Rational Drug Use for Neuropsychiatric Symptoms of Dementia

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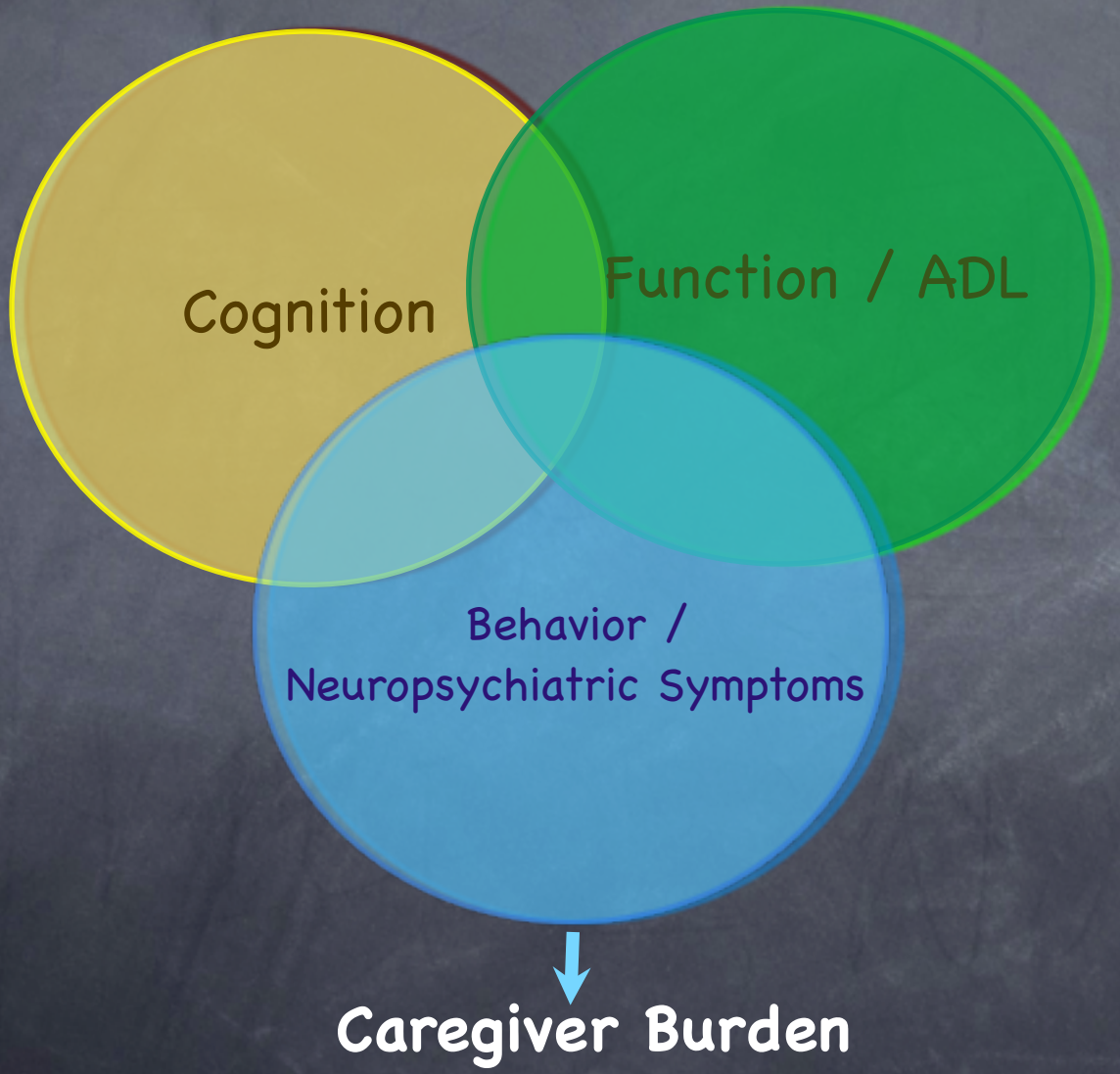
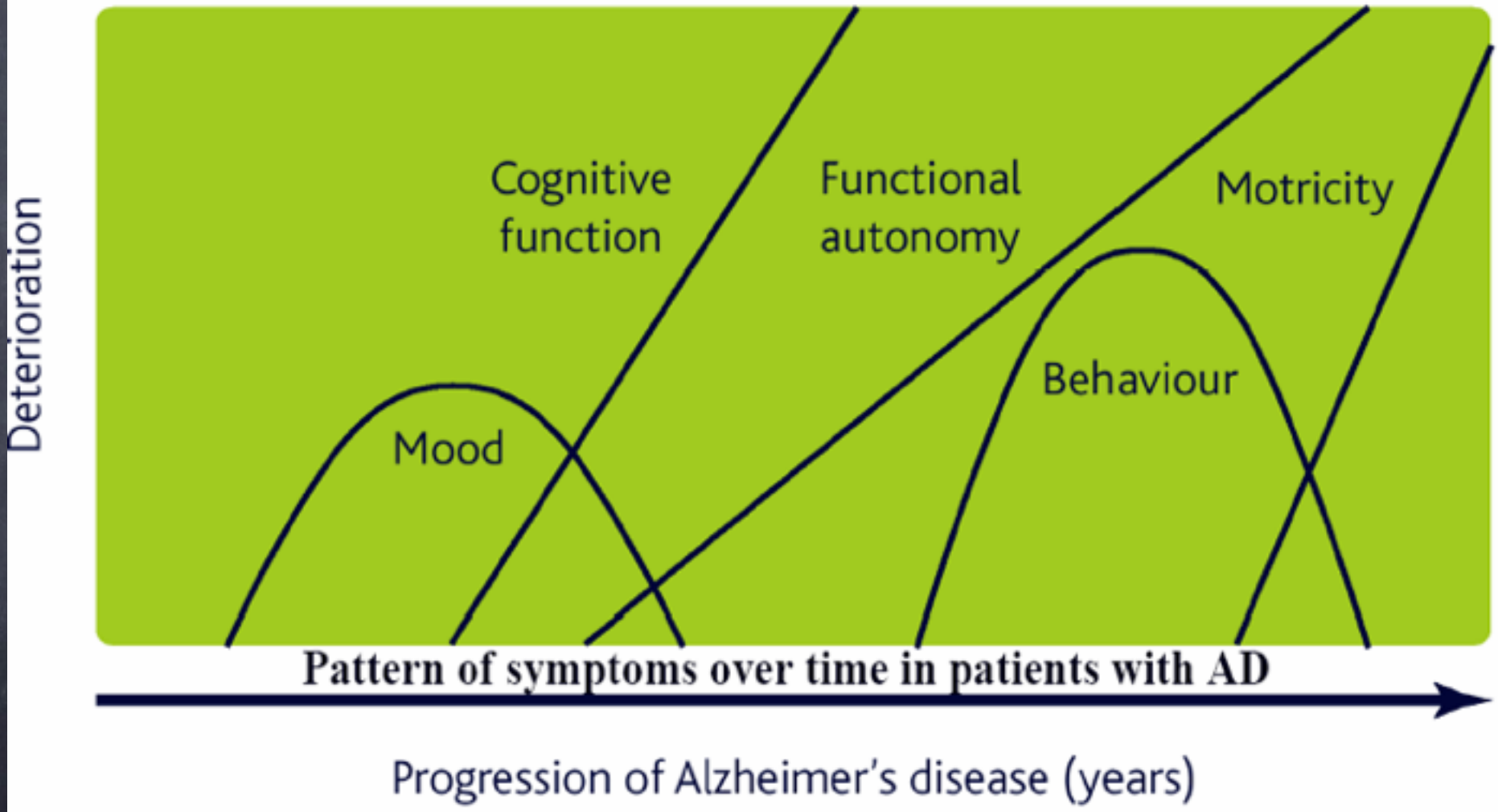
Aspects of AD Affecting Care Requirement



