Treatment development for neuropsychiatric symptoms in Alzheimer dementia

Where are we headed?

Constantine G. Lyketsos, MD, MHS
Chair of Psychiatry, Johns Hopkins Bayview
Elizabeth Plank Althouse Professor, Johns Hopkins University
kostas@jhmi.edu

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Outline

- NPS in Alzheimer disease (AD)
- Focus on agitation
- Treatment development
- The pipeline

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Facing reality: balancing "cure" with "care"

- **Near and medium term outcome**: extend the time course of MCI and dementia→ higher prevalence

- We must take proper care of the100+ million patients & caregivers worldwide with dementia by 2050

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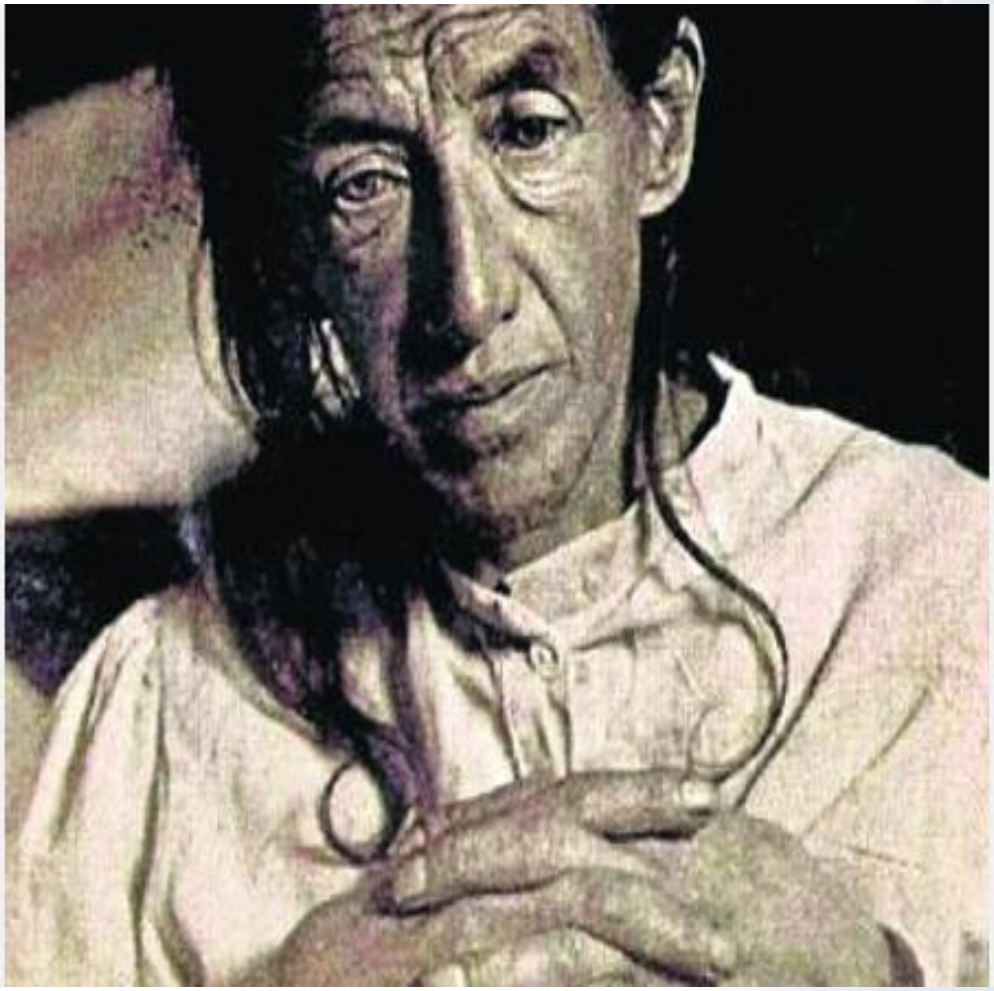
A common presentation

81 year old man with AD. Last few months easily, constantly frustrated with minor matters and “takes it out on family.”

Very agitated when requests made. For example, when hearing its time to eat, he says “I will eat when I want,” gets up and joins at the table while “screaming and yelling.”

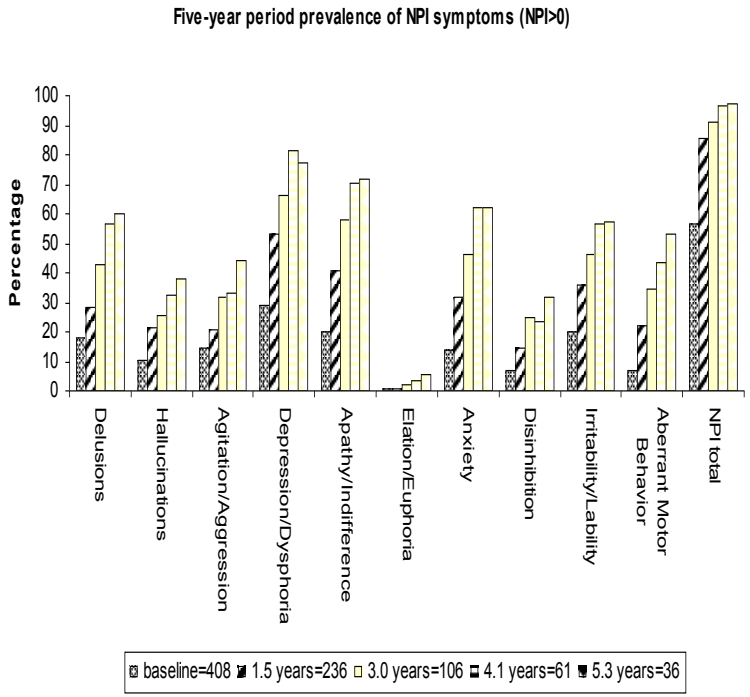
At Thanksgiving he started accusing his daughter of taking his money and not buying her children Christmas gifts. When brother tried to reassure him he raised his fists and threaten to throw him out on the street.

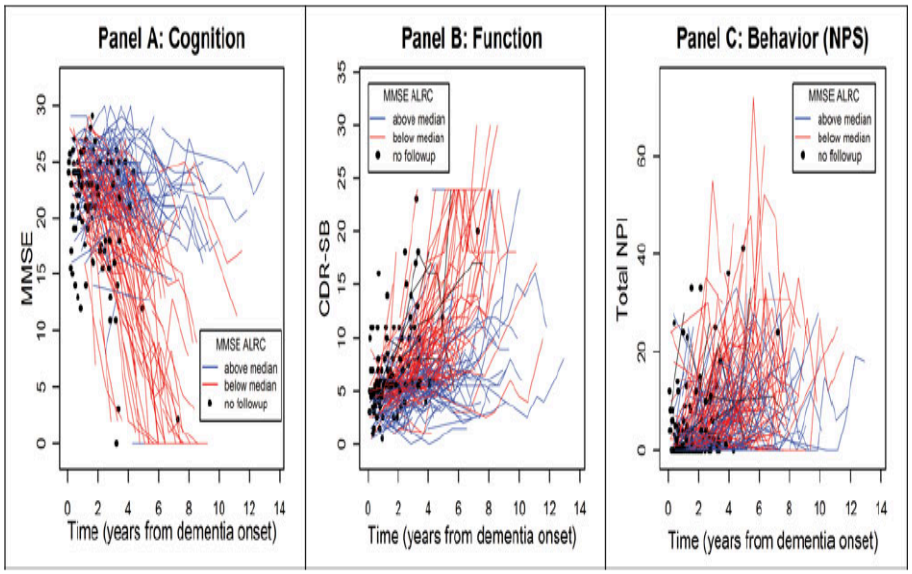
Auguste D: hospitalized for delusions and change in personality, not cognitive impairment



NPS are UNIVERSAL (97%) & fluctuate

Cache County Dementia Progression Study





Steinberg et al, Int J Ger Psychiatry 2008

Tschanz et al, Am J Geriatr Psychiatry 2012

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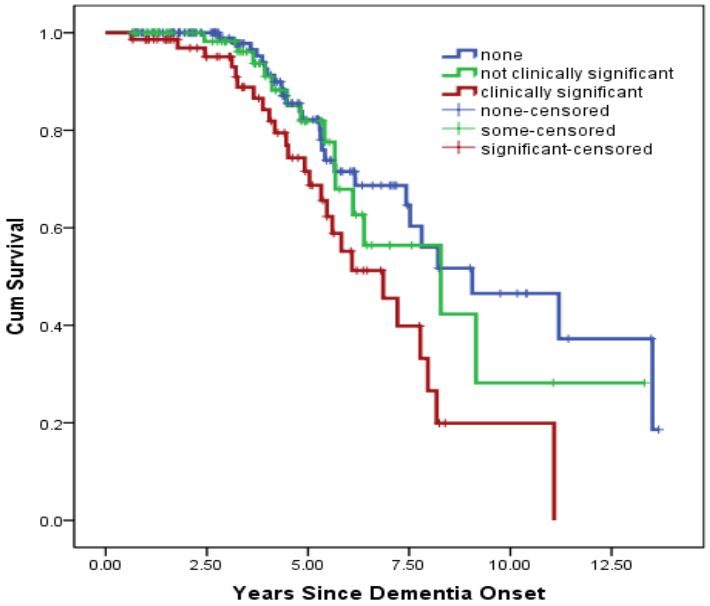
NPS are "bad" for patients & caregivers

- Greater ADL impairment[1]
- Worse quality of life[2]
- Earlier institutionalization[3]
- Major source of burden[4]
- Higher costs[5]
- Faster to severe dementia[6]
- Accelerated mortality[6]



[1]Lyketsos et al, 1997; [2]Gonzales-Salvador et al, 1999; [3]Steele et al, 1990;

