Causes of Cognitive Impairment and Dementia: Diagnosis, Prognosis and Management

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In ancient Egypt it was thought that the heart and the diaphragm were the seats of mental health.

However it was known that old age can be accompanied by major memory problems (Boller & Forbes, 1998).

The ancient Egyptian doctor tried to explain the cognitive decline of old age: 'As to his mind (consciousness?) passes away: it is due to the fact that the vessels of the heart are carrying faeces.' 'As to drying up of the mind: it is due to the fact that the blood coagulates? in the heart.' 'As to debility through senile decay: it is due to the fact that purulency is on his heart' (Ebbell, 1937).

Age is here, old age arrived,
Feebleness come, weakness grows,
Childlike one sleeps all day,
Eyes are dim, ears deaf,
Strength is waning through weariness,
The mouth, silenced, speaks not.
The heart, void, recalls not the past.
The bones ache throughout.

The Ebers papyrus (c. 1550 BC)
## Causes of Cognitive Impairment

### Dementia over the centuries

<table>
<thead>
<tr>
<th>Causes</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual disorders</td>
<td>Wine abuse</td>
</tr>
<tr>
<td>Sequelae of delivery</td>
<td>Masturbation</td>
</tr>
<tr>
<td>Head injuries</td>
<td>Unhappy love</td>
</tr>
<tr>
<td>Progression of age</td>
<td>Fears</td>
</tr>
<tr>
<td>Ataxic fever</td>
<td>Political upheavals</td>
</tr>
<tr>
<td>Hemorrhoids surgery</td>
<td>Unfulfilled ambitions</td>
</tr>
<tr>
<td>Mania</td>
<td>Poverty</td>
</tr>
<tr>
<td>Paralysis</td>
<td>Domestic problems</td>
</tr>
<tr>
<td>Apoplexy</td>
<td>Mercury abuse</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Dietary excesses</td>
</tr>
</tbody>
</table>

Etienne Esquirol, 1838
Causes of Cognitive Impairment

Dementia over the centuries

- At the beginning of the 20\textsuperscript{th} century the distinction between mental disorders caused by identifiable brain diseases and others that lacked a recognisable physical cause became an important issue.
- For the former the German psychiatrist Emanuel Mendel introduced the term „organic“ (1902).
- Attempts were subsequently made to identify symptom patterns within the group of organic mental disorders that were specific to underlying brain diseases.

Emanuel Mendel
1839 - 1907
Dementia is a syndrome due to disease of the brain, usually of a chronic and progressive nature, in which a disturbance of multiple higher cortical functions, including memory, thinking orientation, comprehension, calculations, learning capacity, language and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration of emotional control, social behaviour or motivation.

- Decline in memory (new learning, short-term more than long-term, verbal and non-verbal)
- Decline in other cognitive abilities (e.g. planning, thinking, judgment, etc.)
- No delirium
- Decline in emotional control, motivation, social behaviour (BPSD)
- Present at least for 6 months