Neuropsychiatric Symptoms of Dementia

- Neuropsychiatric&behavioral disturbances
- 50 -90 % at any point in disease process
- May be the presenting symptoms
- Number& severity increase with worsening of cognitive Decline
- Certain behaviors frequently found at different stage

Progression of Symptoms in AD



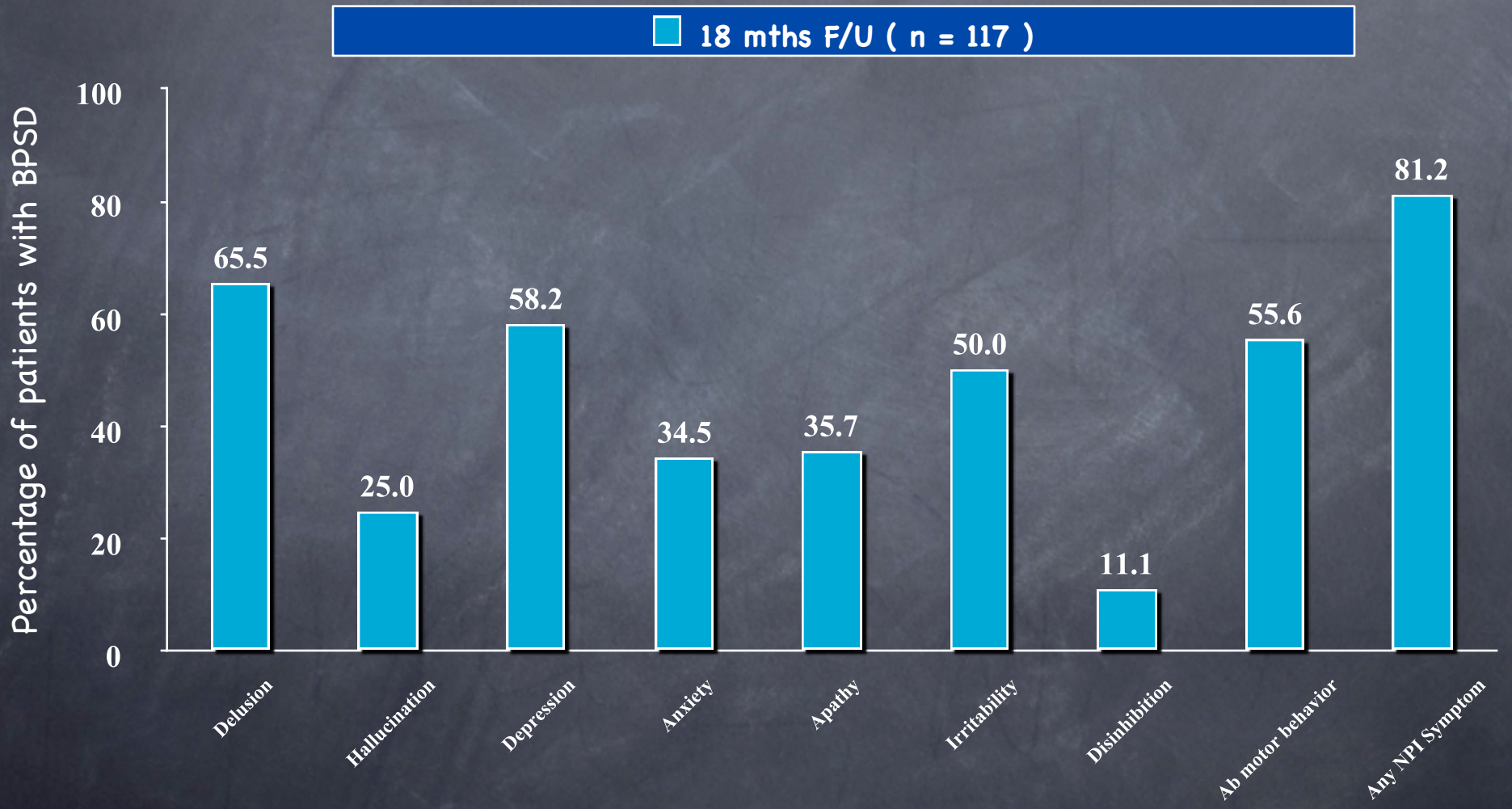
Lovestone & Gauthier. Martin Dunitz Ltd, London, 2001

Neuropsychiatric Inventory (NPI)

	MCI[1]	Mild AD[2]	MSAD[3]	Severe AD[2]
Apathy	37%	47%	67%	92%
Agitation	23%	47%	45%	85%
Aberrant motor	12%	12%	53%	84%
Depression	42%	12%	52%	62%
Anxiety	30%	24%	49%	54%
Irritability	39%	35%	35%	54%
Delusions	7%	12%	37%	31%
Disinhibition	16%	35%	22%	31%
Hallucinations	4%	12%	24%	8%
Euphoria	3%	18%	8%	8%

