Agitation associated with Alzheimer's Disease

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- I receive royalties from Cambridge University Press for my book (co-author George Grossberg MD) titled *Psychiatric Consultation in Long-Term Care: A Guide for Healthcare Professionals*. 2nd Edition. 2017.
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Objectives

- Describe the diagnosis of “agitation associated with Alzheimer’s dementia” (AAD) used by the United States Food and Drug Administration to approve brexpiprazole for its treatment.

- Discuss best practices in prevention, assessment and management of AAD.

AAD

- Excessive motor activity (e.g., pacing, aimless wandering)
- Verbal aggression (e.g., cursing, swearing, use of obscenity, profanity)
- Physical aggression (e.g., hitting, pinching, kicking, banging, throwing)

AAD

- Frequency: rarely (less than once a week), sometimes (once per week), often (several times a week), very often (daily, once or more times)
- Severity: mild (little distress to the patient), moderate (more disturbing but redirectable), severe (very disturbing and difficult to redirect)

ICD 11 codes: Behavioral and Psychological Symptoms in Dementia

- 6D86.0 – Psychotic symptoms in dementia
- 6D86.1 – Mood symptoms in dementia
- 6D86.2 – Anxiety symptoms in dementia
- 6D86.3 – Apathy in dementia
- 6D86.4 – Agitation or Aggression in dementia
- 6D86.5 – Disinhibition in dementia
- 6D86.6 – Wandering in dementia

ICD 10 CM codes

- F02.A11 – Mild dementia due to Alzheimer’s disease with agitation
- F02.B11 – Moderate dementia due to AD with agitation
- F02.C11 – Severe dementia due to AD with agitation

Other terms previously used

- Behavioral and Psychological Symptoms of Dementia (BPSD)
- Neuropsychiatric symptoms (NPS) of Dementia
- Dementia with behavioral disturbances (old ICD diagnostic category)

AAD, BPSD, NPS

- More challenging and distressing symptoms than cognitive symptoms and functional challenges
- Common cause of caregiver burden, ED visits, hospitalizations, premature institutionalization
- Their management with psychiatric medications involves navigating many ethical challenges.

- Beck et al. Ethical issues in psychopharmacology. Focus 2021.

Definition of AAD

- Diagnosis of dementia
- Clinical diagnosis of Dementia due to probable Alzheimer’s Disease
- ”Agitation” that meets the International Psychogeriatric Association (IPA) proposed definition

- Sano et al. Agitation in cognitive disorders: Progress in the International Psychogeriatric Association consensus clinical and research definition. International Psychogeriatrics 2023.

IPA proposed definition

- Criteria A: Dementia
- Criteria B: at least one of the following three: excessive motor activity, verbal aggression, physical aggression for two weeks
- Criteria C: causes distress and or impairment in relationships and or ADL
- Criteria D: not due to other comorbidities

- Sano et al. Agitation in cognitive disorders: Progress in the International Psychogeriatric Association consensus clinical and research definition. International Psychogeriatrics 2023.

Criteria D: not due to other comorbidities

Comorbidities include the following: Delirium, Suboptimal care conditions, Medication adverse effects

- Sano et al. Agitation in cognitive disorders: Progress in the International Psychogeriatric Association consensus clinical and research definition. International Psychogeriatrics 2023.

Prevention of AAD

- High quality medical care
- Comprehensive Wellness Care Plan
- Caregiver STEPS (support, training, empowerment, praise, support)

High quality medical care

- 4Ms of Age-Friendly Care (what Matters, Medications, Mentation, Mobility)
- Goal concordant care

Medications

- Rational deprescribing using AGS 2023 Beers Criteria
- De-intensification of medical treatment based on age and frailty

Comprehensive wellness care plan

- Strengths-based Personalized Psychosocial spiritual Environmental Initiatives and Creative Engagement (SPPEICE)
- Pharmacological interventions as appropriate

- Desai and Grossberg. *Psychosocial spiritual wellness care plan for persons with dementia*. Chapter 13. Psychiatric consultation in long-term care: A guide for healthcare professionals. 2nd Edition. Cambridge University Press. 2017

Caregiver training: DICE training

- Describe
- Investigate
- Create
- Evaluate

- https://diceapproach.com

AAD – The ADEPT tool

- Assess
- Diagnose
- Evaluate
- Prevent
- Treat

- Shenvi C et al. Managing delirium and agitation in older emergency department patient: The ADEPT tool. Ann Emerg Med 2020.

