Pharmacological treatment of behavioral & psychological symptoms of dementia

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November 5, 2022

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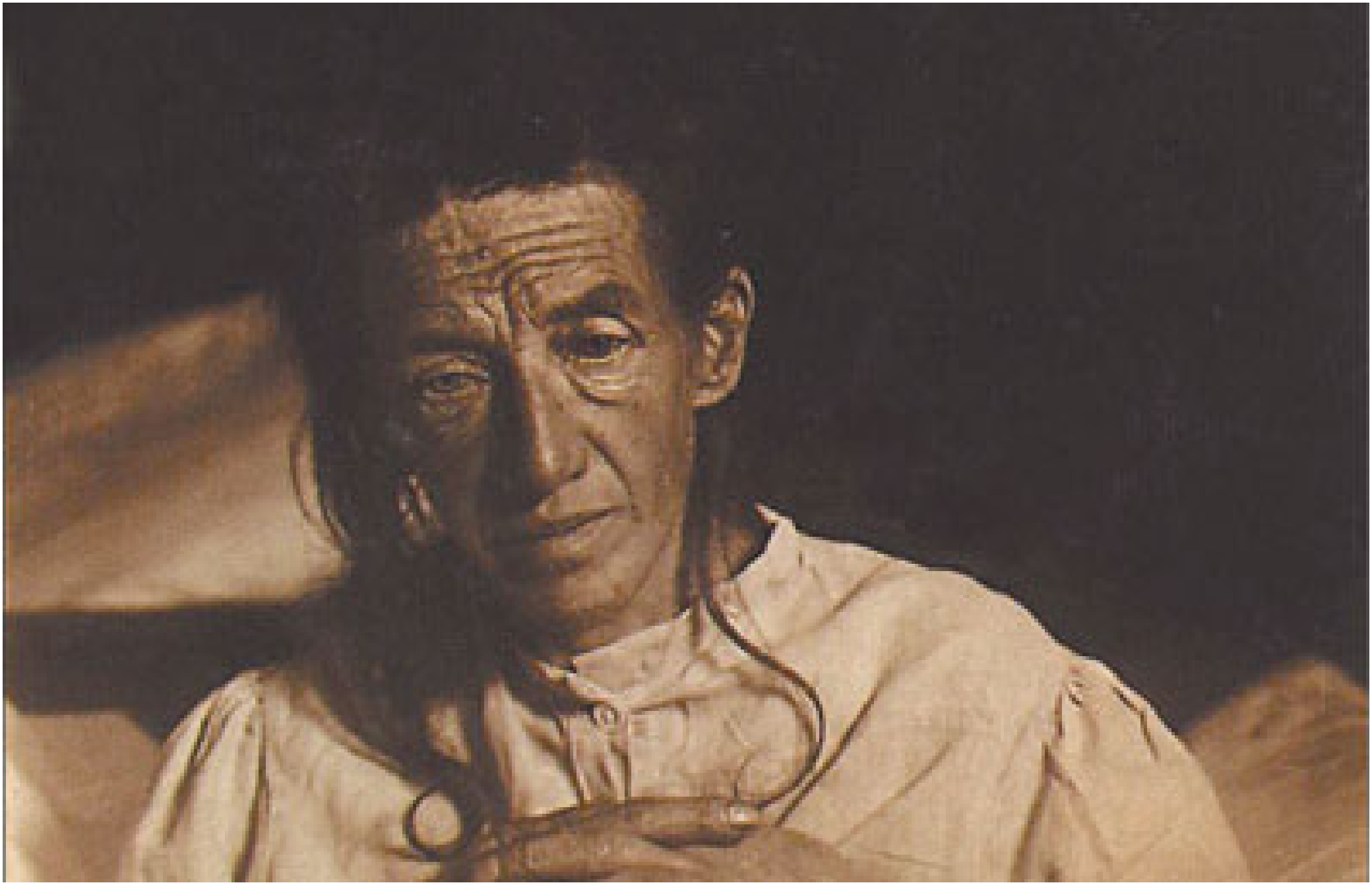
Disclosures

