Pharmacological Treatments for Dementia and Management for Neuropsychiatric Symptoms of Dementia

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OBJECTIVES

- Review current pharmacologic treatment guidelines of Alzheimer's disease (AD)
- Discuss treatment options for other types of dementia
- Review therapies to manage behavioral and psychiatric symptoms of dementia

CLINICAL PRESENTATION

Symptoms show up years before diagnosis

Changes in mood, anxiety, sleep, depressive symptoms, apathy, withdrawal

Underdiagnosed

GOALS OF THERAPY

Maintain cognition & functional status

Manage behavioral & psychological symptoms

Treatment Options for Dementia

Cholinesterase Inhibitors

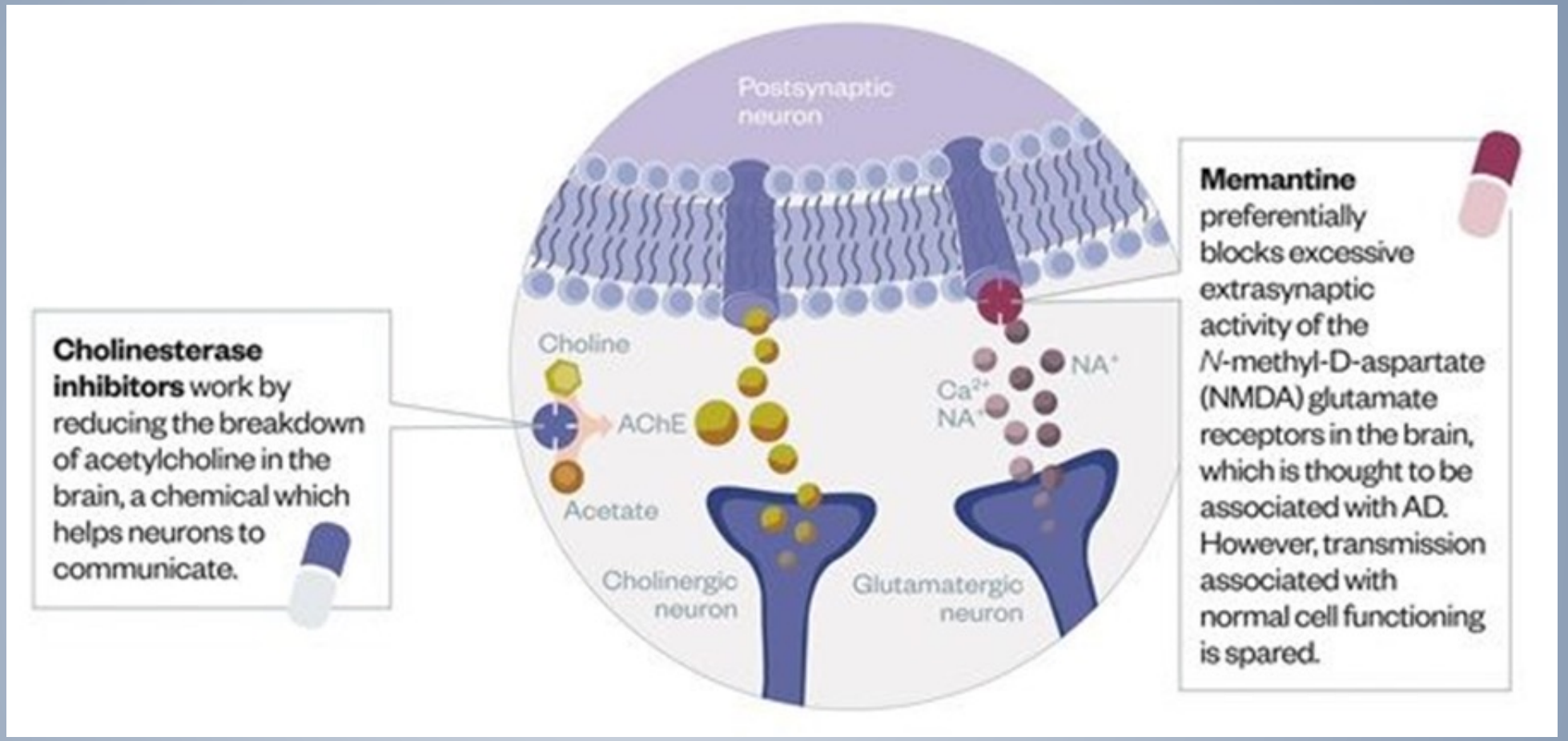
- Donepezil (Aricept™)
- Galantamine (Razadyne™)
- Rivastigmine IR & Transdermal (Exelon™)

