Psychiatric Management in Patients with Dementia

Dr. Katherine Murray

Objectives

- Providers will be able to recognize emerging psychiatric symptoms in patients with dementia and complete a thorough workup for possible underlying causes
- Providers will be knowledgeable about treatment options for psychiatric symptoms in patients will dementia
- Providers will understand the risks associated with psychiatric treatment in geriatric patients, particularly those suffering from dementia

Disclosures

- I have no conflict of interest to disclose for this presentation
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  - Drs. Tampi, Joshi, and Srinivasan and their presentation on Management of Behavioral and Psychological Symptoms of Dementia
  - Dr. Tampi and his presentation on Psychotic Disorders in the elderly
  - Dr. Devanand and his presentation on Neuropsychiatric Symptoms and their Treatment in Alzheimer's Dementia
  - Dr. Small and his presentation on Lifestyle Interventions for Prevention and Treatment of Dementia

Prevalence of Behavioral and Psychological Symptoms of Dementia (BPSD)

- Community
  - 65% have at least 1 disruptive behavior
  - 40% have at least 3 disruptive behaviors
- Nursing Homes
  - 90% have at least 1 disruptive behavior
  - 45% have at least 4 disruptive behaviors
- Behaviors are often chronic with different symptoms emerging as the illness progresses
- Symptoms often fluctuate
- Psychomotor agitation is most common

COMMON BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD)

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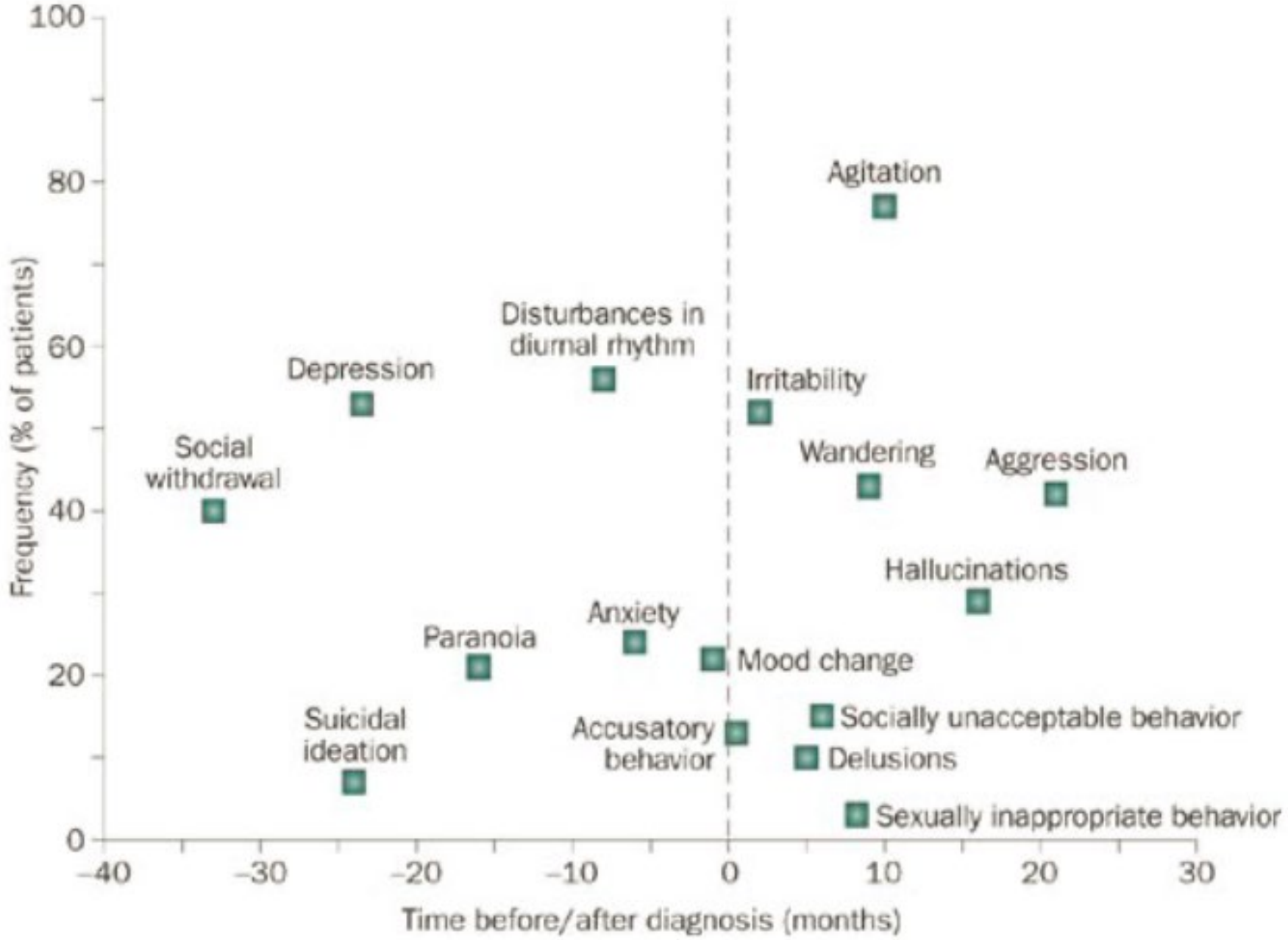
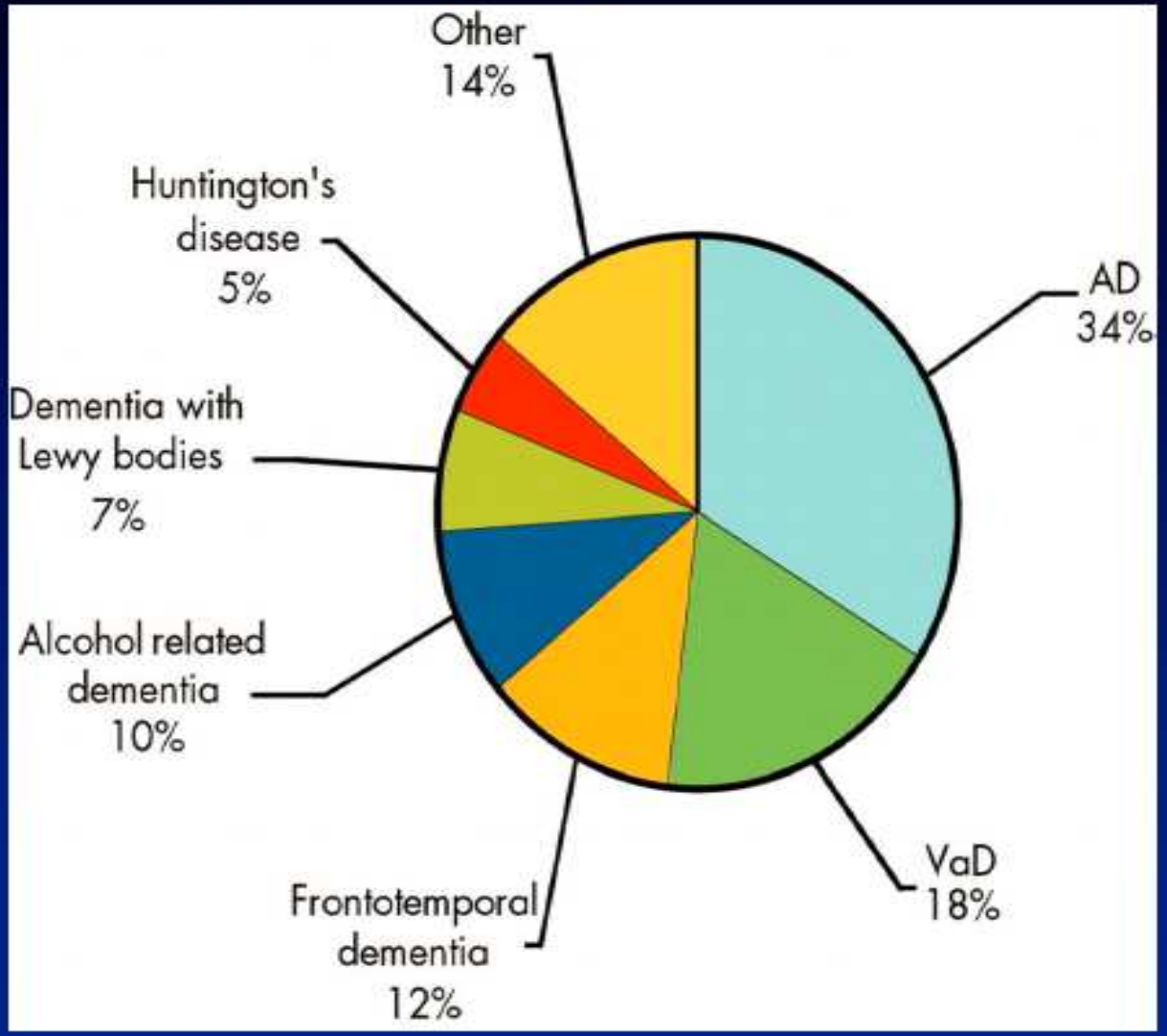
Type of behaviors	Prevalence
Anxiety	21% to 60%
Apathy	48% to 92%
Delusions	16% to 70%
Depression	30% to 50%
Disinhibition/Impulsivity	30% to 35%
Hallucinations	4% to 76%
Inappropriate sexual behaviors	7% to 25%
Mood lability	30% to 40%
Sleep disturbance	20% to 25%
Stereotyped behaviors	12% to 84%
Weight loss	15% to 20%

