Pharmacological Treatments for Neuropsychiatric Symptoms of Dementia

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OBJECTIVES

- Discuss pharmacological therapies to manage behavioral and psychiatric symptoms of dementia
- Use of antipsychotics
- Use of antidepressants
- Use of other pharmacological therapies
- Discuss assessing benefits of therapy-continuation and risks of side effects

Dementia

Estimated prevalence:

- 50 million cases worldwide

- Anticipated to increase to 152 million people by 2050

Majority of patients with Alzheimer's dementia (AD) will experience symptoms of mood or behavioral disturbance at some point in the disease process

Neuropsychiatric Symptoms (NPS) of Dementia

Psychotic symptoms:

Delusion

hallucinations

Paranoia

sleep disturbances

Disruptive/hyperactive behavior:

Agitation

Aggression

Hyperactivity

Hypervocalization

Irritability

Wandering/pacing

Disinhibition

Anxiety

Depression

Apathy

Neuropsychiatric Symptoms (NPS) of Dementia

- One or more of NPS symptoms are observed in **60% - 90%** of patients with dementia
- Prevalence increases with disease severity
- Lead to greater functional and cognitive impairment in patients with dementia
- Diminish quality of life for both patients living with dementia and their care partners
- Cause greater care partner burden, depression, and employment difficulties
- Increase morbidity and mortality, health-care utilization
- Accelerate to earlier institutionalization

Neuropsychiatric Symptoms (NPS) of Dementia

- NPS are common in dementia, but may be under-reported by patients and families
- Screening for NPS in patients with dementia should be done at regular follow-up visits
- Important questions to ask caregivers
  - **Does the patient have any behaviors that worry you?**
  - **Does the patient have hallucinations, see things, or hear voices that aren't there?**

Management of Neuropsychiatric Symptoms (NPS) of Dementia

- Nonpharmacologic therapies
- Other underlying causes
  - Medication side effects
  - Pain
  - Delirium
  - Depression
  - Sleep disorders
  - Poor vision
  - Hearing loss

Best Practices

- **Non-Pharmacological Interventions:** First-line treatment of agitation in dementia for all patients
  - Effective interventions
  - Implementation is difficult due to limited resources, staff availability, and training requirements within institutional and other care settings.
- **Pharmacological agents**
  - When first-line therapies (ie. Non-Pharmacological Interventions) have failed
  - Symptoms are severe and/or distressing
  - When imminent safety is a concern for the patients and those around them

A 2023 Update on the Advancements in the Treatment of Agitation in Alzheimer's Disease

- Agitation: One of the most common, complex, and distressing NPS, resulting from a complex interplay of neurologic, biologic, psychiatric, and environmental contributions
- Proposed mechanisms of agitation in AD include **dysregulation of serotonin, NE, glutamate, sigma-1, and cannabinoid neurotransmission**

- A 2023 update on the advancements in the treatment of agitation in Alzheimer's disease - PubMed (nih.gov)

Management of Neuropsychiatric Symptoms (NPS) of Dementia

- **Atypical antipsychotics – Olanzapine, Quetiapine, Risperidone, Clozapine, Aripiprazole, Brexpiprazole, Pimavanserin**
- Antidepressants – SSRI
- Dextromethorphan/Quinidine & Dextromethorphan/Bupropion
- Prazosin
- Cholinesterase inhibitors/ Memantine
- Anticonvulsants

Antipsychotics (2nd Generation)

- **Off Label Use: Agitation/aggression and psychosis associated with dementia**
  - Olanzapine
  - Risperidone
  - Quetiapine
  - Aripiprazole (Abilify ™)
  - Clozapine
- **FDA approval**:
  - **Brexpiprazole (Rexulti ™) - Agitation associated with dementia due to Alzheimer disease**
  - Pimavanserin (Nuplazid ™) - Parkinson disease psychosis

Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease

- 42 site double blind placebo controlled trial, N=421
- Method: Outpatients with AD and psychosis, aggression, agitation 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) vs placebo in 2:2:2:3 ratio
  - If response is not adequate after 1st 2 weeks, discontinue treatment.
  - If adequate response, continue treatment up to 36 weeks
- Inclusion: AD, MMSE 5-26, ambulatory, live at home or ALF, **delusions, hallucinations aggression or agitation that developed after dementia onset and were severe enough to disrupt their functioning and need antipsychotics**
- Exclusion: primary psychotic disorders (e.g schizophrenia, bipolar), delirium, other dementia like vascular or Lewy body, psychosis agitation aggression due to other medical condition medication or substance, suicidal, receive ACHEi or antidepressant
- **Primary outcome**: Time from initial treatment to the discontinuation of treatment for any reason
- **Secondary outcome**: Number of patients with at least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at **12 weeks**

Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease

Results:

