4th International Alzheimer's Disease Conference

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Strategic Supporting Partner

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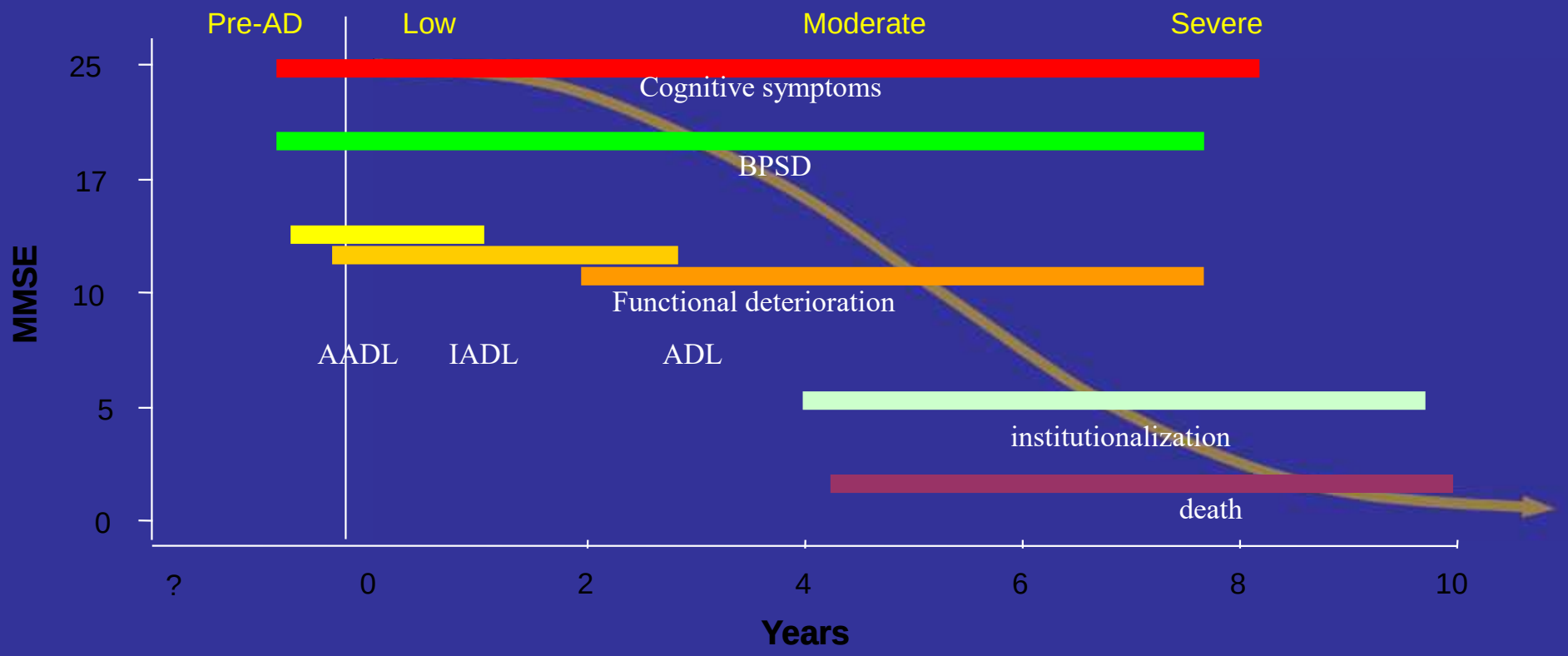
Practical considerations in management of Alzheimer´s Disease

Pálmi V. Jónsson, MD, FACP, FRCP L
Chief of Geriatrics, Landspitali University Hospital,
Professor of Geriatrics, Faculty of Medicine, University of Iceland

Natural History of AD



Modificata da Gauthier S. ed. Clinical Diagnosis and Management of Alzheimer's Disease. 1996.

First:

- Disease modifying medications have not reached the market yet

- Treatment of cognitive symptoms is a symptomatic treatment

- Treat all co-morbidity
    - RO B12 deficiency, Hypothyroidism,
    - Treat all cardiovascular risk factors
        - hypertension
        - hypercholesterolemia
        - smoking
    - Optimize treatment of DM

- Treat depression

  Depression can begin before, with and after the diagnosis of Alzheimer´s disease

Symptomatic treatment of Alzheimer´s disease

•Acetylcholinesterase inhibitors work by inhibiting acetylcholinesterase (the enzyme primarily responsible for synaptic recycling of acetylcholine in gray matter), thereby prolonging the action of endogenous acetylcholine.

•Three such inhibitors are currently in clinical use:
- •donepezil (Aricept)
- •rivastigmine (Exelon)
- •galantamine (Razadyne)

•Overall there is no convincing evidence that acetylcholinesterase inhibitors have any clinically meaningful disease modifying effects, and therefore the decision on timing of initiation of therapy should be individualized based on the preferences of the patient and family.

•However, all three acetylcholinesterase inhibitors have been shown to be safe and to maintain their cognitive benefits over multiple years.

•The acetylcholinesterase inhibitors maintain their efficacy in severe dementia

Cognitive symptoms of Alzheimer's disease: clinical management and prevention

BMJ 2019;367:l6217

Symptomatic treatment of Alzheimer´s disease

•The acetylcholinesterase inhibitors are overall relatively well tolerated.

- •Gastrointestinal side effects—including anorexia, nausea, vomiting, and diarrhea —are fairly common, occurring in 5-33% of patients in clinical trials.
- •These side effects may be more common in individuals with lower body weight,
- •Other adverse effects include dizziness/vertigo, fatigue, insomnia, hallucinations, bradycardia, and muscle cramps.

•Direct comparison of donepezil and oral rivastigmine showed no difference in cognition overall.

