The Place for Treatments and Trial Design Considerations for Associated Neuropsychiatric Symptoms in Alzheimer's Disease

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Disclosures

Rachel Schindler, MD is a full-time employee of Pfizer, Inc. Dr. Schindler has no other relationships to disclose.

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Key Considerations

- The treatment of neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) is a significant unmet medical need
- More research is needed on the underlying neurobiology of NPS to help identify drug targets
- More clinical trials are needed to facilitate the development of effective treatments. Flexibility in acceptance of innovative trial designs will help in making trials more feasible, and hasten the development of drugs for the treatment of NPS in AD

Overview

- Burden of NPS in AD
- Defining and understanding NPS in AD
- Advances in understanding the neurobiologic basis of NPS in AD
- Unmet medical need with current treatment options
- Previous and ongoing clinical trials of pharmacologic treatments for NPS
- Measurement of NPS
- Challenges in the clinical development of treatment options for NPS
- Future directions

Prevalence of NPS Symptoms in AD Dementia

Symptom	Prevalence
Depression	30%-68%[1]
Apathy	42%-74%[1]
Agitation	31%-60%[1]
Psychosis Delusions Hallucinations	12%-74%[2] 18%-38%[1] 7%-24%[1]
Sleep/night time behavior disorders	20%-42%[1]
Anxiety	24%-65%[3]

NPS often co-occur or may recur at different points[4-6]
60% of patients have at least 1 symptom;
over half of patients have at least 4 NPS simultaneously[4,5]

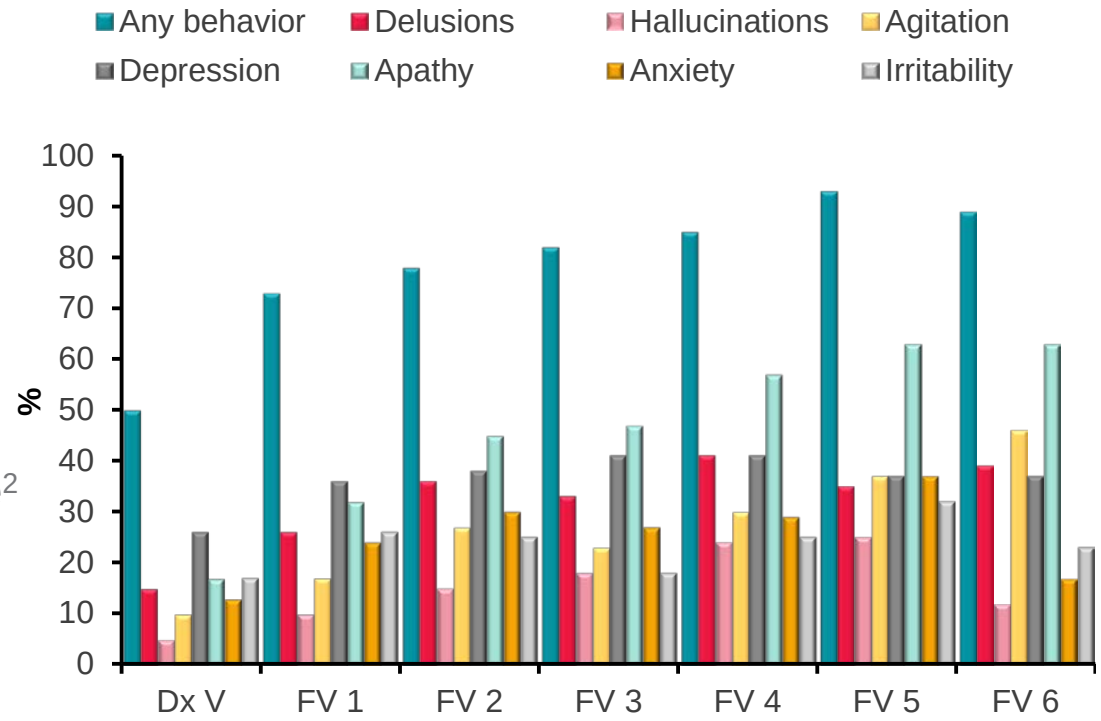
1. As reviewed in Bergh S, Selbaek G. *Norsk Epidemiol*. 2012;22(2):225-232; 2. Ropacki SA, Jeste DV. *Am J Psychiatry*. 2005;162(11):2022-2030; 3. Mega MS, et al. *Neurology*. 1996;46(1):130-135; 4. Lyketsos CG, et al. *Int J Geriatr Psychiatry*. 2001;16:1043-1053; 5. Frisoni GB, et al. *Dement Geriatr Cogn Disord*. 1999;10:130-138; 6. Devanand DP, et al. *Arch Gen Psychiatry*. 1997;54(3):257-263.