Royalties, American Psychiatric Association Publishing

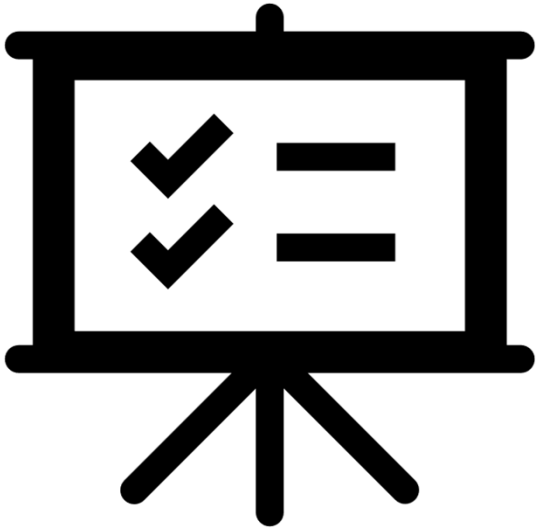


Behavioral & psychological symptoms of dementia (BPSD)

About 90% of people with dementia will experience BPSD sometime over the course of their illness.

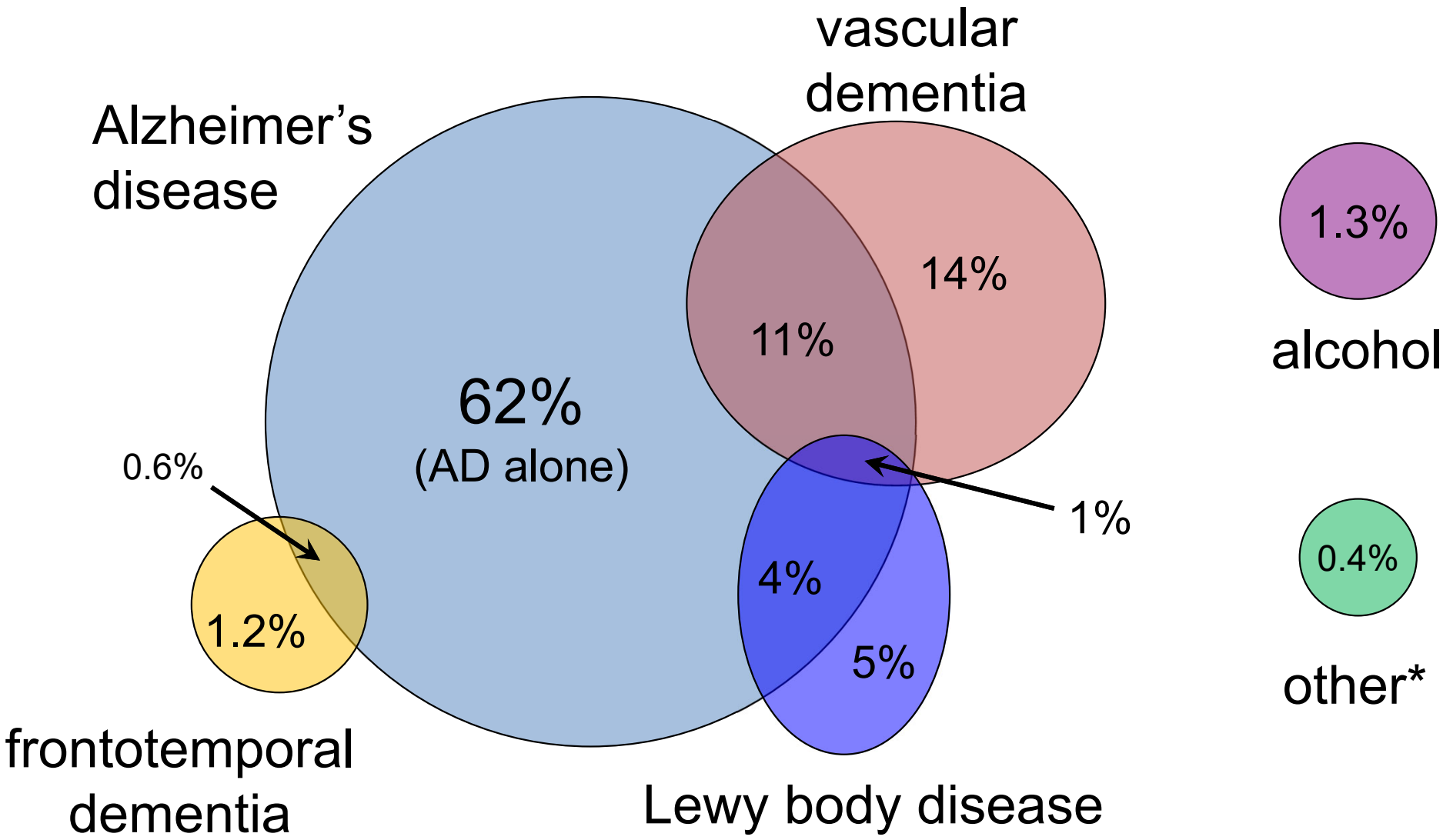
BPSD can be distressing to patients and caregivers, can affect patients' ability to live independently, and can be dangerous.