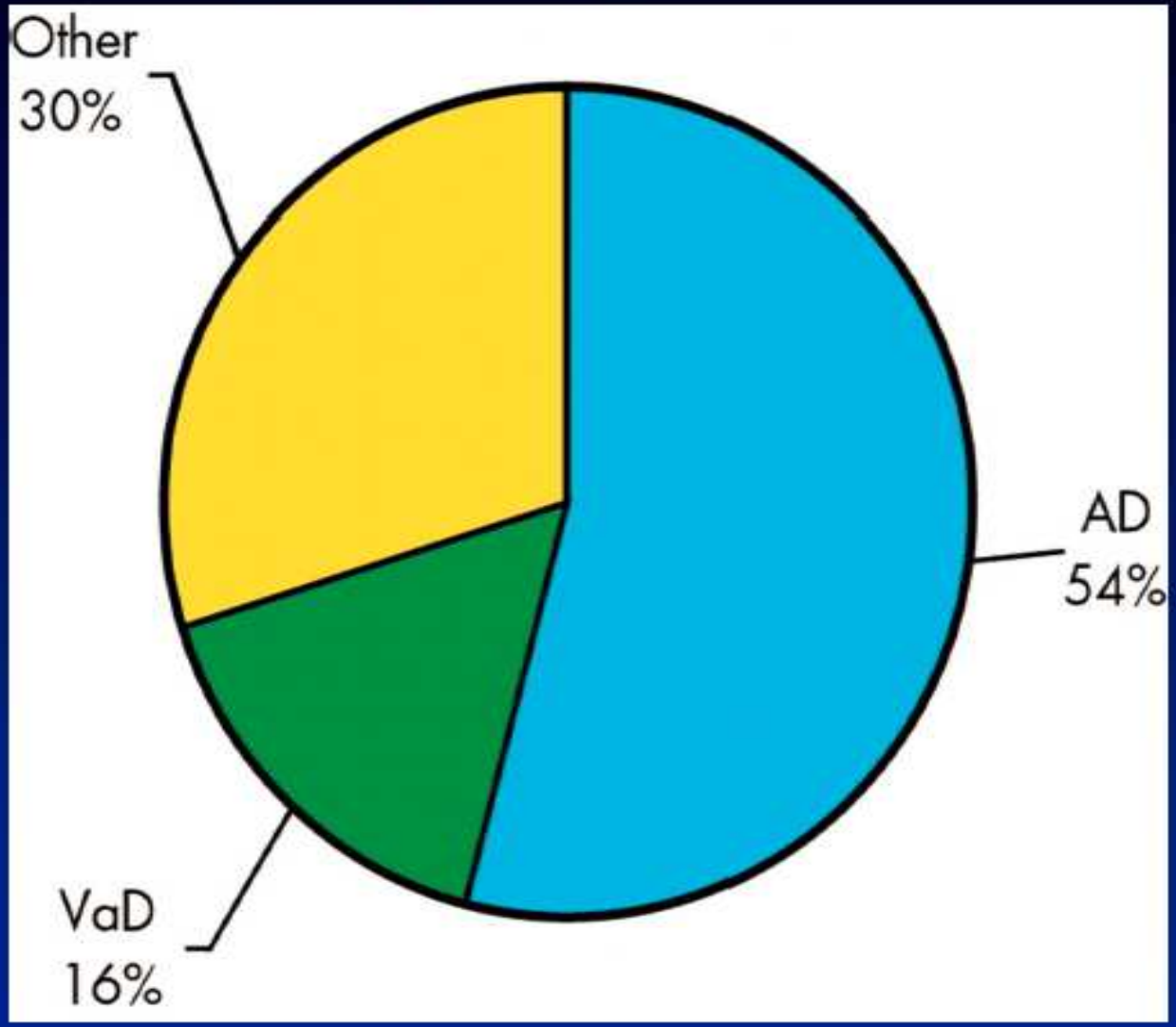
Tampi et al, Curr Psychiatry Rep, 2022


100
80
60
40
20
0
Frequency (% of patients)
Agitation
Disturbances in diurnal rhythm
Depression
Irritability
Social withdrawal
Wandering
Aggression
Hallucinations
Anxiety
Paranoia
Mood change
Socially unacceptable behavior
Suicidal ideation
Accusatory behavior
Delusions
Sexually inappropriate behavior
−40
−30
−20
−10
0
10
20
30
Time before/after diagnosis (months)

Causes of dementia with early onset (≤65 years)



Causes of dementia with late onset (>65 years)



van der Flier WM, Scheltens P. Epidemiology and risk factors of dementia. J Neurol Neurosurg Psychiatry. 2005 Dec;76 Suppl 5(Suppl 5):v2-7.

Clinical differentiation between the various major neurocognitive disorders

Features	Alzheimer's Disease (AD)	Vascular Disease (VD)	Frontotemporal Lobar Degeneration (FTLD)	Lewy Body Disease (LBD)
Symptom onset	Insidious onset	Variable Stepwise progression	Pre-senile onset	Insidious onset
Cognitive features	Memory decline Executive dysfunction	Executive dysfunction	Executive dysfunction	Memory decline Visuospatial deficits Executive dysfunction
Motors symptoms	Rare Apraxia in severe stages	Variable, depends on location of lesions	Parkinsonian-symptoms in some cases	Parkinsonian-symptoms within one year of cognitive symptoms
Progression	8-10 years	3-5 years	6-8 years	6-8 years

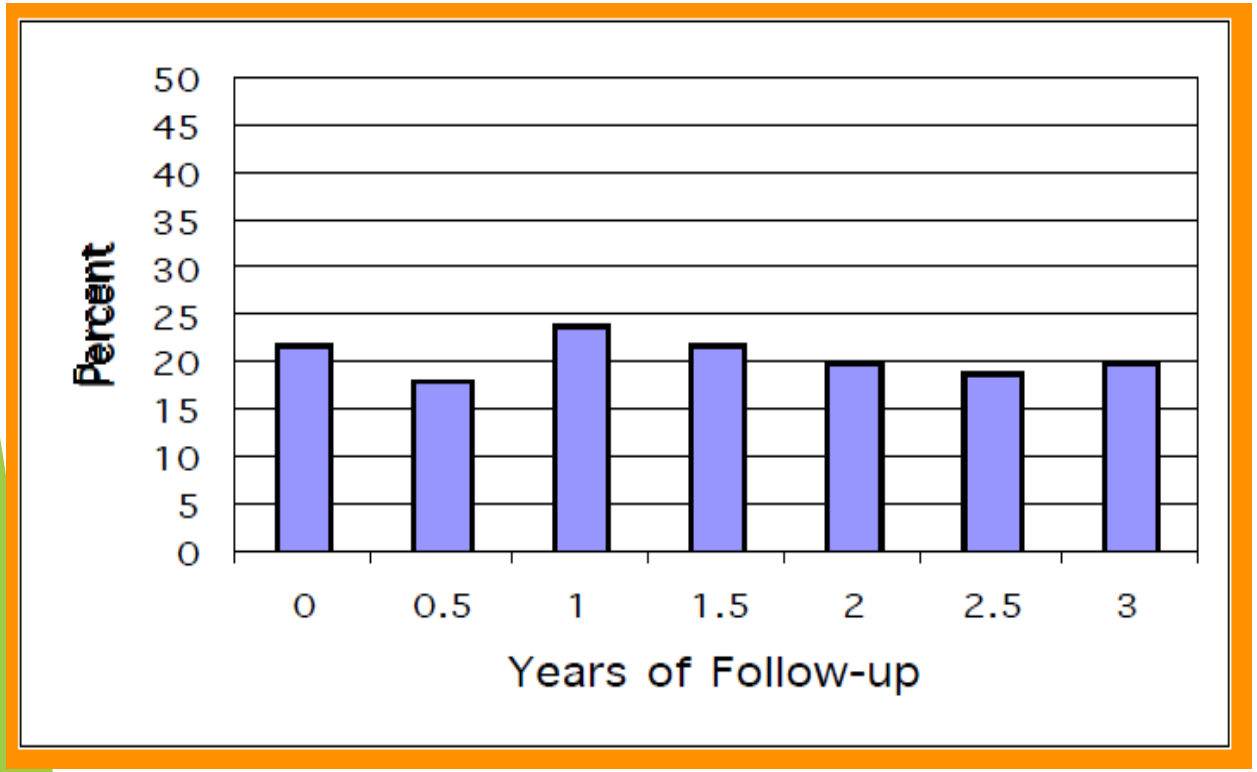
Tampi RR, Tampi DJ. Cognitive Disorders. The Major Neurocognitive Disorders. In: Black DW, editor. Scientific American Psychiatry [online]. Hamilton ON: Decker Intellectual Properties; July 2017. DOI: 10.2310/7800.13047.