Fluctuations in NPS Over Time in AD

NPS may be apparent prior to an AD diagnosis or may manifest in early or later stages of disease[1]

- In a population-based sample of incident AD, 50% of participants experienced NPS at baseline[2]
- Most neuropsychiatric inventory (NPI) symptoms increased over time[2]
  - 89% of survivors experienced NPS by final study visit
- Hallucinations, anxiety, and irritability declined at final visit[2]
- Pattern of NPS shifted over time[2]
  - Depression, irritability or apathy were most common
  - Apathy was most commonly reported symptom by Visit 4

Prevalence of NPS from AD Onset

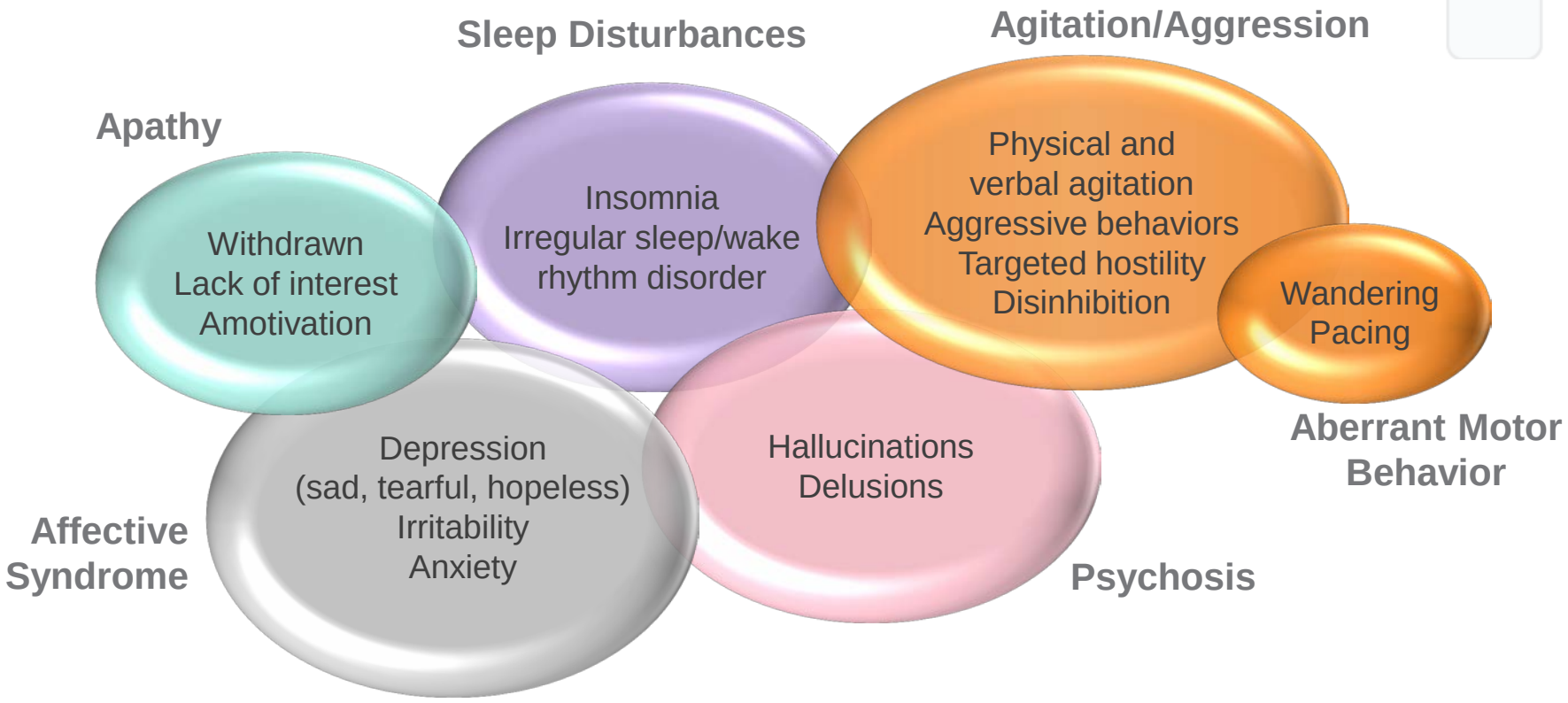


	Dx V	FV 1	FV 2	FV 3	FV 4	FV 5	FV 6
Years from AD onset, mean (SD)	1.71 (1.26)	3.28 (1.47)	4.47 (1.92)	5.20 (1.89)	5.64 (1.83)	6.55 (1.95)	7.72 (2.24)
N	328	216	140	110	84	60	35

Dx V = diagnosis visit; FV = follow-up visit.

1. Lyketsos CG, Miller DS. *Alzheimers Dement*. 2012;8(1):60-64;
2. Tschanz, JT, et al. *Am J Geriatr Psychiatry.* 2011;19(6):532-542.

NPS in AD Often Cluster



1. Lyketsos CG, Miller DS. *Alzheimers Dement*. 2012;8(1):60-64; 2. Lyketsos CG, et al. *Int J Geriatr Psychiatry*. 2001;16:1043-1053; 3. Geda YE, et al. *Alzheimers Dement*. 2013;9(5):602-608; 4. Geda YE, et al. *Alzheimers Dement*. 2013;9(5):602-608 (Appendix C: Ancoli-Israel S, et al. www.ncbi.nlm.nih.gov/pmc/articles/PMC3766403/bin/NIHMS465719-supplement-03.docx; Appendix D: Sultzer DL, et al. www.ncbi.nlm.nih.gov/pmc/articles/PMC3766403/bin/NIHMS465719-supplement-04.docx. Accessed November 3, 2014).

Risk Factors for NPS in Patients With Mild Cognitive Impairment (MCI) and Mild AD

	Affective Behaviors (depression, apathy, and anxiety)	Distress/ Tension Behaviors (irritability and agitation)	Impulse Control Behaviors (disinhibition, elation, and aberrant motor behavior)	Psychotic Behaviors (delusions and hallucinations)
