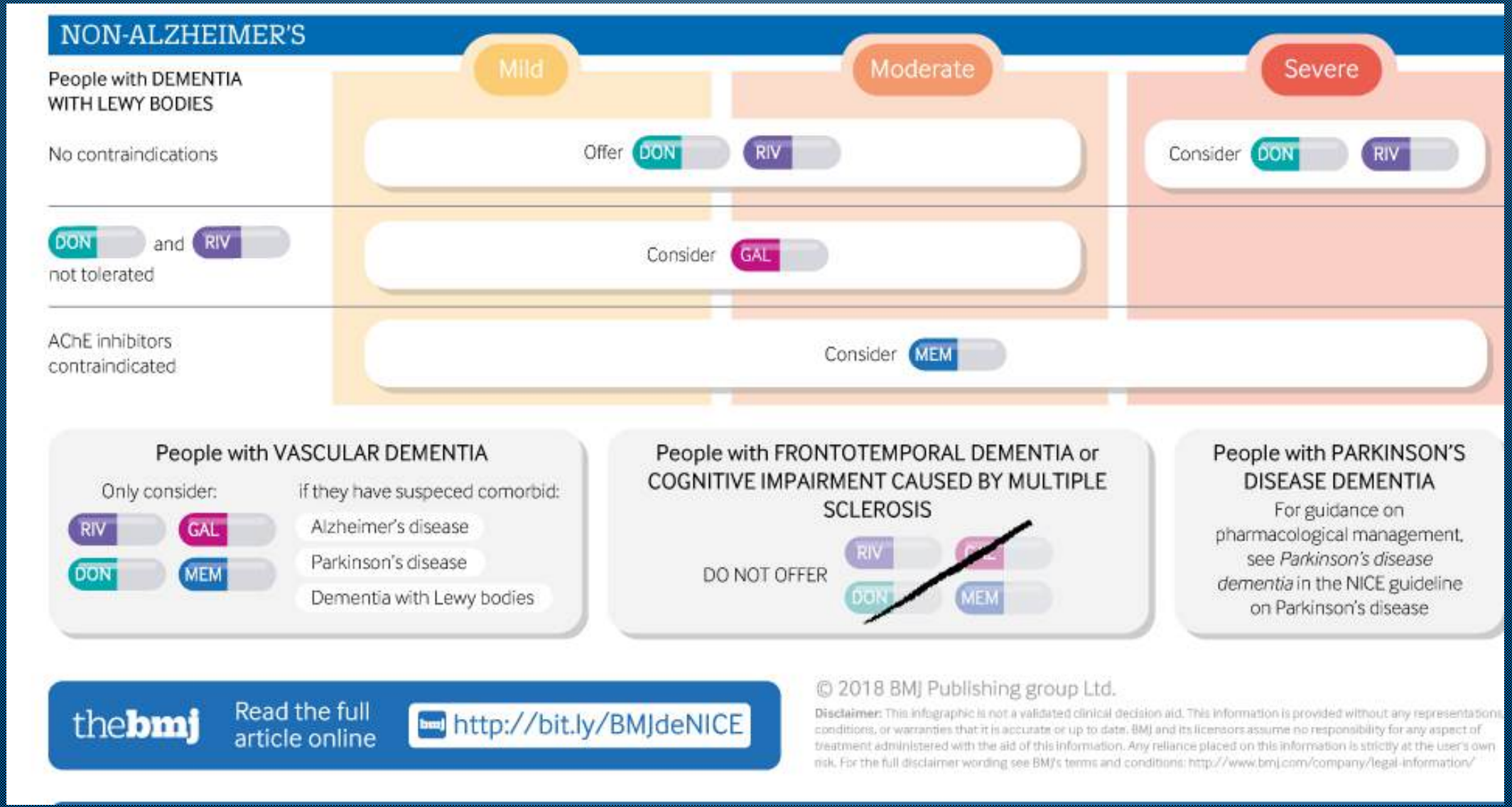
- Abnormalities in serotanin activity and dopaminergic function
- Cholinergic system appears to be relatively preserved
- No role of ChEIs or memantine
- Serotonergic medication can be used for Behavioral variant F.T dementia
  - Citalopram 10-20mg/day
  - Trazodone 25mg/day
  - Sertraline, Paroxetine, Fluvoxamine
  - Decrease disinhibition, anxiety, impulsivity, repeatative behaviour

Other Dementias

- Progressive supranuclear palsy, corticobasal degeneration, prion disease and Huntington's disease
  - Little evidence for efficiency of ChEIs and memantine because of worsening behavioural symptoms

- Posterior cortical atrophy, Logopenic progressive aphasia
  - Worth trying ChEIs or Memantine


thebmj Visual summary
Pharmacological management for people with dementia
This infographic summarises NICE guidance on drugs that can be offered as a part of treatment for people with the most common forms of dementia. An individualised approach is necessary owing to the wide variety of symptoms faced by each person with dementia.
KEY
AChE INHIBITORS
DON Donepezil
GAL Galantamine
RIV Rivastigmine
MEM Memantine
ALZHEIMER'S
Mild
Moderate
Severe
NEWLY DIAGNOSED PATIENTS
Monotherapy is recommended as an option DON GAL RIV
Monotherapy is recommended as an option MEM
PEOPLE INTOLERANT OF, OR WITH A CONTRAINDICATION TO, AChE INHIBITORS
Monotherapy is recommended as an option MEM
PEOPLE ALREADY TAKING AN AChE INHIBITOR
Consider in addition MEM
Offer in addition MEM
Do not stop AChE inhibitors because of disease severity alone