BMJ 2019;367:l6217

Symptomatic treatment of Alzheimer´s disease

Memantine is a low affinity N-methyl-D-aspartate (NMDA) receptor antagonist;

it has been hypothesized to involve mitigation of glutamate-induced excitotoxicity.

it is available as immediate and extended release formulations

A recent meta-analysis of 29 trials including 7885 patients with AD found with a high degree of certainty that memantine showed a clear but modest benefit on global impression, cognition, and activities of daily living for moderate to severe AD

The meta-analysis also found an effect on behavior with patients randomized to the memantine arm being significantly less likely to develop agitation during the treatment period compared with those randomized to placebo. However, this was only true for those without agitation at baseline

The clinical benefit of memantine is smaller than that of the acetylcholinesterase inhibitors. Effect size of 0.65-0.4 points/ MMSE

The benefit of adding memantine to acetylcholinesterase inhibitor therapy has been studied with mixed results.

BMJ 2019;367:l6217

Psycho-social support

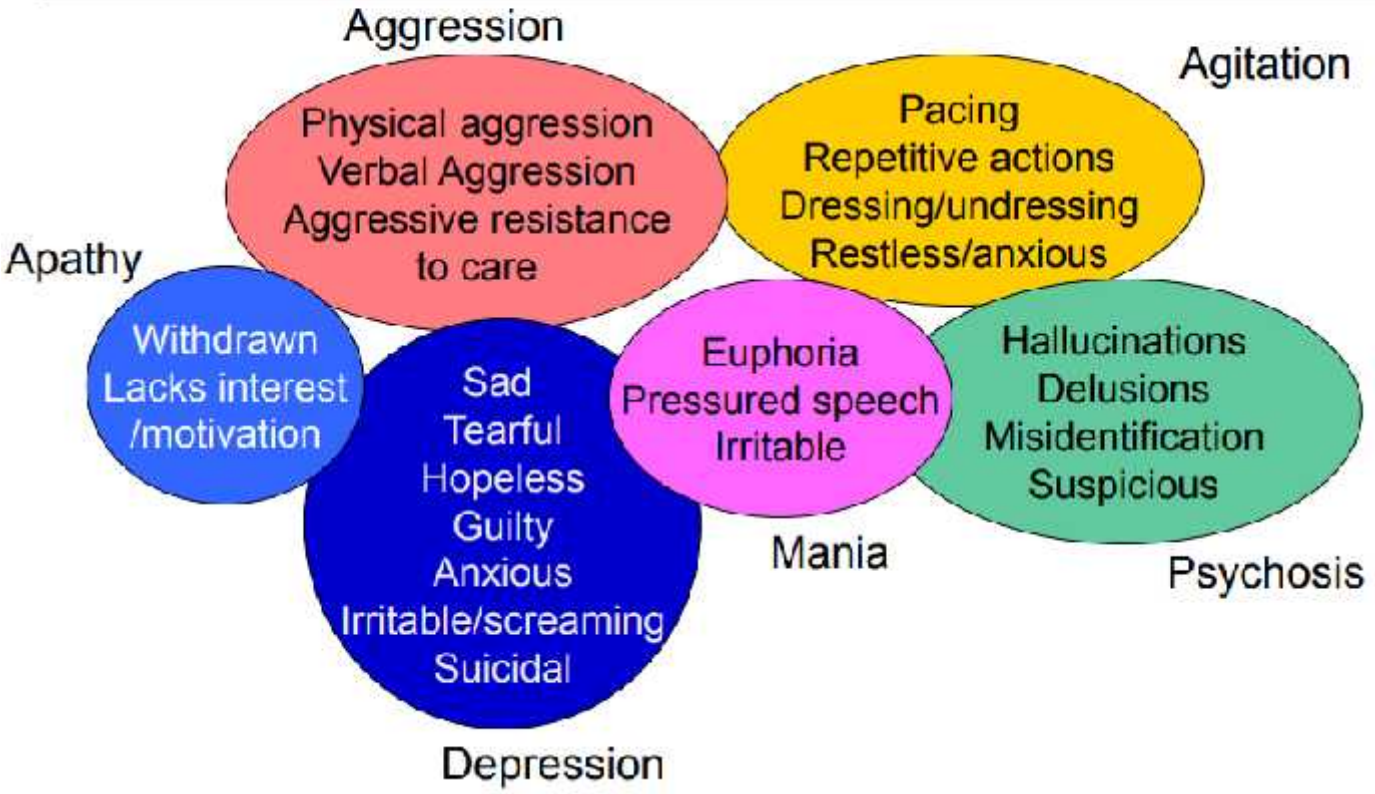
- Psycho- social support is important – several possibilities:
  - Support groups for spouses and children
  - Specialized day care
  - Respite care
  - Nursing Home Care
    - If uncontrolled BPSD
    - When a person has entered well into stage 5 on the Dementia Global Deteriorating Rating Scale

BPSD

Five Domains:

- Cognitive/ perceptual (delusions, hallucinations)
- Motor (e.g. pacing, wandering, repetitive movements, physical aggression)
- Verbal (e.g. yelling, calling out, repetitive speech, verbal aggression)
- Emotional (e.g. Euphoria, depression, apathy, anxiety, irritability)
- Vegetitative (disturbances in sleep and appetite)