Objectives



- Describe the natural history, prevalence & presentation of behavioral and psychological symptoms of dementia (BPSD)
- Develop a plan for assessing BPSD
- List the elements of a plan to manage BPSD, including behavioral, environmental & pharmacological interventions

Causes of dementia in the U.S.



Goodman et al., *Alzheimers Dement* 2017;13:28-37. *Huntington's disease, Creutzfeldt-Jakob disease, drug-induced dementia

Prevalence of specific BPSD

Symptom	Prevalence
apathy	49%
depression	42%
aggression	40%
sleep disorder	39%
anxiety	39%
irritability	36%
appetite disorder	34%
aberrant motor behavior	32%
delusions	31%
disinhibition	17%
hallucinations	16%
euphoria	7%

Zhao et al., *J Affect Disorder* 2016;190:264-271.

BPSD vary by cause of dementia

Cause of dementia	Behavioral and psychological symptoms
Alzheimer's disease	mild dementia=#ghsuhvvlrq/#dq{lhw|/#lqvrp qld p rghudwh#wr#vhyhuh=#kdoxflqdwlrqv/#ghoxvlrqv/# uhshwlwlyhqhvv/#djjuhvvlrq
Lewy body disease*	visual hallucinations, delusions, anxiety, REM sleep behavior disorder
vascular dementia	apathy, amotivation, depression
frontotemporal dementia, behavioral variant	disinhibition, verbal repetitiveness, aggression, hyperorality, apathy
Down syndrome	withdrawal/apathy, impulsivity, anxiety, aggression, tantrums, wandering, hoarding, sleep disturbance, weight change, obsessions/compulsions

Walaszek *Behavioral & Psychological Symptoms of Dementia* 2019.
* includes dementia with Lewy bodies and Parkinson disease dementia

Why do BPSD arise?