**Mild:** interferes with ADLs, but still can live independent (mail problem: new learning)

**Moderate:** only highly learned or very familiar material is retained. Serious handicap for independent living

**Severe:** only fragments of memory left. Often even close relatives are not recognised

ICD-10, 1994
### Causes of Cognitive Impairment

#### Assessment of cognition in old age

- History and collateral history (what is the gold standard? Alone or together?)
- Physical/neurological assessment
- MSE + cognitive assessment
- CT/ MRI (if complicated or young functional imaging)
- Bloods: FBE, U&E, TFTs, glucose, folate, B12, calcium, LFT
- ECG
- Differential diagnosis (e.g. depression, delirium, pain etc.)
- Consider assessment by neuropsychologist if available
<table>
<thead>
<tr>
<th>Feature</th>
<th>Dementia</th>
<th>Delirium</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Slow and insidious – over months or years</td>
<td>Sudden over a few hours or days</td>
<td>Often abrupt – may coincide with life changes</td>
</tr>
<tr>
<td><strong>Course</strong></td>
<td>Symptoms are progressive over a long period of time Not reversible</td>
<td>Short and fluctuating, often worse at night, often lightens with treatment of the underlying condition(s)</td>
<td>Typically worse in the morning, usually managed with treatment</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Months to years</td>
<td>Hours to less than 1 month – where the delirium persists longer than a few days as many as 30% may never completely resolve</td>
<td>At least 2 weeks – can last for months or years, and represents a change from previous functioning</td>
</tr>
<tr>
<td><strong>Psychomotor activity</strong></td>
<td>Wandering / exit seeking or Agitated or Withdrawn (may be related to co-existing depression)</td>
<td>Hyperactive delirium: agitation, restlessness, hallucinations Hypoactive delirium: sleepy, apathetic</td>
<td>Usually withdrawn, apathy</td>
</tr>
<tr>
<td><strong>Alertness</strong></td>
<td>Generally normal</td>
<td>Fluctuates – may be hypervigilant through to very lethargic</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>Generally normal</td>
<td>Impaired – difficulty following conversation, fluctuates</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Mood</strong></td>
<td>Depression may be present in early dementia</td>
<td>Fluctuating emotions – e.g. anger, tearful outbursts, fear</td>
<td>Depressed mood Lack of interest or pleasure in usual activities Change in appetite (increase or decrease) potentially nihilistic</td>
</tr>
<tr>
<td><strong>Thinking</strong></td>
<td>Difficulty in word finding and abstraction</td>
<td>Disorganised, distorted, fragmented</td>
<td>Intact themes of helplessness and hopelessness present</td>
</tr>
<tr>
<td><strong>Perception</strong></td>
<td>Misperceptions usually absent (can be present in Lewy body dementia)</td>
<td>Distorted – illusions, hallucinations, delusions; difficulty distinguishing between reality and misperceptions</td>
<td>Usually intact (hallucinations and delusions only present in severe cases)</td>
</tr>
</tbody>
</table>
Assessment of cognition in old age: how to get started

- Being assessed for cognition is uncomfortable (build bridges, listen, don’t rush)
- Adapt questions to clinical situation (age, level of impairment, education, culture)
- Explain why assessment happens
- Start with open questions and move to closed questions
- Ask for overall health and then narrow down to MSE and cognition
- What change to memory have they (and others) noticed? (ask for examples)
- Check other cognitive functions
- Ask for living situation and coping level, support, driving, pain, falls, their theories
- Explain what should happen next and why

Causes of Cognitive Impairment
Assessment of cognition in old age

- There is no ideal cognitive test for cognitive screening.
- MMSE & clock drawing test are the most commonly used cognitive tests around the globe.
- Others are GPCOG, Mini-Cog, NuCOG, MOCA, CERAD, CAMCOG, etc.
- Additional brief bedside tests can be added (e.g. frontal lobe).
- Rudas is useful for different cultural background.
- KICA is useful for traditional living Indigenous Australians.
- Geriatric Depression Scale (GDS-15) is a useful short depression scale.
- Try to consider impact of other illnesses or medications.

Reutens, Peisah & Brodaty, 2009
Fig. 4.1  An example of a frontal patient’s copy of an alternating sequence.
**Fig. 4.2** Luria three-step Test: the sequence of hand positions (fist—edge—palm) is shown. Figure taken from *Higher cortical functions in man* by A. R. Luria. © 1966, 1979 by Aleksandr Romanovich Luria. Reproduced by permission of Basic Books, a division of Harper Collins Publishers Inc.
Fig. 4.3  Alternating Hand Movements Test: the hand positions (above) and the sequence of movements to demonstrate to the patient (below) are shown. Figure taken from *Higher cortical functions in man* by A. R. Luria. © 1966, 1979 by Aleksandr Romanovich Luria. Reproduced by permission of Basic Books, a division of Harper Collins Publishers Inc.
Causes of Cognitive Impairment

GDS-15

1. Are you basically satisfied with your life?
2. Have you dropped many or your activities and interests?
3. Do you feel that your life is empty?
4. Do you often get bored?
5. Are you in good spirits most of the time?
6. Are you afraid that something bad is going to happen to you?
7. Do you feel happy most of the time?
8. Do you feel helpless?
9. Do you prefer to stay at home, rather than going out and doing new things?
10. Do you feel you have more problems with your memory than most?
11. Do you think it is wonderful to be alive?
12. Do you feel pretty worthless the way you are now?
13. Do you feel full of energy?
14. Do you feel that your situation is hopeless?
15. Do you think that most people are better off than you are?