Male gender	X	X	X	X
Younger age		X	X	X
Lower education		X		
Caucasian	X			
Functional decline	X	X	X	X
Amnestic MCI vs nonamnestic MCI		X (agitation)	X (elation)	

Being married was protective against psychotic behaviors

Apostolova LG, et al. *Dement Geriatr Cogn Disord.* 2014;37(5-6):315-326.

NPS Have Severe and Disabling Consequences for Patients with AD and Their Caregivers

- NPS associated with poor prognosis and outcomes, especially if symptoms occur earlier[1]
  - eg, Individuals who ultimately develop psychosis have more rapid cognitive deterioration during the earliest phases of AD vs individuals with AD not developing psychosis[2]
- Numerous studies demonstrated that NPS are associated with[1,3,4]
  - Reduced quality of life
  - Increased healthcare costs and mortality
  - Nursing home placement
- NPS have a significant impact on caregivers[1,5,6]
  - Loss of work
  - Increased depression, distress
  - Psychological morbidity

1. Lyketsos CG, Miller DS. *Alzheimers Dement*. 2012;8(1):60-64; 2. Emanuel JE, et al. *Am J Geriatr Psychiatry*. 2011;19(2):160-168;
3. Beeri MS, et al. *Int J Geriatr Psychiatry*. 2002;17(5):403-408; 4. Yaffe K, et al. *J Am Med Assoc*. 2002;287(16):2090-2097;
5. Tampi RR, et al. *Neurology*. 2011;1-6; 6. Cerejeira J, et al. *Front Neurol*. 2012;3:73.

Healthcare Cost Implications of NPS in Dementia

- A 1-point increase in the NPI score can result in a $247 - $409 annual increase per patient in direct costs for AD[1]
- 70% of nursing home patients with dementia and NPS
  were at higher care levels
  resulting in additional cost of $382 per patient-year[2]
- NPS were associated with costs of $4115 per patient per year in a community-based study in AD[3]

1. Murman DL, et al. *Neurology*. 2002;59(11):1721-1729; 2. O'Brien et al. *Int Psychogeriatr*. 2000;12:51-57; 3. Beeri MS, et al. *Int J Geriatr Psychiatry*. 2002;17(5):403-408.