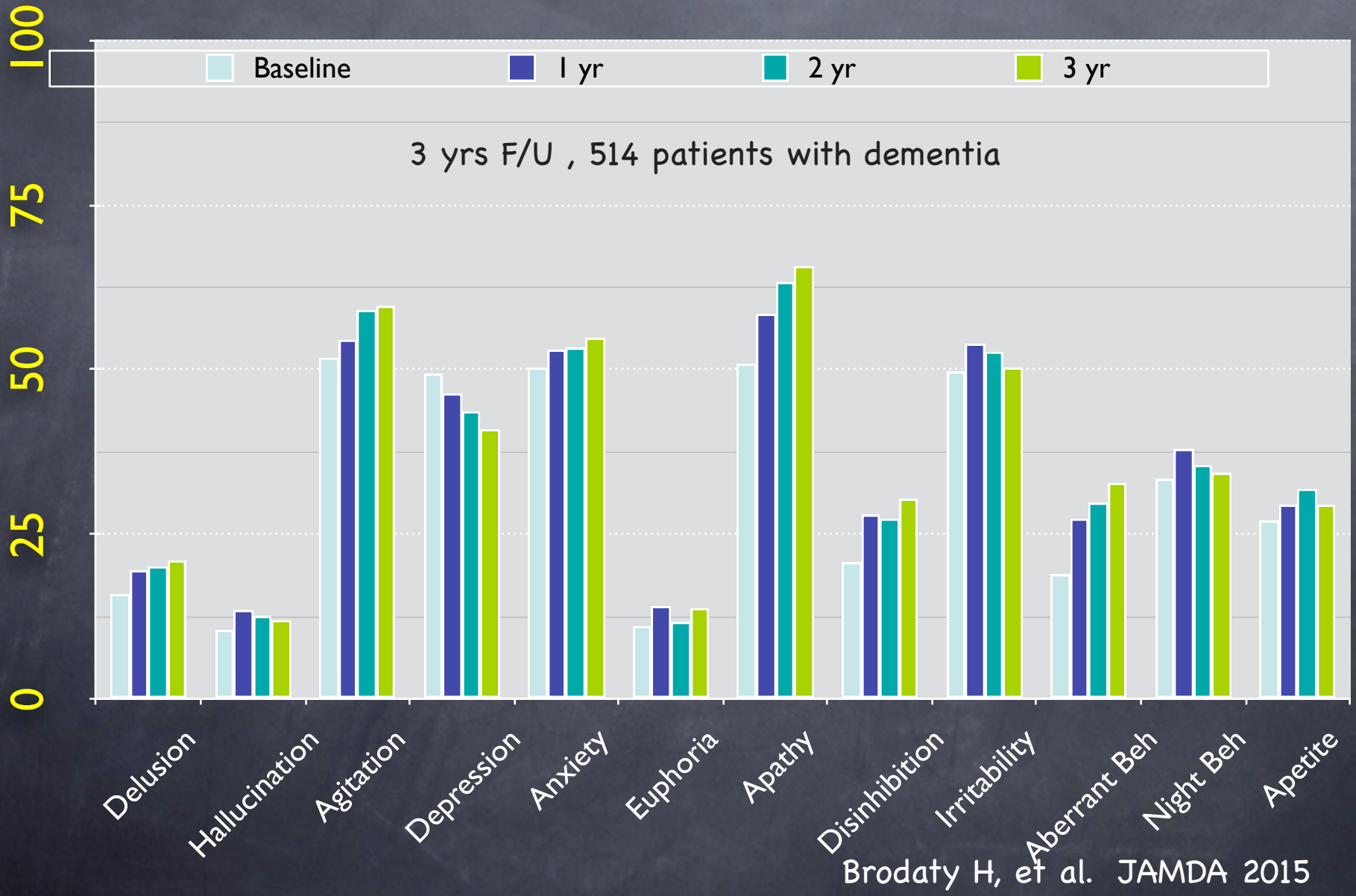
[1]Peters et al *Neurology* S 2002 [2]Mega et al *Neurology* 1996 [3]Gauthier et al *Int Psychogeriatr* 2002