[4]Lyketsos et al, 1999; [5] Murman et al, 2002; [6] Peters et al, 2015

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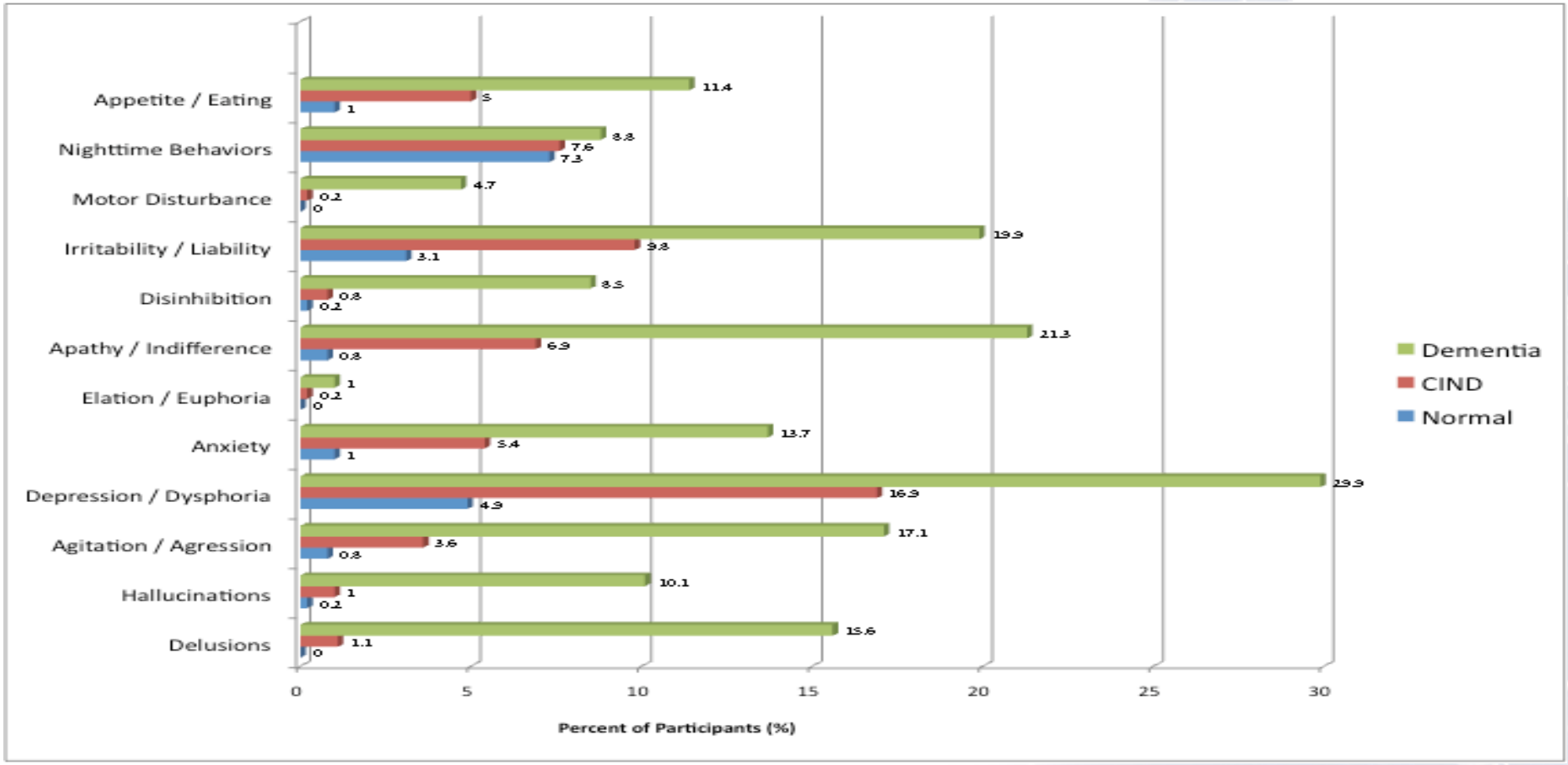
NPS are common in MCI

Cache County Memory Study



Peters et al, AJGP 2011

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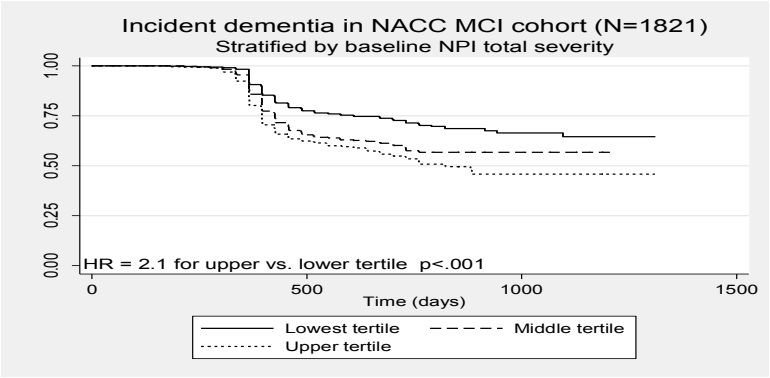
NPS & MBI increase risk of MCI & dementia

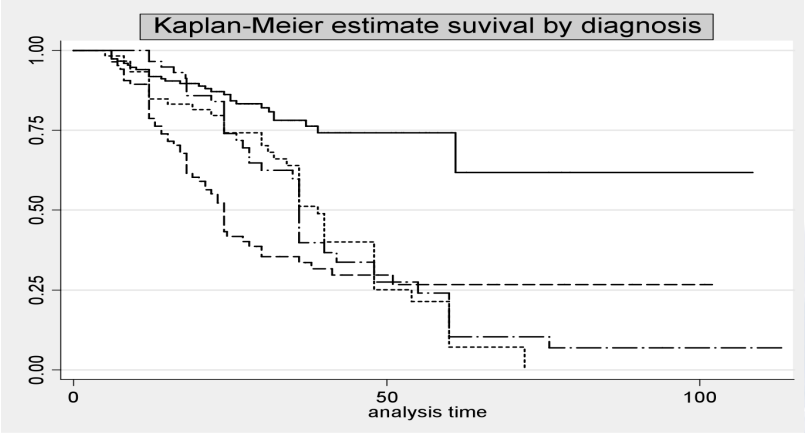
opportunity to prevent dementia

NPS in MCI: greater dementia risk



Rosenberg, Alzh Dem 2012

MBI: greater dementia risk than MCI alone



Taragano, J Clinical Psychiatry 2009

ELSEVIER

Alzheimer's & Dementia ■ (2015) 1-8

Alzheimer's & Dementia

Perspective

Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment

Zahinoor Ismail[a,b,c,d,*], Eric E. Smith[b,d], Yonas Geda[e,f], David Sultzer[g,h], Henry Brodaty[i], Gwenn Smith[j], Luis Agüera-Ortiz[k], Rob Sweet[l,m], David Miller[n], Constantine G. Lyketsos[o], for the ISTAART Neuropsychiatric Symptoms Professional Interest Area

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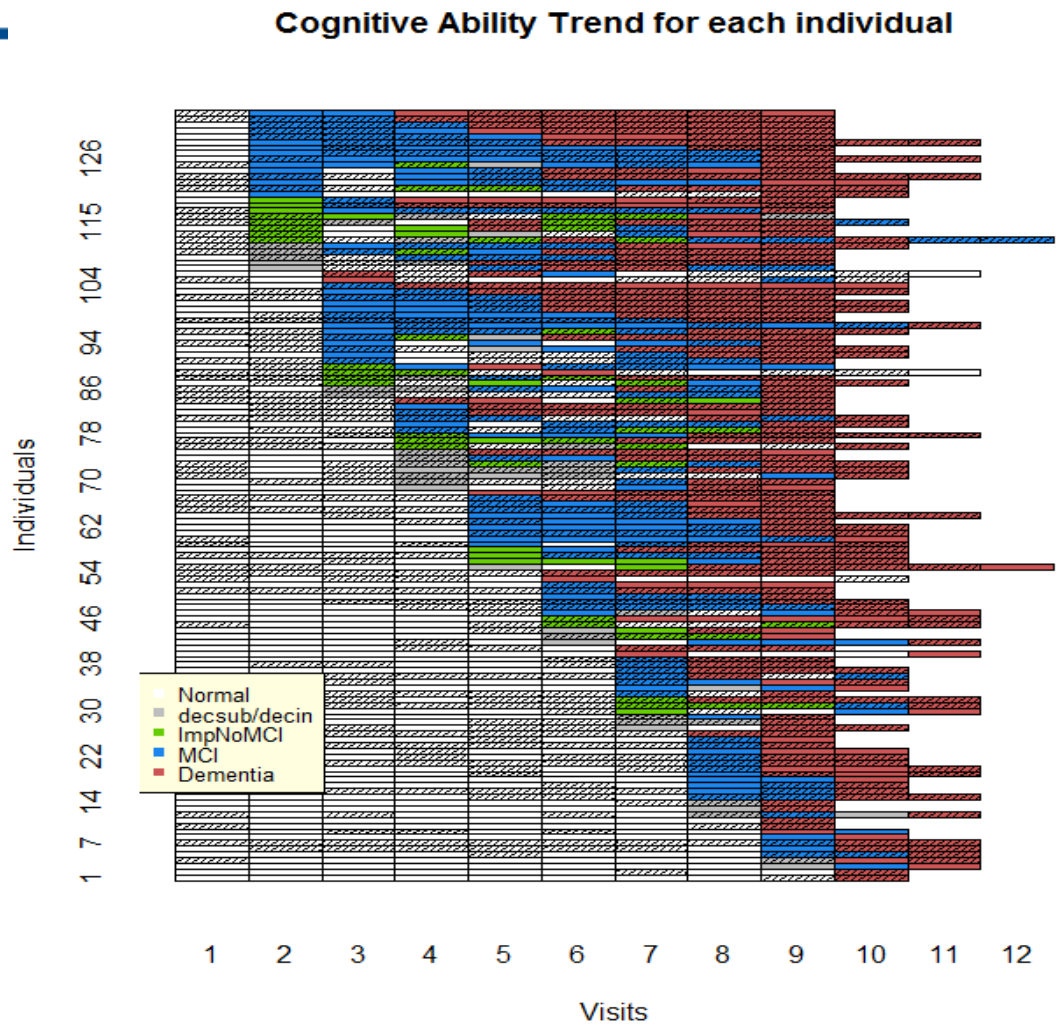
In fact, over half of people who develop dementia develop NPS BEFORE cognitive symptoms



Sequencing of NPS Presence with Cognitive Diagnosis (overall N=1,980)

Normal→ MCI
NPS Onset Before MCI: 55%

Normal→ Dementia
NPS Onset Before MCI 55%

Normal→ Dementia (no MCI)
NPS Before Dementia 64%

Wise et al, under review, from analysis of NACC data

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Medication Rxs are disappointing

few meds have efficacy—many have significant risks

- FDA approved “AD meds” (cholinesterase inhibitors; memantine): ineffective

- Anticonvulsants: ineffective, risky
- Benzodiazepines: ineffective, risky

- Antipsychotics: small benefit, black box warning
- Antidepressants: largely ineffective

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Eco-psychosocial interventions

behavioral, environmental, caregiver focused

Numerous expert bodies recommend first-line

Largely NOT been translated to real-world care

- ***Lack of practical clinical approach***
- Lack of provider training
- Lack of reimbursement
- Lack of guidelines
- Perceived lack of efficacy
- Heterogeneity of interventions

Molinari et al, 2010; Cohen-Mansfield et al, 2013

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How should we develop Rx for NPS?