Challenges With Current Pharmacologic Treatment Options for NPS in AD

"Despite several decades of efforts, few effective treatments are currently available for NPS…redoubled efforts are needed in this area because of their great public health impact"

– iSTAART NPS-PIA roundtable[1]

- Well controlled trials (e.g., AChEI, memantine, antipsychotics) suggest a signal on various behaviors, but findings have been inconsistent[2,3]
  - NPS are difficult to study[1,3]
- Use of antipsychotics in the elderly poses safety risks[2,4]
- Mood stabilizers that may be effective and are widely used (eg, divalproex, lamotrigine) do not have an indication[2,3]
- NPS are often refractory to treatment[5]
- Underlying neurobiology is poorly understood, complicating target identification[1]

ChEI = cholinesterase inhibitor; iSTAART NPS-PIA = International Society to advance Alzheimer's Research and treatment NPS Professional Area of Interest.

1. Lyketsos CG, Miller DS. *Alzheimers Dement*. 2012;8(1):60-64; 2. Wang J, et al. *J Neurol Neurosurg Psychiatry* 2014;0:1-9. doi:10.1136/jnnp-2014-308112; 3. Jeste DV, et al. *Neuropsychopharmacology*. 2008;33(5):957-970; 4. Kales HC, et al. *Am J Psychiatry*. 2007;164(10):1568-1576; 4. Gauthier S, et al. *Int Psychogeriatr*. 2010;22(3):346-372; 5. Lyketsos CG, et al. *Alzheimers Dement*. 2011;7(5):532-539.

Meta-analysis of RCTs Indicates Improvement in NPS in AD Patients Treated with Cholinesterase Inhibitors and Atypical Antipsychotics

Versus Placebo	Favors Medicine	Neutral	Favors Placebo	Test for Overall Effect (*P* Value)
Atypical Antipsychotics	X			<0.00001
AChEI's	X			0.02
Memantine	X			0.13
Antidepressants		X		0.97
Mood stabilizers			X	0.02

ChEI = cholinesterase inhibitor; RCT = randomized controlled trials.
Wang J, et al. *J Neurol Neurosurg Psychiatry* 2014;0:1-9. doi:10.1136/jnnp-2014-308112.

Major Neurobiologic Models Underpinning NPS in AD[1]

- Frontal-subcortical circuits[2,3]
  - ≥3 frontal-subcortical circuits, each including a basal ganglia substrate and thalamic component, link back to frontal cortex
    - **Dorsolateral** circuit: planning, organization, executive function
    - **Apathy** circuit: mediates motivated behavior
    - **Orbitofrontal** circuit: mediates inhibitory control, conformity with social norms
- Cortico-cortical network[4]
  - 5 large-scale, neurocognitive networks
    - With extensive reciprocal connections, including the memory–emotion network
    - Hippocampus & amygdala
- Ascending monoaminergic system[5]
  - Brain stem serotonergic, noradrenergic, or dopaminergic cells with diffuse projections throughout the brain

1. Geda YE, et al, *Alzheimers Dement.* 2013;9(5):602-608; 2. Alexander GE, et al. *Prog Brain Res*. 1990;85:119-146; 3. Cummings JL. *Arch Neurol*. 1993;50(8):873-880; 4. Mesulam MM. *Brain*. 1998;121(Pt 6):1013-1052; 5. Benarroch, EE. *Basic Neurosciences with Clinical Applications*. Philadelphia, PA: Butterworth Heinemann/Elsevier; 2006.