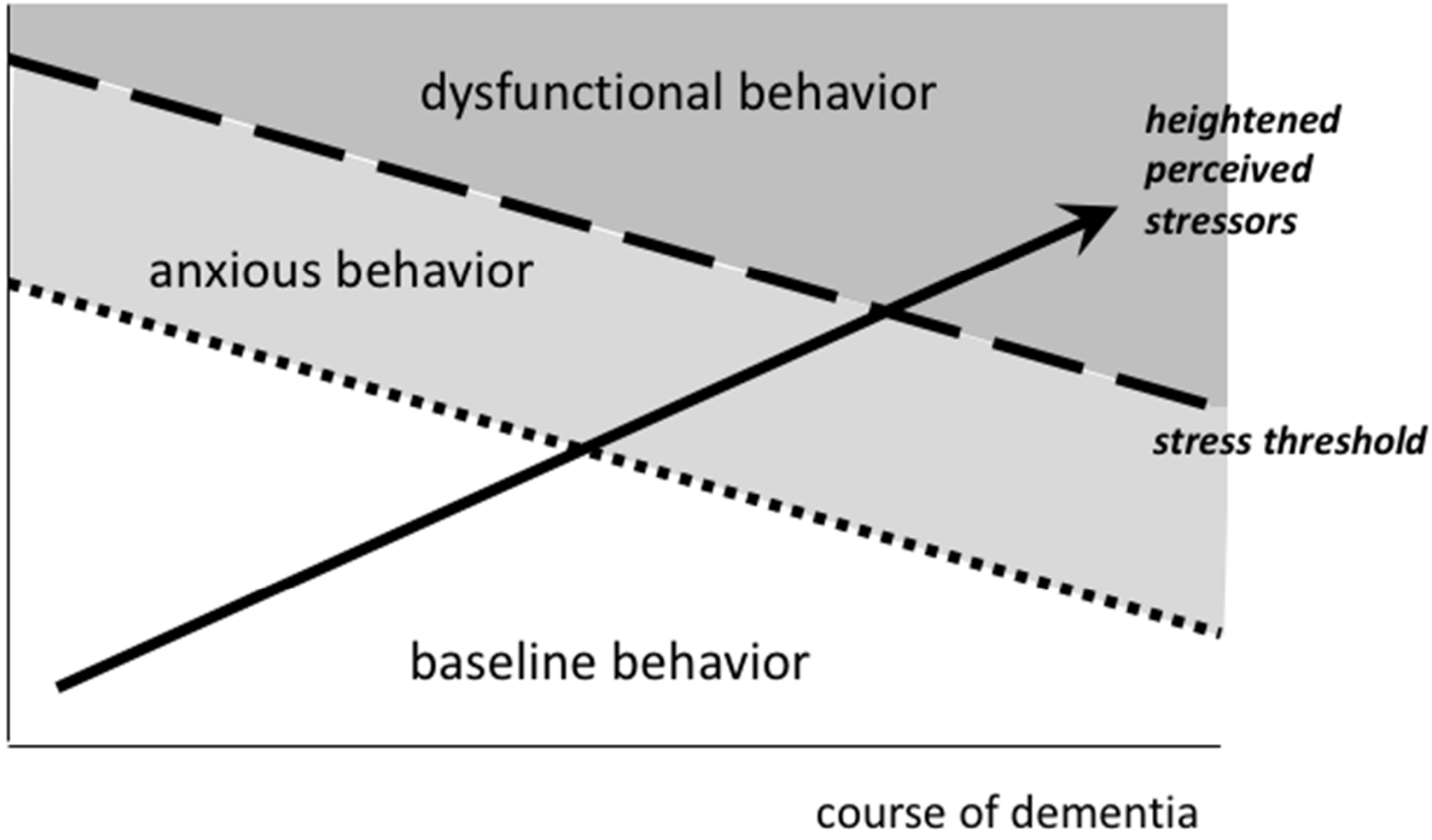
neurobiological model

behavioral model

unmet needs model

progressively lowered stress threshold model

Progressively lowered stress threshold model



Smith et al., *JAGS* 2004; 52:1755-1760.

Assessment of BPSD (1)

- timing: how often? how long does it last? how long has it been present?
- severity: dangerous? distressing? at risk of escalating? other risks (e.g., losing housing)? interfering with care?
- antecedents: precipitants? patterns?
- consequences: how do caregivers respond? what works and doesn't work?
- history: new behavior? if not new, is it different

Assessment of BPSD (2)

- Screen for all BPSD:
  - depression
  - apathy
  - verbal aggression
  - physical aggression & agitation
  - wandering
  - refusing medications or assistance with ADLs
  - disturbances of sleep-wake cycle
  - anxiety & irritability
  - delusions & hallucinations
  - elation, euphoria & disinhibition
  - pathological laughing or crying
  - alterations in appetite & eating
  - sexually inappropriate behaviors

Assessment of BPSD (3)

- screen for caregiver burden
  - consider PHQ-2 to screen for depression
- consider medical contributions
- assess pain
- review medication list & other substances
- screen for elder abuse