Common Psychiatric Symptoms Associated with Dementia Subtypes

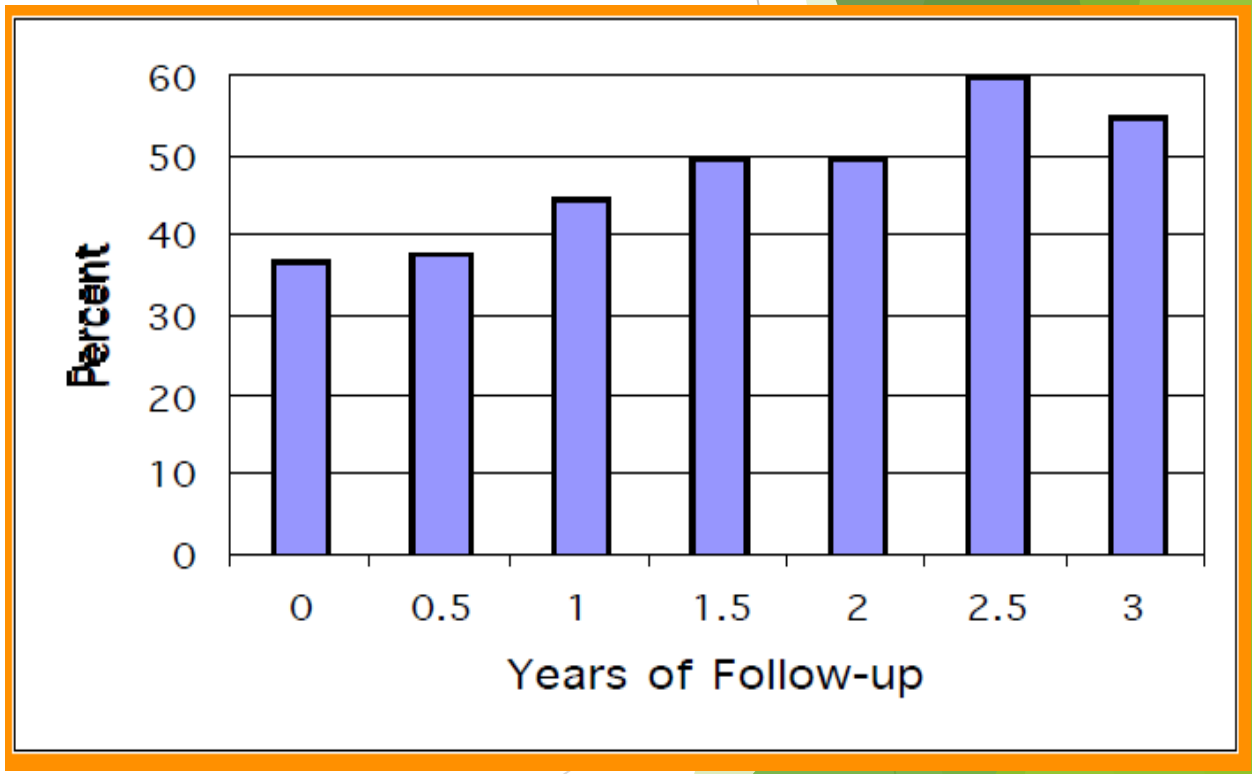
- Alzheimer's
  - Depression, anxiety, insomnia, agitation, delusions, hallucinations, aggression, misidentification
  - Delusions are typically persecutory, paranoid
- Frontotemporal
  - Changes in behavior and personality, for example increasingly inappropriate social behavior, loss of empathy, loss of interpersonal skills, impulsivity
  - Memory may stay relatively intact
- Vascular
  - Depression, anxiety, apathy, agitation, psychosis
  - Reduced speed of thinking and problem-solving
- Lewy Body
  - Recurrent complex visual hallucinations, typically well-formed and detailed
  - REM sleep behavior disorder can often precede onset of dementia by years
  - Increased sensitivity to neuroleptics

Prevalence of Symptoms in Alzheimer's Dementia (AD)

Depression



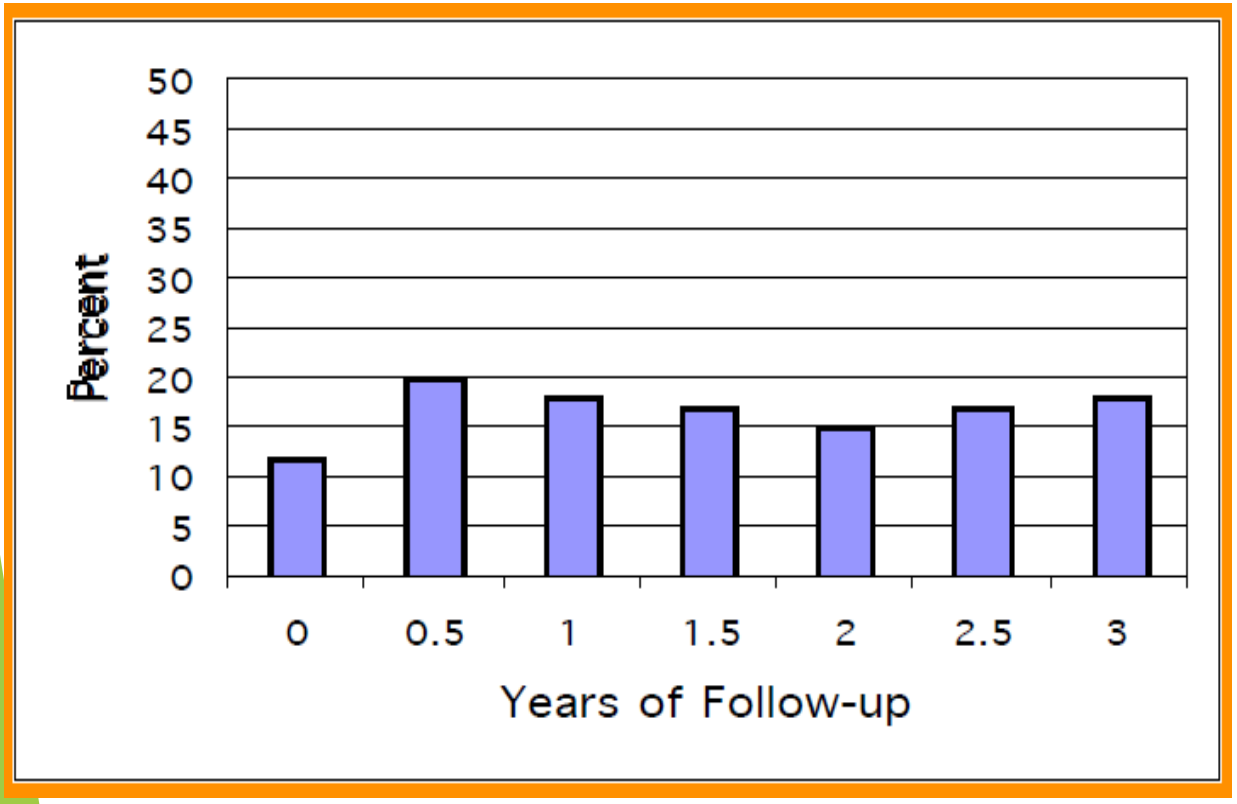
Agitation or Wandering



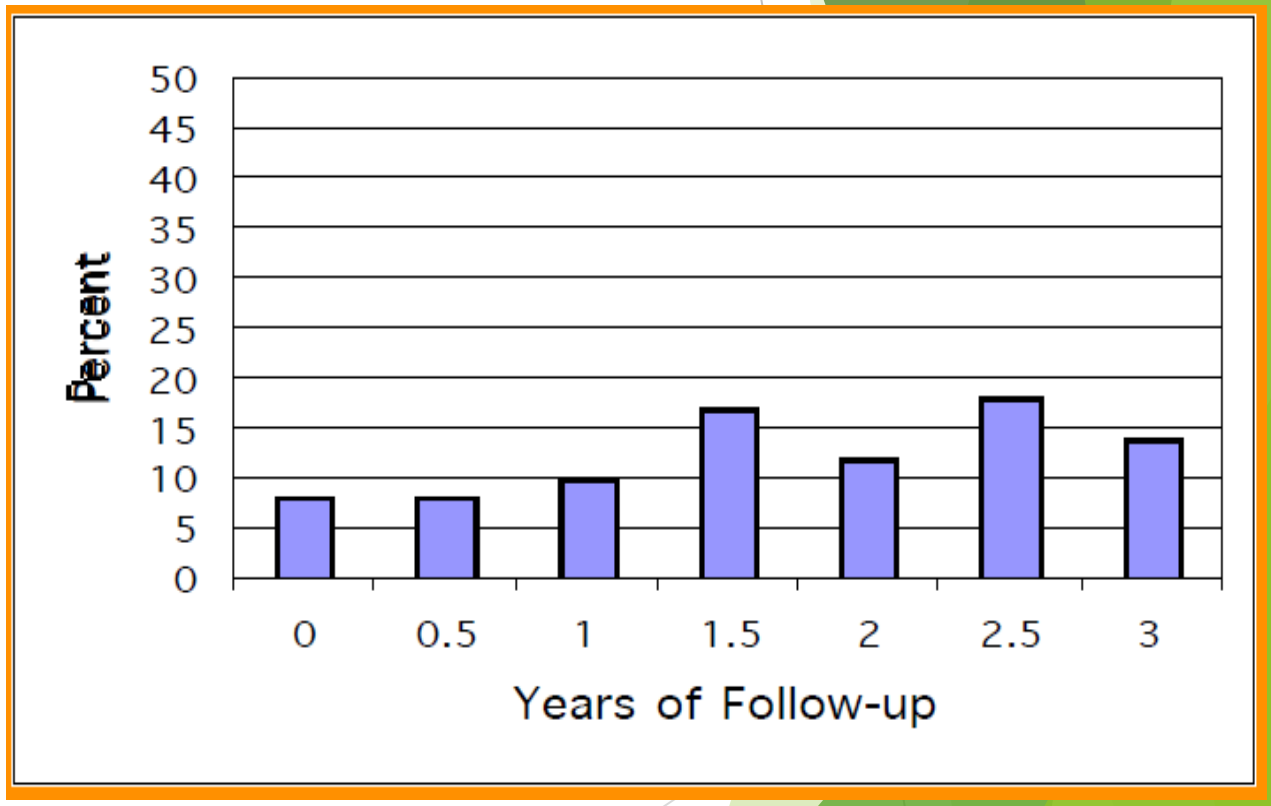
Devanand DP et al. *Arch Neurol* 1992; 49:371-376

Devanand DP et al. *Arch Gen Psychiatry* 1997; 54:257-263

Paranoid Delusions



Hallucinations



Psychopathology in AD

- Most patients with AD develop psychiatric symptoms
- Agitation and psychosis often co-occur and often lead to hospitalization
- Agitation is common, persistent, and increases with disease severity
- Aggression is uncommon in mild stages, but increases with disease severity
- Depressed mood, paranoid delusions, and hallucinations do not change appreciably during mild to moderate stages of disease
- Depressed mood with vegetative signs (changes to sleep, appetite) is uncommon and rarely persists
- Findings have been replicated in community and clinical samples

Devanand DP et al. *Arch Gen Psychiatry* 1997; 54:257-263
Lyketsos CG et al. *Am J Psychiatry* 2000; 157:708-714
Paulsen JS et al. *Neurology* 2000; 54:1965-71

Table 3.