COMBINE

- Disease specific phenotypes (top down)
- Based on cause (bottom up)

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Overlap of disturbances (38/45, p<0.01)

Cache County Dementia Progression Study

	Apathy	Depression	Anxiety	Irritability	Elation	Delusions	Hallucin.	Agitation	Aberrant	Disinh.
Apathy	54 (27.3)	22	17	20	1	19	9	17	17	7
Depression	5.14 (2.45-7.83)	39 (19.7)	19	14	1	14	10	12	14	3
Anxiety	3.95 (1.80-8.66)	10.67 (4.58-24.87)	32 (16.2)	14	1	13	6	11	14	6
Irritability	4.11 (1.96-8.64)	3.15 (1.44-6.91)	3.86 (1.69-8.80)	38 (19.2)	0	15	6	19	18	9
Elation	.269 (.214-.339)	.193 (.145-.257)	.157 (.114-.217)	.807 (.754-.864)	1 (0.5)	1	1	0	1	1
Delusions	2.46 (1.22-4.97)	2.31 (1.08-4.96)	2.87 (1.28-6.40)	2.83 (1.32-6.06)	.223 (.17-.29)	45 (22.7)	15	18	14	12
Hallucinations	1.49 (.62-3.59)	3.08 (1.27-7.47)	1.69 (.62-4.59)	1.31 (.49-3.53)	.127 (.09-.183)	6.46 (2.70-15.44)	26 (13.1)	8	7	3
Agitation	2.30 (1.12-4.73)	1.99 (.90-4.39)	2.38 (1.04-5.44)	6.27 (2.88-13.67)	.792 (.74-.85)	3.77 (1.79-7.92)	1.87 (.75-4.68)	41 (20.7)	14	12
Aberrant	3.43 (1.59-7.38)	3.89 (1.74-8.70)	5.68 (2.45-13.16)	8.1 (3.57-18.39)	.168 (.12-.23)	3.00 (1.37-6.60)	1.98 (.76-5.16)	3.55 (1.60-7.89)	34 (17.2)	9
Disinhibition	2.53 (.87-7.36)	1.02 (.274-3.81)	4.03 (1.32-12.26)	7.97 (2.63-24.09)	.071 (.043-.12)	18.18 (4.86-68.07)	1.74 (.46-6.63)	21.24 (5.64-80.0)	9.48 (3.11-28.93)	15 (7.6)

Lyketsos et al, Int J Ger Psychiatry 2001

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NPS groupings by phenomenology
proposed by the ISTAART NPS-PIA

ELSEVIER

Alzheimer's & Dementia 9 (2013) 602–608

Alzheimer's & Dementia

Neuropsychiatric symptoms in Alzheimer's disease: Past progress and anticipation of the future

Yonas E. Geda[a], Lon S. Schneider[b], Laura N. Gitlin[c], David S. Miller[d,†], Gwenn S. Smith[e], Joanne Bell[f], Javier Evans[g], Michael Lee[h], Anton Porsteinsson[i], Krista L. Lanctôt[j,k], Paul B. Rosenberg[e], David L. Sultzer[l], Paul T. Francis[m], Henry Brodaty[n], Prasad P. Padala[o,p], Chiadikaobi U. Onyike[e], Luis Agüera Ortiz[q,r], Sonia Ancoli-Israel[s], Donald L. Bliwise[t], Jennifer L. Martin[u], Michael V. Vitiello[v], Kristine Yaffe[w], Phyllis C. Zee[x], Nathan Herrmann[j], Robert A. Sweet[y,z,aa], Clive Ballard[bb], Ni A. Khin[cc], Cara Alfaro[cc], Patrick S. Murray[y,aa], Susan Schultz[dd], Constantine G. Lyketsos[e,*,†]; for the Neuropsychiatric Syndromes Professional Interest Area of ISTAART

Novel

- Agitation (IPA, 2014)
- Apathy (Robert, 2010)
- Circadian disorder (TBA)

DSM Legacy

- Psychosis (Jeste, 2000)
- Depression (Olin, 2003)

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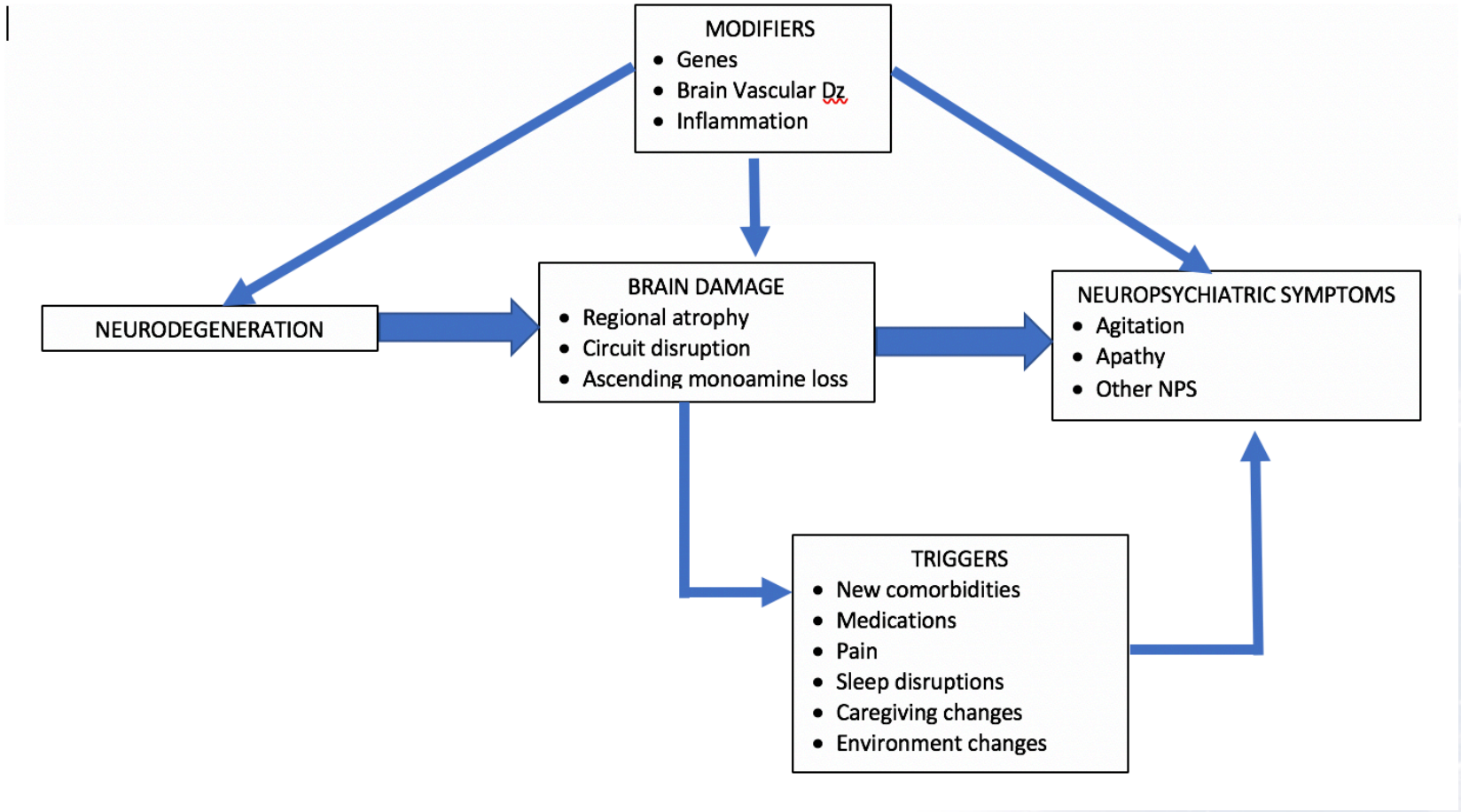
Etiologies of NPS



British Medical Journal 2015; NIMH/NIA Panel May 2017

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Three *(overlapping)* neurobiological models

proposed by the ISTAART NPS-PIA

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1. Fronto-subcortical circuit disruption
2. Cortico-cortical circuit disruption
3. Monoamine regulatory imbalance

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Molecular Aspects of Medicine 43–44 (2015) 25–37

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

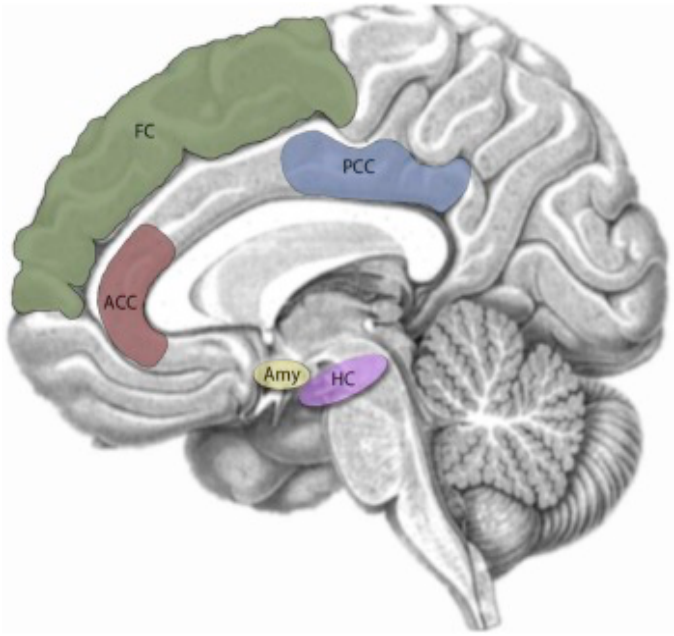
journal homepage: www.elsevier.com/locate/mam

Review

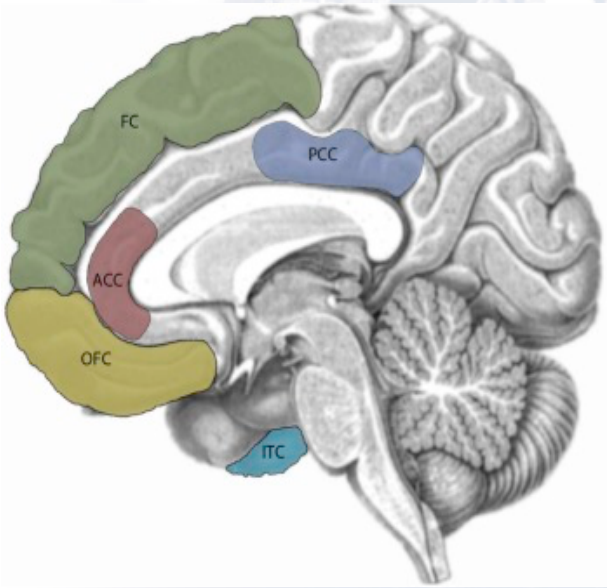
Neuropsychiatric symptoms in Alzheimer's disease: What might be associated brain circuits?