Medications & substances that can cause BPSD

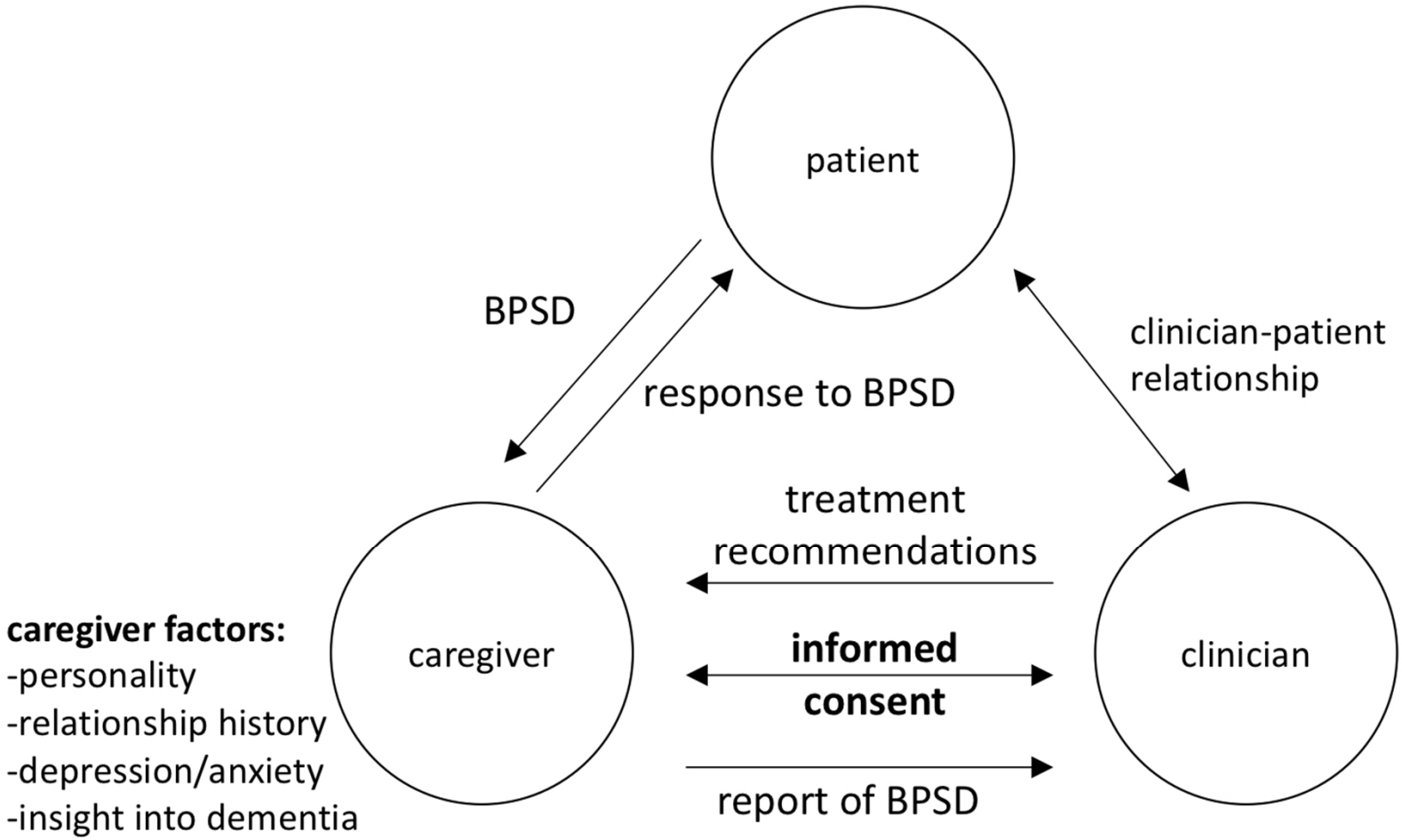
- anticholinergic meds
- antidepressants
- antiepileptic drugs
- antiparkinsonian meds
- antipsychotics
- cholinesterase inhibitors
- opioids
- sedative-hypnotic meds
- steroids
- alcohol
- cannabis

Cultural and spiritual factors

- cultural factors may
  - affect how patients and family members interpret the symptoms of dementia
  - determine whether or not medical attention is sought
  - interfere with access to healthcare, e.g., because of language barriers
- prevalence of BPSD generally similar across various ethnicities in the U.S.
- cultural expectations around the responsibilities of children and grandchildren with respect to the elders may affect the relationships among patients and family caregivers
- consider using APA's Cultural Formulation Interview (CFI)

Dilworth-Anderson & Gibson *Alzheimer Dis Assoc Disord* 2002;16:S56-63. Mukadam et al., *Int J Geriatr Psychiatry* 2011;26:12–20.

The role of caregivers



Walaszek *Behavioral & Psychological Symptoms of Dementia* 2019.