Yesavage et al., 1983
<table>
<thead>
<tr>
<th>Neurodegenerative</th>
<th>Deficiency States</th>
<th>Endocrine disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alzheimer’s disease</td>
<td>• B12</td>
<td>• Diabetes</td>
</tr>
<tr>
<td>• Dementia with Lewy bodies</td>
<td>• Thiamine</td>
<td>• Thyroid disease</td>
</tr>
<tr>
<td>• Frontal dementias</td>
<td>• Nicotinic acid</td>
<td>• Parathyroid disease</td>
</tr>
<tr>
<td>• Huntington’s disease</td>
<td>Neurological disorders/trauma</td>
<td>• Cushing’s disease</td>
</tr>
<tr>
<td>Vascular</td>
<td>• Normal pressure</td>
<td>• Addison’s disease</td>
</tr>
<tr>
<td>• Infarction</td>
<td>hydrocephalus</td>
<td>Potentially reversible</td>
</tr>
<tr>
<td>• Haemorrhage</td>
<td>• Head injury</td>
<td>• Drugs</td>
</tr>
<tr>
<td>• Vasculitis</td>
<td>• Space occupation lesions</td>
<td>• Depression</td>
</tr>
<tr>
<td>• Other</td>
<td>• Multiple Sclerosis</td>
<td>• Metabolic causes</td>
</tr>
<tr>
<td>Alzheimer’s Disease mixed</td>
<td><strong>Infection</strong></td>
<td>• Neoplasm</td>
</tr>
<tr>
<td></td>
<td>• Syphilis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Viral encephalitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• HIV</td>
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</tbody>
</table>
Alzheimer’s Disease

- Causes > 50% of all dementias
- Characterised by insidious onset and slow steady progression of deficits
- Usually new learning is affected first (rapid forgetting), then praxis, language, executive functions
- Typical cortical dementia (amnesia, aphasia, agnosia, apraxia)
- Pathological hallmarks are plaques, tangles, atrophy (hippocampus)
- Main risk factors are unmodifiable – age, family history, APOE ε4, female sex
- No perfect diagnostic test in living patient but clinical diagnosis correlates 80-90% with autopsy findings in experienced hands
- No evidence for other causes of dementia which could be seen to be responsible for clinical presentation
- Typical course duration: 7-10 years (huge variation)
Causes of Cognitive Impairment

Petersen & Jack., 2009
MCI

- Mild subjective
- Objective memory loss
- Normal ADL function

Mild AD

- Forgetfulness
- Short-term memory loss
- Repetitive questions
- Hobbies, interests lost
- Impaired instrumental functions
- Anomia

Moderate AD

- Progression of cognitive deficits
- Aphasia
- Dysexecutive syndrome
- Impaired BADL
- Transitions in care

Severe AD

- Agitation
- Altered sleep patterns
- Total dependence: dressing, feeding, bathing

BADL = basic activities of daily living.

Vascular Dementia

- app. 10-20% of dementias
- Main cause should be cerebrovascular disease
- Often step-wise progression (but can also be slow and gradual)
- For “pure” VaD a neurological deficit is required with temporal relationship (neurology)
- Various subtypes (acute onset, multi-infarct, strategic, subcortical VD, mixed cortical-subcortical, haemorrhagic)
- The older the patient is the more likely it is that AD pathology is present as well (mixed AD)
- There are rare genetic subtypes (CADASIL)
Vascular Dementia

- Cardiovascular risk factors
- Often slowing of mentation (subcortical)
- Problems with retrieval rather than encoding
- Often gait problems, depression
- MRI scan: DWMCH, lacunes, strokes, atrophy, but hippocampi often preserved
Dementia with Lewy bodies