Neuropathology and Neuroimaging Findings

Symptom	Sample	Findings
Depression	Neuropathology	• Possible ↑ monoamine neuron loss, relative preservation ACh neurons
	Neuroimaging	• FDG-PET: primarily deficits in frontal and parietal cortices
Apathy	Neuropathology	• Atrophy & white matter tract Δs, likely → loss of neurons and synapses innervating & connecting frontal cortical circuits
	Neuroimaging	• Structural and functional alterations of frontal circuits (eg, ant. cingulate, orbitofrontal, dorsolateral frontal cortex, frontal white matter) • Evidence for dysfunctional DA circuits linking basal ganglia w/ ant. cingulate & frontal cortices
Agitation	Neuropathology	• Agitation: NFT ↑ orbitofrontal cortex & ant. cingulate • Aggression: ↓ ChAT in superior & middle frontal gyri
	Neuroimaging	• Early studies—aggression, irritability: ↓ metabolism R fronto-temporal and bilateral cingulate cortex
Psychosis	Neuropathology	• May be increased aggregation of neocortical MAPT in AD+P • Ltd evidence: general neocortical synaptic disruption
	Neuroimaging	• Few studies, inconsistent, but all with severe fxnl Δs frontal, parietal, temporal

Geda YE, et al. *Alzheimers Dement*. 2013;9(5):602-608. (Appendix A: Smith GS, et al. www.ncbi.nlm.nih.gov/pmc/articles/PMC3766403/bin/NIHMS465719-supplement-01.docx; Appendix B: Lanctot KL, et al. www.ncbi.nlm.nih.gov/pmc/articles/PMC3766403/bin/NIHMS465719-supplement-02.docx; Appendix D: Sultzer DL, et al. www.ncbi.nlm.nih.gov/pmc/articles/PMC3766403/bin/NIHMS465719-supplement-04.docx; Appendix E: Sweet RA, et al. www.ncbi.nlm.nih.gov/pmc/articles/PMC3766403/bin/NIHMS465719-supplement-05.doc. Accessed November 3, 2014.)

Study Population Considerations

- Overall *total* NPS (all behavioral symptoms) vs *specific* neuropsychiatric symptoms or clusters (eg, agitation and psychosis; depression and anxiety)
  - Mechanism of action (MOA) may implicate particular target behavior(s), leading to greater chance of demonstrating a signal
  - However, most NPS occur concurrently with NPS in other domains/clusters[1-3]
- Minimum level of NPS is needed in the study population at baseline, balancing:
  - Enough NPS to detect a signal/avoid a floor effect vs
  - Too severe a population, which is difficult to manage in a trial and requires concomitant meds that might obscure signal
- Variability/cyclical nature of symptoms
  - Variation between screening and baseline

1. Lyketsos CG, et al. *Int J Geriatr Psychiatry*. 2001;16:1043-1053; 2. Frisoni GB, et al. *Dement Geriatr Cogn Disord*. 1999;10:130-138; 3. Devanand DP, et al. *Arch Gen Psychiatry*. 1997;54(3):257-263.

Study Population Considerations

- Concomitant meds—at baseline and for rescue
  - Many of those used in practice are:
    - Not indicated for behavioral symptoms (eg, divalproex, lamotrigine) or
    - Associated with safety considerations (eg, black box warning for atypical antipsychotics)
  - Flexibility in approving use of these meds in protocols is needed or studies will not be feasible
  - Doses can be controlled
- Diagnostic criteria—in development[1]
  - Currently, limited consensus criteria[1]
  - Recent studies suggest that these populations can be reliably identified
    - Psychosis of AD[2]
    - Depression of AD[3,4]
    - Apathy[5,6]—proposed criteria
    - Agitation[7]

1. Geda YE, et al. *Alzheimers Dement*. 2013;9(5):602-608; 2. Jeste DV, Finkel SI. *Am J Geriatr Psychiatry*. 2000;8(1):29-34; 3. Lyketsos CG, et al. *Biol Psychiatry*. 2002; 52(3):243-252; 4. Lyketsos CG, Lee HB. *Dement Geriatr Cogn Disord*. 2004;17(1-2):55-64; 5. Robert P, et al. *Eur Psychiatry*. 2009;24(2):98-104; 6. Geda YE, et al. *Alzheimers Dement*. 2013;9(5):602-608 (Appendix B: Lanctôt KL, et al. www.ncbi.nlm.nih.gov/pmc/articles/PMC3766403/bin/NIHMS465719-supplement-02.docx. Accessed November 3, 2014); 7. Cummings J, et al. *Ann Neurol.* 2014;76(Supplement S18):Abstract M1336