- **Median time to discontinuation due to lack of efficacy**: **Favored olanzapine (22.1 weeks) and risperidone (26.7 weeks) vs quetiapine (9.1 weeks) and placebo (9.0 weeks) (P=0.002)**
- **No significant differences in improvement on the Clinical Global Impression of Change (CGIC) scale:** Improvement in the Olanzapine group (32%), Risperidone group (29%), Quetiapine group (26%), placebo group (21%) (P=0.22)
- Median time to discontinuation due to AE/intolerability: Favored placebo - Olanzapine 24%, quetiapine 16%, risperidone 18%, placebo 5% (p=0.009)
- **Higher rate of parkinsonism or EPS in olanzapine and risperidone (12% each) vs quetiapine (2%) vs placebo (1%)**
- **Cognitive disturbances and psychotic symptoms: more common with olanzapine (5% and 7%, respectively) than with the other medications or placebo (0 to 2%)**
- **Body weight and BMI increased with antipsychotic drugs (0.4 to 1.0 lb per month)** and decreased slightly with placebo (by −0.9 lb per month and −0.2 BMI unit)
  - Olanzapine > Risperidone > Quetiapine > Placebo

Conclusion

- Atypical antipsychotic drugs were more effective than placebo
- Adverse effects may limit their overall effectiveness
- Usage may be restricted to patients who have few or no side effects and for whom benefits are demonstrated.
- Clinicians, patients, and family members must consider both risks and benefits in order to optimize a patient's care.

- https://www.nejm.org/doi/full/10.1056/NEJMoa061240

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 (EPS) 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

Antipsychotics for NPS

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 are associated with increased side-effects (drug-induced parkinsonism, etc.)**
- **Risperidone should not be used in patients with DLB**

Clozapine

- Conflicting results for NPS treatment
- **Off Label Use: Agitation/aggression and psychosis associated with dementia**
- 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

Aripiprazole (Abilify ™)

Mechanism of Action (MOA): Functions as a partial agonist at the D_2 and 5-HT_{1A} receptors, and as an antagonist at the 5-HT_{2A} receptor

Psychosis nursing home patients with AD (RCT, multicenter, parallel group, double blinded placebo controlled), N=256, duration 10 weeks (2008)

- **Method**: AD patients age 55-95 with psychotic symptoms (delusions/hallucination at least intermittently for > 1 month) associated with AD randomized to receive aripiprazole 2 mg/day (could be titrated to 5, 10, 15 mg/day based on efficacy and tolerability vs placebo
- **Primary outcome**: Mean change from baseline to Week 10 (last-observation-carried-forward [LOCF] dataset) on Neuropsychiatric Inventory (NPI-NH Psychosis subscale and CGI-S scores)
- **Secondary outcome**: Mean changes from baseline in the scores for the NPI-NH Total scale, BPRS, CMAI, Cornell Scale for Depression in Dementia, NPI-NH Psychosis and Total Caregiver Distress Scores, and Alzheimer's Disease Cooperative Study–mActivities of Daily Living (ADCS-ADL-SEV)

Aripiprazole (Abilify ™)

Results:

- **Primary outcome**
  - **NPI-NH psychosis scores improved in both groups but no difference in mean change from baseline to week 10** (aripiprazole, -4.53 [9.23] vs placebo, -4.62 [9.56] p = 0.883
  - **CGI Severity score improved in both groups but no difference** (aripiprazole, -0.57 [1.63] vs placebo, -0.43 [1.65]; p = 0.198 at endpoint.
- **Secondary outcome**
  - **Significant improvement in several secondary efficacy measures** (NPI-NH Total, BPRS Total, CGI – improvement, CMAI and Cornell Depression Scale scores) indicated that aripiprazole may confer clinical benefits beyond the primary outcome measures.
  - Greater percentage of responders with aripiprazole vs placebo at Week 8 (47% vs 31%; p= 0.010) and endpoint (46% vs 28% p= 0.006 [CMH])
  - All other secondary endpoint not significant difference
- **Adverse Events**: **Similar in both groups, except for mild-moderate somnolence** (aripiprazole, 14%; placebo, 4%).
  - **EPS symptoms incidence: aripiprazole (5%) and placebo (4%)**

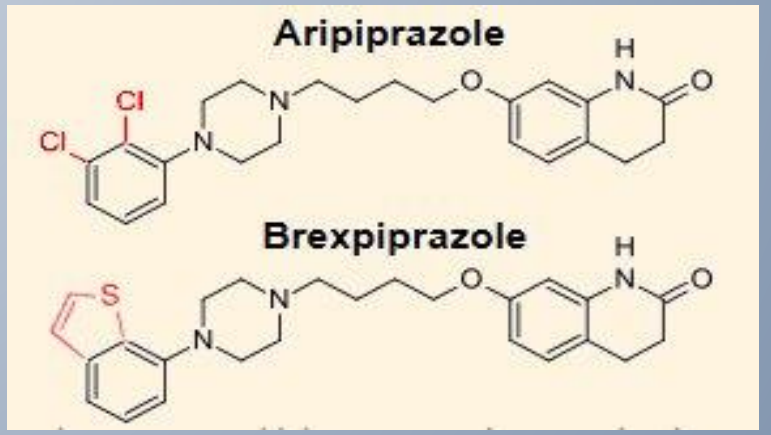
Aripiprazole

- **Conclusion**: No benefit in psychotic symptoms, but improved psychological and behavioral symptoms (agitation, anxiety, depression). Low EPS incidence with Aripiprazole.
- **Off-Label Use**
  - **Agitation/aggression and psychosis associated with dementia, severe or refractory** (alternative agent)
  - Agitation/Aggression (acute, severe) associated with psychiatric disorders (eg, schizophrenia, bipolar disorder), substance intoxication, or other organic causes (alternative agent)