NMDA Receptor Antagonist

- Memantine (Namenda™)

Anti-Amyloid Monoclonal Antibody

- Aducanumab (Aduhelm™)



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Meta-analysis of 13 randomized trials

Methods: Blinded RTC comparing **Donepezil, Galantamine, Rivastigmine** vs placebo in 3000 patients with AD

Objectives: Assess the effects of Donepezil, Galantamine, Rivastigmine in people with mild, moderate or severe dementia due to Alzheimer's disease

Results:

- At 6-12 months, cholinesterase inhibitors showed modest improvements
  - ADAS-Cog Scale: Mean difference -2.7 points **(**95% CI: -3.0 to -2.3)
  - MMSE: Mean difference 1.37 points (95% CI 1.13-1.61) as well as global impression by caregivers and ADLs.
  - "**One analysis estimated that these effects would be similar to preventing a two-months-per-year decline in a typical patient with AD**"
  - "**Another analysis concluded that for every 12 patients treated, one would benefit by achieving minimal improvement or better and one would develop a treatment-related adverse effect**"
  - More patients withdrew from the cholinesterase inhibitors treatment due to adverse events (29 %) compared to placebo (18%)

Meta-analysis of 13 randomized trials

Results:

- Two studies compared **donepezil with galantamine** & two studies compared **donepezil with rivastigmine**
  - No difference between donepezil and galantamine at 52 weeks for cognition, ADL, adverse drug events (ADE)
  - No difference between donepezil and rivastigmine for cognitive function, ADL and behavioral disturbance at 2 years.
    - ADE is higher in the rivastigmine group during the titration phase, but similar in the maintenance phase. AED of rivastigmine 31.7% vs. AED of donepezil 32.5%

Conclusion

- Cholinesterase inhibitor treatment may offer continued therapeutic benefit for up to 2 years in patients with AD
- No difference in efficacy among the cholinesterase inhibitors

AD2000 Trial

Methods:

- 565 community-resident patients with mild to moderate Alzheimer's disease
- randomly received donepezil (5 mg/day) or placebo x 12 weeks
- 486 who completed this period were re-randomized to either donepezil (5 or 10 mg/day) or placebo, with double-blind treatment continuing as long as judged appropriate.

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Primary endpoints:

- Entry to institutional care and progression of disability, defined by loss of either two of four basic, or six of 11 instrumental activities on the Bristol activities of daily living scale (BADLS)

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FINDINGS:

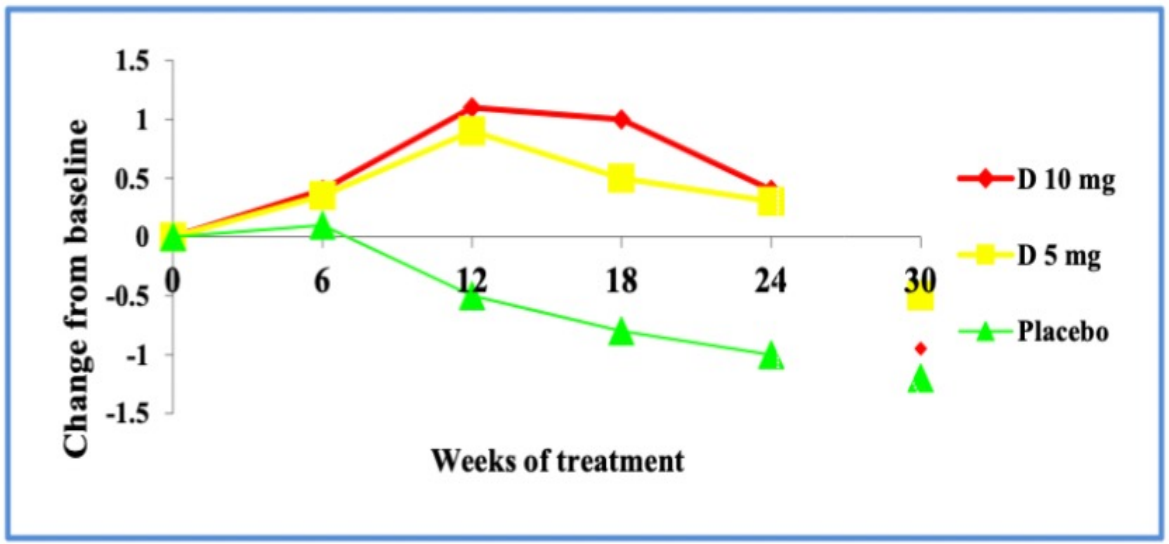
- Cognition averaged 0.8 MMSE points better (95% CI 0.5-1.2; $p<0.0001$) and functionality 1.0 BADLS points better (0.5-1.6; $p<0.0001$) with donepezil over the first 2 years.
- **No significant benefits with donepezil compared with placebo in institutionalization (42% vs 44% at 3 years; p=0.4) or progression of disability (58% vs 59% at 3 years; p=0.4).**
- **No significant differences between donepezil and placebo in behavioral and psychological symptoms**
- **No significant differences were seen between 5 mg and 10 mg donepezil.**