Paul B. Rosenberg *, Milap A. Nowrangi, Constantine G. Lyketsos

Department of Psychiatry and Behavioral Sciences, Division of Geriatric Psychiatry and Neuropsychiatry, Johns Hopkins School of Medicine, USA



Agitation circuit



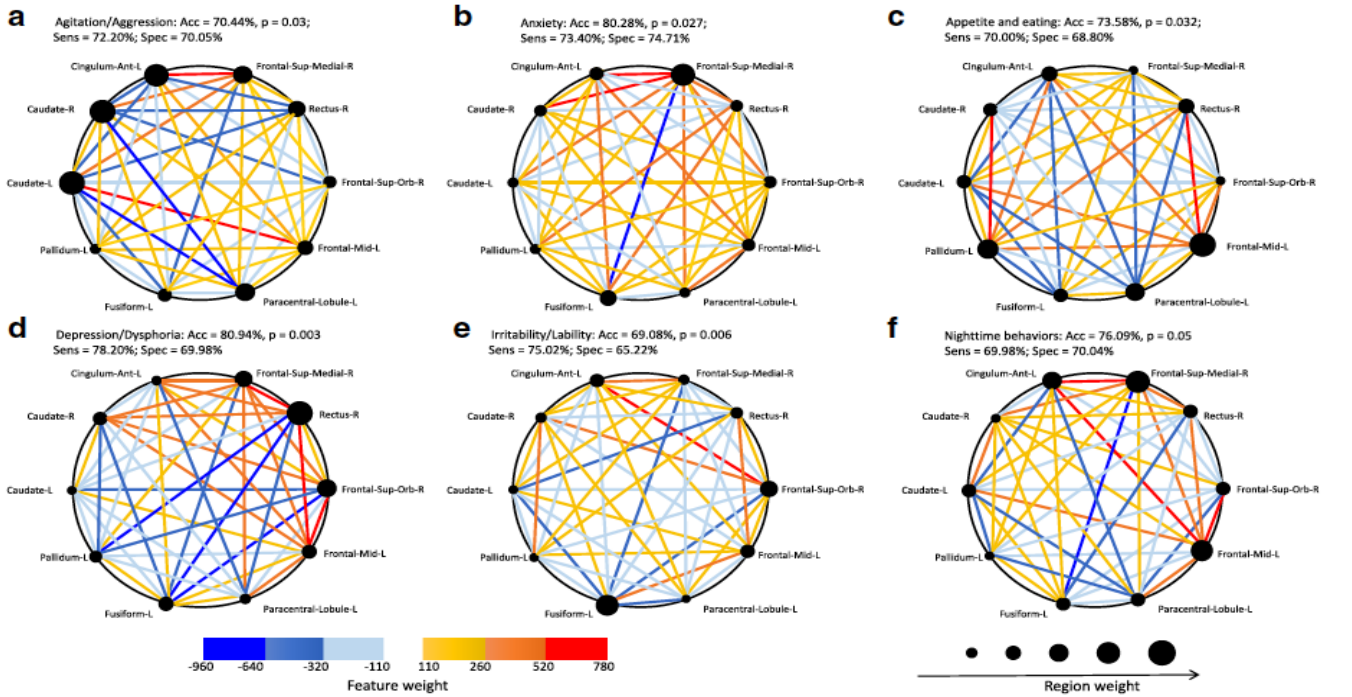
Apathy circuit

Brain Imaging and Behavior
DOI 10.1007/s11682-017-9767-y

ORIGINAL RESEARCH

Identify a shared neural circuit linking multiple neuropsychiatric symptoms with Alzheimer's pathology

Xixi Wang[1] · Ping Ren[2] · Mark Mapstone[3] · Yeates Conwell[4] · Anton P. Porsteinsson[4] · John J. Foxe[5] · Rajeev D. S. Raizada[6] · Feng Lin[2,4,5,6] · and the Alzheimer's Disease Neuroimaging Initiative



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Monoamine regulatory imbalance

serotonergic agents for "Agitation in AD"

J Alzheimers Dis. 2014;41(3):819-33. doi: 10.3233/JAD-140309.

Brain region-specific monoaminergic correlates of neuropsychiatric symptoms in Alzheimer's disease.

Vermeiren Y[1], Van Dam D[1], Aerts T[1], Engelborghs S[2], De Deyn PP[3].

Neuropsychologia. 2005;43(3):442-9.

Cholinergic-serotonergic imbalance contributes to cognitive and behavioral symptoms in Alzheimer's disease.

Garcia-Alloza M[1], Gil-Bea FJ, Diez-Ariza M, Chen CP, Francis PT, Lasheras B, Ramirez MJ.

Arch Neurol. 2004 Aug;61(8):1249-53.

Association of the serotonin transporter and receptor gene polymorphisms in neuropsychiatric symptoms in Alzheimer disease.

Assal F[1], Alarcón M, Solomon EC, Masterman D, Geschwind DH, Cummings JL.

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Novel

- Agitation (IPA, 2014)
- Apathy (Robert, 2010)
- Sleep disorder (pending)

DSM Legacy

- Psychosis (Jeste, 2000)
- Depression (Olin, 2003)

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Table 3. Recommendations for future RCTs targeting A/A in patients with AD

METHODOLOGICAL ASPECT	RECOMMENDATIONS
Population studied	
Age	• No limit
Dementia severity	• Mild to severe based on CDR rating of 1–3; stratification
Settings	• Different RCTs for NH or CD preferred; or stratification
Clinically significant A/A	• A/A needs consensus criteria • "Clinically significant" = medication is needed based on judgment of experienced clinician combined with severity rating above a cut-off on a A/A scale
Concomitant medications	• "AD treatments" allowed on stable doses for 30–60 days • APs not allowed; or allowed stable doses for 30–60 days • Antidepressants, mood stabilizers, anticonvulsants: allowed on stable doses for 30–60 days
Caregiver participation	• Caregiver needs a consensus definition • Standardized training in recognizing NPS and in rating behavior scales • Use of a caregiver diary for real time observations
Study design	
Pharmacological intervention	• Run-in-period before randomization (2–4 weeks) • 8–12-week treatment period • Consolidation response: to assess time to relapse within responders in each group during a 6–12-month period
Non-pharmacological intervention	• Psychosocial intervention during the run-in and the treatment periods in both groups. • Etiologic, non-pharmacologic, person-centered approach during run-in and treatment periods in both groups
Allowed rescue medication	• Defined allowable dosing, monitored use
Outcome measures	
Primary	• Global measure of A/A as primary • Validated scales assessing A/A, co-primary or secondary • Rated by clinicians with patient and caregiver input
Secondary	• Consider actigraphy • Agitation symptoms • Aggression symptoms • Other NPS: irritability, anxiety, depression, psychosis • Cognition, functional ability, quality of life • Caregiver distress, other caregiver measures • Allowed rescue medication cumulative dose
Analytic strategies	
	• Intention to treat analysis • Mixed models: LMM or MMRM

Abbreviations: AD = Alzheimer's disease; NPS = neuropsychiatric symptoms; A/A = agitation/aggression; CD = community dwelling; NH = nursing home; CDR = clinical dementia rating; MMRM: mixed model of repeated measures; linear mixed models.

International Psychogeriatrics (2015), 27:2, 181–197 © International Psychogeriatric Association 2014
doi:10.1017/S1041610214001720

REVIEW

Medication development for agitation and aggression in Alzheimer disease: review and discussion of recent randomized clinical trial design

Maria Soto,[1] Sandrine Andrieu,[1,2] Fati Nourhashemi,[1] Pierre Jean Ousset,[1] Clive Ballard,[3] Philippe Robert,[4] Bruno Vellas,[1] Constantine G. Lyketsos[5] and Paul B. Rosenberg[5]

[1] *Gerontopôle, INSERM U 1027, Alzheimer's Disease Research and Clinical Center, Toulouse University Hospital, France*
[2] *Department of Epidemiology, Toulouse University Hospital Toulouse, France*
[3] *Wolfson Centre for Age-Related Diseases, King's College, London, UK*
[4] *EA CoBTeK / ICMRR University of Nice Sophia Antipolis -CHU, France*
[5] *Department of Psychiatry, The Johns Hopkins Bayview Medical Center, Baltimore, MD, USA*

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Agitation: *core* phenotype

- **Emotional agitation**: distress, upheaval, anger, tension, anxiety, worry, inability to relax
- **Lability**: rapid changes in mood, irritability, unexpected outbursts, overreacting, catastrophizing
- **Psychomotor agitation**: pacing, rocking, restless, gesticulating, pointing fingers,
- **Verbal aggression**: yelling, excessively loud voice, screaming, use of profanity, threats, "in your face"
- **Physical aggression**: grabbing, shoving, pushing, resisting, hitting, kicking, getting in the way

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Antipsychotics for agitation: small benefit