- A Randomized, Double-Blind, Placebo-Controlled Study of Aripiprazole for the Treatment of Psychosis in Nursing Home Patients with Alzheimer Disease - ScienceDirect

Brexpiprazole (Rexulti™)

- Brexpiprazole (Rexulti ™) – 2nd generation antipsychotic
- FDA approval
  - Schizophrenia
  - Major depressive disorder (Adjunctive therapy)
  - **Agitation associated with dementia due to Alzheimer disease**
- Mechanism of action: Brexpiprazole exhibits partial agonist activity for 5-HT_{1A} and D_2 receptors and antagonist activity for 5-HT_{2A} receptors
- Akathisia in major depression disorder studies:
  - Aripiprazole 25% vs. Placebo 4%
  - Brexpiprazole 9% vs. Placebo 2%



Brexpiprazole (Rexulti™)

- 12 weeks randomized double blind, placebo controlled fixed dose study.
- Participants with diagnosis of Alzheimer's, Mini Mental State Examination score of >5 and < 22, score of > 4 on the agitation/aggression of the NPI (Neuropsychiatric Inventory)
- Primary endpoint was Cohen Mansfield Agitation Inventory (CMAI) total score
- Outcome:
  - Significant reduction in CMAI score for 2mg and 3mg doses
    - After 12 weeks of treatment with brexpiprazole 2mg or 3 mg/day (2 mg/d, n = 75; 3 mg/d, n = 153; or placebo, n = 117), brexpiprazole showed significant improvement relative to placebo on the CMAI total score (least square mean difference [LSMD], −5.32; p = 0.0026) and CGI-S score (LSMD, −0.27; p = 0.0078)
  - 1mg dose did not show improvement compared to placebo
- Safety Data:
  - Brexpiprazole compared to placebo: insomnia (3.7% vs. 2.8%), somnolence (3.4% vs. 1.8%), nasopharyngitis (2.7% vs. 2.6%), UTI (2.6% vs. 1.5%). Falls were seen more commonly on placebo (1.7% vs. 2.6%).

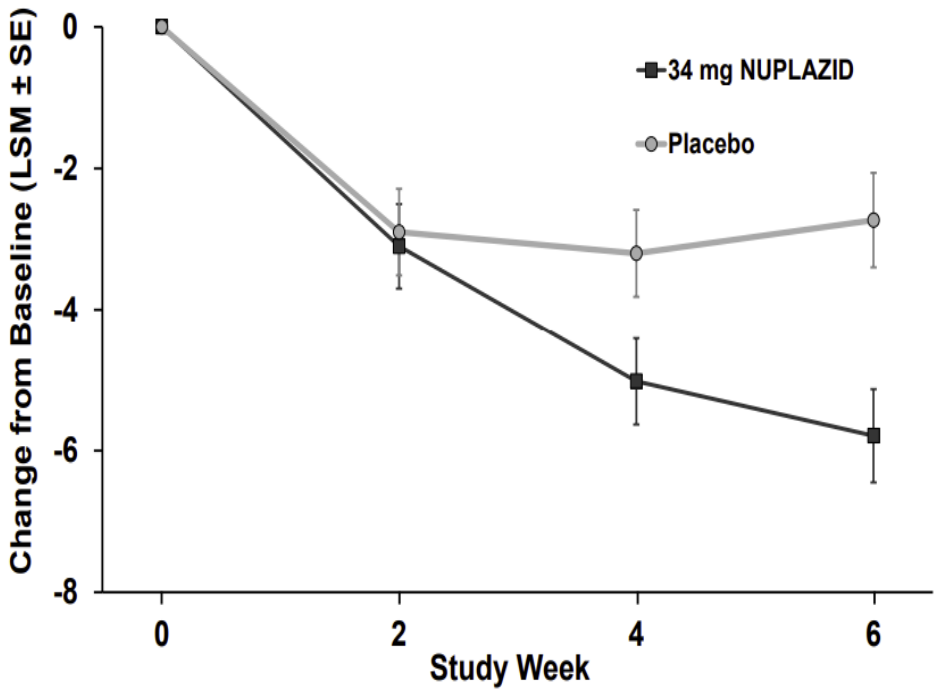
Pimavanserin (Nuplazid ™)

- Class: Atypical antipsychotic
- MOA: inverse 5-HT2A agonist and antagonist, **no dopamine activity**
- Indication: **Treatment of hallucinations and delusions associated with Parkinson's disease psychosis (FDA approved)**. Broader dementia related psychosis indication being pursued
- Harmony Trial: N = 199, randomized placebo controlled, parallel group study, 1:1 ratio. **>40 years old**, **diagnosis of Parkinson's Disease 1 year prior**, and **psychiatric symptoms**, Mini Mental State Examination > 21
- To assess efficacy, Scale for the Assessment of Positive Symptoms (SAPS) was used