BPSD Symptom Clusters



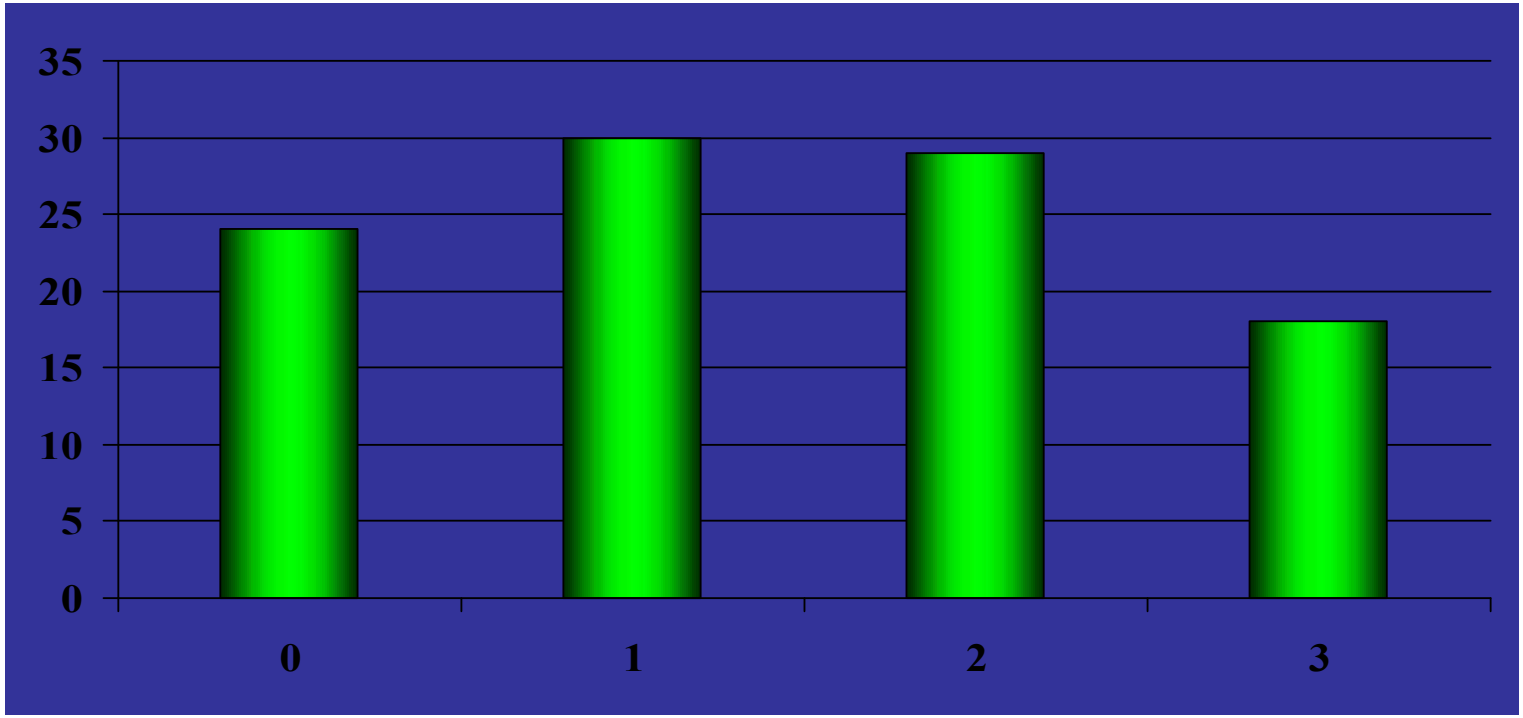
Effects of BPSD

- Residents with BPSD are more likely to[1]:
  - be physically restrained
  - receive antipsychotic medication
  - negatively influence care staff
  - negatively influence other residents
- BPSD increase the cost of caring[2]
- BPSD increase nurse stress, especially aggression[3]
- BPSD exacerbates cognitive and functional deficits[4]
- BPSD increase morbidity and mortality[5]

1 Maslow K 1994
2 O'Brien JA, Shomphe LA,Caro JJ 2000
3 Rodney, 2000
4 J Clin Psychiatry 2004;65:5-10
5 Arch Neurol 2005;62:1601-8

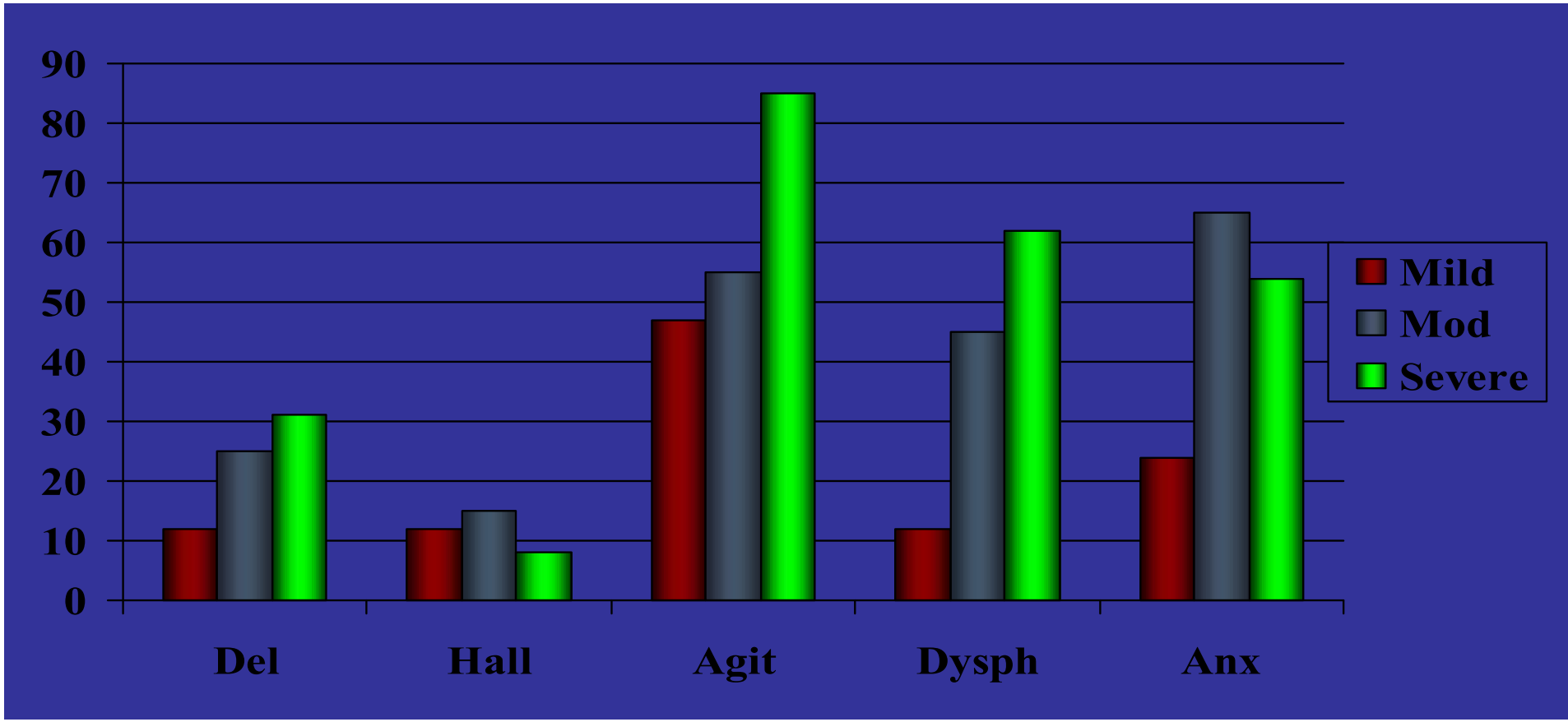
Multiple Behavioral Changes Occur Simultaneously