Antipsychotics carry BLACK BOX warning

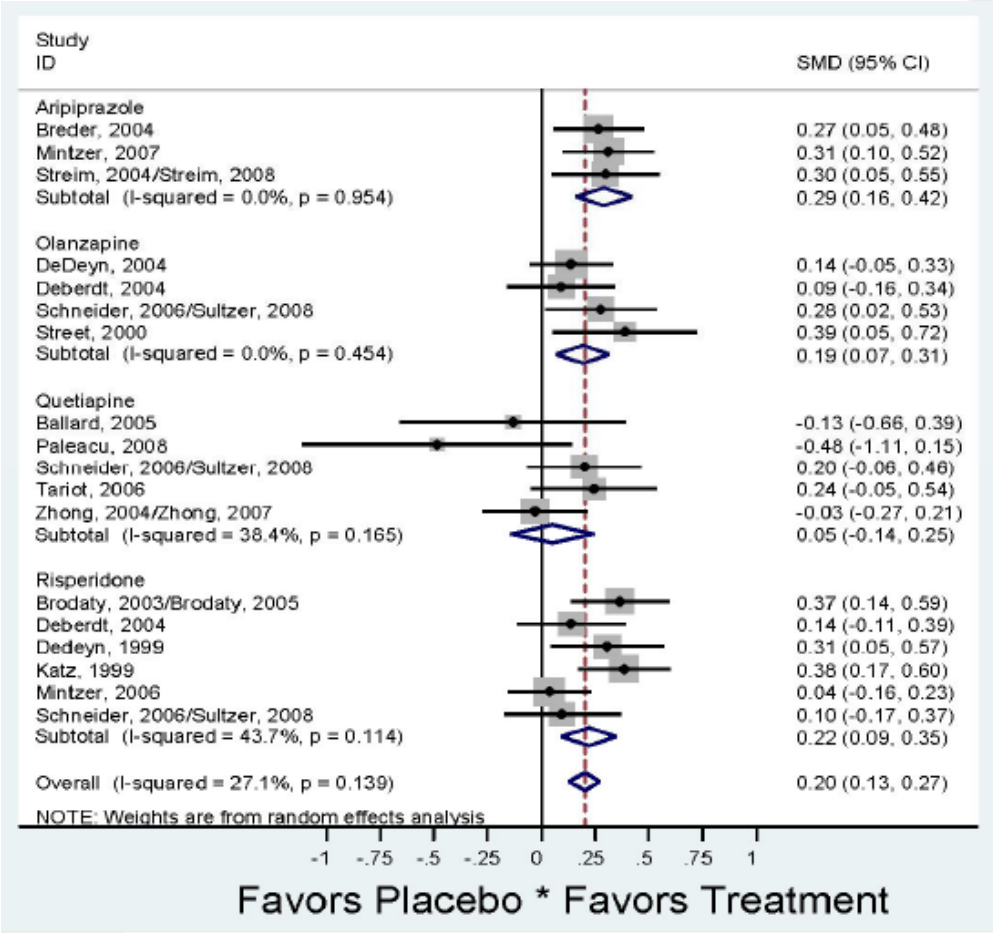
Aripiprazole

Olanzapine

Quetiapine

Risperidone

Effect Size (SMD) = 0.20



AHRQ Comparative Effectiveness Review 2011

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Rationale for serotonergic agents for Agitation in AD

- Serotonin is an inhibitory modulator of agitation, aggression
- Serotonergic dysfunction associated with aggression in animals & humans

- Serotonergic loss widespread in the brains of AD patients even in early disease
- Serotonergic system loss, genetic variation, or dysfunction associated with agitation in AD patients
- SSRIs have favorable side-effect profiles

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Original Investigation

Effect of Citalopram on Agitation in Alzheimer Disease
The CitAD Randomized Clinical Trial

Anton P. Porsteinsson, MD; Lea T. Drye, PhD; Bruce G. Pollock, MD, PhD; D. P. Devanand, MD; Constantine Frangakis, PhD; Zahinoor Ismail, MD; Christopher Marano, MD; Curtis L. Meinert, PhD; Jacobo E. Mintzer, MD, MBA; Cynthia A. Munro, PhD; Gregory Pelton, MD; Peter V. Rabins, MD; Paul B. Rosenberg, MD; Lon S. Schneider, MD; David M. Shade, JD; Daniel Weintraub, MD; Jerome Yesavage, MD; Constantine G. Lyketsos, MD, MHS; for the CitAD Research Group

IMPORTANCE Agitation is common, persistent, and associated with adverse consequences for patients with Alzheimer disease. Pharmacological treatment options, including antipsychotics are not satisfactory.

OBJECTIVE The primary objective was to evaluate the efficacy of citalopram for agitation in patients with Alzheimer disease. Key secondary objectives examined effects of citalopram on function, caregiver distress, safety, cognitive safety, and tolerability.

DESIGN, SETTING, AND PARTICIPANTS The Citalopram for Agitation in Alzheimer Disease Study (CitAD) was a randomized, placebo-controlled, double-blind, parallel group trial that enrolled 186 patients with probable Alzheimer disease and clinically significant agitation from 8 academic centers in the United States and Canada from August 2009 to January 2013.

INTERVENTIONS Participants (n = 186) were randomized to receive a psychosocial intervention plus either citalopram (n = 94) or placebo (n = 92) for 9 weeks. Dosage began at 10 mg per day with planned titration to 30 mg per day over 3 weeks based on response and tolerability.

MAIN OUTCOMES AND MEASURES Primary outcome measures were based on scores from the 18-point Neurobehavioral Rating Scale agitation subscale (NBRS-A) and the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC). Other outcomes were based on scores from the Cohen-Mansfield Agitation Inventory (CMAI) and the Neuropsychiatric Inventory (NPI), ability to complete activities of daily living (ADLs), caregiver distress, cognitive safety (based on scores from the 30-point Mini Mental State Examination [MMSE]), and adverse events.

RESULTS Participants who received citalopram showed significant improvement compared with those who received placebo on both primary outcome measures. The NBRS-A estimated treatment difference at week 9 (citalopram minus placebo) was −0.93 (95% CI, −1.80 to −0.06), $P = .04$. Results from the mADCS-CGIC showed 40% of citalopram participants having moderate or marked improvement from baseline compared with 26% of placebo recipients, with estimated treatment effect (odds ratio [OR] of being at or better than a given CGIC category) of 2.13 (95% CI, 1.23-3.69), $P = .01$. Participants who received citalopram showed significant improvement on the CMAI, total NPI, and caregiver distress scores but not on the NPI agitation subscale, ADLs, or in less use of rescue lorazepam. 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; $P = .01$) were seen in the citalopram group.

CONCLUSIONS AND RELEVANCE Among patients with probable Alzheimer disease and agitation who were receiving psychosocial intervention, the addition of citalopram compared with placebo significantly reduced agitation and caregiver distress; however, cognitive and cardiac adverse effects of citalopram may limit its practical application at the dosage of 30 mg per day.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00898807

JAMA. 2014;311(7):682-691. doi:10.1001/jama.2014.93

Editorial page 677

Author Video Interview at jama.com

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The CitAD Research Group members are listed at the end of this article.

Corresponding Author: Anton P. Porsteinsson, MD, Department of Psychiatry, University of Rochester School of Medicine and Dentistry, 435 E Henrietta Rd, Rochester, NY 14620 (anton_porsteinsson@urmc.rochester.edu).

CitAD: model design

- Biologically informed
- Agitation syndrome
- Psychosocial intervention
- 30mg/day vs. placebo
- 9 weeks of treatment
- Sensitive outcomes
  - mADCS-CGIC
  - NBRS-A/A

NIH-funded multi-center trial (R01AG031348; PI: Lyketsos)

Use The DICE Approach

Describe

- Caregiver **describes** problematic behavior
  - Context (who, what, when and where)
  - Social and physical environment
  - Patient perspective
  - Degree of distress to patient and caregiver

Investigate

- Provider **investigates** possible causes of problem behavior
  - Patient
    - Medication side effects
    - Pain
    - Functional limitations
    - Medical conditions
    - Psychiatric comorbidity
    - Severity of cognitive impairment, executive dysfunction
    - Poor sleep hygiene
    - Sensory changes
    - Fear, sense of loss of control, boredom
  - Caregiver effects/expectations
  - Social and physical environment
  - Cultural factors

Create

- Provider, caregiver and team **collaborate to create** and implement treatment plan
  - Respond to physical problems
  - Strategize behavioral interventions
    - Providing caregiver education and support
    - Enhancing communication with the patient
    - Creating meaningful activities for the patient
    - Simplifying tasks
    - Ensuring the environment is safe
    - Increasing or decreasing stimulation in the environment

Evaluate

- Provider **evaluates** whether "CREATE" interventions have been implemented by caregiver and are safe and effective

Consideration of Psychotropic Use (Acuity/Safety)

Kales, Gitlin, Lyketsos, JAGS 2014

CitAD: main outcomes

Table 2. Primary and Secondary Outcomes[a]

	Citalopram		Placebo	*P* Value
No. randomized	94		92	
No. with any week-9 data	86		83	
Primary Agitation Outcomes				
NBRS-A[b]				
No. with ≥1 follow-up measurement	90		85	
No. with week-9 data	86		81	
Estimated score at 9 weeks, mean (SE)	4.33 (0.31)		5.26 (0.31)	
Estimated treatment effect, mean (95% CI)		−0.93 (−1.80 to −0.06)[c]		.04
ADCS-CGIC, No. (%)				
No. with week-9 data	86		81	
Marked improvement	12 (14)		2 (3)	
Moderate improvement	22 (26)		19 (23)	
Minimal improvement	25 (29)		20 (25)	
No change	17 (20)		23 (28)	
Minimal worsening	6 (7)		11 (14)	
Moderate worsening	3 (4)		5 (6)	
Marked worsening	1 (1)		1 (1)	
Estimated treatment effect, OR (95% CI)[d]		2.13 (1.23 to 3.69)[e]		.007

Porsteinsson et al, JAMA 2014

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Benefit to "psychotic" symptoms

Table 2 Neuropsychiatric Inventory (NPI) domains at week 9

	All participants*						Participants reporting symptom**		
	Citalopram		Placebo				Citalopram	Placebo	
	n†	(%)	n†	(%)	OR* (95% CI)	p-value	Median (IQR)**	Median (IQR)**	p-value
Number with week 9 NPI data	86		83						
Individual domains									
Delusions	22	(26 %)	35	(42 %)	0.40 (0.18, 0.91)	0.03	4 (2, 8)	4 (3, 8)	0.46
Hallucinations	11	(13 %)	13	(16 %)	1.53 (0.50, 4.71)	0.46	1 (1, 3)	6 (4, 6)	<0.01
Agitation/aggression	66	(77 %)	70	(84 %)	0.63 (0.28, 1.41)	0.26	3 (2, 8)	6 (3, 8)	0.05
Depression/dysphoria	24	(28 %)	30	(36 %)	0.69 (0.34, 1.39)	0.30	3 (1, 6)	3 (2, 6)	0.35
Anxiety	36	(42 %)	54	(65 %)	0.43 (0.22, 0.84)	0.01	4 (2.5, 8)	4 (3, 6)	0.78
Elation/euphoria	3	(3 %)	5	(6 %)	0.45 (0.09, 2.21)	0.32	1 (1, 8)	3 (2, 6)	0.55
Apathy/indifference	41	(48 %)	42	(51 %)	0.92 (0.47, 1.80)	0.82	4 (3, 8)	6 (4, 8)	0.36
Disinhibition	27	(31 %)	34	(41 %)	0.71 (0.35, 1.46)	0.35	4 (2, 8)	4 (2, 6)	0.73
Irritability/lability	49	(57 %)	61	(73 %)	0.38 (0.19, 0.76)	0.01	4 (2, 6)	6 (3, 8)	0.13
Aberrant motor behavior	34	(40 %)	47	(57 %)	0.49 (0.24, 0.99)	0.05	4 (3, 8)	4 (3, 8)	0.96
Sleep and nighttime behavior	21	(24 %)	30	(36 %)	0.56 (0.27, 1.16)	0.12	4 (3, 12)	3 (2, 6)	0.03
Appetite and eating disorders	22	(26 %)	18	(22 %)	1.32 (0.62, 2.82)	0.47	4 (4, 8)	4 (3, 8)	0.84
Summary scores									
Non-mood score	78	(91%)	79	(95%)	††0.48 (0.10, 2.00)	0.41	8.5 (5, 17)	14 (8, 24)	<0.01
Affective score	72	(84%)	78	(94%)	0.33 (0.11, 1.03)	0.06	7 (4, 14.5)	12 (6, 20)	0.04
Psychotic score	28	(33%)	37	(45%)	0.67 (0.31, 1.44)	0.30	4 (2, 6)	6 (4, 9)	0.02