Rogers, et al: results

› Donepezil 10mg and 5mg have similar efficacy at 24 weeks

Efficacy

▸ 1.5 difference on MMSE after 24 weeks of donepezil compared with placebo[1]



High Dose of Donepezil 23mg

Farlow, et al Results:

- 1467 patients with moderate AD received Donepezil 10 mg once daily
- Randomized to stay on Donepezil 10 mg daily or increase to 23 mg daily
- After 24 weeks
  - SMALL benefit (2.2 difference on Severe Impairment Battery (SIB) scale)
  - MORE nausea and vomiting with Donepezil 23 mg
  - GI side effects were over 3 times higher (21%) in the first month in the donepezil 23mg group compared to the donepezil 10mg group (5.9%)

› High dose of Donepezil 23 mg can result in more GI side effects with little clinical benefit.

Cholinesterase Inhibitors

Variable responses to cholinesterase inhibitors

- 30 -50% of patients show no observable benefits
- Individualized decisions for each patient are based on clinical response and side effects
- Consider a trial at time of diagnosis

Duration of Therapy

- No consensus on how long to continue cholinesterase inhibitors in patients who are tolerating therapy, and even patients who respond initially will ultimately progress.

Current Dementia Guidelines (ACP)

1. Decision to initiate a trial of therapy with cholinesterase inhibitors/ memantine should be based on individualized assessment. (weak recommendation, moderate quality evidence)
2. Choice of pharmacologic agents should be based on tolerability, adverse effects, ease of use, and cost. (weak recommendation, low quality evidence)
3. There is urgent need for further research on clinical effectiveness of pharmacologic management of dementia.

"Don't prescribe cholinesterase inhibitors for dementia without periodic assessment for perceived cognitive benefits and adverse GI effects"

American Geriatrics Society

AGS Geriatrics Healthcare Professionals

Leading Change. Improving Care for Older Adults.

Ten Things Clinicians and Patients Should Question

http://www.choosingwisely.org/societies/american-geriatrics-society/

Discontinuation of Cholinesterase Inhibitors

Avoid

- Avoid abrupt discontinuation UNLESS severe adverse drug reactions to minimize withdrawal symptoms

Taper

- Taper using 50% dose reduction or stepwise reduction via available dose formulations every 4 weeks to lowest dose prior to discontinuation

Reinitiate

- Reinitiate if worsening of conditions after withdrawal

CHOLINESTERASE INHIBITORS

Use	Modestly improve symptoms of **Alzheimer's disease** Delay in symptom progression. Maintain current level of cognition & function No change in disease progression
MOA	Increase cholinergic transmission by inhibiting cholinesterase at the synaptic cleft
Dosing	Dosing interrupted < 3 days → restart at SAME or LOWER dose Dosing interrupted for > 3 days → restart treatment w/ LOWEST dose & titrate
Adverse Effects	N/V/diarrhea (drug initiation & dose escalation) Weight loss, anorexia (common with donepezil 23 mg) Dizziness, dyspepsia, agitation, bradycardia/ syncope, urinary incontinence, abnormal dreams
Precautions	**Bradycardia:** Vagotonic effects on SA nodes → bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. **Peptic Ulcers Disease:** ↑gastric acid secretion due to increased cholinergic activity. **COPD/asthma:** Cholinomimetics → bronchi are contracted

Clinical Trial: **Memantine in moderate-to-severe Alzheimer's disease**

Population: 252 patients with moderate-to-severe AD (average age 76)

Intervention: Memantine 20mg daily for 28 weeks

Comparison: Placebo for 28 weeks

Outcomes

Primary endpoints:

- Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus)
- Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia (ADCS-ADLsev)

Efficacy: Patients receiving memantine had a better outcome than those receiving placebo per CIBIC(P=0.06) and ADCS-ADLsev (P=0.02)