Persistence of NP of Dementia : The Cache County Study



Steinberg M et al . Int J Geriatric Psychiatry. 2004 19-26

3 Years - Persistent NP Symptoms



Brodaty H, et al. JAMDA 2015

Objectives of NPs management

- Maintain and maximize ADL
- Promote autonomy and dignity
- Improve quality of life of patients and caregiver
- Prevent stress on caregiver and relief burden

General Principles For Treatment of NPs

- Careful assessment for medical/physical cause
- Correction - any physical , psychological environmental triggers
- Need drug treatment ?
- Which category of medication ?
- What are side effects, drug interaction ?
- Pharmacological treatment : start low , go slow short-term use

Non-pharmacological Management

- **Behavioral intervention :Antecedent (A) → Behavior (B) → Consequences**
- **Environmental & physical Interventions**
- **Sensory&nutritional consideration**
- **Recreational /Adjunctive/ Social Therapies & Psychological Interventions**
- **& caregiver intervention**

Pharmacological treatment

- Antipsychotics : psychosis , delirium , agitation

  Conventional : ~~haloperidol, phenothiazines~~

  Atypical : risperidone, olanzapine, quetiapine, ~~clozapine~~, aripiprazole

- Antidepressants : depression, agitation , disinhibition
- Benzodiazepines : anxiety , insomnia
- Anticonvulsants : agitation/ aggression
- ChEIs : BPSD ?
- Memantine : BPSD ?

Summary of controlled trials in dementia atypical antipsychotics

Antipsychotic	Study	n	Duration	Results
Risperidone	Katz *et al.*	625	12 weeks	Improved symptoms
	De Deyn *et al.*	344	13 weeks	Improved symptoms
	Brodaty *et al.*	345	12 weeks	Improved aggression, agitation, psychosis > controls
Olanzapine	Satterlee *et al.*	238	8 weeks	No difference
	Street *et al.*	206	6 weeks	Improved symptoms
Quetiapine (VS haloperidol)	Tariot *et al.*	284	10 weeks	Improved symptoms
				no difference with haloperidol
Aripiprazole	De Deyn et al	208	10 weeks	No difference for NPI subscale
				Improve BPRS subscale

Katz IR et al. J Clin Psychiatry 1999; 60: 107–15

De Deyn et al. Neurology 1999; 53: 946–55

Brodaty et al J Clin Psychiatry 2003;64 : 134 - 143

Satterlee WG et al. Psychopharmacol Bull 1995; 31: 534

Street et al. Arch Gen Psychiatry 2000; 57: 968–76

Tariot et al. Am J Geriatr Psychiatry 2006;14:767-776

De Deyn et al. J Clin Psychopharmacology 2006; 463-67

Mortality Risk and NNH of US VA Registries

sCrude death Rates During 180 day Observation Period Starting Therapy with a New Medication

Medication	% user death	% Nonuser death	Risk Diff. % (95% CI)	NNH (95 % CI)
Haloperidol	20.7	8.4	3.8 (1.0-6.6)	26 (15-99)
Olanzapine	13.9	9.8	2.5 (0.3 - 4.7)	40 (21 - 312)
Quetiapine	11.8	8.2	2.0 (0.7 - 3.3)	50 (30 - 150)
Risperidone	13.9	8.5	3.7 (2.2-5.3)	27 (19 - 46)
Valproic acid	12.2	7.2	4.1 (-1 - 9.2)	NA
Antidepressant	8.3	8.0	0.6 (0.3 - 0.9)	166 (107 - 362)

Maust D T et al. JAMA Psychiatry 2017

Atypical Antipsychotics and mortality risk in dementia

- The FDA conducted a meta-analysis of 17 placebo-controlled studies in 5,106 patients with dementia-related psychosis with 4 atypical antipsychotic drugs (aripiprazole, olanzapine, quetiapine, and risperidone)
- In this meta-analysis, they found:
  - An approximate 1.6–1.7 fold increase in overall mortality with drug treatment versus placebo
  - In a typical 10-week trial, the rate of death with drug treatment was 4.5% versus 2.6% with placebo treatment
  - Causes of death were varied, but the majority appeared to be cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature

FDA talk paper, April 11, 2005.