% with 0,1,2,3 Symptoms (Psychosis, Agitation, Depression)



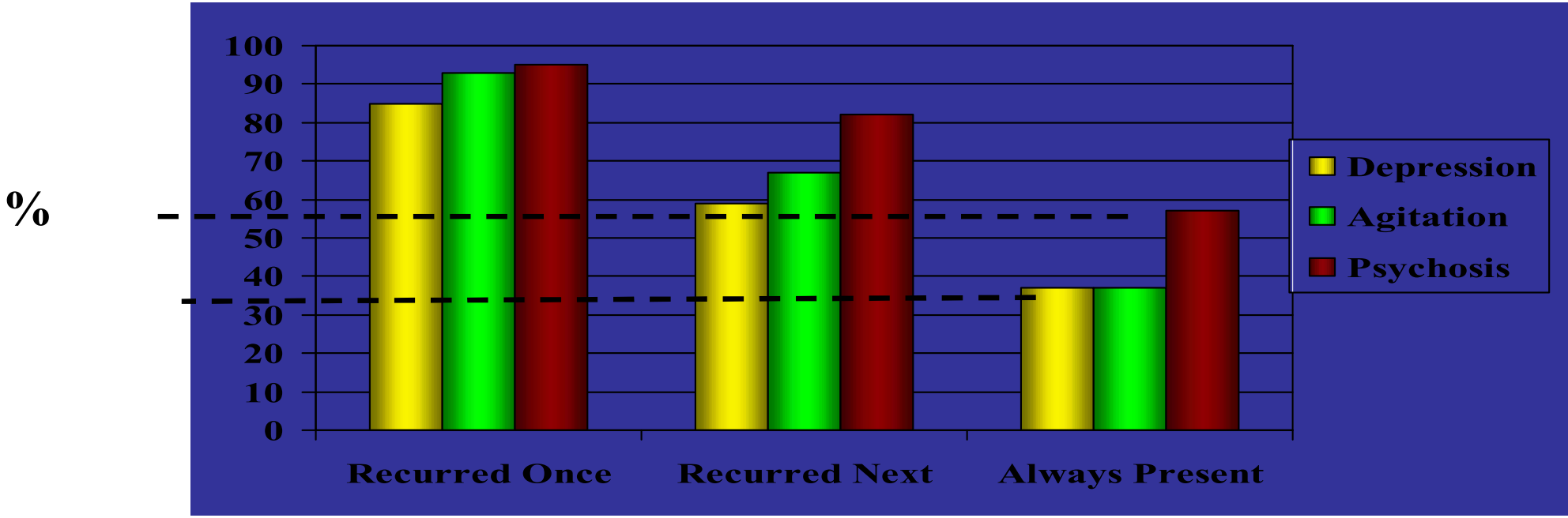
(Levy et al, Am J Psychiatry, 1996)