Differences between delirium, AD, LBD, and depression.[9-11,37]

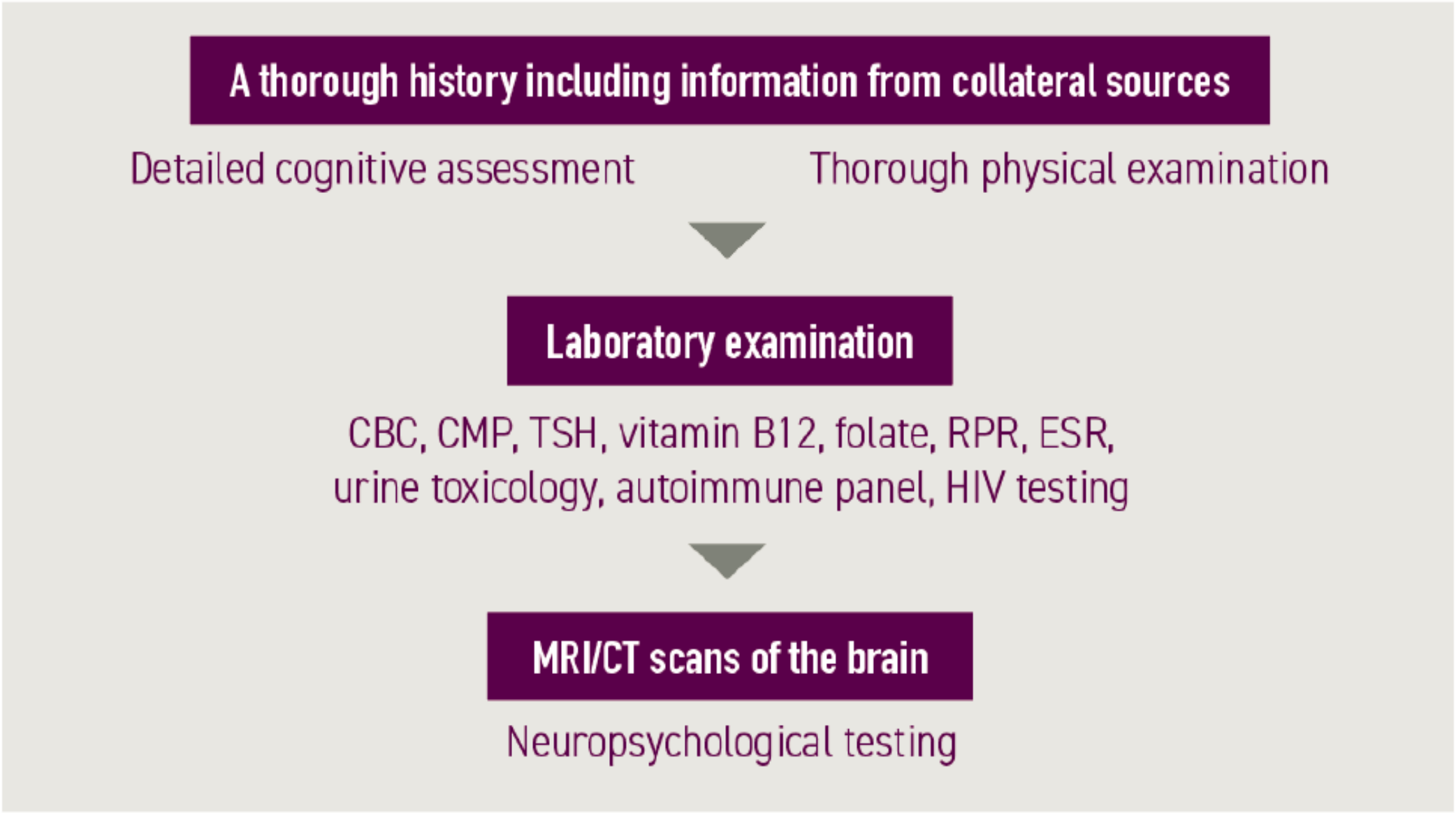
Characteristics	Delirium	AD	LBD	Depression
Presenting symptoms	Unfamiliarity with the environment with short term memory loss; "confusion"	Short term memory loss	Motor symptoms may appear before cognitive impairment; fluctuating cognition, visual hallucinations, and REM-sleep behavior disorder are part of core clinical features	Subjective complaints of poor memory and concentration
Onset	Sudden	Insidious	Insidious	Recent
Alertness	Fluctuating	Normal except in late phases	Fluctuating	Preserved
Duration	Hours to weeks	Months to years	Months to years	Variable
Orientation	Disorientation with onset	Disorientation occurs late in course	Fluctuating	Intact
Hallucinations	From onset	May occur late in course	From onset; visual hallucinations well-formed	Could occur in depression with psychotic features
Cognitive functioning	Fluctuating with alertness	Progressive deterioration	Progressive deterioration	Initially intact with efforts to perform cognitive tasks. May deteriorate without treatment progression
Mood	Fluctuate	Labile	Labile	Usually sad
Sundowning	Present	Present	Present	Absent, mood improve as day progress
Course	Usually reversible with treatment	Irreversible with progressive deterioration	Irreversible with progressive deterioration	Completely reversible

AD, Alzheimer's disease, LBD, Lewy Body dementia; REM, rapid eye movement.

Diagnostic Evaluation

- History from patient
- Collateral information from family, caregivers, etc
- History of substance use (alcohol, drugs, supplements, etc)
- Medications, both prescription and OTC
- Family history of psychiatric illness, dementia
- Psychosocial assessment (developmental history, education, trauma, etc)
- Physical and neurological exam
- Full lab workup including UDS
- Neuroimaging, EEG
- Neuropsychological testing

Figure. Workup for Psychotic Disorders in Late Life[5-7]



Tampi. 2021

Differential diagnoses in case of dementia-related agitation and other conditions.

Neurological	• Stroke • CNS tumors • Intracranial hemorrhage • Meningitis • Encephalitis
Psychiatric	• Bipolar disorder • Schizophrenia • Delusions
Metabolic	• Electrolyte abnormalities • Hyperglycemia • Hypoglycemia
Toxicological	• Anticholinergic agents • Serotonergic agonists • Benzodiazepines • Steroids • Neuroleptics • Alcohol abuse • Alcohol withdrawal • Carbon monoxide toxicity
Infections	• Systemic infections • Fever-Related delirium • Sepsis

Front Neurol. 2021; 12: 644317.
Published online 2021 Apr 16. doi: 10.3389/fneur.2021.644317