Safety:

- More patients receiving placebo than patients receiving memantine discontinued the study early because of adverse events (17 %) vs (10 %)
- Agitation was the most common reason for discontinuation (7 % of those receiving placebo and 5 % of those receiving memantine)

Clinical Trial: Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial

- Population: Patients with moderate to severe AD already receiving stable treatment with donepezil.
- Intervention: Participants were randomized to receive memantine (starting dose 5 mg/d, increased to 20 mg/d, n = 203) for 24 weeks
- Comparison: Placebo (n = 201) for 24 weeks
- *Primary Outcomes:*
  - Change from baseline on the Severe Impairment Battery (SIB), possible score range, 0-100, Memantine 0.9 (0.67) vs Placebo -2.5 (0.69), (P<.001)
  - AD Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL19), possible score range, 0-54, Memantine -2.0 (0.50) vs Placebo -3.4 (0.51), (P =.03)

Clinical Trial: Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial

- *Secondary Outcomes*
  - Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), possible score range, 1-7, Memantine 4.41 (0.074) vs Placebo 4.66 (0.075), (P =.03)
  - Neuropsychiatric Inventory (NPI) was lower for the memantine group compared with the placebo group at week 24 (*P* = .01) → Fewer behavioral disturbances & psychiatric symptoms in the memantine group
  - Behavioral Rating Scale for Geriatric Patients (BGP Care Dependency Subscale) was improved for the memantine group compared with the placebo group (*P* = .001)
- *Safety Data*:
  - Adverse Events: Memantine (7.4%) vs placebo (12.4%). Confusion was the most commonly reason for discontinuation.
- Conclusion: Patients with moderate to severe AD receiving stable doses of donepezil, Memantine has shown improvement than placebo on measures of cognition, ADL, and behavior and is well tolerated.

Memantine Mysteries

- Half-life: ~60 to 80 hours
- Why is memantine immediate release (IR) dosed twice daily?
- What is the value of the memantine extended release (ER) product?

Anti-Amyloid Monoclonal Antibody Aducanumab (Aduhelm™)

- Refer to previous ECHO Dementia recording on 3/12/2021 from Dr. Charles Bernick
- **EMERGE Study and ENGAGE Study**
- Both studies have shown to reduce amyloid plaque in MCI and early stage of Alzheimer's disease
- Statistical assessment is still lacking for meaningful clinical benefits to patients
- ARIA-E and ARIA-H are safety concerns
- FDA accelerated approval can be based on the drug's effect on a surrogate endpoint (biomarker – amyloid plaque) with a required post-approval trial to verify that the drug provides the expected clinical benefit.
- Biogen manufacturer hopes to have the clinical trial completed by 2030 or earlier.

	Donepezil	Galantamine	Rivastigmine	Memantine	Aducanumab
Alzheimer Disease (Mild-Moderate)	**X**	**X**	**X** Oral tablet Transdermal Patch		**X** For MCI or mild dementia who have elevated amyloid beta by PET imaging
Alzheimer Disease (Moderate-Severe)	**X**	Off-label use	**X** Transdermal Patch	**X** Monotherapy or in combination with a cholinesterase inhibitor	
Vascular Dementia	Off-label use		Off-label use	Off-label use	
Dementia with Lewy Bodies	Off-label use	Off-label use	Off-label use	Off-label use	
Parkinson Disease dementia	Off-label use	Off-label use	**X** Oral tablet and Transdermal Patch for mild to moderate PD dementia	Off-label use	
Frontal Temporal Dementia					

Frontal Temporal Dementia

- **Cognitive dysfunction** — No medications have been demonstrated to improve cognitive deficits in patients with FTD.
- “When there is uncertainty about whether the patient has FTD or AD, a trial of a cholinesterase inhibitor is reasonable.”
- **Galantamine** shows some benefit in patients with primary progressive aphasia of FTD at a 8-week trial.
- **Rivastigmine** shows benefit on executive function but not global cognition as measured by MMSE.
- **Donepezil:** An open-label study found no benefit of treatment on cognitive measure. Some patients developed worsened behaviors.