- 2nd most common neurodegenerative dementia
- Often misdiagnosed
- Fluctuating cognition (often looks like delirium)
- Recurrent visual hallucinations, delusions, Parkinsonism
- Impaired attention, visuo-spatial, frontal-subcortical abilities
- Temporal relationship of parkinsonism and cognitive impairment is important
- Often overlap with AD and PD pathology
Dementia with Lewy bodies

- Often repeated falls, depression
- Often syncopes, transient loss of consciousness
- Often REM sleep behaviour disorder
- Often neuroleptic sensitivity
- Often responds very well to cholinesterase inhibitors
- Often M > F, onset > 65 y, usually shorter duration than AD
Mainly affect the frontal and anterior temporal lobes
Parietal cortex and basal ganglia can be involved as well
With or without Amyotrophic Lateral Sclerosis (ALS)
Frontotemporal lobar degeneration (FTLD)

- 2-5% of all dementing illnesses
- In people < 65 y as common as AD
- Presentation varies depending to location of pathology
- Often asymmetrical atrophy
- Positive family history in 1/3 to 1/2 of cases
- Preservation of memory and orientation for a long time
- Often early prominent personality changes
- Apathy, euphoria, irritability, obsessive-compulsive, loss of empathy
- Often insight and judgment impaired early
- Often hyperorality, hypersexuality
- Executive dysfunction, often language problems
- Tauopathy (chr. 17, + Parkinsonism) can be present
- Duration: 2-16 years
CADASIL

- CADASIL is an autosomal-dominant inherited non-amyloid systematic angiopathy caused by mutations in the notch 3 gene on chromosome 19. Named in 1993, it is the most common cause of inherited stroke and vascular cognitive impairment in adults.
- Genetic testing and skin test available.
- More than 150 mutations in over 500 families worldwide.
- Average age for symptom onset is 37 years, 80% have dementia in the end.
- Highly variable phenotype: migraine, mood disturbances, apathy, epileptic seizures, TIA’s, strokes, vascular cognitive impairment and dementia.
- Hypothesis: the angiopathy leads to a reduced ability of the blood vessels to autoregulate, resulting in reduced cerebral perfusion. Most patients have 2-5 recurrent strokes.
- But additional modulating environmental factors contribute to exacerbate the situation triggering a stroke. Smoking has been identified in a genotype-phenotype study with 65 CADASIL families.

Singhal et al., 2004; Starkstein et al., 2005; Lautenschlager & Martins, 2005; Chabriat et al., 2009.
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

Cause of Cognitive Impairment

Figure 1: Natural history of the main clinical manifestations of CADASIL

The exact age at earliest onset or of first MRI abnormalities is uncertain (dotted line). The frequency of T2 white-matter abnormalities increases progressively and becomes constant by around 35 years in all patients.

Chabriet et al., 2009
First described in 1988 by Benson et al. Usually presenile onset

Described as “posteriorly shifted variant of AD (“visual variant AD”)

Leading symptoms are visuospatial complaints: blurry vision, movement of objects, reading difficulties, problems recognising objects → ophtalmologist

Visual agnosia, dressing apraxia

Balint’s syndrome (oculomotor apraxia, optic ataxia)

Gerstmann’s syndrome (agraphia, acalculia, finger agnosia, right/left disorientation)

Testing: Visuoconstructive difficulties in drawing to copy or to command

Compared to AD better on memory and verbal tests

More depression and better insight compared to AD
Causes of Cognitive Impairment

Posterior Cortical Atrophy (PCA)

Neuropathology: AD, Lewy-body disease, CJD (“Heidenhain variant”), progressive subcortical Gliosis, corticobasal degeneration

Figure 1. Serial MR images of a patient with posterior cortical atrophy (sagittal T1, axial FLAIR, coronal T1). Note the occipitoparietal atrophy (large white arrows) and the relative preservation of the hippocampus (small black arrow).