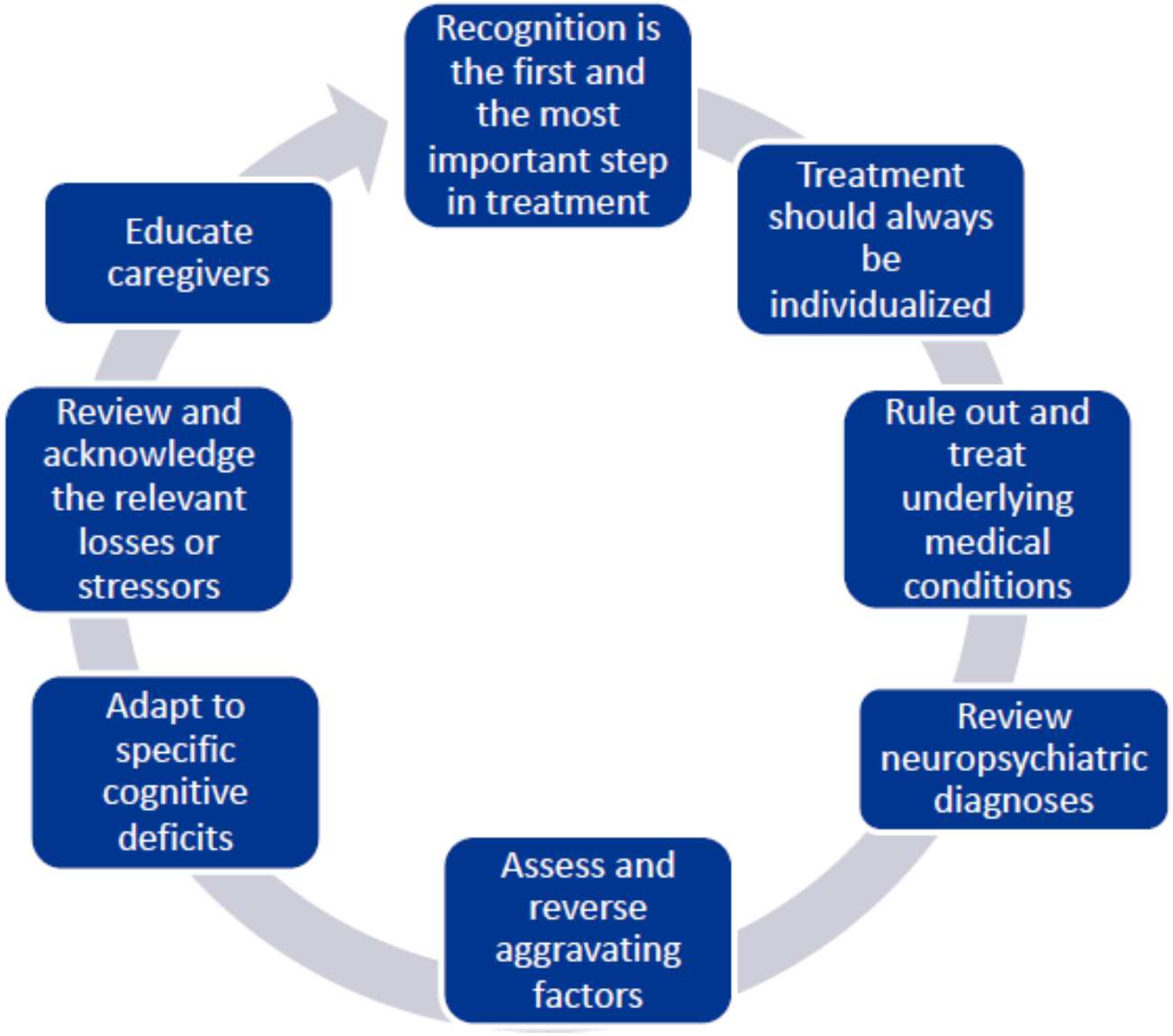
Charles Bonnet Syndrome

- Condition that causes patients with vision loss to experience complex, recurrent, and vivid visual hallucinations
- Lilliputian hallucinations: hallucinations in which characters/objects appear smaller than normal
- Images of complex colored patterns and images
- Animals, plants, trees, inanimate objects
- Hallucinations often fit into person's surroundings
- Rarely experience auditory hallucinations or delusions
- Insight is often preserved
- Prevalence between 10-40%, mainly occurs in women
- Correction of ocular pathology may resolve hallucinations

Medications Associated with Psychosis

- **Antiparkinsonian drugs**
  - L-dopa or carbidopa
  - Amantadine
  - Bromocriptine
- **Anticholinergic/antihistamines agents**
  - Diphenhydramine
  - Hydroxizine
- **Analgesics and antiinflammatory drugs**
  - Indomethacin
- **Antineoplastic agents**
- **Oral or parenteral steroids**
  - Prednisone
  - Dexamethasone
- **Antiarrythmic and cardiac drugs**
  - Digitalis
  - Quinidine
  - Procainamide
  - Propranolol
- **Tricyclic antidepressants**
  - Amitriptyline
- **Stimulants**
  - Amphetamine
  - Thyroid
  - Ephedrine
- **Sedative-hypnotics**
  - Benzodiazepines
  - Barbiturates
  - Chloral hydrate

Treatments



Tampi et al, Curr Psychiatry Rep, 2022

Non-pharmacological Interventions

- Livingston G, et al. 2005 Systematic Review
  - Effective interventions: psychoeducation, instruction for staff
  - May be effective: cognitive stimulant therapy, therapeutic activities
  - Not consistently beneficial: specialized dementia units (but may reduce wandering)

- Livingston G, Lewis-Holmes E, Baio S, et al. 2014 Systematic Review
  - Person-centered care, communication skills training, adapted dementia care mapping reduced agitation in care homes both immediately and for up to 6 months
  - Activities and music therapy reduced agitation
  - Sensory intervention reduced agitation
  - Aroma- and light-therapy were ineffective

Tampi et al, Curr Psychiatry Rep, 2022

Pharmacological Interventions

- Only for symptoms that persist after use of non-pharmacological interventions
- Choice of medication is often influenced by the urgency of the situation
- Behaviors can be classified as emergent vs non-emergent

Emergent behaviors

May need to be treated with medications i.e., antipsychotics

or

need inpatient psychiatric treatment

Non-emergent behaviors

Cluster the most salient features into patterns that is roughly analogous to a drug responsive syndrome

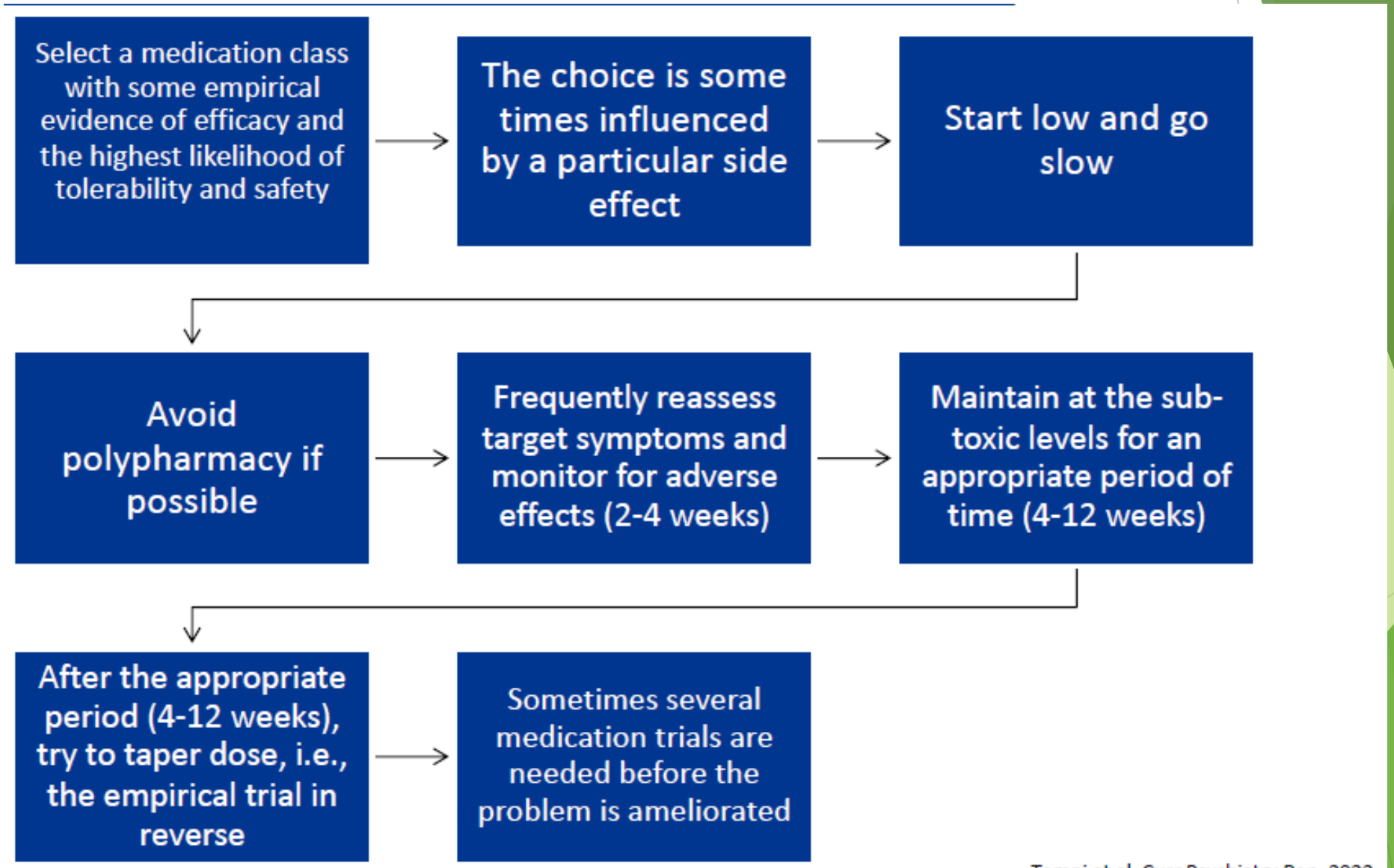
Appears depressed: Use antidepressants

Appears hypomanic/manic: Use mood stabilizers or antipsychotics

Appears psychotic: Use antipsychotics

Tampi et al, Curr Psychiatry Rep, 2022

Prescribing Guidelines



Tampi et al, Curr Psychiatry Rep, 2022

Treating Depression in Dementia

- Prevalence of MDD in Alzheimer's dementia: 10-40%
- MDD accounts for 25-50% of all geriatric psychiatric inpatient admissions
- Caregiver's report of depression in the patient with AD can often indicate depression in the caregiver
- Can be difficult to assess for depression as depressive symptoms are also commonly seen in dementia
  - Apathy, anhedonia, insomnia, memory loss, poor concentration, agitation
- Can be difficult to assess for depressive symptoms in severe dementia

Schulz R et al. Am J Geriatr Psychiatry 2013; 21:14-25

Authors	Type of Study	Outcomes
Martinon-Torres G, Fioravanti M, Grimley EJ. 2004	Meta-analysis	• Two studies were included, comprising 104 participants with dementia • 16 and 6 weeks duration, trazodone from 50 to 300mg daily • Compared to placebo, no statistically significant benefit for behaviors, cognition or function • No difference between placebo and trazodone for adverse effects
Seitz DP, Adunuri N, Gill SS, et al. 2011	Meta-analysis	• 5 studies compared SSRIs to placebo • 2 studies were combined in a meta-analysis • In 2 studies sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo • No effect on trazodone compared to placebo and equal efficacy to haloperidol • Both SSRIs and trazodone appear to be tolerated reasonably well when compared to placebo, typical antipsychotics and atypical antipsychotics
Henry G, Williamson D, Tampi RR. 2011	Literature review	• 19 placebo controlled trials • 11 trials, 8 using a selective serotonin reuptake inhibitor (SSRI) compound and 3 using trazodone showed benefit in the treatment of BPSD • The antidepressant drug was well tolerated in at least 14 of the 19 trials

Complications when Treating Depression in Patients with Dementia

- Despite widespread use of antidepressant medications in patients with dementia, there is little evidence of therapeutic benefit
- Most studies involving treatment of depression dementia focus on AD
- Lack of therapeutic benefit cannot be explained by age alone as depressed older adults without dementia respond as well to antidepressants as other age groups
- Antidepressant use can be potentially harmful with increased risk of falls, hospitalizations, and higher risk of mortality
- Only 1 RCT with 14 patients examining SSRI use in patients with LBD - showed no efficacy and higher burden of side effects
- Antidepressants can be use in post-stroke depression in patients without dementia
- SSRI use is widely advocated in patients for FTD for treatment of depression and disinhibition; however, studies have mixed results
- Common side effects of SSRIs: N/V/D, dry mouth, changes to sleep, sweating, sexual dysfunction, hyponatremia (worst with citalopram), increased bleeding risk. Paroxetine has most anti-cholinergic side effects.