Study Population Considerations: Approaches in Recent Studies

- Inclusion criteria
  - CiTAD, scylloinositol: NPI agitation/aggression ≥4[1-3]
  - AVP-923: Clinical Global Impression of Agitation Severity (CGI-S) ≥4, a clinician impression of severity (qualitative)[4]
    → All 3 studies had similar baseline severity (NPI agitation/Aggression ~7)
- Although all 3 studies were only evaluating aggression and agitation, the average total NPI was ~30 to 50[1-4]
  - Consistent with reports that most patients have more than 1 symptom
  - Scylloinositol baseline NPI Agitation/Aggression score = 7.2. NPI-C Agitation and Aggression scores = 12.7 and 5.5[3]
    → Population can be consistently identified using quantitative and qualitative measures

1. Porsteinsson AP, et al. *J Am Med Assoc*. 2014;311(7)682-691; 2. Abushakra SR, et al. *J Nutr Health Aging*. 2012;16(9):795-872;
3. Abushakra SR, et al. *Alzheimers Dement*. 2014;10(4):P458; 4. Cummings J, et al. *Ann Neurol.* 2014;76(Supplement S18):Abstract M1336.

Study Design Considerations

- Amelioration of existing symptoms vs preventing or delaying the emergence of NPS
  - Different trial designs
    - Delay to emergence requires much longer studies
- Should a distinction be made between frequency and severity of NPS?
- Parallel design vs. sequential parallel comparison design[1,2]?
- Agreement on trial methodology (eg, choice of scales, consistent definition of behaviors) might allow conclusions to be drawn from a larger dataset

1. Fava, M, Schoenfeld, D. System and method for reducing the placebo effect in controlled clinical trials, *US 7647235 B1,* January 2010; 2. Ivanova, A, Qaquish, B, Schoenfeld, D. Optimality, sample size, and power calculations for the sequential parallel comparison design. *Statistics in Medicine (*30) 23: 2793-2803.

Outcome Measures

- Numerous validated scales available and fit for purpose
- Advantages to using scales with well-known characteristics
  - (eg, NPI has ~20 years of use and data)
- Concurrent nature of varying symptoms suggests that a broad scale should be used to assess full impact
  - (eg, NPI, BEHAVE-AD, CERAD, BPRS)
- Interest in a single domain suggests the use of a more detailed/expanded scale to better understand changes in the target symptoms (eg, Cohen-Mansfield, CSDD, NPI-C)
- Current scales may be sufficient for detecting drug effect
  - For the AVP-923 study, the traditional NPI agitation/aggression subdomain was employed, and statistically significant changes were demonstrated with a range of 0 to 12[1]
- Environment is important, and available scales may not take this into account

BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease; BPRS = Behavior Rating Scale; CERAD = Consortium to Establish a Registry for Alzheimer Disease; CSDD = Cornell Scale for Depression in Dementia; NBRs = Neurobehavioral Rating Scale; NPI-C = Neuropsychiatric Inventory-Clinician rating scale.

Cummings J, et al. *Ann Neurol.* 2014;76(Supplement S18):Abstract M1336.

Scales Available for Assessment of NPS

Symptom	Assessment Scale	Informant	Type	Rating
Multiple symptoms	**Neuropsychiatric Inventory (NPI)**[1-3]	Patient/Caregiver	Interview	Severity/Frequency
	NPI-C[4]	Clinician	Interview	Severity/Frequency
	Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)[5]	Caregiver	Interview	Presence/Severity
	Brief Psychiatric Rating Scale (BPRS)[3]	Clinician	Self-report	Severity
	Consortium to Establish a Registry for Alzheimer's Disease Behavior Rating Scale for Dementia (CERAD-BRSD)[5,6]	Caregiver	Interview	Severity
Depression	Cornell Scale of Depression in Dementia (CSDD)[4,5,7]	Patient/Caregiver	Interview	Severity
	Geriatric Depression Scale (GDS)[7,8]	Patient	Self-report	Presence/Severity
Apathy	Apathy Evaluation Scale (AES)[3]	Patient/Caregiver/ Clinician	Self-report/Interview	Severity
	Apathy Inventory (AI)[3,5,9]	Patient/Caregiver	Interview	Presence/Severity/ Frequency
	Apathy Scale (AS)[3]	Caregiver	Self-report	Severity
	Dementia Apathy Interview and Rating (DAIR)[3,9]	Caregiver	Interview	Severity
	Irritability-Apathy Scale (IAS)[3]	Caregiver	Interview	Severity
	Lille Apathy Rating Scale (LARS)[3]	Patient	Interview	Severity
Agitation/ Aggression	Cohen-Mansfield Agitation Inventory (CMAI)[5,10]	Caregiver/Nurse	Self-report/Interview	Severity/Frequency
	Overt Aggression Scale (OAS)[11]	Caregiver	Report	Severity
Psychosis	Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD)[5,12,13]	Caregiver	Interview	Presence/Frequency