Tang-Wai, et al., 2004
First case description by Huntington in 1872
Prevalence varies: e.g. in Europe 4-8/100 000, but also hotspots, e.g. in Tasmania and Scotland
Autosomal-dominant disorder with an expansion in the CAG repeat within exon 1 of the gene encoding huntingtin on chromosome 4 (Triplet repeat disorder). The normal length is 36 or less repeats. An expansion of 40 or more causes HD. Large expansions tend to result in earlier onset. “Anticipation” more often in children of male HD patients
How the expansion causes HD is not fully understood (? toxic gain-of-function)
Genetic testing is available, but strict protocol
Average age of onset is mid-forties, average duration 15-20 years
Usually more severe when earlier onset and with more psychiatric symptoms
Choreiform movements, unsteadiness of gait, tendency to fall, psychiatric symptoms, personality change, dementia

Lovestone, 2009
Causes of Cognitive Impairment

HD: psychiatric symptoms

- Apathy
- General inefficiency at work
- Executive dysfunction
- Decreased attention and distractibility
- Deficits in immediate memory and planning
- Slowing of cognitive responses
- Reduced verbal fluency
- Judgement often impaired
- Subcortical dementia
- Dysphoria, irritability, apathy, anxiety, aggression, depression, delusions

Lovestone, 2009
Challenges about uncommon causes of dementia

- patients present in various settings
- to consider that this could be dementia
- often requires thorough and highly specialised assessments
- almost always requires the involvement of several disciplines
- high percentage of unknown ethiologies
- often long period of uncertainty before dementia trajectory is confirmed
- often lack of effective treatment
- often limited knowledge on suitable management approach
- often lack of effective support network for patient and family
- cause might be relevant to prognosis for other family members
## Causes of Cognitive Impairment

### Clinical skills

- Almost all patients with mild dementia wish to be told
- But ethical need to ask patient prior to disclosure of diagnosis
- Family member might be more ambivalent and in some cases ask the clinician not to disclose the diagnosis, placing the clinician in a difficult decision
- Disclosing a diagnosis of dementia is a sensitive task – needs skills
- Reassurance is not reassurance when inappropriate
- Unnecessary pessimistic attitude due to sinister outlook is not helpful
- Clinician should convey an attitude of care and attention, share facts and information, should have time to address fears and concerns, and will be guided by the family and patient in regards to management approach

Lovestone, 2009
Causes of Cognitive Impairment

How to manage once dementia is diagnosed?

- Education
- Driving
- Legal considerations
- ? Cholinesterase Inhibitors and Memantine
- Lifestyle factors and general health
- Services
- Look out for BPSD
- Carer burden
Treatment of vascular risk factors in AD: does it make a difference?

Observational study, memory clinic
301 patients with AD without CVD
Mean follow-up: 2.3 years

Figure 2: Multivariate mixed random effects regression model of MMSE progression over time in patients with AD without CVD

Model is adjusted for age, sex, education level, first Mini-Mental State Examination (MMSE) score, cholinesterase inhibitor use, number of vascular risk factors (VRF), year of first visit, duration of symptoms before first visit, and propensity score. AD = Alzheimer disease; CVD = cerebrovascular disease.

Deschaintre et al., 2009
Causes of Cognitive Impairment

Drugs

4 drugs approved - all symptomatic:

- Aricept (donepezil) - cholinesterase inhibitor
- Exelon (rivastigmine) - cholinesterase inhibitor
- Reminyl (galantamine) - cholinesterase inhibitor
- Ebixa (memantine) - NMDA receptor antagonist
- ChE contraindications: active peptic ulcer, bradyarrhythmias eg sick sinus syndrome, ?asthma, previous adverse response
- ChE: nausea, anorexia, vomiting, insomnia, dizziness, muscle cramps, nightmares
- ChE benefits: period of modest cognitive enhancement, Symptomatic treatments not cures, 2 in 3 maintain baseline or improve, functional and behavioural benefits, mean 38 to 52 weeks before patients cross baseline of cognitive decline