- Costello H, Roiser JP, Howard R. Antidepressant medications in dementia: evidence and potential mechanisms of treatment-resistance. Psychol Med. 2023 Feb;53(3):654-667. doi: 10.1017/S003329172200397X. Epub 2023 Jan 9. PMID: 36621964; PMCID: PMC9976038.

Treatment of Anxiety in Patients with Dementia

- Anxiety can be difficult to identify in patients with dementia; however, anxiety is incredibly common in this population - some studies have shown prevalence of up to 70%
- Anxiety often decreases in more severe stages of dementia
- Anxiety is more common in Vascular, FTD, and Parkinson's dementia compared to Alzheimer's
- Overall lack of large RCT for treatment of anxiety in dementia
- Anxiety disorders more common in elderly women without dementia, no gender differences in patients with dementia
- Patients with more significant symptoms of anxiety often present with higher rates of depression, agitation, and sleep disturbance
- CBT can be helpful in earlier stages of dementia, limited utility in later stages
- Medications: antidepressants (SSRIs, SNRIs), cholinesterase inhibitors, memantine, atypical antipsychotics (Seroquel, Risperdal), benzodiazepines (with extreme caution)

- Kwak YT, Yang Y, Koo MS. Anxiety in Dementia. Dement Neurocogn Disord. 2017 Jun;16(2):33-39. doi: 10.12779/dnd.2017.16.2.33. Epub 2017 Jun 30. PMID: 30906368; PMCID: PMC6427954.

Treatment of Agitation and Psychosis in Patients with Dementia

- Agitation commonly occurs in patients with Alzheimer's dementia
- Agitation is associated with accelerated disease progression, increased risk of institutionalization, and mortality
- Behavioral strategies may help with mild symptoms, but medications are typically needed for moderate to severe symptoms
- FDA-approved medications:
  - For agitation in Alzheimer's dementia - brexpiprazole
  - For psychosis associated with Parkinson's disease - pimavanserin

Brexpiprazole

- Approved for treatment of agitation in AD in 2023
- Dopamine and serotonin receptor partial agonism similar to aripiprazole
- Based on 2 initial clinical trials and a 3rd clinical trial that tested 2mg and 3mg doses identified as likely to be efficacious in the first 2 trials
- Doses of 2-3mg daily showed efficacy compared to placebo with small effect size. Lower doses did not distinguish from placebo in the first 2 clinical trials
- Side effects were minimal: headache, insomnia, somnolence
- EPS did not differ between drug and placebo

- Grossberg G et al, Am J Geriatr Psychiatry 28: 383-400; 2020
- Lee D et al. JAMA Neurol 80:1307-1316; 2023.

Pimavanserin

- Approved in 2016 for treatment of Parkinson's disease psychosis (PDP)
- Mechanism of action: potent serotonin 5-HT2A receptor antagonist/inverse agonist. Can also interact with serotonin 5-HT2C receptors
- Approximately half of patients with PD will develop psychotic symptoms
- Antipsychotics worsen motor symptoms in patients with PD
- Based on available clinical trials, efficacy of pimavanserin is inferior to clozapine; however, has significantly less side effects compared to clozapine
- 35% lower mortality compared to other atypical antipsychotics
- 3 separate clinical trials showed efficacy in the use of pimavanserin for PDP (measured in reduction of SAPS score - Scale for the Assessment of Positive Symptoms)
- Study evaluating long-term use of pimavanserin showed that beneficial effects were maintained up to 2 years. Studies also showed that MCI and DBS do not alter the effects of pimavanserin
- Currently no clinical trials comparing pimavanserin to atypical antipsychotics in the treatment of PDP

- Rissardo JP, Durante Í, Sharon I, Fornari Caprara AL. Pimavanserin and Parkinson's Disease Psychosis: A Narrative Review. Brain Sci. 2022 Sep 23;12(10):1286. doi: 10.3390/brainsci12101286. PMID: 36291220; PMCID: PMC9599742.

TYPICAL ANTIPSYCHOTICS

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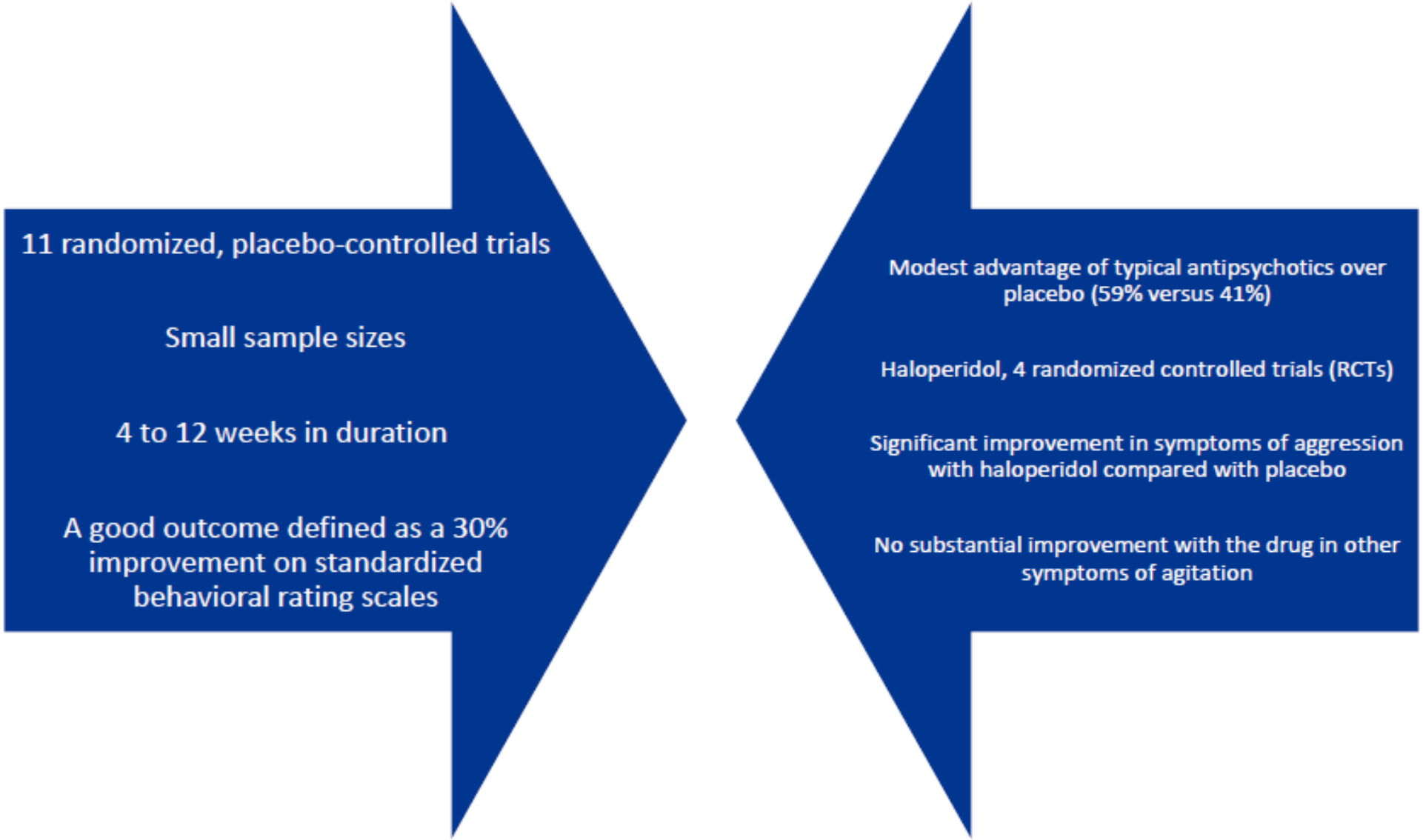

Ballard et al, Nat Rev Neurol, 2009

Atypical Antipsychotics

Risperidone	Olanzapine	Quetiapine
625 patients with AD or mixed dementia	206 nursing home patients randomly assigned to tx groups	No dose-comparison study in dementia
50% reduction in BEHAVE-AD scores	Placebo, 5mg, 10mg, 15 mg groups for 6 weeks	EPS minimal
Placebo 33%, Risperdal 1 mg 45%, 2 mg 50%	All 3 doses superior to placebo	Dosage 25-400mg tolerated by elderly AD patients
Dose for optimal benefit/risk ratio: 1mg daily	5mg dose as effective as higher doses with less side effects	Low doses preferred to minimize sedation
3 of 4 studies in nursing home patients (n=941) with AD or mixed dementia	EPS did not differ among groups	
Advantage with use of Risperdal compared to placebo for psychosis and/or agitation	Sedation and weight gain were not prominent (however it was a short trial)	
Katz I et al. J Clin Psychiatry 1999; 60:107-115 Katz I et al. Int J Geriatr Psychiatry 2007; 22:475-484	Street J et al. Arch Gen Psychiatry 2000; 57: 968-967	Tariot P et al. Am J Ger Psychiatry 14:767-776, 2006 Schneider L et al. Am J Ger Psychiatry 14:191-210, 2006

CATIE-AD Study

- CATIE-AD (Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease) Study
- 421 patients with Alzheimer's dementia with psychosis, agitation, and/or aggression followed for 36 weeks
- Cognitive assessments performed at 12, 24, and 36 weeks
- Randomly assigned to treatment groups including olanzapine, quetiapine, risperidone, and placebo
- Based on clinician's judgement, patients could discontinue the originally assigned medication and receive another randomly assigned medication
- Results: Cognitive function declined more in patients receiving antipsychotic medication than those receiving placebo at a magnitude of 1 year's deterioration
- EPS more common with olanzapine and risperidone
- No significant improvement in agitation and/or psychosis
- The Quality of Antipsychotic Drug Prescribing in Nursing Homes, Becky A. Briesacher; M. Rhona Limcangco; Linda Simoni-Wastila; Jalpa A. Doshi; Suzi R. Levens; Dennis G. Shea; Bruce Stuart, *Arch Intern Med.* 2005;165:1280-1285.