1. Geda YE, et al. *Alzheimers Dement*. 2013;9(5):602-608; 2. Cummings JL, et al. *Neurology*. 1994;44(12):2308-2314; 3. Clarke DE, et al. *J Psychosom Res*. 2011;70(1):73-97; 4. de Medeiros K, et al. *Int Psychogeriatr*. 2010;22(6):984-994; 5. Tampi RR, et al. *Neurology*. 2011;1-6; 6. Gearing M, et al. *Neurology*. 1995;45:461-466; 7. Geda YE, et al. *Alzheimers Dement*. 2013;9(5):602-608 (Appendix A: Smith GS, et al. www.ncbi.nlm.nih.gov/pmc/articles/PMC3766403/bin/NIHMS465719-supplement-01.docx. Accessed November 3, 2014); 8. Hollingworth P, et al. *J Am Geriatr Soc*. 2006;54(9):1348-1354; 9. Cipriani G, et al. *J Nerv Ment Dis*. 2014;202(10):718-724; 10. Cohen-Mansfield J. *J Psychiatr Res*. 2008;43(1):64-69; 11. Yudofsky SC, et al. *Am J Psychiatry*. 1986;143(1):35-39; 12. Holtzer R, et al. *J Am Geriatr Soc*. 2003;51(7):953-960; 13. Geda YE, et al. *Alzheimers Dement*. 2013;9(5):602-608 (Appendix E: Sweet RA, et al. www.ncbi.nlm.nih.gov/pmc/articles/PMC3766403/bin/NIHMS465719-supplement-05.doc. Accessed November 3, 2014).

Recent and Ongoing Clinical Trials Evaluating Pharmacologic Treatment Options for NPS in AD

Class	Drug	Studied in AD for	Study Design	Results
Antidepressant	Citalopram	Agitation	N=186, double-blind w/placebo, CitAD[1]	Signif. improvement in NBRS agitation subscale, CMAI, total NPI No sig difference on NPI agitation subscale. Worsening of cognition and cardiac AEs
NMDA receptor + antiarrhythmic	AVP-923	Agitation	N=220, double-blind w/ placebo[2]	Signif. improvement in NPI agitation subscale and NPI total. No evidence of cognitive decline on MMSE or ADAS-cog.
Antihypertension	Prazosin	Agitation/ aggression	N=22, double-blind w/ placebo[3]	Signif. improvement in NPI and BPRS
		Agitation	N=120 (estimated)[4]	Currently recruiting Primary endpoints: NPI and ADCS-CGIC Secondary endpoint: BPRS
Inositol stereoisomer	Scylloinositol (ELND005)	Agitation/ aggression	N=400 (estimated)[5]	Currently recruiting Primary endpoint: NPI-C agitation/aggression subscale Secondary endpoints: mADCS-CGIC, NPI total, MMSE, ADCS-ADL
Dopamine agonist	Brexpiprazole	Agitation	N=420 (estimated)[6] N=230 (estimated)[7]	2 studies currently recruiting Primary endpoint: CMAI Secondary endpoint: CGI-S agitation
Nicotinic receptor agonist	Encenicline	Cognition NPS Function	N=790 (estimated)[8]	2 studies currently recruiting Primary endpoint: ADAS-cog-13, CDR-SB, Secondary endpoints NPI total, DAD, COWAT, MMSE
5-HT2A receptor inverse agonist	Pimavanserin	Psychosis	N=212 (estimated)[9]	Currently recruiting Primary endpoint: NPI Nursing Home version (NPI-NH)
5-HT6 receptor antagonist	SAM-760	Cognition NPS	N=342 (estimated)[10]	Currently recruiting Primary endpoint: ADAS-cog Secondary endpoint: NPI total
5-HT6 receptor antagonist	Idalopirdine	Cognition NPS Function	N=4260 (estimated)[11-14]	4 studies currently recruiting Primary endpoint: ADAS-cog Secondary endpoints: NPI total, single NPI items, NPI anxiety, CGIC, ADL-23, EuroQoL 5D 3L, C-SSRS