Pimavanserin (Nuplazid ™) Harmony Trial

› Efficacy Data

Figure 2 SAPS-PD Change from Baseline through 6 Weeks Total Study Treatment



› Safety Data

Table 1 Adverse Reactions in Placebo-Controlled Studies of 6-Week Treatment Duration and Reported in ≥2% and >Placebo

	Percentage of Patients Reporting Adverse Reaction	
	NUPLAZID 34 mg	Placebo
	N=202	N=231
Gastrointestinal disorders		
Nausea	7%	4%
Constipation	4%	3%
General disorders		
Peripheral edema	7%	2%
Gait disturbance	2%	<1%
Psychiatric disorders		
Hallucination[a]	5%	3%
Confusional state	6%	3%

[a] Hallucination includes visual, auditory, tactile, and somatic hallucinations.

Pimavanserin (Nuplazid ™) and Alzheimer's

- FDA rejection in 2021 for broader psychosis indication
- Manufacturer is concerned that relapse may be due to dopaminergic medications used in Parkinson's treatment
- Newer study (Study 19) showed modest benefit of 1.8 on NeuroPsychiatric Inventory Scale
- FDA rejected again in 2022

Antipsychotics for NPS

Aripiprazole (Abilify ™)

- **Off-label use**
  - **Agitation/Aggression and psychosis associated with dementia, severe or refractory**
  - **Agitation/Aggression (acute, severe) associated with psychiatric disorders (eg, schizophrenia, bipolar disorder), substance intoxication, or other organic cause**
- Initial Dose: 2 to 5 mg PO once daily. May increase dose based on response and tolerability in 5 mg increments at intervals ≥1 week up to 15 mg once daily

Brexpiprazole (Rexulti™)

- **Indication**: **Agitation associated with dementia due to Alzheimer disease**
- Dose: 0.5 mg once daily for 7 days. Increase dose on days 8 to 14 to 1 mg once daily, then on day 15 to the target dose of 2 mg once daily. Based on response and tolerability, may increase dose after at least 14 days to the maximum dose of 3 mg once daily

Pimavanserin (Nuplazid ™)

- **Indication: Parkinson disease psychosis**
- Dose: 34 mg PO once daily.

Comparison: Side Effects of Antipsychotics

	EPS/TD	Dyslipidemia	Weight gain/T2DM	Elevated prolactin	Anticholinergic effects	Orthostatic hypotension	QTC prolongation
*First generation**							
chlorpromazine	+	+++	+++	++	+++	+++	+++
haloperidol	+++	+	+	+++	+/-	-	++ (+++ if IV)
fluphenazine	+++	+	+	+++	+/-	-	+/-
*Second generation**							
aripiprazole	+	-	+	-	-	-	+/-
asenapine	++	-	++	++	-	+	++
brexpiprazole	+	+	+	+/-	+/-	+/-	+/-
lurasidone	++	+/-	+/-	+/-	-	+	+/-
olanzapine	+	++++	++++	+	++	+	++
paliperidone	+++	+	+++	+++	-	++	++
pimavanserin	+/-	-	+	-	+	++	+
quetiapine	+/-	+++	+++	+/-	++	++	+++
risperidone	+++	+	+++	+++	+	+	++
ziprasidone	+	+/-	+/-	+	-	+	+++ (BBW!)
clozapine	+/-	++++	++++	+/-	+++	+++	++

Cost Comparison

Drug Name	Brand Name	Dosage Form	Frequency	Dose	Cost $ (30 day supply)
Aripiprazole	Abilify	Tab, ODT, solution, LAI	Daily, LAI (4 weeks)	2-15mg	11.80-16.20
Brexpiprazole	Rexulti	Tab	Daily	1-3mg	**1504**
Olanzapine	Zyprexa	Tab, ODT, LAI	Daily, LAI (2-4 weeks)	2.5-10mg	15.60-27.60
Pimavanserin	Nuplazid	Capsule	Daily	34mg	**5269**
Quetiapine	Seroquel	Tab, XR	Daily or BID	25QHS-75mg BID	16.50
Risperidone	Risperdal	Tab, ODT, solution, LAI	Daily, LAI (2 weeks)	0.25mg - 0.5mg BID	14.77

Antipsychotics for NPS

Both typical and atypical antipsychotics may potentially increase mortality and strokes

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

"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."

In patients without a clinically significant response after an adequate trial (eg, up to 4 weeks), taper and withdraw therapy.

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.