BPSD in Alzheimer's Disease



Lancet Neurol 2005;4:735-42

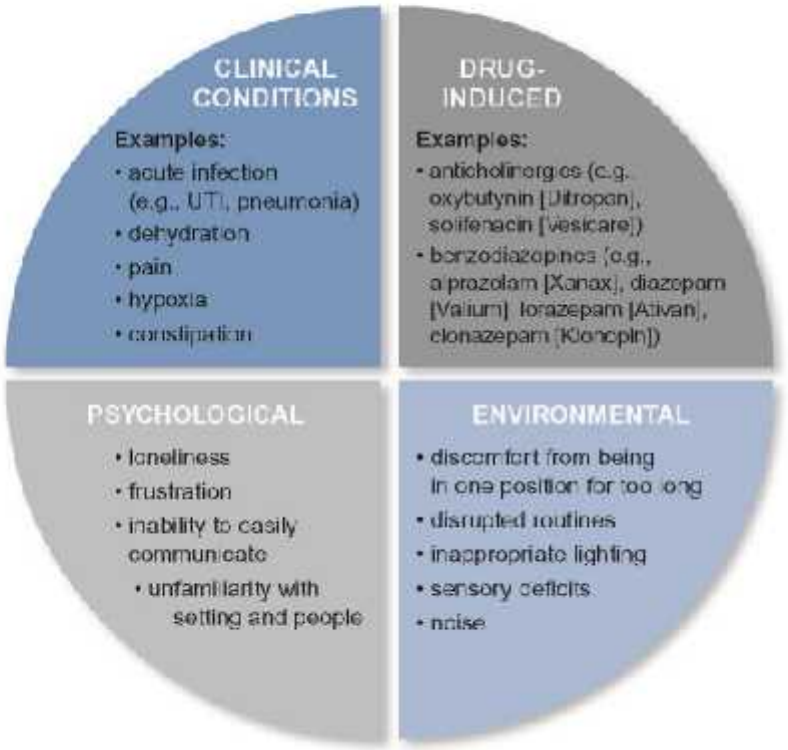
Once Present, BPSD Recur



Patients Re-Examined Five times in One Year

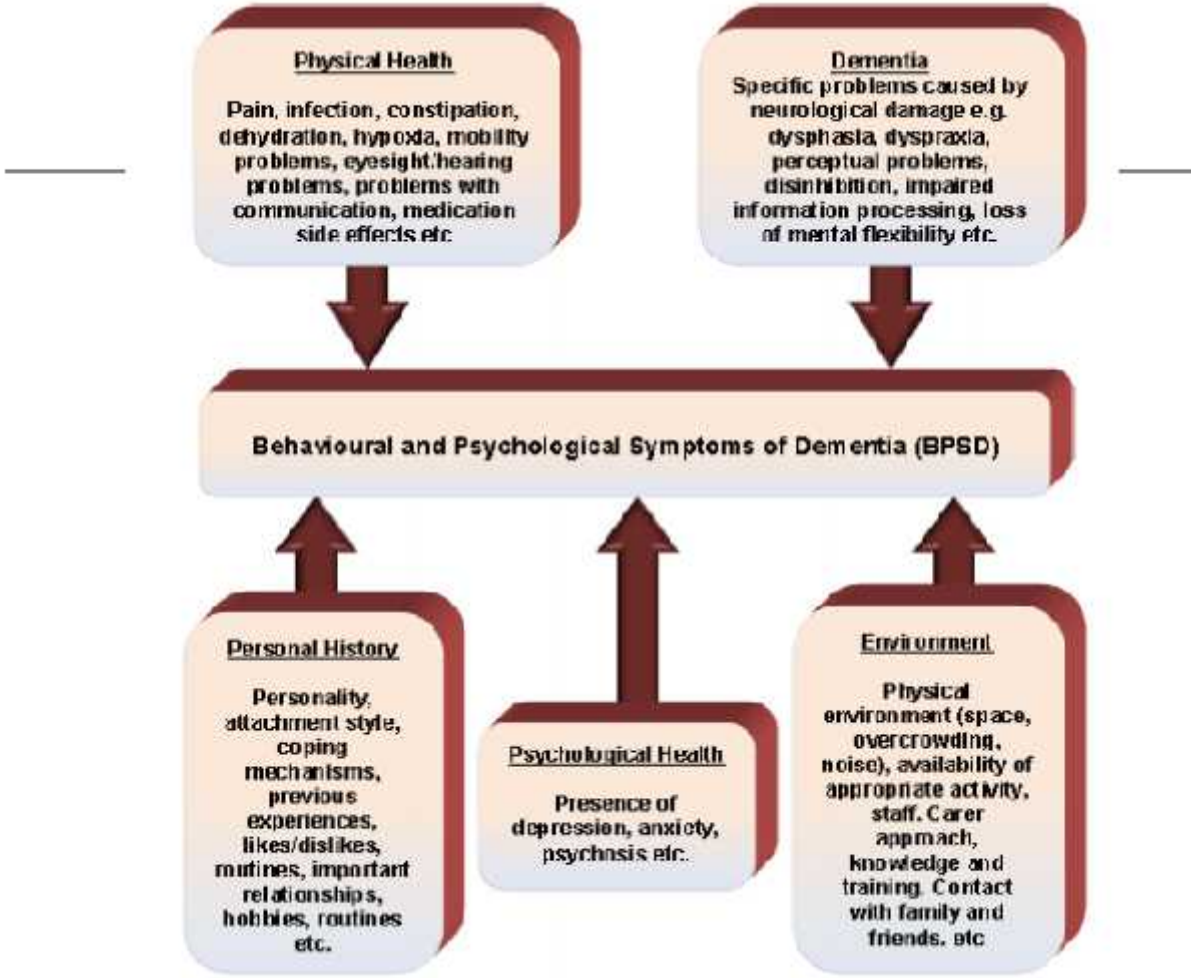
Levy et al. - Am J Psychiatry 1996;153:1438-43

Understanding the Reasons for BPSD



The importance of considering physical (biological) psychological and social factors