1. Porsteinsson AP, et al. *J Am Med Assoc*. 2014;311(7)682-691; 2. ALZFORUM. www.alzforum.org/news/conference-coverage/new-drug-calm-agitation-uncontrollable-laughing-and-crying-alzheimers. Accessed November 3, 2014; 3. Wang LY, et al. *Am J Geriatr Psychiatry*. 2009;17(9):744-751; 4. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT01126099. Accessed November 3, 2014; 5. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT01735630. Accessed November 3, 2014; 6. ClinicalTrials.gov. www.clinicaltrials.gov/show/NCT01862640. Accessed November 3, 2014; 7. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT01922258. Accessed November 3, 2014; 8. ClinicalTrials.gov. www.clinicaltrials.gov/show/NCT01969123. Accessed November 17, 2014; 9. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT02035553. Accessed November 3, 2014; 10. ClinicalTrials.gov. www.clinicaltrials.gov/show/NCT01712074. Accessed November 3, 2014; 11. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT02006641. Accessed November 17, 2014; 12. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT01955161. Accessed November 17, 2014; 13. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT02006654. Accessed November 17, 2014; 14. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT02079246. Accessed November 17, 2014.

Future Directions

- Lack of recognition and understanding of association between AD and NPS
  - Education is needed on the impact of NPS
  - Consider opportunities to define impact, discuss clinical trial design issues, and review emerging data
- To date, the amount of research has been somewhat limited
- Treatment options that are both indicated and not associated with significant safety concerns are limited
- More research is needed to better understand the underlying neurobiology to provide direction for better targets
- Consensus on trial methodology (choice of scales, definition of patient population) would enable better data comparison
- More data will be available within the next year—to provide guidance
  - Scylloinositol (Elan) and AVP-923 trials for agitation/aggression will be reported within ~1 year[1,2]
  - Pimavanserin study for AD Psychosis[3]

1.ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT01735630. Accessed November 3, 2014; 2. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT01584440. Accessed November 3, 2014; 3. ClinicalTrials.gov. www.clinicaltrials.gov/show/NCT01712074. Accessed November 3, 2014; 3. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT02035553. Accessed November 3, 2014.

Key Regulatory Questions (1/3)

Discussion Paper, page 11, “Stand-alone symptoms (e.g., neuropsychiatric symptoms..) states:

“It is recommended to address such stand-alone indications in separate dedicated trials;”

Concerns with this approach:

- It will not be practical to conduct a separate trial(s) for each symptom and thus a deterrent to developing treatments for some NPS
- Some symptoms are biologically related. Approving treatment for only one might be overlooking the interrelationships of these symptoms
- Cholinesterase inhibitors & memantine have already shown effects on multiple behaviors.

Questions:

- If a study demonstrated positive endpoints for multiple symptoms, or clusters of symptoms, would an indication be considered for:
  - More than 1 symptom (e.g., apathy and delusions)
  - A cluster of (related) symptoms (e.g., “affective” for depression, anxiety; “psychosis” for hallucinations, delusions)
  - Behavior in general (e.g., more than 1 cluster or many symptoms)?
- If not acceptable, please indicate why not.
- What would be necessary to obtain an indication for “Behavior”?

Key Regulatory Questions (2/3)

- Would delay to emergence of behavioral symptoms be an acceptable outcome measure?
  - For specific domains or clusters?
  - For an overall behavioral effect as has been seen with the cholinesterase inhibitors?
- If not acceptable, please indicate why not.

Key Regulatory Questions (3/3)

- Would regulators consider allowing use of medications at baseline (stable doses) and for rescue (controlled doses) that are standard of care for these NPS but which may be associated with safety concerns (ie, atypical antipsychotics) or not indicated (mood stabilizers e.g., divalproex, lamotrigine)?

- If not acceptable, please indicate why not.

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