Leonpacher et al, Am J Psychiatry 2016

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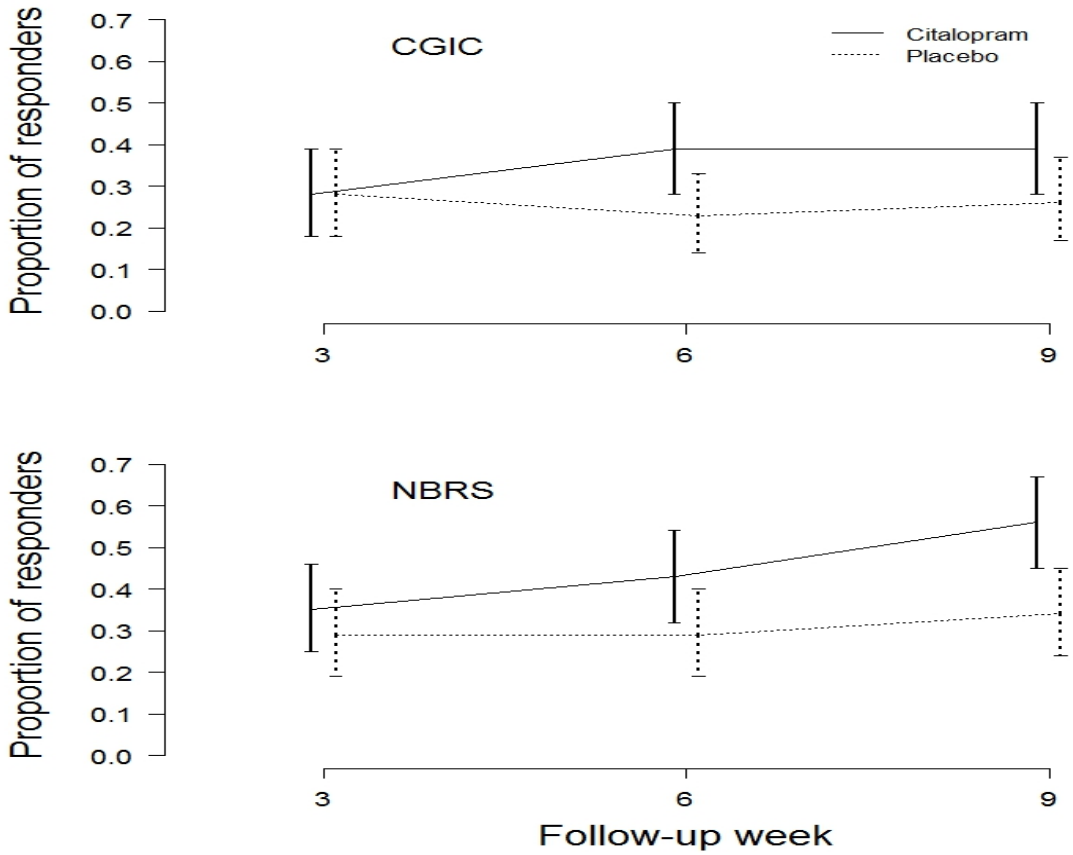
Placebo response (28%) by week 3
Citalopram (40%) response 9+ weeks



Weintraub et al, Am J Geriatric Psych 2015

JOHNS HOPKINS MEDICINE

Response limited to a subgroup

Heterogeneity of Treatment Response to Citalopram for Patients With Alzheimer's Disease With Aggression or Agitation: The CitAD Randomized Clinical Trial

Lon S. Schneider, M.D., M.S., Constantine Frangakis, Ph.D., Lea T. Drye, Ph.D., D.P. Devanand, M.D., Christopher M. Marano, M.D., Jacob Mintzer, M.D., M.B.A., Benoit H. Mulsant, M.D., M.S., Cynthia A. Munro, Ph.D., Jeffery A. Newell, B.A., Sonia Pawluczyk, M.D., Gregory Pelton, M.D., Bruce G. Pollock, M.D., Ph.D., Anton P. Porsteinsson, M.D., Peter V. Rabins, M.D., Lisa Rein, Sc.M., Paul B. Rosenberg, M.D., David Shade, J.D., Daniel Weintraub, M.D., Jerome Yesavage, M.D., Constantine G. Lyketsos, M.D., M.H.S., for the CitAD Research Group

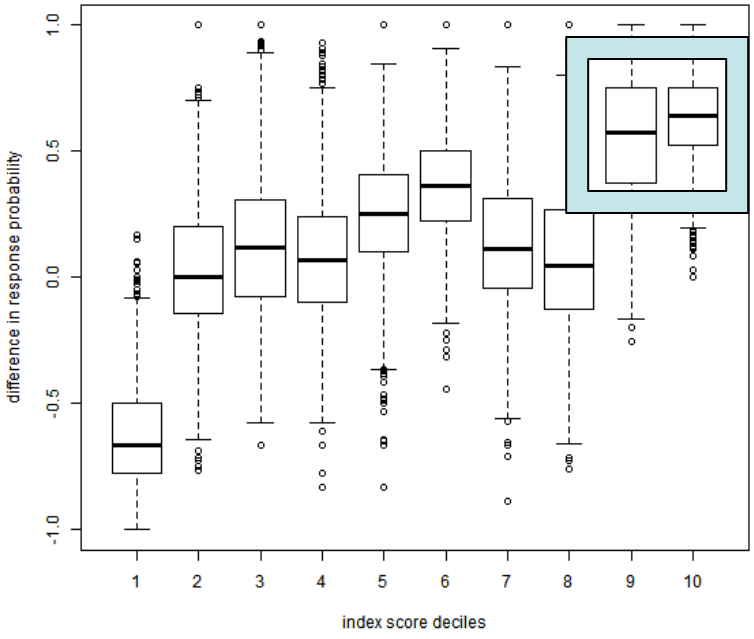
Objective: Pharmacological treatments for agitation and aggression in patients with Alzheimer's disease have shown limited efficacy. The authors assessed the heterogeneity of response to citalopram in the Citalopram for Agitation in Alzheimer Disease (CitAD) study to identify individuals who may be helped or harmed.

Method: In this double-blind parallel-group multicenter trial of 186 patients with Alzheimer's disease and clinically significant agitation, participants were randomly assigned to receive citalopram or placebo for 9 weeks, with the dosage titrated to 30 mg/day over the first 3 weeks. Five planned potential predictors of treatment outcome were assessed, along with six additional predictors. The authors then used a two-stage multivariate method to select the most likely predictors; grouped participants into 10 subgroups by their index scores; and estimated the citalopram treatment effect for each.

Results: Five covariates were likely predictors, and treatment effect was heterogeneous across the subgroups. Patients for whom citalopram was more effective were more likely to be outpatients, have the least cognitive impairment, have moderate agitation, and be within the middle age range (76–82 years). Patients for whom placebo was more effective were more likely to be in long-term care, have more severe cognitive impairment, have more severe agitation, and be treated with lorazepam.

Conclusions: Considering several covariates together allowed the identification of responders. Those with moderate agitation and with lower levels of cognitive impairment were more likely to benefit from citalopram, and those with more severe agitation and greater cognitive impairment were at greater risk for adverse responses. Considering the dosages used and the association of citalopram with cardiac QT prolongation, use of this agent to treat agitation may be limited to a subgroup of people with dementia.

AJP in Advance (doi: 10.1176/appi.ajp.2015.15050648)



Schneider et al, Am J Psychiatry 2016

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Response depends on Affective vs. Executive phenotype

ADS (Affective)	EDS (dysexecutive) 0	1	2	3	4	5	6
0	0	1	0	2	1	0	1
1	2	5	8	2	0	1	1
2	2	8	8	6	4	7	2
3	1	6	10	12	4	12	3
4	4	3	8	4	13	8	6
5	1	3	4	6	3	4	5
6	0	0	0	1	1	0	0
7	0	0	0	0	2	1	0