Management of Neuropsychiatric Symptoms (NPS) of Dementia

- **Atypical antipsychotics – Olanzapine, Quetiapine, Risperidone, Aripiprazole, Brexpiprazole, Pimavanserin**
- Antidepressants – SSRI
- Dextromethorphan/Quinidine & Dextromethorphan/Bupropion
- Prazosin
- Cholinesterase inhibitors/ Memantine
- Anticonvulsants

Citalopram (Celexa™)

Effect of citalopram on agitation in Alzheimer disease: CitAD (N=186), randomized, placebo-controlled, double-blind, parallel group (2014), Duration 9 weeks

Method: Patients with probable Alzheimer, with MMSE score from 5 to 28, had clinically significant agitation for which a physician determined that medication was appropriate

› Randomized to receive psychological intervention + citalopram 10 mg daily then titrate to 30 mg over 3 weeks VS psychological intervention + placebo

Primary Outcome: Neurobehavioral Rating Scale Agitation (NBRS-A) & modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC)

Secondary outcome: Cohen-Mansfield Agitation Inventory (CMAI), and Neuropsychiatric Inventory (NPI), ADLs, caregiver distress, cognitive safety (based on scores from the 30-point MMSE)

› https://jamanetwork.com/journals/jama/fullarticle/1829989

Effect of Citalopram on Agitation in Alzheimer disease

Results

› **Primary outcome**: Citalopram had significant improvement vs placebo on both primary outcomes

- NBRS-A difference at week 9: -0.93 (95% CI, -1.80 to -0.06), P = .04
- mADCS-CGIC: 40% of citalopram had moderate or marked improvement from baseline compared with 26% placebo. 2.13 (95% CI, 1.23-3.69), P = .01

› **Secondary outcome:**

- CMAI, total NPI, caregiver distress: Significant improvement
- NPI agitation subscale, ADLs, less use of lorazepam: No difference

› **Adverse effects**: Citalopram had worsening of cognition (-1.05 points; 95% CI, -1.97 to -0.13; P = .03) and QT interval prolongation (18.1 ms; 95% CI, 6.1-30.1; P = .01)

Escitalopram (Lexapro™)

- Escitalopram (S-enantiomer of citalopram): Its high selectivity for serotonin reuptake inhibition allows for a more specific and targeted action on serotonin reuptake, leading to increased levels of serotonin in the brain

S-CitAD study evaluates the safety and efficacy of escitalopram in a phase 3, multicenter, randomized, sequential-phase trial design **funded by the National Institute of Aging (NIA)**

- First phase, all patients and their care partners will receive structured non-pharmacologic psychosocial intervention (PSI) X3 weeks, after which patients will be determined as PSI responders and non-responders.
- In the randomized controlled trial phase, PSI non-responders will be randomized to **escitalopram 5–15 mg/d (target: 15 mg/day)** or matching placebo for 12 weeks
- **Primary outcome:** mADCS-CGIC; other outcome measures include the agitation, aggression, and dysphoria domains of the NPI-C, domains of the NPI, Alzheimer's Disease Cooperative StudyActivities of Daily Living (ADCS-ADL) scale, and safety.
- **The S-CitAD study is currently enrolling participants** – stay tuned

Comparative efficacy and safety of antidepressant therapy for the agitation of dementia: A systematic review and network meta-analysis

- **Method**:
  - 8 databases (PubMed, Cochrane Library, Web of Science, Embase, Wanfang Database, China National Knowledge Infrastructure, VIP Database and China biomedical literature service) from 11/6/22.
  - Patients with any dementia type, any antidepressant (TCA, SSRI, etc), antidepressants vs placebo or other antidepressants, RCT, incidence of total AE
  - **Any RCTs reporting efficacy and safety of antidepressant drugs in treating agitated behavior symptoms in patients with dementia**
  - **12 articles with 1146 patients included**
  - **Efficacy measured by CMAI. If not available, then NBRS, NPI, or Agitated Behavior in Dementia Scale could be used**

Comparative efficacy and safety of antidepressant therapy for the agitation of dementia: A systematic review and network meta-analysis

Results:

- All are antidepressants vs placebo, no head to head
- **Citalopram**: Efficacy (standardized mean difference (SMD) = −0.44, 95% CI = −0.72 to −0.16) was significantly higher vs placebo
- No significant effect on **sertraline** (SMD = −0.08, 95% CI −0.43 to 0.27), **mirtazapine** (SMD = −0.04, 95% CI −0.45 to 0.37), **trazodone** (SMD = 0.03, 95% CI −0.43 to 0.49) and **fluoxetine** (SMD = 0.31, 95% CI −0.87 to 1.49) vs placebo
- The area under the surface of the cumulative ranking curve (**SUCRA**) was used to express the efficacy and safety ranking of the various treatments.
- **Efficacy ranking by SUCRA: Citalopram (94.8%) > sertraline (53.9%) > mirtazapine (46.8%) > placebo (40.3%) > trazodone (38.2%) > fluoxetine (26.1%)**
- Detailed data on efficacy of escitalopram were not available

Comparative efficacy and safety of antidepressant therapy for the agitation of dementia: A systematic review and network meta-analysis

- **Adverse Events (AE):** trazodone (OR = 4.58, 95% CI = 1.12–18.69) was significantly higher than placebo
- Most common AE: dizziness, tremors, weakness
- **Probability of adverse events ranking highest to lowest: Trazodone (96.5%) > sertraline (51.7%) > mirtazapine (48.8%) > citalopram (41.3%) > placebo (40.3%)** > escitalopram (21.2%)
  - Low AE with Escitalopram was probably due to small number of participants in this study according to the meta-analysis
- **Conclusion**: **Citalopram is probably the effective antidepressant for the treatment of agitation symptoms in patients with dementia according to this comparative study**
- **Limitations**: Sample size of available RCTs, other potential risks of bias, and some variation in study design, such as different doses and durations of interventions, higher-quality RCTs with large sample sizes are needed to confirm the results in the future.