Neuropsychiatric Symptoms (NPS) of Dementia

Psychotic symptoms: psychosis, delusions, hallucinations, sleep disturbances

Depression

Hyperactive/ disruptive behavior: agitation, aggression, hyperactivity, hypervocalization, disinhibition

Anxiety

Apathy

Management of Neuropsychiatric Symptoms (NPS) of Dementia

- Nonpharmacologic therapies
- Medication side effects
- Pain assessment
- Delirium
- Depression
- Sleep disorders
- Poor vision
- Hearing loss

Management of Neuropsychiatric Symptoms (NPS) of Dementia

- NO MEDICATIONS ARE APPROVED TO TREAT NPS
- Antidementia drugs: cholinesterase inhibitors, Memantine
- Atypical antipsychotics – Olanzapine, Quetiapine, Pimavanserin, Risperidone
- Antidepressants – SSRI
- Anticonvulsants
- Prazosin ?

Management of Neuropsychiatric Symptoms (NPS) of Dementia

Cholinesterase inhibitors

- A 2015 systematic review and meta-analysis:
  - 15 randomized placebo-controlled trials
  - Cholinesterase inhibitors have shown a small efficacy for NPS in mild to moderate dementia

- For NPS in mild to moderate dementia
- Patients with DLB may have a more beneficial response

Memantine

- Post hoc analyses: Patients on memantine treatment may have diminished agitation/aggression, irritability, and other behavioral disturbances
- However, systematic reviews shows that studies have not demonstrated a clinically significant effect of memantine for NPS of dementia

Antipsychotics for NPS

Both typical and atypical antipsychotics may potentially increase mortality

Not FDA approved for the treatment of behavioral disorders in patients with dementia.

"American Psychiatric Association (APA) recommends that if a risk/benefit assessment favors the use of an antipsychotic for behavioral/psychological symptoms in patients with dementia, treatment should be initiated at a low dose to be titrated up to the **minimum effective dose** as tolerated."

Use antipsychotics cautiously after informing patient/caregiver/family of the potential risks, including the risk of increased mortality

Antipsychotics for NPS

Olanzapine (Zyprexa™)

- 2.5 mg daily and titrated up to 5 mg BID.
- Modestly effective for treating NPS in AD or vascular dementia
- Olanzapine shows statistically significant benefit for the primary endpoints in 4 out of 7 trials studied
- Less extrapyramidal symptoms at doses ≤ 5 mg per day
- More metabolic side effects (eg, weight gain, diabetes, and hypercholesterolemia)

Quetiapine (Seroquel™)

- 25 mg QHS & titrate up to 75 mg BID
- Fewer data regarding the effectiveness of quetiapine in NPS
- Conflicting results

Antipsychotics for NPS

Pimavanserin (Nuplazid™)

- Approved for Parkinson disease-related psychosis
- 34 mg daily
- Tariot et al. Trial: 351 patients with dementia-related psychosis were treated with open-label pimavanserin (20mg or 34 mg once daily)
  - 217 had a clinical response at 12 weeks
  - Followed by a randomized trial of drug continuation versus placebo
  - Relapse rate: Placebo 28% vs. Pimavanserin 13%
- Adverse effect: QT prolongation, orthostatic hypotension, etc.

Risperidone (Risperdal™)

- Risperidone shows statistically significant benefit for the primary endpoint in 4 out of 7 trials studied
- Initial: 0.5 mg/day in 2 divided doses; titrate up to 1 mg/day
- Higher doses may be associated with increased side-effects (drug-induced parkinsonism, etc.)
- **Risperidone should not be used in patients with DLB**

Antipsychotics for NPS

Clozapine

- Clinical trials found no evidence that Clozapine shows benefit for NPS
- Many adverse drug reactions (severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, Increased mortality in elderly patients with dementia-related psychosis, etc.)
- Risk Evaluation and Mitigation Strategy (REMS) program requirements

Antidepressants for NPS

Clinical trials of SSRIs for depression in patients with dementia have shown mixed results

- **Citalopram**:
  - Two multicenter trials with citalopram demonstrated efficacy for NPS with mild side effects.
  - In one study that used Citalopram 30mg daily, QT prolongation and worsening cognitive scores were noted in the citalopram-treated patients
  - It is recommended not to exceed Citalopram 20 mg daily in older adults
- **Escitalopram:** Stereoisomer, S-citalopram (escitalopram) can inhibit reuptake of serotonin more potently compared with the other stereoisomer.
- **Sertraline**: A study in 131 patients with AD and depression found no efficacy for sertraline after 12 and 24 weeks of therapy
- **Fluoxetine:** Long half-life and more drug interactions than other SSRIs → less desirable for older adults
- **Paroxetine**: The most anticholinergic of the SSRIs → affect cognition