NON-ALZHEIMER'S
Mild
Moderate
Severe
People with DEMENTIA WITH LEWY BODIES
No contraindications
Offer DON RIV
Consider DON RIV
DON and RIV not tolerated
Consider GAL
AChE inhibitors contraindicated
Consider MEM
People with VASCULAR DEMENTIA
Only consider:
RIV GAL DON MEM
if they have suspeced comorbid:
Alzheimer's disease
Parkinson's disease
Dementia with Lewy bodies
People with FRONTOTEMPORAL DEMENTIA or COGNITIVE IMPAIRMENT CAUSED BY MULTIPLE SCLEROSIS
DO NOT OFFER
RIV DON MEM
People with PARKINSON'S DISEASE DEMENTIA
For guidance on pharmacological management, see Parkinson's disease dementia in the NICE guideline on Parkinson's disease
thebmj
Read the full article online
http://bit.ly/BMJdeNICE
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MANAGEMENT OF NEUROPSYCHIATRIC SYMPTOMS

- Screening – clinicians should routinely ask about them because symptons may not be volunteered
- Assessment of underlying causes
- Non pharmaccological management
- Pain management
- Depression
  - ✓SSRI : Citalopram (not exceeded 20mg)
    Sertraline (Alternative)
    Tricyclic should be avoided

- Severe or refractory agitation
  - ✓ Antipsychotic agents have limited efficacy and associated with mortality in patients with dementia
  - ✓ When symptoms are severe and threatening patients or care giver safty, Low dose olenzapine or quetiapine can be tried (Grade 2C)
  - ✓ DLB
    - ➢ Risk of severe S.E with neuroleptic medications
    - ➢ Very low dose of Quetiapine/ clozapine.
- Sleep disturbances – Non pharmacological strategies are preferred to pharmacotherapy; sleep hygiene, morning natural light

VASCULAR RISK FACTOR CONTROL

- Identification and treatment of risk factors for stroke, CVD and dementia
- Antihypertensive for hypertension
- Statin or fibrate for dyslipidaemia
- Antiplatelet for CVD and atherosclerosis
- Insulin or OHA for DM
- Drugs and exercise for obesity

MANAGEMENT OF MEDICAL CO-MORBIDITIES

- Mistake that all problems arising in people with dementia are due to dementia
- Most people with Dementia are older and likely to have other medical conditions:
  - ✓Infection
  - ✓Constipation
  - ✓Electrolyte imbalance

MANAGEMENT OF MEDICAL CO-MORBIDITIES: CONT.

- Dementia is a significant independent determinant of non-treatment with Asprin or Warfarin
- No good reason to avoid anticoagulant therapy in patients with A.F if they live with caring relatives

AVOIDING ADVERSE DRUG EFFECTS

- Adverse effects of prescribed medications can contribute to cognitive impairment and exacerbate dementia
- Increased risk for adverse drug events of polypharmacy due to metabolic changes and decreased drug clearance associated with aging
- Clinician who makes medication change should notify all other clinicians who are actively following the patient

- Important to periodically review patient's drug regimen, use minimal required dose, consider adverse drug effects as a cause of new symptom before prescribing another drug and consider non pharmacological approach when appropiate
- Avoidance of drugs that can exacerbate cognitive impairment; benzodiazepines, opoids, anticholinergic drugs, antipsychotic drugs and antihypertensive drugs in patients with PD and other disorders associated with autonomic dysfunction

Adverse effects of excessive antipsychotic use for behavioural symptons in Dementia

- Health report (U.K) – at least 180,000 people with Dementia are being prescribed antipsychotics each year
- Extra 1800 death/year and 1620/year cerebrovascular adverse events
- Risperidone is only drug specifically licensed for use in Dementia and only for short term (6weeks) who are unresponsive to non-pharmacological approach
- DLB show severe sensitivity to neuroleptic drugs, atypical antipsychotics and fatal reactions, need to ovoid neuroleptic drug in these patients

IS IT WORTH TREATING MCI?

- Cholinesterase inhibitors – not recommended for routine treatment of MCI
- Aducanumab – clinical trials supported to consider that treatment in patients with MCI (MMSE>24) and positive amyloid PET scan
- Furture new drug – Lecanemab
- Treatment of reversible causes of MCI
  - Treating other conditions– hypertension, sleep apnoea, depression
  - Stopping certain medicines – benzodiazepines, anticholinergics, antihistamines, opioids and PPI.

SUMMARY

- No treatment can cure dementia and disease specific drugs can help slow down the progression of disease and ease some symptoms
- Main disease specific drugs are ChEIs and NMDA receptor antagonists and disease modifying drug; Aducanumab is emerging to use
- Management of neuropsychiatric symptoms, control of vascular risk factors and management of medical comorbidities are important issues in patient with dmentia
- Caring physician should consider not only prescribing necessary medication but also avoiding adverse drug effects and polyphamacy

THANK YOU