42-site, double-blind, placebo-controlled trial for 36 weeks

421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation

Randomly assigned to receive:

Olanzapine (mean dose, 5.5 mg per day)

Quetiapine (mean dose, 56.5 mg per day)

Risperidone (mean dose, 1.0 mg per day)

- Time to the discontinuation of treatment for any reason no different for drugs compared to placebo (P=0.52)
- The median time to the discontinuation of treatment due to lack of efficacy placebo =quetiapine, risperidone and olanzapine >placebo
- 3-5 times more individuals discontinued the drugs due to side-effects when compared to placebo (P=0.009)
- Improvement on the CGIC scale no different between drugs and placebo (P=0.22)

The main outcomes were:

1. The time from initial treatment to the discontinuation of treatment for any reason.
2. The number of patients with at least minimal

improvement on the Clinical Global Impression of

Change (CGIC) scale at 12 weeks

- No significant differences between antipsychotics and placebo on functioning, care needs, or quality of life
- Cognitive function declined more in patients receiving antipsychotics on multiple cognitive measures
- Treatment groups had significantly higher costs
- There were no cerebrovascular events or deaths that could be attributable to the drugs

CATIE: Dementia study

ALGORITHM FOR TREATING EMERGENT AGITATION

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- Offer Risperidone: 0.25 mg-1.0 mg dose
- Or Aripiprazole 2.0-5.0 mg dose
- Or Quetiapine 25 mg-50 mg dose
- Or Olanzapine 2.5 mg-5 mg dose
- Can repeat dose in 0.5-1 hour if needed
- May need 1-2 repeats before the patient responds. **Avoid Benzos!**

- **If patients is refusing PO medications and is very agitated or aggressive**
- Give IM Olanzapine: 2.5 mg-5.0 mg dose
- Or IM Haloperidol: 0.5 mg-2.0 mg dose
- Can repeat dose in 0.5-1 hour if needed
- May need 1-2 repeats before the patient responds. **Avoid Benzos!**

Discontinuation of antipsychotics in AD

- Federal regulations require discontinuation of antipsychotics in nursing homes 4 months after initiating treatment unless the physician provides a written rationale to continue treatment
- Requirement is based on concerns about side effects
- Placebo-controlled studies of antipsychotic discontinuation showed mixed results and some recent studies showed little difference on drug vs placebo
- Largest study (n=100) that discontinued AD patients from different antipsychotics showed greater worsening on placebo by 12 months in patients with greater baseline psychopathology
- Ballard C et al. Plos Med 5(4): e76, 2008

APA PRACTICE GUIDELINE

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- Use antipsychotics only if the benefit outweigh the risks
- Initiated treatment at a low dose and titrate to the minimum effective dose as tolerated
- If adverse effects occur, risks vs. benefits should be reviewed to determine if taper and discontinuation of the medication is indicated
- If there is no response after a 4-week trial on an adequate dose, then the medication should be tapered and discontinued
- When there is a positive response the decision to possibly taper the medication should be discussed with the patient and/or the surrogate decision maker
- When there is adequate response, an attempt to taper and withdraw the medication should be made within 4 months of initiation of treatment unless there is a recurrence of symptoms with previous attempts at tapering the medication
- While tapering the medication assess symptoms at least every month during the taper and for at least 4 months after the medication discontinuation
- In the absence of delirium, haloperidol should not be used as a first-line agent
- Long-acting injectable antipsychotic medication should not be used unless for a co-occurring chronic psychotic illness

Reus et al, Am Psychiatr Publ, 2016

RISKS OF ANTIPSYCHOTIC MEDICATIONS IN OLDER ADULTS

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- Sedation
- Anticholinergic symptoms
- Orthostatic hypotension
- Extrapyramidal symptoms
- QTc prolongation
- Metabolic side effects
- Acute kidney injury
- Cerebrovascular adverse events*
- Death*
- Cognitive decline*

* Increased risk specifically in dementia patients

Toxicity of antipsychotics in patients with dementia

- Increased risk of EPS, tardive dyskinesia in elderly patients with dementia
- Risk varies based on which antipsychotic is prescribed
- Orthostatic hypotension, autonomic effects are rare with low doses
- FDA black box warning: increased risk of mortality in patients with dementia
- 15 placebo-controlled trials, pooled analyses showed increased mortality risk in studies conducted mostly in nursing homes
- Some more recent nursing home studies do not show increased mortality risk
- Outpatient study: increased antipsychotic mortality risk disappeared after controlling for baseline psychosis and agitation which themselves increase mortality risk

- Raivio MM et al. Am J Geriatr Psychiatry 2007; 15:416-424
- Simoni-Wastilla L et al. Am J Geriatr Psychiatry 2009; 17:417-427
- Lopez O et al. Am J Psychiatry 2013; 170:1051-1058

Community Practice Data

- 75,445 patients in CMS (Medicare/Medicaid) database
- Mortality risk greatest for haloperidol compared to risperidone
- Quetiapine slightly lower risk
- High-dose haloperidol associated with double the mortality risk of low-dose haloperidol
- High-dose risperidone associated with 35% greater mortality risk compared to low-dose risperidone
- High doses used were above the therapeutic window identified in dose-comparison studies
- Huybrechts KF et al. Br Med J 2012; 344: e977

SCHNEIDER L, ET AL. RISK OF DEATH WITH ATYPICAL ANTIPSYCHOTIC DRUG TREATMENT FOR DEMENTIA: META-ANALYSIS OF RANDOMIZED PLACEBO-CONTROLLED TRIALS. JAMA. 2005 OCT 19;294(15):1934-43

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Medication	No. events in treatment group	No. events in placebo group	Odds ratio, 95% CI
Aripiprazole	21/603	6/348	1.73, 0.70-4.30
Olanzapine	31/1184	6/478	1.91, 0.79-4.59
Quetiapine	21/391	7/246	1.67, 0.70-4.03
Risperidone	45/1175	22/779	1.30, 0.76-2.23
Overall	**118/3353 (3.5%)**	**41/1851 (2.3%)**	**1.54, 1.06-2.23 P=0.02**

COGNITIVE ENHANCERS

AMERICAN PSYCHIATRIC ASSOCIATION

Authors	Type of Study	Outcomes
Rodda J, Morgan S, Walker Z. 2009	Meta-analysis	• 14 studies were identified • 9 were of donepezil, 3 of galantamine and 2 of rivastigmine • Median study treatment length was 24 weeks • Four studies were specifically designed to assess behavioral outcomes • Three studies found statistically significant but modest (2.1 to 6.2), differences in the change of NPI total score between drug and placebo
Maidment ID, Fox CG, Boustani M, et al. 2008	Meta-analysis	• 6 randomized, parallel-group, double-blind studies • Five of the 6 studies identified had NPI outcome data • 868 patients were treated with memantine and 882 patients were treated with placebo • Patients on memantine improved by 1.99 on the NPI scale compared to the placebo group

MOOD STABILIZERS

AMERICAN PSYCHIATRIC ASSOCIATION

Authors	Outcomes	Bottom-line
Lonergan E, Luxenberg J. 2009	• Total of 3 RCTs • 2 were included in the meta-analysis	• Valproate preparations are ineffective in treating agitation among demented patients • Valproate therapy is associated with an unacceptable rate of adverse effects
Konovalov S, Muralee S, Tampi RR. 2008	• Total of seven RCTs • 2 for carbamazepine and 5 for valproate • 1 study showed statistically significant improvement • 5 studies showed no significant differences • 1 study showed statistically significant worsening • Majority of the studies reported significantly more frequent adverse effects in the medication group	• Although clearly beneficial in some patients, anticonvulsant mood stabilizers cannot be recommended for routine use in the treatment of BPSD at the present time
Kim Y, Wilkins KM, Tampi RR. 2008	• 11 case reports, 3 case series and 1 retrospective chart review; no controlled studies	• Well tolerated and effective treatment • Less well tolerated in patients with dementia with Lewy bodies

PROPRANOLOL

AMERICAN PSYCHIATRIC ASSOCIATION

Name of study	Dosing	Results	Tolerability
Petrie &Ban, 1981	60-160 mg/day	• Improvement in symptoms of wandering in all 3 patients and agitation in 2 of the patients where it was present	• Propranolol was well tolerated except for a reduction of pulse rate in 2 of the 3 patients
Weiler et al, 1988	80-560 mg/day	• Agitated behaviors improved significantly in all participants	• Well tolerated with no adverse effects reported
Shankle et al, 1995	10-80 mg/day	• The overall response rate was 67% (8/12) • 60% response rate for agitation • 71% response rate for agitation and aggression	• Well tolerated, bradycardia in 1 participant with heart disease, symptoms resolved when the dose of propranolol was reduced from 60 mg/day to 30 mg/day
Peskind et al, 2005	106±38 mg/day	• At week 6 ▪ NPI total score ➢ Propranolol vs Placebo (P=0.01) ▪ NPI items ➢ Propranolol vs Placebo "agitation/aggression" (P=0.06) ▪ CGIC mean score ➢ Propranolol vs Placebo (P=0.005) ▪ CGIC ➢ Markedly improved (n=1), moderately improved (n=7) (P<0.02)	• One individual in the propranolol group discontinued treatment due to rash • Two individuals in the placebo group treatment discontinued treatment due to hypotension (n = 1) or bradycardia (n = 1) when compared to none in the propranolol group
Summers, 2006	80-180 mg/day	• Significant improvements in disruptive vocalizations and episodic violent outbursts	• No adverse effects noted from propranolol

Dementia Prevention, Intervention, and Care

- 2020 Lancet Commission
- 12 potential modifiable risk factors
- Interventions should be individualized. Consider the person “as a whole” and include family members/caregivers
- Keeping people with dementia physically healthy is important for their cognitive health

Livingston G, et al. *Lancet*. 2020;396(10248):413-446.