Frontiers | Comparative efficacy and safety of antidepressant therapy for the agitation of dementia: A systematic review andnetwork meta-analysis (frontiersin.org)

Antidepressants for NPS

- **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
- **Bupropion and Venlafaxine/other SNRI** have not been well studied in AD.
- **Tricyclic antidepressants**
  - Anticholinergic side effects → can cause worsening confusion
  - Not as well tolerated as SSRI
  - Should be avoided

Antipsychotics for NPS

Citalopram

- **Off-label use: Aggressive or agitated behavior associated with dementia**
- Initial Dose: 10 mg once daily; increase to 20 mg once daily after ≥3 days.
- In adults ≤60 years, may further increase dose based on response and tolerability up to 30 mg/day
- For adults >60 years, do not exceed the maximum dose of 20 mg/day due to risk of QT prolongation

Monitoring

- ECG in patients at increased risk for QT-prolonging effects due to certain conditions or medications
- Electrolytes (**Sodium**, **potassium, magnesium**) prior to initiation and periodically during therapy in patients at increased risk for electrolyte abnormalities
- Liver and renal function tests (baseline; as clinically indicated);
- CBC (as clinically indicated)
- Closely monitor patients for depression, clinical worsening, suicidality, psychosis, or unusual changes in behavior (the initial 1 to 2 months of therapy or during periods of dosage adjustments)

Management of Neuropsychiatric Symptoms (NPS) of Dementia

- **Atypical antipsychotics – Olanzapine, Quetiapine, Risperidone, Aripiprazole, Brexpiprazole, Pimavanserin**
- Antidepressants – SSRI
- Dextromethorphan/Quinidine & Dextromethorphan/Bupropion
- Prazosin
- Cholinesterase inhibitors/ Memantine
- Anticonvulsants

Dextromethorphan Combination Products

- Dextromethorphan hydrobromide (DM) acts on glutamate modulation in two ways:
  - Inhibits presynaptic glutamate release
  - N-methyl-D-aspartate (NMDA) receptor antagonist modulates post-synaptic glutamate response.
- DM is combined with quinidine or bupropion which prevents DM CYP-450 metabolism, increasing DM plasma and CNS bioavailability
- **Dextromethorphan/quinidine** 20mg/10mg **(Nuedexta ™)**-Approved in 2010
  - Approved for the treatment of pseudobulbar affect
  - **Off-label use: Agitation/aggression in Alzheimer disease**
- **Dextromethorphan/bupropion** 45mg/105mg **(Auvelity™)**
  - Approved for the treatment of MDD in adults in 2022

Dextromethorphan/Quinidine (Nuedexta ™)

- **Study**: Phase 2, multicenter, randomized, double-blind, placebo-controlled, sequential parallel comparison design (SPCD) study with two consecutive 5-week treatment stages.
  - Stage 1, patients were randomized to Dextromethorphan/Quinidine (DM/Q) or placebo.
  - Stage 2, Patients receiving DM/Q remained on treatment and those receiving placebo were stratified by their treatment response and non-responders were rerandomized to DM/Q or placebo.
- 194 patients aged 50–90 years old with probable AD per the National Institute of Aging – Alzheimer's Association (NIA-AA) criteria, MMSE of 8–28, agitation meeting the International Psychogeriatric Association (IPA) criteria, and screening and baseline Clinical Global Impression Scale (CGIS) scores of ≥4 were recruited.

Dextromethorphan/Quinidine (Nuedexta ™)

- **Results**:
  - **Dextromethorphan/Quinidine showed greater numeric reductions on NPI-Agitation/Aggression domains at Week 5** in both stages 1 (from 7.1 to 3.8) and 2 (from 5.8 to 3.8) compared to placebo
  - Combined analysis of both stages showed significant reductions on NPI-Agitation/ Aggression domains for Dextromethorphan/Quinidine compared to placebo, −3.95; $p < 0.001$)
- **Dose:** Dextromethorphan 20 mg/quinidine 10 mg once daily X 7 days, then increase to dextromethorphan 20 mg/quinidine 10 mg BID
- **ADR:** diarrhea, dizziness, peripheral edema, UTI, flatulence, QT prolongation
- **Drug Interactions**: Check drug interactions especially with other cardiac meds
- **Monitoring**: QT interval at baseline and 3 to 4 hours after the first dose in patients at risk for QTc prolongation; potassium and magnesium prior to and during therapy; CBC, liver and renal function tests.