snowdrop bulb
## Causes of Cognitive Impairment

### Table 1. Molecular Classification of Dementing Disorders

<table>
<thead>
<tr>
<th>Clinical Disorder</th>
<th>Protein</th>
<th>Term</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>β-Amyloid</td>
<td>β-Amyloidopathy</td>
<td>PSEN1, PSEN2, APP, APOE, others</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Tau</td>
<td>Tauopathy</td>
<td>MAPT</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Tau</td>
<td>Tauopathy</td>
<td>MAPT</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Tau</td>
<td>Tauopathy</td>
<td>MAPT</td>
</tr>
<tr>
<td>Lewy body dementia</td>
<td>α-Synuclein</td>
<td>α-Synucleinopathy</td>
<td>GBA, TARDP, PGN, C9orf72, SNCA, LRRK2, GBA</td>
</tr>
<tr>
<td>Parkinson disease dementia</td>
<td>α-Synuclein</td>
<td>α-Synucleinopathy</td>
<td>GBA, TARDP, PGN, C9orf72, SNCA, LRRK2, GBA</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Prion protein</td>
<td>Prionopathy</td>
<td>PRNP, HTT</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>Huntingtin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: TDP-43, TAR DNA-binding protein 43.

aNeurodegenerative dementing disorders are characterized by derangements in particular proteins, with characteristic deposition of abnormal proteins in neurons, glia, or brain extracellular space. In some diseases, there are co-pathologies. For example, Alzheimer disease is marked by abnormal deposits of both β-amyloid and tau. Various genes have been shown to be involved in these disorders, either through mutations with autosomal dominant or recessive inheritance, or through risk factors of polymorphisms or mutations.
Table 3. Clinical Investigational Drug Studies in Alzheimer Disease

<table>
<thead>
<tr>
<th>Objectives and Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase β-amyloid clearance</td>
</tr>
<tr>
<td>Active immunization</td>
</tr>
<tr>
<td>AN-1792, ACC-001 (vanutide cridificar), a CAD-106, UB-311, V-950</td>
</tr>
<tr>
<td>Passive immunization</td>
</tr>
<tr>
<td>Bapineuzumab (AAB-001), a solanezumab (LY2062430), a crenezumab (MABT-5102A), a gantenerumab (R-1450), a ponezumab (PF-04360365), GSK-933776</td>
</tr>
<tr>
<td>Immunoglobulin therapy</td>
</tr>
<tr>
<td>Human immunoglobulin intravenous therapy a</td>
</tr>
<tr>
<td>Decrease β-amyloid production</td>
</tr>
<tr>
<td>γ-Secretase modulators (tarenflurbil [R-flurbiprofen])</td>
</tr>
<tr>
<td>γ-Secretase inhibitors (semagacestat [LY450139], begacestat [GSI-953], avagacestat [BMS-708163], a GSI-136, PF-3084014, MK0752)</td>
</tr>
<tr>
<td>α-Secretase enhancers (acitretin [etretinate, varenicline])</td>
</tr>
<tr>
<td>β-Secretase inhibitors (CTS-21166)</td>
</tr>
<tr>
<td>Decrease β-amyloid fibril formation or aggregation</td>
</tr>
<tr>
<td>Tramilprostate</td>
</tr>
<tr>
<td>Scylo-inositol (D-005) a</td>
</tr>
<tr>
<td>Deter tau aggregation</td>
</tr>
<tr>
<td>Methylthioninium (methylene blue)</td>
</tr>
<tr>
<td>Inhibit tau phosphorylation</td>
</tr>
<tr>
<td>GSK-3 Inhibitors (lithium, valproic acid)</td>
</tr>
<tr>
<td>Deter neurodegeneration</td>
</tr>
<tr>
<td>Davunetide a (NAP, AL-108)</td>
</tr>
<tr>
<td>Nerve growth factor (NGF)</td>
</tr>
<tr>
<td>NGF-adeno-associated virus, AAV2-NGF (CERE-110)</td>
</tr>
<tr>
<td>Brain-derived neurotrophic factor (BDNF)</td>
</tr>
<tr>
<td>Exenatide</td>
</tr>
</tbody>
</table>

a Currently under development in phase 2 or phase 3 trials.
First description of BPSD in Alzheimer’s Disease

“The first noticeable symptoms of illness shown by this 51-year old woman was suspiciousness of her husband. Soon, a rapidly increasing memory impairment became evident; she could no longer orient herself in her own dwelling, dragged objects here and there and hid them, and at times, believing that people were out to murder her, started to scream loudly.”