Principles of management

- treat underlying medical causes
- discontinue offending medications & substances
- support & educate caregivers & other family members
- develop a psychological, behavioral & environmental management plan
- avoid adding new medications, unless there is risk of harm to patient or others
- if a medication is added, regularly monitor outcomes & attempt discontinuation
- ensure that patients & caregivers are in a safe environment

Psychological, behavioral & environmental interventions

patients

- structured activities
- music therapy
- multisensory stimulation, e.g., Snoezelen
- reminiscence therapy
- problem-solving therapy

facilities

- training programs for formal caregivers, e.g., DICE
- dementia care mapping or other quality improvement tools

families

- supporting family caregivers

Walaszek *Behavioral & Psychological Symptoms of Dementia* 2019.

When to turn to medications for BPSD

"Nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, are dangerous, and/or cause significant distress to the patient"

(*emphasis added*)

The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia 2016

Caveats to using medications for BPSD

- patients with dementia may already have significant polypharmacy (which could be contributing to cognitive impairment or BPSD)
- clinical trials have shown only modest efficacy for medications in treating BPSD
- there are significant risks associated with the use of medications for BPSD, esp. mortality with antipsychotics
- no medications approved for use in BPSD, except
  - pimavanserin for Parkinson's disease psychosis
  - dextromethorphan-quinidine for pseudobulbar affect

Walaszek *Behavioral & Psychological Symptoms of Dementia* 2019.

Informed consent

"Before treatment, the potential risks and benefits from antipsychotic medication should be assessed by the clinician and discussed with the patient, surrogate decision maker, or other family member."

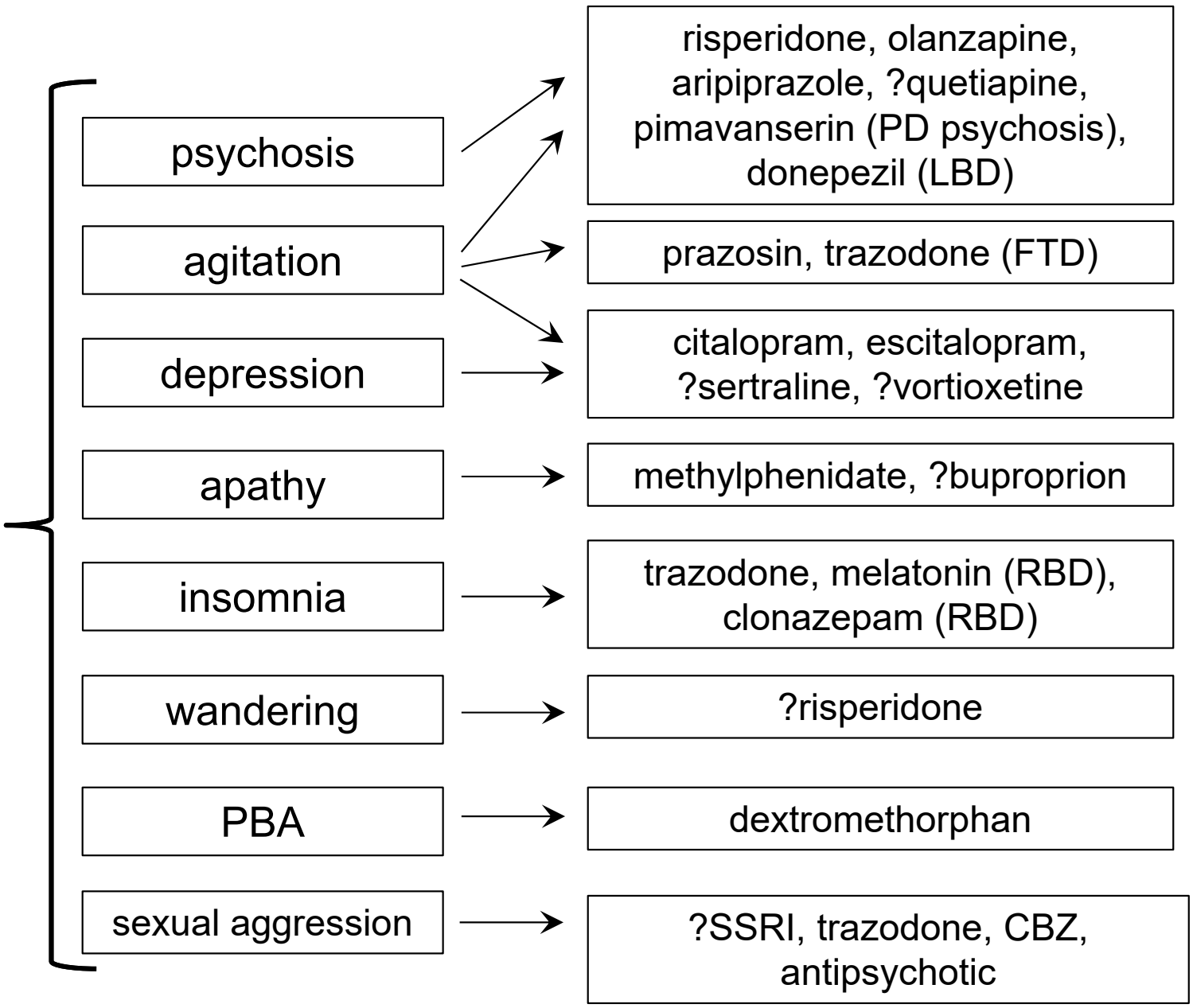
The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia 2016