Assess: Differential diagnosis

- Delirium and medical condition (e.g., pain) induced agitation
- Psychosis in dementia
- Primary mental illness (e.g., major depression [agitated depression], PTSD, schizophrenia, bipolar disorder)
- Substance / medication intoxication (includes caffeine)
- Substance / meditation withdrawal (includes caffeine)
- Pseudobulbar affect
- Parkinson’s disease psychosis

Evaluation of AAD after confirming diagnosis

- Get details about “agitation”: type, frequency, severity, duration, triggers (e.g., pain), context, relieving factors.
- Use quantitative measures to track response to treatment.

- American Psychiatric Association Practice Guidelines on the use of antipsychotics for the treatment of agitation or psychosis for patients with Dementia. 2016

Evaluate cause and context of AAD

- History
- Physical exam including neurological exam, mental status exam
- Standardized tests to assess cognition (e.g., SLUMS), function (e.g., FAQ, PSMS) and behavior (e.g., NPI-Q)
- Workup as appropriate: CBC, CMP, TSH, B12, vit D, Mag, medication blood levels, etc.

Comprehensive Treatment Plan

- Treat the cause
- Person-centered non-pharmacological interventions
- Pharmacological interventions as appropriate

- American Psychiatric Association Practice Guidelines on the use of antipsychotics for the treatment of agitation or psychosis for patients with Dementia. 2016

Primary / First line agitation interventions

- Treat the cause (biopsychosocial spiritual unmet needs)
- Deprescribing of deliriogenic / agitation inducing medications
- Multi-domain intervention (includes personalized non-drug interventions)
- Consults

- Desai and Grossberg. *Neurocognitive Disorders*. Chapter 3. Psychiatric consultation in long-term care: A guide for healthcare professionals. 2nd Edition. Cambridge University Press. 2017.

Treat the cause: Suboptimal care conditions

- Caregiver education
- Caregiver support
  - Support groups
  - Respite
  - Individual counseling
- Caregiver DICE training

- Sano et al. Agitation in cognitive disorders: Progress in the International Psychogeriatric Association consensus clinical and research definition. International Psychogeriatrics 2023.

Deprescribing

Identify and reduce / taper and discontinue deliriogenic medications (e.g., anticholinergics, benzodiazepines, opioids)

- Desai and Grossberg. *Psychiatric aspects of rational deprescribing*. Chapter 12. Psychiatric consultation in long-term care: A guide for healthcare professionals. 2nd Edition. Cambridge University Press. 2017.

Personalized non-drug interventions

- Collaborative de-escalation
- Ensure adequate hydration and nutrition
- Hearing and vision aids
- Calm, low stimulation environment
- Calming music, lavender or other soothing lotion
- Validation
- Humanitude approach: gaze, speech, touch, verticality
- Meaningful activities

Consults

- PT, OT, speech therapy
- Pharmacist
- Geriatrician
- Psychiatrist / Geriatric Psychiatrist / Neuropsychiatrist
- Neuropsychologist / Gerontologist
- Palliative Medicine

European Academy of Neurology Guideline

- AAD should be treated with antipsychotics only after all non-pharmacological measures have been proven to be without benefit or in the case of severe self harm or harm to others (weak recommendation)
- Antipsychotics should be discontinued after cessation of behavioral disturbances and in patients in whom there are side effects (good practice recommendation).

- Frederikson et al. A European Academy of Neurology guideline on medical management issues in dementia. European Journal of Neurology 2020

APA Guidelines for nonemergency antipsychotic medication

- For treatment of severe and dangerous agitation or psychosis
- For treatment of agitation or psychosis if they cause significant distress

- American Psychiatric Association Practice Guidelines on the use of antipsychotics for the treatment of agitation or psychosis for patients with Dementia. 2016

APA Guidelines for nonemergency antipsychotic medication

- Haloperidol should not be used as first line
- Long-acting injectable antipsychotic should not be utilized

- American Psychiatric Association Practice Guidelines on the use of antipsychotics for the treatment of agitation or psychosis for patients with Dementia. 2016

AGS Beers Criteria: Pharmacotherapy for AAD

Reserve pharmacotherapy for severe agitation, which poses a substantial danger for self-injury or danger to others; or for cases of severe distressing psychotic symptoms (e.g., hallucinations, delusions) and nonpharmacological interventions are not effective or not possible.

- American Geriatrics Society AGS 2023 Beers Criteria.

Dementia with agitation Rx

- Emergent setting:
  - First choice: IM olanzapine
  - Second choice: IM haloperidol
  - Third choice: IM lorazepam

- Chen A et al. Harvard South Shore Algorithm for management of behavioral and psychological symptoms of dementia. Psychiatry Res 2021.