BPSD

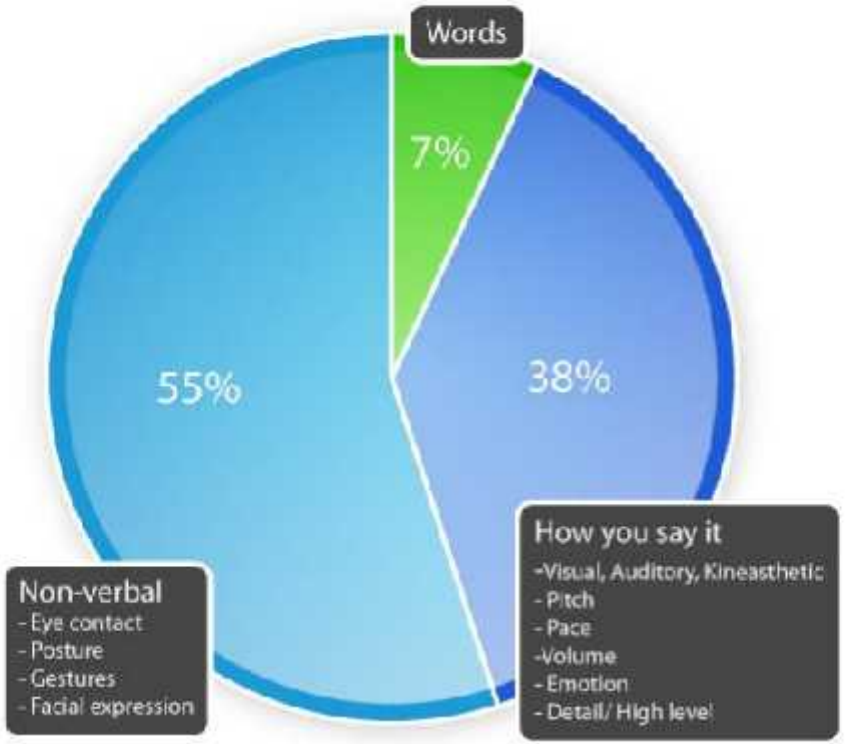

Physical Health
Pain, infection, constipation, dehydration, hypoxia, mobility problems, eyesight/hearing problems, problems with communication, medication side effects etc
Dementia
Specific problems caused by neurological damage e.g. dysphasia, dyspraxia, perceptual problems, disinhibition, impaired information processing, loss of mental flexibility etc.
Behavioural and Psychological Symptoms of Dementia (BPSD)
Personal History
Personality, attachment style, coping mechanisms, previous experiences, likes/dislikes, routines, important relationships, hobbies, routines etc.
Psychological Health
Presence of depression, anxiety, psychosis etc.
Environment
Physical environment (space, overcrowding, noise), availability of appropriate activity, staff. Carer approach, knowledge and training. Contact with family and friends. etc

Types of Non Pharmacological Approaches

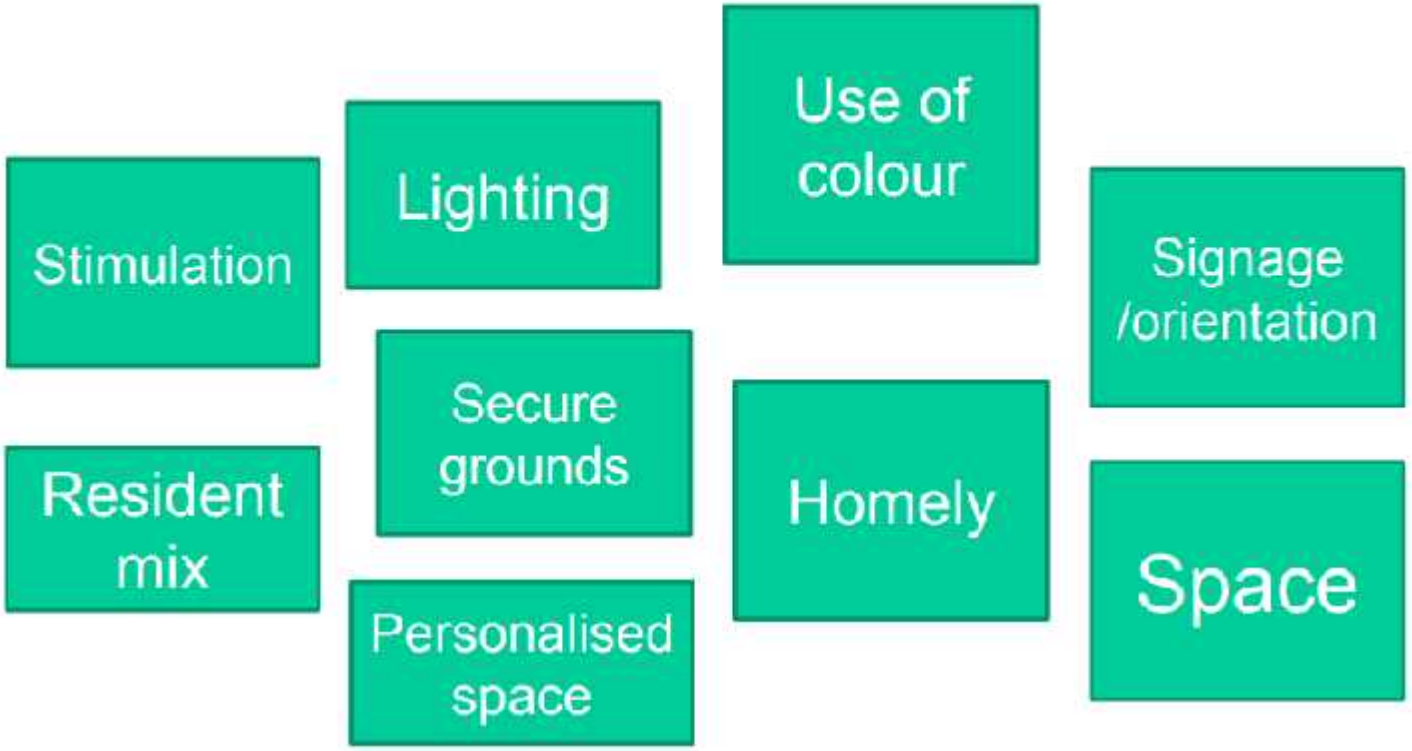
- Standard Preventative/Wellbeing Interventions
  - reality orientation, reminiscence and validation
  - cognitive stimulation,
  - Music, dance, aromatherapy, art
  - Multi-sensory, tool box, doll therapy, pet therapy.
- Social contact/simulated presence
- Staff training/communication and care techniques
- Activity based interventions
- Environmental interventions
- Individualised treatment programmes/Person centred care

We do not only communicate with words:

Communication



Environmental Interventions



The goal of history is to establish:

- Priorities regarding the nature and urgency of intervention
  - Safety of patient and others
  - RO delirium
- Characterize the symptoms
  - What symptom, onset, timing, severity
- Identify potentially reversible exacerbating factors
  - Environmental change
  - Medications review
  - Discomfort (pain, constipation, urinary retention)
- Review psychiatric history and substance use
- Create a baseline for measuring the effectiveness of treatment
  - NPI, BHAVE-AD, CMAI – scales, time consuming
  - Ask caregiver to identify major symptom, quantify, related distress

The goal of physical examination and investigations

• Confirm historical data and identify alternative contributing psychiatric and general medical conditions:

•Is there a painful condition?

•Is this a delirium superimposed on dementia?

•Is there a primary psychiatric disorder co-existent?