Start low

Go slow

Specific BPSD

Implement caregiver, behavioral & environmental interventions first; if ineffective and BPSD dangerous or distressing…



Walaszek *Behavioral & Psychological Symptoms of Dementia* 2019; CBZ = carbamazepine, FTD = frontotemporal dementia, LBD = Lewy body disease, PBA = pseudobulbar affect, PD = Parkinson's disease, RBD = REM sleep behavior disorder

Antipsychotics

atypical antipsychotics

risperidone

olanzapine

aripiprazole

quetiapine

clozapine

brexpiprazole

typical antipsychotics

haloperidol

Atypical antipsychotics: side effects

Side effect	Comments
death	antipsychotic 3.5% vs. placebo 2.2% in first 12 weeks, plus continued risk over first three years
sedation	antipsychotic 20% vs. placebo 8%
cognitive impairment	equivalent to one year of cognitive decline
extrapyramidal symptoms	haloperidol > risperidone > aripiprazole > olanzapine > quetiapine = clozapine
falls & fractures	1.5-2.5x increased risk
metabolic	weight gain: olanzapine > quetiapine & risperidone
stroke	risperidone 2.2% vs. placebo 1.1%; also higher risk with olanzapine
others	edema, neutropenia, ?venous thromboembolism

Schneider et al JAMA 2005; 294: 1934-43; Walaszek *Behavioral & Psychological Symptoms of Dementia* 2019.

Atypical antipsychotics: efficacy

- best evidence for risperidone, olanzapine and aripiprazole
  - mixed evidence for quetiapine
  - evidence for clozapine in very specific scenarios
  - early evidence for brexpiprazole
- overall, small effect on behavioral symptoms:
  - pooled effect size = 0.16
  - number needed to treat = 6
  - significant placebo effects (30-50% response rates)
- response usually in first 2-4 weeks
- no studies of other antipsychotics

Maglione et al., *Comparative Effective Review* 43, 2011. Schneider et al., *Am J Geriatr Psych* 2006;14:191-210.

Starting antipsychotics

1. Start at a low dose and titrate up to the minimum effective dose as tolerated
2. Include a plan for stopping antipsychotic within 4-6 months
3. If the patient experiences a clinically significant side effect, re-review risks/benefits and determine whether medication should be tapered & stopped
4. If there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic drug, the medication should be tapered & stopped

The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia 2016

Dosing of antipsychotics

	Starting dose	Maximum dose
risperidone	0.25 mg qhs	0.5 mg bid
olanzapine	2.5 mg qhs	10 mg qhs
aripiprazole	2.5 mg qhs	10 mg qhs
quetiapine	25 mg qhs	100 mg bid
clozapine	6.25-12.5 mg qhs	50 mg qhs
brexpiprazole	0.5 mg qhs	2 mg qhs

Walaszek *Behavioral & Psychological Symptoms of Dementia* 2019; Grossberg et al., *Am J Geriatr Psychiatry* 2020

Stopping antipsychotics

- **An attempt to taper and withdraw the drug should be made within 4 months of initiation**, unless the patient experienced a recurrence of symptoms with prior attempts at tapering of antipsychotic medication
- Make sure to involve patient, surrogate decision maker or other family member in decision-making about tapering off medication.
- During the taper, assess BPSD at least monthly. Continue to assess for at least 4 months after medication to stopped to see if BPSD recur or worsen.