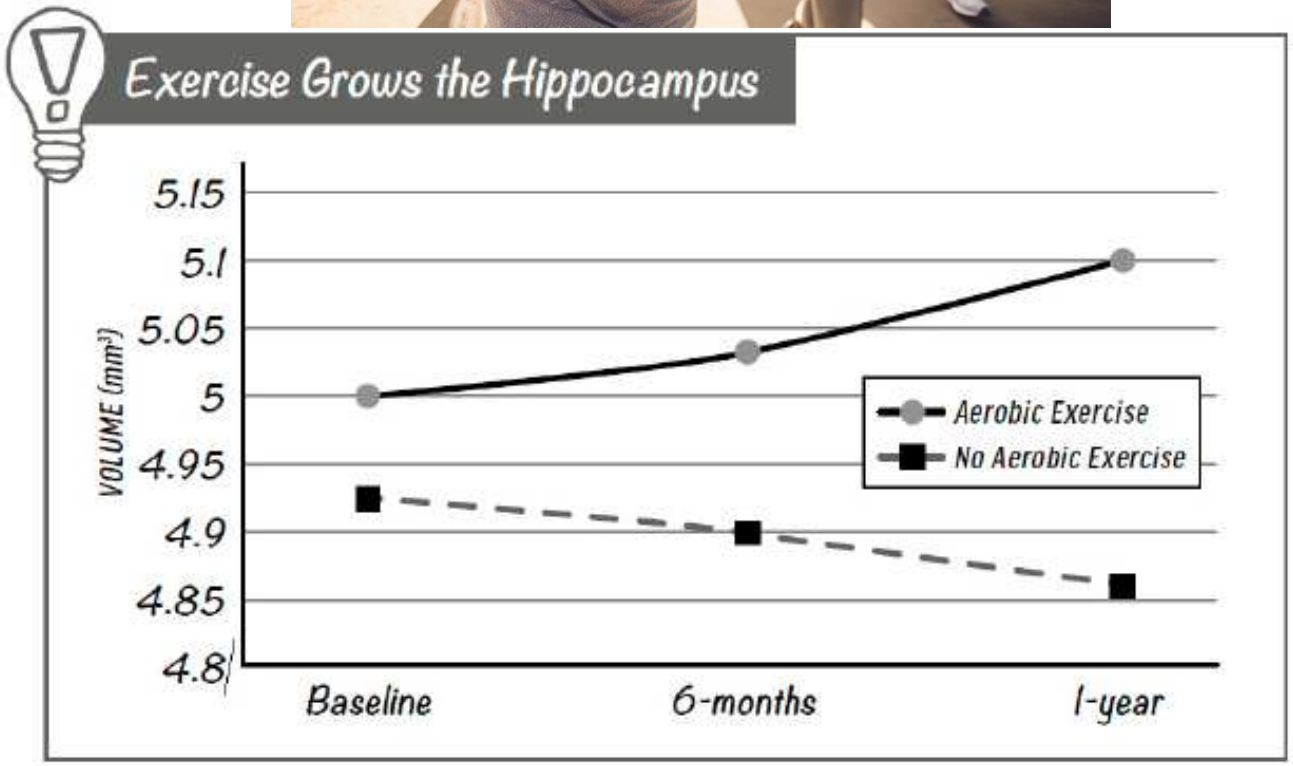
FINGER Study

- 1200 participants at risk for cognitive decline
- 2-year multi-domain intervention
  - Nutritional guidance
  - Exercise
  - Cognitive training
  - Social activity
  - Management of metabolic and vascular risk factors
- Primary outcome: Cognitive performance
- Secondary outcomes:
  - Dementia, depressive symptoms, vascular factors, quality of life, health-resource usage
- Findings suggest that multi-domain could improve or maintain cognitive functioning in at-risk elderly people in the general population

Ngandu T, et al. *Lancet*. 2015;385(9984):2255-2263.

Physical Exercise

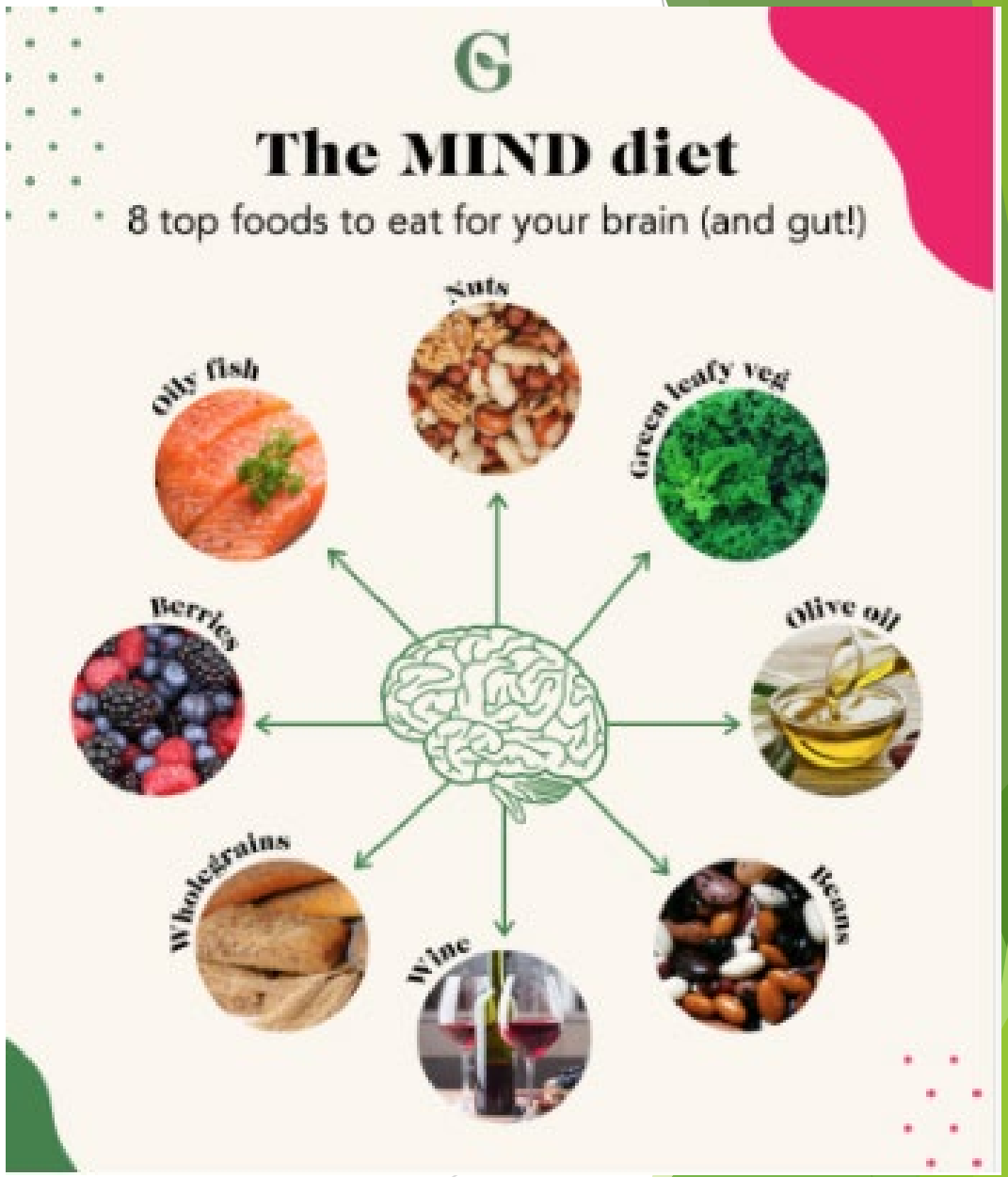
- Animal and human studies:
  - Larger brains
  - Better memory
  - Lower risk for dementia
- Increased brain-derived neurotrophic factor, endorphins
- Cardiovascular, strength, and balance training



Kramer AF, et al. *J Gerontol A Biol Sci Med Sci*. 2004;59(9):M940-M957. Erickson KI, et al. *Proc Natl Acad Sci U S A*. 2011;108(7):3017-3022; Alty et al. *Practical Neurology*. 2020;20(3):234-240.

The MIND Diet

- Nutritional choices that protect the brain:
  - Emphasize: beans, fruits, vegetables, nuts, olive oil, poultry, fish, whole grains
  - Minimize: butter, margarine, cheese, fried foods, fast food, sweets
- 5-year study (> 900 older adults) showed that adherence to the MIND diet significantly slowed cognitive decline, equivalent to a 7.5-year younger brain age
- MIND diet is associated with better memory and thinking independent of AD disease pathology



Klodian Dhana, et al. MIND Diet, Common Brain Pathologies, and Cognition in Community-Dwelling Older Adults. *Journal of Alzheimer's Disease*, 2021; 83 (2): 683 DOI: 10.3233/JAD-210107