Antidepressants for NPS

- **Venlafaxine and Bupropion** have not been well studied in AD.
- **Mirtazapine**: Randomized trial of 219 patients with depression and AD, mirtazapine was no more effective than placebo after 13 or 39 weeks of therapy.
- **Tricyclic antidepressants**
  - Anticholinergic side effects → can cause worsening confusion
  - Not as well tolerated as SSRI
  - Should be avoided

Anticonvulsants

- Carbamazepine
  - A placebo-controlled study of agitation in nursing home patients with advanced dementia: Low doses (300 mg/day) achieving a mean serum level of 5.3 mcg/mL were used and has showed some efficacy.
  - Subsequent trial found no benefit
  - Systematic review: Not enough evidence of benefit for carbamazepine to recommend its use for NPS
- Valproate
  - Improved aggressive behavior in several earlier reports
  - Subsequent systematic review: Three randomized controlled trials and two studies of valproate concluded that Valproate was ineffective for NPS treatment
- Gabapentin
  - One open-label prospective study shows little benefit
  - For patients receiving Gabapentin for postherpetic or neuropathic pain, Gabapentin can help with pain and agitation.
- Lamotrigine:
  - No randomized, placebo-controlled studies have been published to date.

Drugs to Avoid

Benzodiazepines

- Not recommended for the NPS of dementia
- Randomized controlled trial: Using IM lorazepam and IM olanzapine for NPS shows benefit 2 hours after treatment. However, the benefit of lorazepam was not sustained at 24 hours.
- Benzodiazepine side effects: Worsening gait, potential paradoxic agitation, and physical dependence.
- **"Benzodiazepine should be limited to brief and stressful events, such as a change in residence or an anxiety-provoking medical event". Benzodiazepine with shorter half-lives such as Lorazepam is preferred**.

Older Antihistamines

- Not recommended due to high rates of anticholinergic side effects

Other Sedatives

- Not recommended due to sedation, fall risks, worsening confusion

Prazosin ?

PEACE-AD trial (Prazosin for Disruptive Agitation in Alzheimer's Disease)

› Purpose: Determine safety and efficacy of prazosin on agitation in adults with AD

  - Prazosin is FDA approved for HTN: Not recommended for initial management. May be considered as additional therapy for resistant HTN in patients who do not respond to combination therapy with preferred agents.
  - PTSD-related nightmares and sleep disruption (off-label use): Dose range: 3 to 15 mg at bedtime
  - Prazosin doesn't have side effects that atypical antipsychotics have (sedation, stroke risk, increased mortality in dementia patients, etc.)

› Study Design: Multicenter, randomized, double blind, placebo controlled. phase 2, 20 long term memory care communities

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› Start date: October 23, 2018, End date: February 2022

› Enrolled 186 nursing home residents with dementia, probable Alzheimer's disease

PEACE-AD trial (Prazosin for Disruptive Agitation in Alzheimer's Disease)

- Inclusions:
  - Agitation significant enough to interfere with caregiving
  - Any combination of the behaviors: Irritability, physically and/or verbally aggressive behavior, physically resistant to necessary care, restlessness, pacing, or other movement symptoms of agitation
  - If taking psychotropic medication, dosage must be stable for at least two weeks prior to starting the study
  - If taking a cholinesterase inhibitor and/or memantine, dosage must be stable for three months prior to starting the study

- Intervention: Prazosin BID x 12 wks (Titration schedule starting with 1mg QHS and titrating up to 4mg QAM & 6mg QHS on day 29)

- Comparison: Placebo BID x 12 weeks (titration schedule)

- Primary outcome: ADAS-Clinical Global Impression of Change in Agitation (CGIC)

- Results: No results published yet

Ongoing Evaluation and Monitoring

American Psychiatric Association recommends: “An attempt to taper and withdraw antipsychotic therapy be made within **four months of initiation** in patients who have responded to therapy and who have no prior history of relapse with medication taper.”

Use of antipsychotic medications should only continue if the medication provides benefit.

Discontinuation of antipsychotics should be considered on regular basis while assessing the risk of relapse versus risk of adverse effects from continued use of medication

Some patients may not be able to taper-off antipsychotic medications due to relapse.

Patients with severe baseline symptoms may be at an increased risk of relapse upon medication discontinuation.

Summary

- Assessment for underlying causes for cognitive changes and NPS
- Nonpharmacologic approaches
- Adequate Pain management
- Cholinesterase inhibitors do not improve NPS clinically, but these drugs have modest improvement in cognition.
- Cautious use of Antipsychotics
- SSRI
- Ongoing monitoring of benefits versus harms must be conducted regularly

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- Up to Date
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