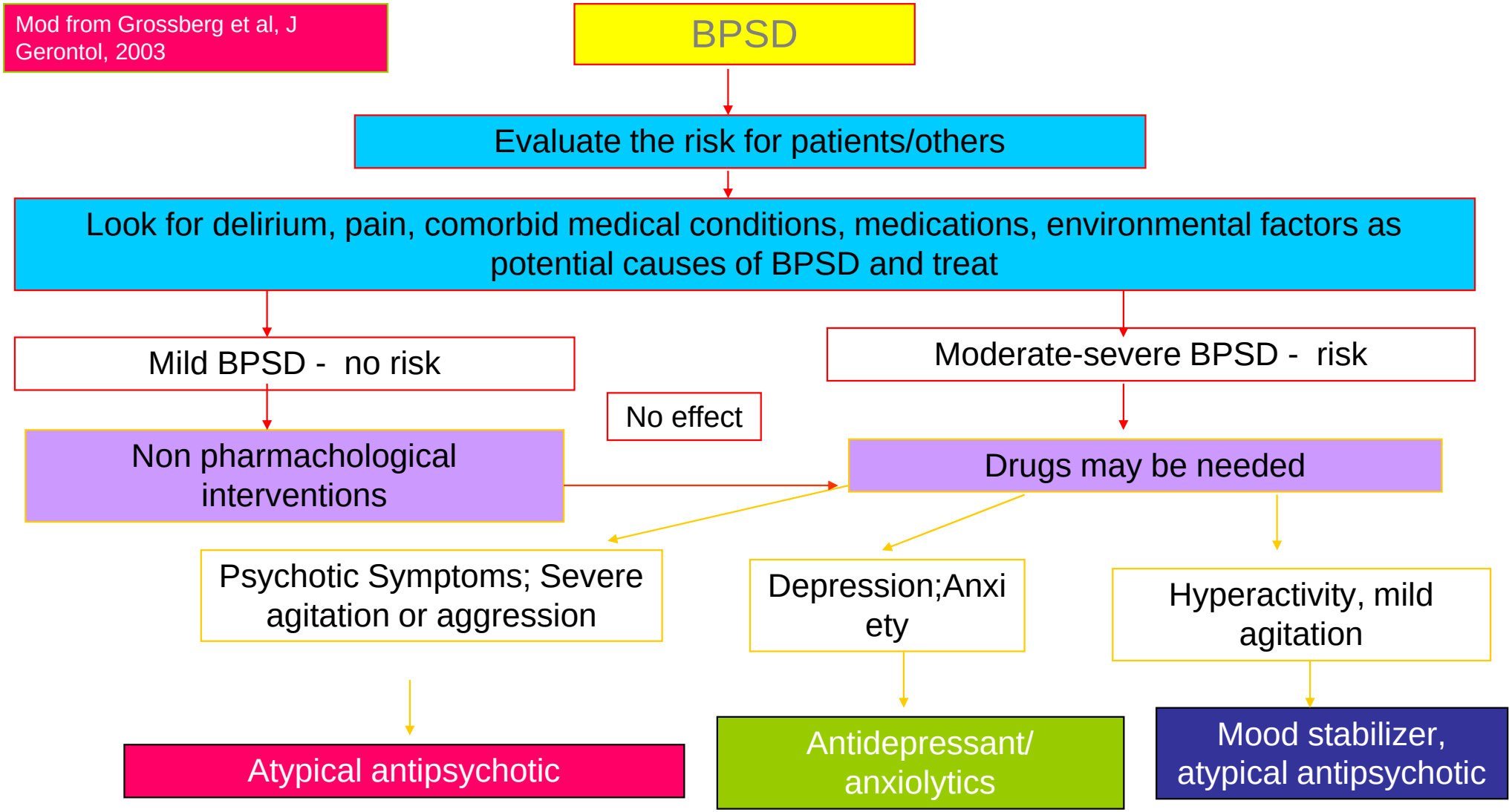
•Could there be a CNS neoplasm masquerading as BPSD?

Management of behavioral problems in Alzheimer's disease.

Abstract

Alzheimer's disease (AD) is a complex progressive brain degenerative disorder that has effects on multiple cerebral systems. In addition to cognitive and functional decline, diverse behavioral changes manifest with increasing severity over time, presenting significant management challenges for caregivers and health care professionals. Almost all patients with AD are affected by neuropsychiatric symptoms at some point during their illness; in some cases, symptoms occur prior to diagnosis of the dementia syndrome. Further, behavioral factors have been identified, which may have their origins in particular neurobiological processes, and respond to particular management strategies. Improved clarification of causes, triggers, and presentation of neuropsychiatric symptoms will guide both research and clinical decision-making. Measurement of neuropsychiatric symptoms in AD is most commonly by means of the Neuropsychiatric Inventory; its utility and future development are discussed, as are the limitations and difficulties encountered when quantifying behavioral responses in clinical trials. Evidence from clinical trials of both non-pharmacological and pharmacological treatments, and from neurobiological studies, provides a range of management options that can be tailored to individual needs. We suggest that **non-pharmacological interventions** (including psychosocial/psychological counseling, interpersonal management and environmental management) **should be attempted first, followed by the least harmful medication for the shortest time possible**. **Pharmacological treatment options**, such as antipsychotics, antidepressants, anticonvulsants, cholinesterase inhibitors and memantine, **need careful consideration of the benefits and limitations of each drug class.**

Gauthier S et. al. Int Psychogeriatr. 2010 May;22(3):346-72. Epub 2010 Jan 25.