Real world prescription of antipsychotics in dementia

- Longitudinal study in UK * , primary care database :

  Conventional ATP 8.9 % in 2001 —> 1.4 % in 2014

  Atypical ATP 6.6 % in 2001 —> 6.9 % in 2014

- French National AD Database ** : 2010 - 2014

  6.5 % in 2010 —> 7.7 % in 2014 ;

  Associated factor : male , more severe dementia, long-term care

- Dutch population-based study ***: 2008 - 2013

  13 % in 2008 —> 11 % in 2009 ; haldol& risperidone

* Stocks S J et al Drug Safe 2017, ** Titratene K. et al. Alzheimer's Research& Therapy 2017
*** Sultana J et al. Epidemic Psychiat Science 2016

Rate of Inappropiate antipsychotics Use in Canada

Kirknam J et al. Canadian J of Psychiatry 2017

A consensus guideline for antipsychotic drug use for dementia in care homes. Bridging the gap between scientific evidence and clinical practice

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International Psychogeriatrics (2015), 27:11, 1849–1859

Practice Guideline for ATP use in Dementia

1. General prescription stipulations.
   - Antipsychotics should never be used as a first-line approach. Non-pharmacological interventions should be tried first. The benefits should be expected to outweigh the adverse events.
   - APs should only be prescribed in
     (a) symptoms caused by underlying psychotic disorder that causes severe distress to patient/risk to others,
     (b) in non-psychotic patients in an extreme and acute situation with risk i.e. severe and harmful physical aggression to oneself or other, severe physical exhaustion, and severe eating/drinking disorders with a risk of malnourishment or dehydration.
   - The behavior is not caused by another somatic disorder (such as pain, infection, hunger, constipation) or psychiatric disorder (anxiety/depression),
   - only antipsychotics with proven evidence should be prescribed,
   - start low, go slow.
2. Assessment prior to prescription.
   - Investigation of underlying syndromes, neurological, psychiatric, environmental (interaction) factors.
   - Assessment of medical state and risk (cardiovascular and subtype of dementia (Lewy Body/Parkinson) and symptoms (motor symptoms, cardiac arrhythmias, orthostatic hypotension, urine retention).
   - ECG should be carried out in patients with history of cardiovascular diseases, cardiac arrhythmia, and combination of medication that prolong QT-interval.
3. Care and treatment plan.
   - Use APs always in combination with non-pharmacological and preventive measure aimed at increasing carers competence.
   - Care and treatment plan should draw expertise form multidisciplinary team/with regular consultation.
   - Family caregiver should be informed and consulted throughout treatment and discontinuation.
   - Improvement and lack of improvement should be included as a clinical criterion for modifying care and treatment plan.

International Psychogeriatrics (2015), 27:11, 1849–1859

Practice Guideline for ATP use in Dementia

4. Discontinuation.
   - Discontinuation should be a standard principle as part of a withdrawal plan.
   - If APs are prescribed for sedative purposes, drug should be withdrawn when situation has calmed down.
   - Discontinuation through tapering rather than immediate discontinuation unless Malign Neuroleptic Syndrome, cardiovascular complication, infections, severe side effect at low dose.
5. Long-term treatment (> 12 weeks).
   - Long-term antipsychotic treatment is only acceptable in patients with
     - long history or high severity of psychotics/concurrent schizophrenia,
     - at least two unsuccessful discontinuation attempts + psychosocial interventions has been shown not to be effective + alternative medication is not available/has been shown ineffective/expected to cause severe adverse events.
   - Restarting can be acceptable – under supervision of a specialist – in extreme situation in case of
     - recurrence of severe symptoms after withdrawal resulting in risk/distress that had previously improved with AP treatment,
     - recurrence of severe symptoms after withdrawal if withdrawal was before completing a 12-week course,
     - a distinct separate new episode.

International Psychogeriatrics (2015), 27:11, 1849–1859

Adverse Effects of ATP

Adverse effect	*Aripiprazole (Abilify)*	*Haloperidol*	*Olanzapine (Zyprexa)*	*Quetiapine (Seroquel)*	*Risperidone (Risperdal)*	*Ziprasidone (Geodon)*
Anticholinergic effects	0	+	+	+	0	0
Dyslipidemia	0	++	+++	++	+	0
Extrapyramidal symptoms	+	++	+	0	++	+
Hyperprolactinemia	0	+	+	0	+++	+
Neuroleptic malignant syndrome	+	+	+	+	+	+
Postural hypotension	+	++	+	++	++	+
Prolonged QT interval	+	++	+	+	+	++
Sedation	+	++	++	++	+	+
Seizures	+	0	+	+	+	+
Sexual dysfunction	+	++	+	+	++	+
Type 2 diabetes mellitus	+	+	++	+	+	+
Weight gain	0	+	+++	++	++	0