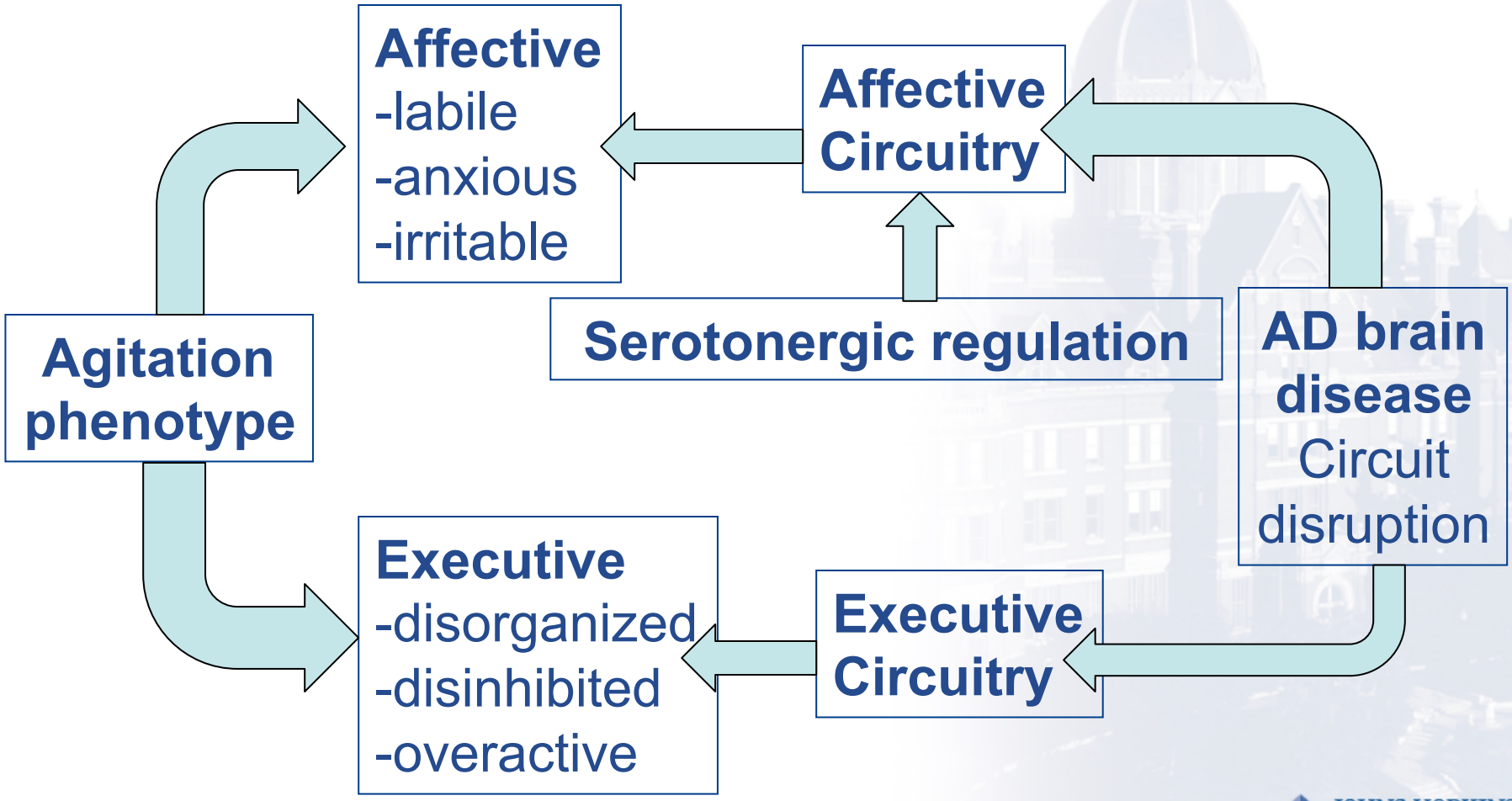
Group	% Response at 9w Placebo	Citalopram	# of Patients
overall	**26**	**40**	**186**
blue	29	26	27
white	31	32	51
red	14	52	53

Charu et al, Int J Biostat 2017

JOHNS HOPKINS MEDICINE

Linking Top Down to Bottom up

etiologic model for agitation



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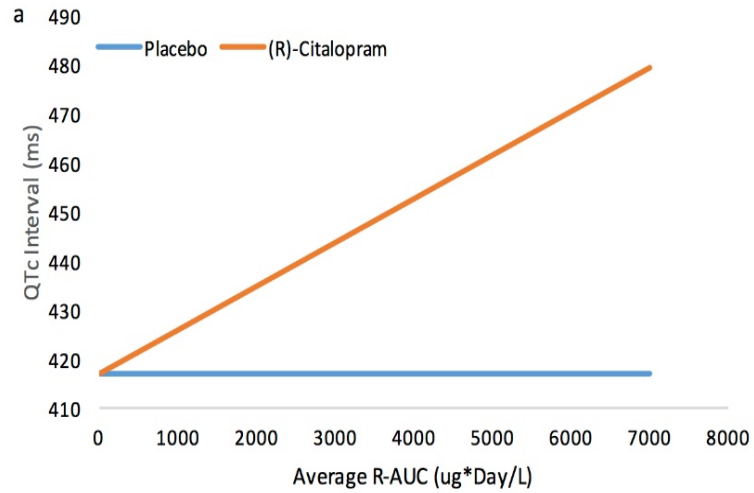
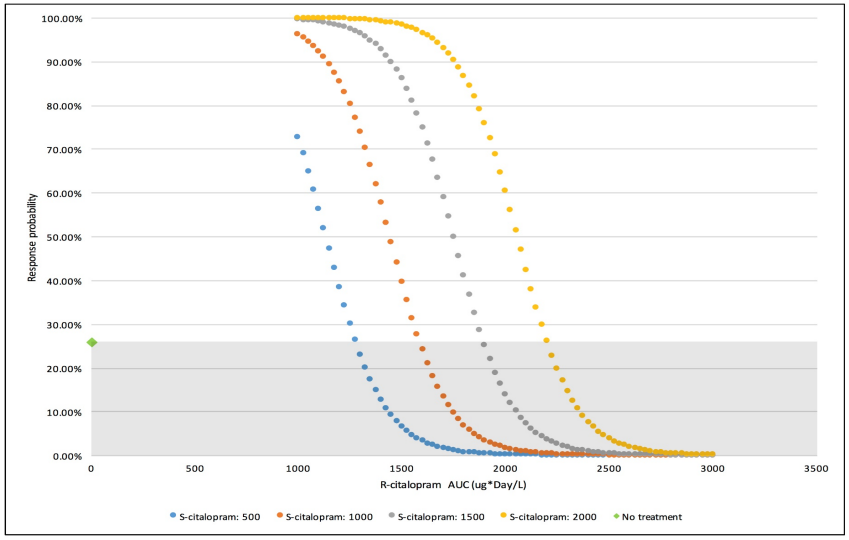
R- vs. S-citalopram have DIFFERENT effects

R-citalopram→QTc prolong.

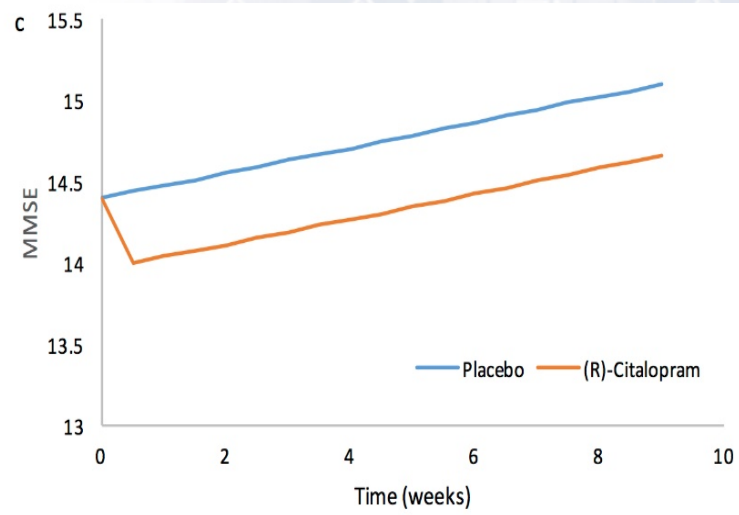


S-citalopram→clinical benefit

Response probability



R-citalopram→MMSE decline

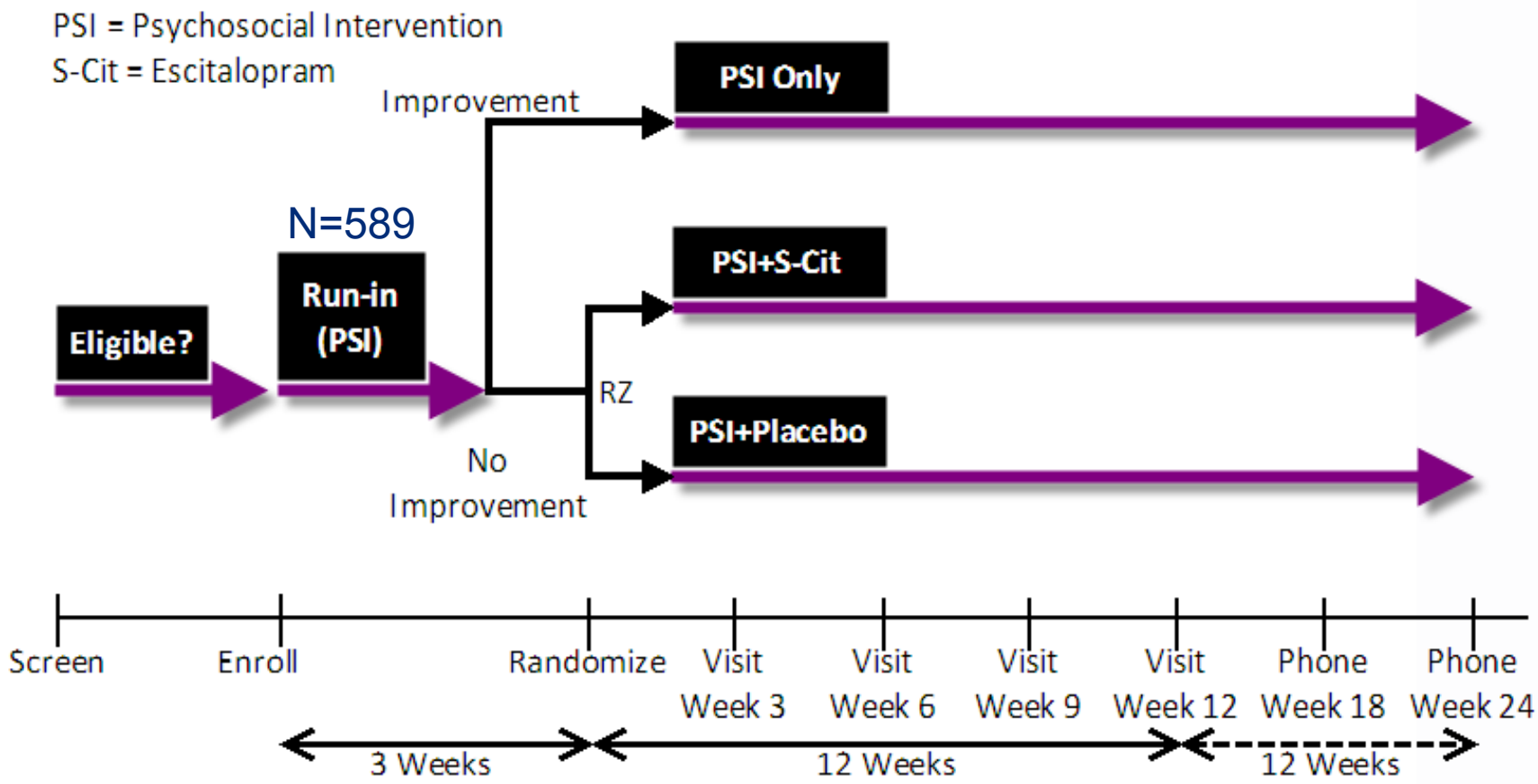


Ho et al, Br J Clin Pharmacol 2016

JOHNS HOPKINS MEDICINE

What's next? S-CitAD

relevant subgroups: Precision Medicine



R01AG052510; PI: Lyketsos

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Novel medications for agitation
in study or under development

- Citalopram
- S-citalopram
- Brexpiprazole
- D’-dextromethorphan
- Dronabinol
- Prazosin

- Several other compounds being considered

JOHNS HOPKINS MEDICINE

Otsuka and Lundbeck announce results of brexpiprazole on symptoms of agitation related to Alzheimer's-type dementia

Otsuka Pharmaceutical Co., Ltd. (Otsuka) and H. Lundbeck A/S (Lundbeck) announce top-line results from two phase III clinical trials evaluating the efficacy, safety and tolerability of brexpiprazole in the treatment of agitation in patients with dementia of the Alzheimer's type.