Antidepressants (1)

- best risk-benefit profile of any drug class for pharmacological treatment of BPSD, specifically of agitation and depression
- **citalopram** 30 mg/d has the strongest evidence for efficacy for agitation, but it is associated with QT prolongation
- **escitalopram** may be effective, without QT prolongation as a side effect and with good cardiac safety
- **sertraline:** after initial (50-150 mg/d) for treating depression, more recent trials have not demonstrated efficacy (but well tolerated)

Farina et al., *Int J Geriatr Psychiatry* 2017

Antidepressants (2)

- **trazodone:** fairly strong evidence base for agitation in frontotemporal dementia; start 25-50 mg/d, titrate up to 250 mg/d as tolerated
- **vortioxetine**: maybe beneficial for cognition as well as mood
- **bupropion:** very little evidence, but could be considered for apathy (though most recent study was negative); antidepressant least likely to cause hyponatremia
- **mirtazapine:** negative trials, but could be considered for insomnia or anorexia
- **duloxetine, fluoxetine, venlafaxine:** negative trials or very little evidence of efficacy
- **paroxetine, tricyclic antidepressants:** avoid (anticholinergic)

Farina et al., *Int J Geriatr Psychiatry* 2017; 32:32–49; Maier et al., *JAMA Netw Open* 2020; 3(5):e206027; Cumbo et al., *J Prev Alzheimers Dis* 2019; 6(3):192-197

Antidepressants (3)

- safety concerns
  - hyponatremia
    - risk factors include: female gender, age > 65, use of diuretics
    - possible with any antidepressant, but least likely with bupropion (and perhaps mirtazapine)
    - check baseline sodium, then 2-3 weeks after starting and after each dose increase
  - QT prolongation: citalopram
  - falls
  - GI side effects, weight loss

Other pharmacological options (1)

Medication	Comments
acetaminophen	consider for all patients with BPSD, 1000 mg twice or three times daily
carbamazepine	risks include drug-drug interactions, hyponatremia, neutropenia/agranulocytosis
clonazepam	avoid, except in REM sleep behavior disorder
dextromethorphan	best evidence for pathological laughing & crying, combined with quinidine to increase half-life
donepezil	first choice for LBD, otherwise likely not effective for BPSD
gabapentin	very little evidence to support use
lorazepam	avoid, except in emergency situations

Other pharmacological options (2)

Medication	Comments
melatonin	1-3 mg 2-3 hours before bedtime, not likely to be effective except perhaps for REM sleep behavior disorder (may need higher doses)
memantine	not effective for BPSD
methylphenidate	modestly effective for apathy; start at 5 mg morning & noon, titrate to 10 mg morning & noon; monitor blood pressure, weight, restlessness
pimavanserin	only for psychosis associated with Parkinson disease; increases mortality
prazosin	one small study indicated efficacy, start 1 mg qhs, may increase to 2 mg qam and 4 mg qhs
valproate	do not use

Walaszek *Behavioral & Psychological Symptoms of Dementia* 2019; Hwang et al., *Neurology* 2021

Pharmacological options, by diagnosis

Diagnosis	Comments
Lewy body disease	• donepezil is first-line • if antipsychotic needed, consider clozapine, quetiapine or olanzapine • pimavanserin could be an option for PD psychosis
vascular dementia	• consider methylphenidate for apathy, but need to monitor blood pressure & irritability • may be more prone to vascular side effects of antipsychotics
FTD, behavioral variant	• trazodone or SSRIs are first line • stimulant could be considered • avoid cholinesterase inhibitors

Conclusions

- Behavioral and psychological symptoms are nearly universal in dementia, affect patients and caregivers, and can be distressing and dangerous.
- Treatment should always involve non-pharmacological interventions. If BPSD are dangerous and/or distressing, medications options can be considered.
- **We can improve the lives of persons with BPSD and their caregivers.**

Questions?

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