Reese TR et al. AM Fam Physician 2016

Monitoring Recommendation for Long-term Antipsychotic Use

Adverse effect	*Monitoring*
Cataracts	Slit lamp examination at treatment initiation and every six months if patient is receiving quetiapine (Seroquel)
Diabetes mellitus or metabolic syndrome	Lipid panel; check fasting plasma glucose level at treatment initiation, at 12 weeks, then annually if receiving atypical antipsychotics; measure waist circumference and BMI at initiation and when dosage changes, then at every visit for six months; initiate quarterly nutrition counseling if BMI increases by more than 1 kg per m^2; check blood pressure at initiation and when dosage changes, then every three months for first year
Extrapyramidal symptoms	Assess for symptoms, including tardive dyskinesia and restlessness, at treatment initiation and when dosage changes, then weekly until dose is stable for two weeks, then yearly if receiving an atypical antipsychotic
Prolonged QT interval	Baseline electrocardiography if patient has history of heart disease, syncope, sudden death in a family member younger than 40 years, congenitally prolonged QT interval, or polypharmacy

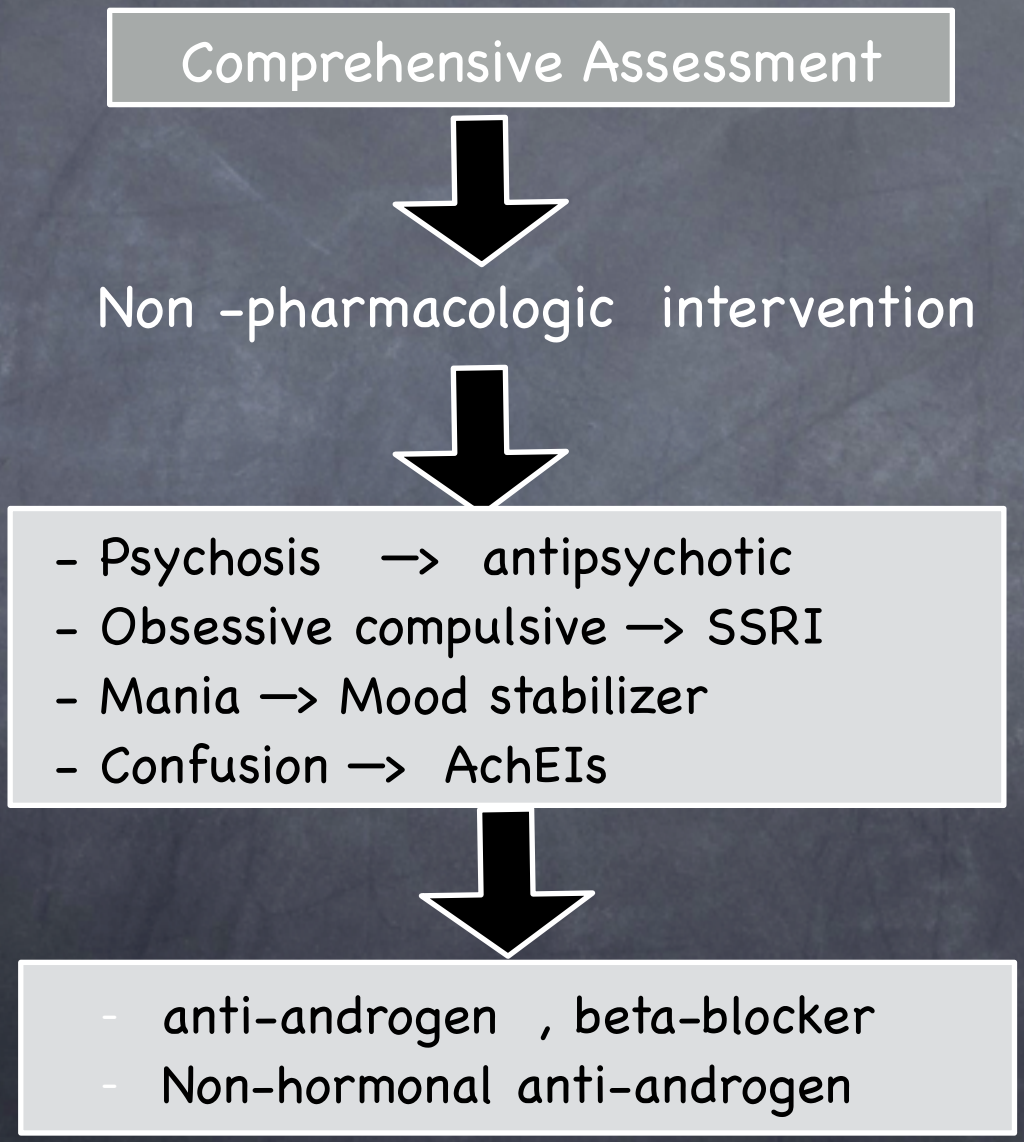
Reese TR et al. AM Fam Physician 2016

Alternative Medication for treatment of Agitation

Medications	Applications/comments
Cholinesterase inhibitors	
Galantamine (8–24 mg/day)	Evaluated in multiple randomized controlled trials
Donepezil (5–10 mg/day)	Can improve agitation, mood, anxiety, apathy and psychotic symptoms
Rivastigmine (3–9 mg/day)	Especially effective in patients with Lewy body dementia
	Gastrointestinal adverse effects can limit tolerability
NMDA-glutamate receptor antagonist	
Memantine (10–20 mg/day)	Evaluated in multiple randomized controlled trials
	Small-to-moderate effect size
	Can stabilize cognition, function and agitation
	Possible antipsychotic-sparing effect
	May worsen agitation or psychotic symptoms in some patients
Antidepressants	
Citalopram (10–40 mg/day)	Evaluated in multiple randomized controlled trials