Dextromethorphan/bupropion (Auvelity™)

- **ADVANCE-1** studied the safety and efficacy of dextromethorphan/bupropion (DM/BUP) for agitation in AD
  - Phase 2/3, 5-week, multicenter, randomized, double-blind, placebo-controlled trial.
  - 366 patients were randomized to DM/BUP 30/105 mg once daily and titrated to DM/BUP 45/105 mg BID (n = 159), bupropion 105 mg twice daily (n = 49), or placebo (n = 158)
  - Participants were ages 65–90 from the community, with a diagnosis of probable AD per the NIAAA criteria, MMSE scores between 10 and 24, agitation meeting the IPA provisional criteria, and a ≥ 4 score on the Agitation/Aggression domains on the NPI
- Primary outcome: Measure change in CMAI from baseline to week 5
- Results: **After 5 weeks, Dextromethorphan/bupropion significantly reduced CMAI score** by −15.4 points compared to bupropion alone (−10.0; $p < 0.001$) or placebo (−11.5; $p = 0.010$) [51,55].
- **Following these positive findings, DM/BUP was granted Breakthrough Therapy Designation for the treatment of AD agitation in June 2020.**

Dextromethorphan/bupropion (Auvelity™)

ACCORD study

- **Clinicians reported agitation improvements** in 66.3% of the patients at week 2 and 86.3% at week 5 on the modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation (mADCS-CGIC) [56].
- **Care partners reported improvements in agitation** in 67.5% of the patients at week 2 and 89.3% at week 5 on caregiver-rated Patient Global Impression of Change (PGI-C) [56].
- **Care partner distress and burden, patient's quality of life, and depressive symptoms were improved compared to baseline** in stage 1 on the NPI Agitation and Aggression Caregiver Distress score ($p < 0.001$, at weeks 4 and 8
- Adverse Event: 28.3% with DM/BUP and 22% with placebo. Discontinuation rates due to AEs were low in both groups (0% with DM/BUP and 1.9% with placebo)
- Common adverse reactions: **GI (Nausea) and dizziness**

Dextromethorphan/bupropion (Auvelity™)

ADVANCE-2

- Phase 3, 5-week, multicenter, randomized, double-blind, placebo-controlled trial evaluating DM/BUP for agitation by a primary endpoint of change in CMAI after 5 weeks.
- The study aims to recruit 350 patients aged 65–90 years old with a diagnosis of probable AD per the NIA-AA criteria and agitation meeting the IPA provisional definition.
- The study is anticipated to conclude by **June 2025**

Dextromethorphan/Quinidine (Nuedexta ™)

- **Off Label Use: Agitation/aggression in Alzheimer disease** Dextromethorphan 20 mg/quinidine 10 mg PO once daily for 7 days, then increase to dextromethorphan 20 mg/quinidine 10 mg twice daily.
- **Indication**: **Pseudobulbar affects -** Dextromethorphan 20 mg/quinidine 10 mg daily X7 days, then increase to dextromethorphan 20 mg/quinidine 10 mg Q12 hours. Reassess patient periodically to determine if continued use is necessary.
- **Cost**: 20-10 mg tablets, #30 ~ **$944 for 1 month**

Dextromethorphan/Bupropion (Auvelity™)

- **Indication:** Major depressive disorder (unipolar)
- The clinical trial for assessing agitation in patients with dementia is anticipated to conclude by **June 2025**
- **Cost**: 45-105 mg tablet, #30 ~ **$666 for 1 month**

Management of Neuropsychiatric Symptoms (NPS) of Dementia

- **Atypical antipsychotics – Olanzapine, Quetiapine, Risperidone, Aripiprazole, Brexpiprazole, Pimavanserin**
- Antidepressants – SSRI
- Dextromethorphan/Quinidine & Dextromethorphan/Bupropion
- Prazosin
- Cholinesterase inhibitors/ Memantine
- Anticonvulsants

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

- Prazosin is FDA approved for HTN (resistant HTN)
- Off-label use: Post-traumatic stress disorder (PTSD) related nightmares and sleep disruption

› **PEACE-AD Trial**: Multicenter, randomized, double blind, placebo controlled trial. phase 2, 12 weeks (n=35)

› **Method:**

- Patients from community dwelling settings and long-term care facilities with a diagnosis of probable or possible AD and clinically significant agitation randomized to receive **prazosin 4 mg QAM and 6 mg QPM** vs placebo
- Stable doses of psychotropic medications for ≥2 weeks and stable doses of ChE-I or memantine were allowed

› **Primary Outcome:** ADCS-CGIC-A (A for agitation), NPI score, NPI-NH scores, ADCS-DL-Severe

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

Results: (After 12 weeks)