Mod from Grossberg et al, J Gerontol, 2003
BPSD
Evaluate the risk for patients/others
Look for delirium, pain, comorbid medical conditions, medications, environmental factors as potential causes of BPSD and treat
Mild BPSD - no risk
Moderate-severe BPSD - risk
No effect
Non pharmachological interventions
Drugs may be needed
Psychotic Symptoms; Severe agitation or aggression
Depression;Anxiety
Hyperactivity, mild agitation
Atypical antipsychotic
Antidepressant/ anxiolytics
Mood stabilizer, atypical antipsychotic

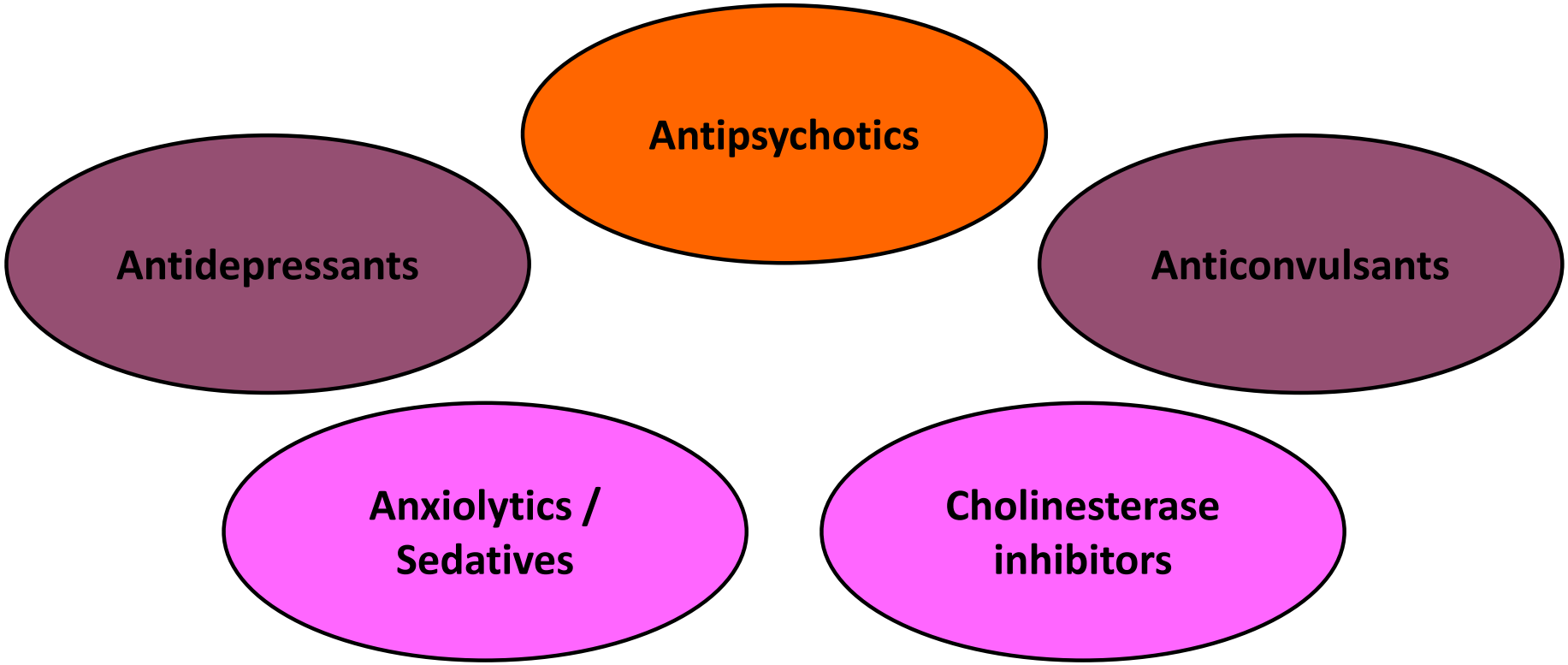
Non-pharmacologic treatment

• May suffice for mild BPSD symptoms but should always accompany pharmacological treatment.

•Caregiver training:

- •Understanding the behavior as a response to discomfort, unmet needs or attempt to communicate
- •Create soothing environment with optimal levels of stimulation and respond to the patient in a nonthreatening calm way
- •Aromatherapy, massage, musical therapy, reminiscence therapy
- •Give the patients simple tasks to perform: fold laundry or give a busy quilts (with interesting objects: zippers, Velcro, beads, ties etc)
- •Weighted blanket

Treatment Options



Pharmacologic intervention for agitation and aggression

- Wandering and repetitive vocalizations rarely respond to pharmacotherapy

- Empiric treatment of pain:
  - paracetamol 1g x 3
  - buprenorphine transdermal (up to 10 mcg hourly
  - possibly pregabalin (up to 300 mg daily)

- Selective serotonin reuptake inhibitors (SSRI)
  - citalopram, 10 mg to 20 mg QD
  - sertraline, 25 mg to 100 mg QD
  - recall nausea, hyponatremia and prolonge QT interval

Pharmacologic intervention for agitation and aggression

- Antipsychotics, effect size 0.15-0.30
  - risperidone, 0,25 mg x 2 to 1 mg x 2 QD
  - olanzapine, 2,5 mg to 10 mg QD
  - quetiapine, 12,5 mg to 100 mg x 2 QD
  - aripiprazole, 2 mg to 15 mg QD

- For people with Lewy Body Dementia or Dementia with Parkinsons disease
  - clozapine, 6,25 mg to 25 mg per day
  - quetiapine, low dose

- Not much help from:
  - cholinesterase inhibitors, memantine, valproate or benzodiazepines

Atypical antipsychotics: advantages in the elderly

- Lower incidence of EPS and less TD
- Lower incidence of central and peripheral anticholinergic adverse effect
- Favorable safety profile
- Lower potential for drug interactions
- Lower risk of liver dysfunction
- Less or no induction of prolactin
- Better compliance, less relapse

Risk associated with antipsyhotic medications

- Tardive dyskinesia
- Ventricular Arrhytmias
- Pneumonias
- DVT
- Femur Fractures
- Stroke
- Death

Pharmacologic intervention for Depression and Apathy

For depression:

- Selective serotonin reuptake inhibitors (SSRI)
  - citalopram, 10 mg to 20 mg QD
  - sertraline, 25 mg to 50 mg QD
  - recall nausea, hyponatremia and prolonge QT interval
  - Consider methylphenidate (average dose 16 mg QD), start with 2,5 mg x QD
- For apathy
  - Consider methylphenidate (average dose 16 mg QD), start with 2,5 mg x QD
    modest effect