Dementia with agitation Rx

- Urgent setting:
  - First choice: ODT risperidone or aripiprazole
  - Second choice: Prazosin
  - Third choice: ECT can be considered

- Chen A et al. Harvard South Shore Algorithm for management of behavioral and psychological symptoms of dementia. Psychiatry Res 2021.

Dementia with agitation Rx

- Non-urgent:
  - Trazodone
  - Donepezil and memantine
  - Escitalopram and sertraline
  - Second generation antipsychotics
  - Prazosin
  - Carbamazepine

- Chen A et al. Harvard South Shore Algorithm for management of behavioral and psychological symptoms of dementia. Psychiatry Res 2021.

Pharmacotherapy for Dementia related agitation

Brexpiprazole is the only drug approved by the FDA for treatment of dementia related agitation (AAD = Agitation in Alzheimer’s Dementia)

Pharmacotherapy for Dementia related agitation

Risperidone is approved in European Union, Canada, Australia and New Zealand for treatment of dementia related agitation (AAD = Agitation in Alzheimer's Dementia) – specifically for physical aggression management.

European Academy of Neurology Guideline

- Risperidone may be considered first line treatment when pharmacological treatment is necessary.
- Haloperidol and aripiprazole are also options.

- Frederikson et al. A European Academy of Neurology guideline on medical management issues in dementia. European Journal of Neurology 2020

Brexpiprazole dosing

- 0.5mg daily at bedtime for 7 days
- 1 mg daily at bedtime from 8-14 days
- 2 mg daily at bedtime from 15th day onwards
- 3 mg daily at bedtime from 22nd day onwards if necessary

- Lee et al. Brexpiprazole for the Treatment of Agitation in Alzheimer Dementia: A Randomized Clinical Trial. JAMA Neurology 2023.

When to expect a response?

- Within four weeks of the final dose
- If response not clinically significant or adverse effects more than benefits, taper and discontinue brexpiprazole

- Lee et al. Brexpiprazole for the Treatment of Agitation in Alzheimer Dementia: A Randomized Clinical Trial. JAMA Neurology 2023.

How long to prescribe?

Attempt to taper and discontinue within four months unless prior efforts to taper failed.

- American Psychiatric Association Practice Guidelines on the use of antipsychotics for the treatment of agitation or psychosis for patients with Dementia. 2016.

The FDA has issued Black Box Warnings

In dementia patients, use of antipsychotics carries black box warnings for increased risk of death and strokes – need to share this with patient and family

Dementia with agitation

Citalopram

- Livingston G, Huntley J, Sommerland A, et al.: Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 396, Aug 8, 2020, 413 – 446.

Dementia with agitation and antipsychotics

- Risperidone first choice
- Aripiprazole or Quetiapine second choice

- Academy of Consultation Liaison Psychiatry. How to manage acute agitation in medical setting. 2020.

Sequential treatment algorithm in an inpatient setting by Canadian experts

- First line: risperidone
- Second line: aripiprazole or quetiapine
- Third line: carbamazepine (100mg, after three days, 200mg and after four more days, 300mg at bedtime)
- Fourth line: citalopram (10mg, after a week to 20mg)
- Fifth line: gabapentin (200mg, up to 900mg, may go to 1800mg)
- Sixth line: prazosin (1-6mg, first dose at bedtime)
- Seventh line: combination of medications or ECT

- Davies et al. Sequential drug treatment algorithm for agitation and aggression in Alzheimer's and mixed dementia. Journal of Psychopharmacology 2018, Vol. 32(5) 509–523.

Sequential treatment algorithm in an inpatient setting by Canadian experts

- Risperidone (initial dose 0.5mg [0.25mg in frail patients], may be increased to 1mg [0.5 in frail] and if necessary 1.5mg [0.75 mg in frail]) – all doses given at bedtime
- Aripiprazole (2.5mg initial dose, initial target dose 10mg, may reach 12.5mg daily) – given as single evening dose
- Quetiapine (25mg initial dose [12.5mg if frail], initial target dose 100mg, and if necessary 200mg [100mg if frail]).

  - Davies et al. Sequential drug treatment algorithm for agitation and aggression in Alzheimer's and mixed dementia. Journal of Psychopharmacology 2018, Vol. 32(5) 509–523.

Sequential treatment algorithm in an inpatient setting by Canadian experts

As needed meditations:

- Trazodone (25mg every hour as needed with max of 150mg / day and option to go up to 300 mg / day in non-frail patients)
- Lorazepam (0.5mg as needed up to a max of 2mg / day)

- Davies et al. Sequential drug treatment algorithm for agitation and aggression in Alzheimer's and mixed dementia. Journal of Psychopharmacology 2018, Vol. 32(5) 509–523.