Sertraline (25–200 mg/day)	SSRIs are the most effective and best tolerated antidepressants
Trazodone (12.5–200 mg/day)	Target agitation resulting from co-morbid depressive disorders
	May reduce agitation via enhancement of frontal serotonin neurotransmission
	Monitor for SIADH-related hyponatraemia and movement disorders
Antiepileptics	Fair evidence base
Valproic acid (250–1500 mg/day)	Valproic acid may have a narrow therapeutic dosage window for the treatment of agitation (750–1000 mg/day)
Carbamazepine (100–600 mg/day)	Carbamazepine use may be complicated by numerous adverse effects and hepatic auto-induction
Gabapentin (200–2700 mg/day)	Gabapentin dosage must be reduced in patients with renal impairment

Drugs and aging 2008 . P 381-398

Inappropriate Sexual Behaviors



INTERNATIONAL GUIDELINE

Recommendations (grading)[b]	Included guidelines[a]					Sufficient agreement?
	DCCG (2005)	NICE (2006)	SIGN (2006)	CCC (2007)	MOH (M) (2009)	
Antipsychotics	•	•	•	•	•	
For (severe) psychosis and/or aggression/agitation	+(1)	+	-	+(A1)	+(A)	Yes
Use of atypical antipsychotics (risperidone, olanzapine)	+(1)	-	+(gpp)	+(A1)	+(A)	Yes
Use of conventional antipsychotics (haloperidol)	+(1)	-	+(A)	-	-	Yes
Choice based on individual risk/benefit analysis	-	+	-	-	+(C)	Yes
Start at low dose and titrate upwards	-	+	-	+(B3)	+(C)	Yes
Time-limited use and regular reassessment (every 3 months or according to clinical need)	+(4)	+	-	+(B3)	+(C)	Yes
Withdrawal after behavioural stability	-	-	-	+(A1)	+(C)	Yes
Benzodiazepines	•	•	/	•	/	
For acute agitation or agitation based on anxiety (short-term use)	+(3,4)	+	-	+(B1)	-	Yes
Antidepressants	•		•	•	•	
For comorbid depression use of selective serotonine reuptake inhibitors	+(2)	+(moderate)	+(D)	+(B3)	+(A)	Yes
Acetylcholinesterase inhibitors (A-Chl)	•	•	•	•	•	
Use of A-Chl	?	+(moderate)	+(B)	+(B3)	+(B)	No
Memantine	/	•	•	•	•	
Use of memantine	-	?	?	+(B3)	B	No

Azermai M et al Aging Research Review 2012

Thank You For Your Attention