- **No difference between prazosin vs placebo on ADCS-CGIC in Agitation** (3.5 ± 1.3 vs. 3.4 ± 1.4, p=NS) **and on NPI scores**, NPI-NH scores, ADCS-ADL-Severe, days of study survivorship, and total dose of rescue lorazepam
- **Prazosin had statistically significant benefits on change in the Cohen-Mansfield Agitation Inventory (CMAI) vs placebo** (baseline 54.8 ± 14.2 vs. 66.3 ± 12.1, 12 Weeks 51.1 ± 14.6 vs. 73.3 ± 20.1; p = 0.04).
  - **NPI-5 and percent CGIC-A responders** showed benefits, indicating potential efficacy to be explored in future studies.
- CV effect: No differences on supine or standing SBP, DBP, HR at any time point
- Common AEs: nausea (7.7% vs. 0%), postural dizziness (7.7% vs. 0%), syncope (11.5% vs. 0%), somnolence (11.5% vs. 0%), and dizziness (19.2% vs. 12.5%)

Prazosin

- **Indication**: **Hypertension, chronic (alternative agent)**
  - Not recommended for initial management but may be considered as additional therapy for resistant hypertension in patients who do not respond adequately to combination therapy with preferred agents
- **Off Label Use:**
  - **PTSD-related nightmares and sleep disruption**
  - **Raynaud phenomenon**

Management of Neuropsychiatric Symptoms (NPS) of Dementia

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- Antidepressants – SSRI
- Dextromethorphan/Quinidine & Dextromethorphan/Bupropion
- Prazosin
- Cholinesterase inhibitors/ Memantine
- Anticonvulsants

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
  - 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 show that studies have not demonstrated a clinically significant effect of memantine for NPS of dementia

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

Management of Neuropsychiatric Symptoms (NPS) of Dementia

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- Anticonvulsants

Lamotrigine

- Retrospective medical record review in 2008 of lamotrigine for manic-like symptoms and **agitation in older adults** (average age 77) with dementia in ALF (n=5, duration 5 months)
- Clinician started lamotrigine based on symptoms or failure to respond to atypical antipsychotics
- Patients received doses of lamotrigine between 100-300 mg/day, average 190 mg/day x 5 months
- Outcome: change in MMSE, HAM-D (Hamilton Depression Rating Scale), and YMRS (Young-Mania Rating Scale)
- Results:
  - MMSE decreased from 19.6 to 18.2 (non significant)
  - HAM-D decreased from 12.8 to 9 (non significant)
  - YMRS decreased from 10.4 to 5 (significant)
  - None of the patients had to discontinue lamotrigine due to side effects, suggesting safe profile
- Limitations: Results are limited by small sample size, retrospective nature, and YMRS scale which is normally used for bipolar

- https://www.cambridge.org/core/journals/international-psychogeriatrics/article/lamotrigine-for-agitation-in-older-patients-with-dementia/137FD4A28C2A407A36C629310CD62B6A

Lamotrigine

Case Study: Aggression in Frontal Lobe Dementia With Lamotrigine Treatment (2000)

- 65 yo F with a 12 year history of chronic recurrent episodes for MDD
- Treatment of depression included antidepressants with some improvement but not sustained
- Her last admission was after a 3-month history of repeatedly asking the same questions, picking her nose until it bled, and being verbally and physically aggressive.
  - Treated with fluvoxamine, buspirone, lorazepam, vitamin E, thiamine, loxapine, risperidone, and divalproex with little/no improvement
- On admission, in addition to problem above, she was extremely aggressive and disinhibited, with moderate deterioration in concentration and cognition
  - Medication at admission: divalproex 1500 mg/day, lorazepam 2-4 mg/day
- She convinced psych staff that she would not harm them, but when approached she hit them and left some with facial bruises and black eyes
- Diagnosis: Frontal lobe dementia
- Treated with lamotrigine 12.5 mg/day, which increases to 100 mg/day over 4 weeks. Symptoms dramatically improved and she went back to premorbid self. Maintained this dose over 6 months without relapse and no side effects.

› .

› https://ajp.psychiatryonline.org/doi/full/10.1176/appi.ajp.157.7.1178

Lamotrigine

- Anticonvulsant: Inhibits presynaptic glutamate release
- **Indications**:
  - Bipolar disorder
  - Focal onset seizures and generalized onset seizures
- **Off-Label Use**
  - Short-lasting unilateral neuralgiform headache attacks, prophylaxis
  - Trigeminal neuralgia
- **No published reports regarding its potential efficacy in controlling psychotic symptoms in dementia**

Skin Hypersensitivity reactions

- Skin rash
- Multiorgan hypersensitivity reactions include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS)
- **Lamotrigine-induced skin eruptions generally occur between 5 days and 8 weeks after initiation of therapy**
- **Lamotrigine doses must be tapered up gradually to avoid severe skin hypersensitivity reactions**
- If patients have missed Lamotrigine more than 3 days, some experts want to restart low dose of Lamotrigine to avoid severe skin hypersensitivity reactions

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 (Depakote™)
  - Several earlier reports showed improved aggressive behavior
  - 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.

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

Summary

- Assessment for underlying causes for cognitive changes and neuropsychiatric symptoms of dementia
- Nonpharmacological approaches (First line treatment)
- Use of pharmacological treatment should only continue if the medication provides benefit
- Ongoing monitoring of benefits versus harms must be conducted regularly