Pharmacotherapy – Other Antipsychotics

- Risperidone 0.5-1mg ODT (orally dissolvable tablet) – may cause orthostatic hypotension
- Olanzapine 2.5-5mg ODT – may cause orthostatic hypotension, caution in intoxicated patients
- Quetiapine 25-50mg at night – may cause orthostatic hypotension
- Haloperidol 1-2mg – may have more extrapyramidal adverse effects than atypical antipsychotics

- Shenvi C et al. Managing delirium and agitation in older emergency department patient: The ADEPT tool. Ann Emerg Med 2020.

Anticholinergic activity and antipsychotics

Brexpiprazole, risperidone, haloperidol and aripiprazole preferred as they have low / mild anticholinergic activity whereas quetiapine has moderate anticholinergic activity and olanzapine has severe anticholinergic activity

- Thom R et al. Delirium in hospitalized patients. Risks and benefits of antipsychotics. Cleveland Clinic Journal of Medicine 2017.

Parkinson’s disease, Lewy body dementia and antipsychotics – Delirium management

- Quetiapine is the preferred antipsychotic.
- Risperidone and haloperidol are contraindicated.

- Thom R et al. Delirium in hospitalized patients. Risks and benefits of antipsychotics. Cleveland Clinic Journal of Medicine 2017.
- Angel C et al. Standardizing management of adults with delirium hospitalized on medical-surgical units. Perm J. 2016.

Prolonged QTc and antipsychotics

Prolonged QTc: Aripiprazole is the preferred antipsychotic

- Thom R et al. Delirium in hospitalized patients. Risks and benefits of antipsychotics. Cleveland Clinic Journal of Medicine 2017.

Renal dose adjustments

Risperidone – caution / avoid in renal impairment

- Thom R et al. Delirium. Am J Psychiatry 2019.

Olanzapine and anticholinergic effects

- Constipation
- Inverted dose-response relationship: lower efficacy with 15mg/d for agitation/psychosis in dementia compared to 5mg/d.
- Delirium
- Worsening cognition in dementia patients.

- Mulsant and Pollock. Psychopharmacology. Textbook of Geriatric Psychiatry. American Psychiatric Association Publishing. 2023.

Olanzapine and anticholinergic effects

AGS 2023 Beers Criteria recommends us to avoid it in delirium patients (as part of avoiding anticholinergic medications)

- American Geriatrics Society. AGS 2023 Beers Criteria.

Special population and antipsychotics

- Orthostatic hypotension: Minimal risk: aripiprazole and ziprasidone; Mild risk: haloperidol and olanzapine; Moderate risk: risperidone and quetiapine
- Hyperglycemia – olanzapine has greatest risk, quetiapine has moderate risk, risperidone and haloperidol has low risk.

- Thom R et al. Delirium in hospitalized patients. Risks and benefits of antipsychotics. Cleveland Clinic Journal of Medicine 2017.
- 3D clinical practice guidelines – Delirium, Depression, Dementia in Post-Acute and Long-term Care Setting. AMDA 2023.

Haloperidol

Risk of akathisia is attenuated with 4.5 mg / day or less dose

- Thom R et al. Delirium. Am J Psychiatry 2019.

Clinical pearls - antipsychotics

- Even a single dose of olanzapine can trigger insulin resistance – so avoid in patients with brittle / labile / unstable diabetes (severe, frequent blood sugar swings)
- Haloperidol plus lorazepam orally may not work as quickly as ODT olanzapine

Anxiety management

- Chamomile (1,500 mg daily in two or three divided doses)
- Lavender (80 mg twice daily)
- These have not been studied in the elderly

- Garakani A et al. Pharmacotherapy for anxiety disorders: Current and emerging treatment options. Focus 2021.

Pharmacotherapy – IM meds

- Ziprasidone 10-20mg IM – caution in patients with heart disease, intoxicated patients
- Olanzapine 2.5-5mg IM – may cause orthostatic hypotension, caution in intoxicated patients, avoid in patients receiving parenteral benzodiazepines
- Haloperidol 0.25-1mg IM – may have more extrapyramidal adverse effects than atypical antipsychotics, may redose if needed

- Shenvi C et al. Managing delirium and agitation in older emergency department patient: The ADEPT tool. Ann Emerg Med 2020.

Pharmacotherapy – Benzodiazepines

Benzodiazepines are appropriate for alcohol withdrawal delirium, sedative-hypnotic withdrawal delirium, stimulant intoxication and in patients with active seizures

- Shenvi C et al. Managing delirium and agitation in older emergency department patient: The ADEPT tool. Ann Emerg Med 2020.