Alois Alzheimer, 1907 (translated by Jarvik and Greenson, 1987)
IPA definition of BPSD

- Symptoms of disturbed perception, thought content, mood or behaviour that frequently occur in patients with dementia

- **Behavioural symptoms:** identified on the basis of observation of the patient: aggression, screaming, agitation, wandering, cursing, disinhibition, hoarding, shadowing and restlessness

- **Psychological symptoms:** assessed on the basis of interviews with the patient and relatives: anxiety, depressive mood, hallucinations and delusions

- Also referred to as neuropsychiatric symptoms or non-cognitive symptoms

- Non-pharmacological interventions are the recommended first-line treatments

Finkel & Burns, 1999
Why are BPSD important?

- Very common at some point in the course of the illness (90-100)
- Multiple aetiologies: genetic, neurobiological, psychological, environmental
- Often distressing to the patient expressing these symptoms
- Correlates poorly with cognitive deficits
- More influential than cognition upon patient outcomes (e.g. functional, QoL, etc.)
- Frequently occurring, but intermittently
- Key contributor to caregiver burden (mental health, QoL, loss from workforce)
- Associated with increased and often premature institutionalisation
- Costly and associated with staff burnout in nursing homes
- Common reason for psychiatric referral
- May result in inappropriate or over-medication

Tariot et al., 1993; Lyketsos et al., 2000; Aupperle PM, 2004; Figiel G et al., 2008; Rodda J et al., 2009; Savva et al., 2009
Dementia and the hospital environment

- Patient most likely will be confused and anxious (high care need)
- Involvement of carer (if available) is crucial ("partnership")
- Often the existing dementia has not been diagnosed yet
- Patient is vulnerable (safety, lack of insight, reduced orientation, medication, diet)
- Effective communication (verbal & non-verbal) is essential

"it is unrealistic to expect a patient with dementia to adapt to, and accommodate, the hospital environment!"
Causes of Cognitive Impairment

BPSD: basic concepts

- Avoid to argue or reason with the patient (don’t take it personally & be flexible)
- Safety (patient, other patients, family, staff): get help
- Reassurance & Distraction (activities)
- Show interest for the individual and use humour
- Explain what is happening and give choices (lack of control)
- Repeat information in different ways & don’t rush
- Consider basic causes of discomfort (pain, hunger, thirst, bowels, bladder, temperature, fatigue, noise, clothes etc.)
- Avoid restraints and allow mobilisation in safe environment
Management of BPSD

- Non-pharmacological (i.e. behavioural, environmental and social) interventions are first-line
- Medications only to be used as an adjunct and if necessary
- Limited evidence
- Does the BPSD warrant treatment? For whom? Why?
- Is the BPSD drug-responsive?
- Do the benefits outweigh the risks?
Non-pharmacological management

- Environmental interventions
- Behavioural management
- Structured activities
- Sensory enhancement: music, massage, aroma
- Social contact: pets, one to one, family videos
- Medical/nursing interventions: light therapy, hearing aids, pain management

- Staff training
- Mental health care for caregiver
- Day treatment
- Exercise program
- Respite care

Cohen-Mansfield, 2001; O’Connor et al., 2009 A+B
In AUS only Risperidone is approved for the treatment of behavioural disturbances in dementia characterised by aggression and/or psychosis (dosage up to 2 mg/day).

Other options include antidepressants, mood stabilisers, benzodiazepines, ChEIs, memantine.

Limited evidence overall, no consensus.

Detailed treatment plan and frequent reviews are important.

NOK need to be informed about risks with written documentation.
**Causes of Cognitive Impairment**

**Depression**

**Participants:** 218 patients with AD and depression  
**Intervention:** RCT, 39 weeks, placebo vs 150mg sertraline vs 45mg mirtazapine  
**Results:** no sig. difference, but sig. more adverse events compared to placebo
Conclusion

- Concerns should be taken seriously and assessed early
- Pharmacological options still limited
- Management plan with involving the family is crucial
- Maintaining general health is important
- Ongoing relationship makes a big difference
- Care for the carers