Pharmacotherapy – Avoid Benzodiazepines

- Risk of precipitating delirium
- Risk of prolonged sedation
- Risk of paradoxical agitation
- Risk of worsening delirium or prolonging delirium
- If used, use 0.5mg lorazepam

- Shenvi C et al. Managing delirium and agitation in older emergency department patient: The ADEPT tool. Ann Emerg Med 2020.

Other options

- Aripiprazole 1-10 mg – may cause akathisia
- Melatonin 1-3 mg 60 minutes before bedtime

- Thom R et al. Delirium. Am J Psychiatry 2019.

Acute Agitation Rx in non-delirium situations in adults (research did not have enough older adults)

- Oral:
  - Tier 1: lorazepam, olanzapine, haloperidol plus lorazepam
  - Tier 2: haloperidol plus promethazine, risperidone, loxapine (inhaled)
  - Tier 3: asenapine, quetiapine
- Parenteral:
  - Tier 1: olanzapine, haloperidol plus promethazine
  - Tier 2: lorazepam, haloperidol plus lorazepam
  - Tier 3: droperidol, ziprasidone

    - Stetson and Osser. Current Opin Psychiatry 2022.

Acute Agitation Rx in non-delirium situations in adults (research did not have enough older adults)

- B52: Intramuscular Benadryl 25mg, Haloperidol 5mg, Lorazepam 2mg – No controlled studies. Hence NOT recommended.
- Midazolam effects don't last very long and repeated use can lead to respiratory suppression. Okay to use in ED settings.
- Dexmedetomidine (Igalmi) sublingual is approved by the FDA for acute agitation treatment in patients with Schizophrenia or Bipolar disorder.

- Stetson and Osser. Current Opin Psychiatry 2022.

Acute agitation pharmacotherapy in ED – adults (average age 40 years)

- IM midazolam 5 mg achieved best sedation at 15 min
- IM olanzapine 10mg did better than IM haloperidol 10mg
- IM ziprasidone 20mg

- Klein et al. Intramuscular midazolam, olanzapine, ziprasidone, and haloperidol for treating acute agitation in the emergency department. Annals of Emergency Medicine 2018.

Risks of B52 vs 52

B52 (Benadryl + 5mg haloperidol + 2mg lorazepam) resulted in more oxygen desaturation, hypotension, physical restraint use, and longer length of stay compared to 52 combination.

- Jeffers T et al. Efficacy of combination haloperidol, lorazepam and diphenhydramine vs. combination haloperidol and lorazepam in the treatment of acute agitation. A multicenter retrospective cohort study. J Emerg Med 2022.

Parkinson’s Disease Psychosis

- Pimavanserin (Nuplazid) approved by the FDA
- Quetiapine may be considered
- Clozapine has grade A level evidence (highest quality evidence)

Pseudobulbar Affect (PBA)

Dextromethorphan – Quinidine (Nuedexta) approved by the FDA for PBA

Insomnia in Alzheimer’s Dementia

Suvorexant (Belsomra) is the only FDA approved medication

Patient with AAD not improving regarding aggressive behaviors

- Re-assess for pain as thoroughly as is possible and treat it well
- Do a whole new thorough assessment as if you are seeing the patient for the first time – you are most likely missing one or more reversible causes
- Get a second opinion

Resources

- American Geriatrics Society. AGS 2023 Beers Criteria.
- Anticholinergic Burden Calculator website (acbcalc.com)
- American Delirium Society

Resources: PsychUsim AAD simulator

- Website: https://psychusim.org

- Simulator available for Agitation Associated with Dementia (AAD), Schizophrenia, Major Depression and Bipolar disorder

Resources: PsychUsim AAD simulator

- In AAD simulator: Several nodes available to click and learn more: Cognitive impairment and screening tools, Prevalence, Agitation assessment (they use CMAI – Cohen Mansfield Agitation Inventory, freely available as pdf on the internet), Pathophysiology, Clinical presentation and diagnosis, Caregiver burden, Patient burden, Economic burden, Treatment guidelines, Non-pharmacological treatment, Pharmacological treatment.

- My take: This is good for education purposes. You will do better getting prevention and treatment of dementia including AAD from a dementia expert team such as our Saint Alphonsus Memory Center with clinics in Boise, Eagle and Nampa and we offer telemedicine consultation.

Free eBooks by Dr. Desai (available upon email request)

- Agitation associated with Dementia
- Delirium in older adults
- Dementia Prevention
- Dementia Family Caregiver Wellness
- Overcoming anxiety, depression and anger
- Fearless, Strong, Patient, Kind: A book of meditations
- Mindfulness and Meditation

Namaste