The primary endpoint of both trials was change from baseline in the Cohen-Mansfield Agitation Inventory (CMAI) total score, a 29-item scale to systematically assess the symptoms of agitation.[i] The key secondary endpoint was the change from baseline in the Clinical Global Impression-Severity of Illness (CGI–S) score, a 7-point scale assessing overall severity of the patient's agitation. [i] These studies were conducted in multiple countries in North America and Europe, and in the Russian Federation.

In both studies, patients treated with brexpiprazole showed improvements in symptoms of agitation relative to placebo. In the first study, the improvement in the primary endpoint of CMAI for 2 mg brexpiprazole was statistically better than placebo ($p<0.05$) and appeared more robust than the improvements on the key secondary endpoint of CGI-S ($p>0.05$). In the second study, the improvements in the primary endpoint of CMAI ($p>0.05$) appeared less robust than improvements observed on the key secondary endpoint of CGI-S ($p<0.05$). In both studies, there was variability in the data from different countries, perhaps associated with differing standards of care; the data from Russian sites showed especially poor separation between placebo and drug.

Original Investigation

Effect of Dextromethorphan-Quinidine on Agitation in Patients With Alzheimer Disease Dementia
A Randomized Clinical Trial

Jeffrey L. Cummings, MD, ScD; Constantine G. Lyketsos, MD, MHS; Elaine R. Peskind, MD; Anton P. Porsteinsson, MD; Jacobo E. Mintzer, MD, MBA; Douglas W. Scharre, MD; Jose E. De La Gandara, MD; Marc Agronin, MD; Charles S. Davis, PhD; Uyen Nguyen, BS; Paul Shin, MS; Pierre N. Tariot, MD; João Siffert, MD

IMPORTANCE Agitation is common among patients with Alzheimer disease; safe, effective treatments are lacking.

OBJECTIVE To assess the efficacy, safety, and tolerability of dextromethorphan hydrobromide–quinidine sulfate for Alzheimer disease–related agitation.

DESIGN, SETTING, AND PARTICIPANTS Phase 2 randomized, multicenter, double-blind, placebo-controlled trial using a sequential parallel comparison design with 2 consecutive 5-week treatment stages conducted August 2012–August 2014. Patients with probable Alzheimer disease, clinically significant agitation (Clinical Global Impressions-Severity agitation score ≥4), and a Mini-Mental State Examination score of 8 to 28 participated at 42 US study sites. Stable dosages of antidepressants, antipsychotics, hypnotics, and antidementia medications were allowed.

INTERVENTIONS In stage 1, 220 patients were randomized in a 3:4 ratio to receive dextromethorphan-quinidine (n = 93) or placebo (n = 127). In stage 2, patients receiving dextromethorphan-quinidine continued; those receiving placebo were stratified by response and rerandomized in a 1:1 ratio to dextromethorphan-quinidine (n = 59) or placebo (n = 60).

MAIN OUTCOMES AND MEASURES The primary end point was change from baseline on the Neuropsychiatric Inventory (NPI) Agitation/Aggression domain (scale range, 0 [absence of symptoms] to 12 [symptoms occur daily and with marked severity]).

RESULTS A total of 194 patients (88.2%) completed the study. With the sequential parallel comparison design, 152 patients received dextromethorphan-quinidine and 127 received placebo during the study. Analysis combining stages 1 (all patients) and 2 (rerandomized placebo nonresponders) showed significantly reduced NPI Agitation/Aggression scores for dextromethorphan-quinidine vs placebo (ordinary least squares z statistic, −3.95; $P < .001$). In stage 1, mean NPI Agitation/Aggression scores were reduced from 7.1 to 3.8 with dextromethorphan-quinidine and from 7.0 to 5.3 with placebo. Between-group treatment differences were significant in stage 1 (least squares mean, −1.5; 95% CI, −2.3 to −0.7; $P<.001$). In stage 2, NPI Agitation/Aggression scores were reduced from 5.8 to 3.8 with dextromethorphan-quinidine and from 6.7 to 5.8 with placebo. Between-group treatment differences were also significant in stage 2 (least squares mean, −1.6; 95% CI, −2.9 to −0.3; $P=.02$). Adverse events included falls (8.6% for dextromethorphan-quinidine vs 3.9% for placebo), diarrhea (5.9% vs 3.1% respectively), and urinary tract infection (5.3% vs 3.9% respectively). Serious adverse events occurred in 7.9% with dextromethorphan-quinidine vs 4.7% with placebo. Dextromethorphan-quinidine was not associated with cognitive impairment, sedation, or clinically significant QTc prolongation.

CONCLUSIONS AND RELEVANCE In this preliminary 10-week phase 2 randomized clinical trial of patients with probable Alzheimer disease, combination dextromethorphan-quinidine demonstrated clinically relevant efficacy for agitation and was generally well tolerated.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01584440

JAMA. 2015;314(12):1242-1254. doi:10.1001/jama.2015.10214

Editorial page 1233

Author Video Interview and JAMA Report Video at jama.com

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jeffrey L. Cummings, MD, ScD, Cleveland Clinic Lou Ruvo Center for Brain Health, 888 W Bonneville Ave, Las Vegas, NV 89106 (cumminj@ccf.org).

Dronabinol for the Treatment of Agitation and Aggressive Behavior in Acutely Hospitalized Severely Demented Patients with Noncognitive Behavioral Symptoms

Matthew R. Woodward, B.A., David G. Harper, Ph.D., Arkadiy Stolyar, M.D., Brent P. Forester, M.D., M.Sc., James M. Ellison, M.D., M.P.H.

Objective: *Behavioral disturbances occur frequently in demented individuals and greatly increase the burden of their care. The efficacy of pharmacotherapeutic treatment options is modest. This study was conducted to explore the efficacy and safety of dronabinol as an adjunctive treatment for agitation and aggressive behavior in severely demented patients.* **Methods:** *Using a retrospective systematic chart review, we studied 40 inpatients from the McLean Hospital Geriatric Neuropsychiatry Inpatient Unit diagnosed with dementia and treated with dronabinol for behavioral or appetite disturbances. A group of geriatric psychiatrists consulted medical records to rate the patients' behaviors prior to initiation of dronabinol treatment and following up to seven days of treatment, using the Pittsburgh Agitation Scale, Clinical Global Impression, and Global Assessment of Functioning. Data on percentage of food consumed at each meal, sleep duration, and adverse events were also collected from medical records.* **Results:** *The addition of dronabinol to patients' treatment regimens was associated with significant decreases in all domains of the Pittsburgh Agitation Scale. There were also significant improvements in Clinical Global Impression scores, sleep duration and percentage of meals consumed during the treatment periods. Twenty-six adverse events were recorded during dronabinol treatment, none of which led to medication discontinuation.* **Conclusion:** *This report represents the largest studied cohort of dementia patients treated with dronabinol to date and confirms earlier reports that dronabinol can serve as an adjunctive treatment for neuropsychiatric symptoms in dementia. Further research, including prospective controlled trials, is needed to clarify dronabinol's role in treating noncognitive behavioral symptoms of demented individuals.* (Am J Geriatr Psychiatry 2014; 22:415–419)

Key Words: Dementia, behavioral disturbances, dronabinol

Behavioral disturbances are highly prevalent among both community-dwelling and institutionalized demented individuals, with reported rates as high as 88%.[1] Among behaviorally disturbed patients, agitated and aggressive behaviors, irritability, and aberrant motor behavior are frequent.[1] For community-dwelling demented individuals, rates of agitation and aggression are estimated to be approximately 35%.[1]

Agitated behavior, defined as "inappropriate verbal, vocal, or motor activity that is not explained by needs or confusion per se" can be characterized as either aggressive or nonaggressive.[2,3] Aggressive behavioral symptoms, which can occur with or without agitation, include fighting, throwing, grabbing, destroying items, verbal outbursts, cursing, and screaming, whereas nonaggressive symptoms include restlessness, pacing, wandering, repetitive questioning, chatting, inappropriate disrobing, and verbal outbursts.[3] Neuropsychiatric symptoms, including restlessness, anxiety, disinhibition, and unusual motor behavior, have been reported to more strongly predict caregiver burden

Received July 12, 2011; revised November 21, 2012; accepted November 27, 2012. From the McLean Hospital Geriatric Psychiatry Research Program, Harvard Medical School (MRW, DGH, AS, BPF, JME), Belmont, MA. Send correspondence and reprint requests to Matthew R. Woodward, B.A., McLean Hospital, Geriatric Psychiatry Research Program 115 Mill St., Belmont, MA 02478. e-mail: matthew.woodward@alumni.tufts.edu

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PRAZOSIN FOR THE TREATMENT OF BEHAVIORAL SYMPTOMS IN ALZHEIMER'S DISEASE PATIENTS WITH AGITATION AND AGGRESSION

Lucy Y. Wang, MD[1,2,*], Jane B. Shofer, MS[2], Kirsten Rohde, RN[1], Kim L. Hart, PA-C[1], David J. Hoff, PA-C[1], Yun H. McFall, RPh[1], Murray A. Raskind, MD[1,2], and Elaine R. Peskind, MD[1,2]

[1]VA Northwest Network Mental Illness Research, Education, and Clinical Center (MIRECC)

[2]Alzheimer's Disease Research Center and Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA

Abstract

Objectives—Agitation and aggression in Alzheimer's disease (AD) is a major cause of patient distress, caregiver burden, and institutionalization. Enhanced behavioral responsiveness to central nervous system norepinephrine release may contribute to the pathophysiology of agitation and aggression in AD. Prazosin, a nonsedating generic medication used for hypertension and benign prostatic hypertrophy, antagonizes norepinephrine effects at brain postsynaptic alpha-1 adrenoreceptors. This pilot study examined the efficacy and tolerability of prazosin for behavioral symptoms in patients with agitation and aggression in AD.

Design—Double-blind, placebo controlled, parallel group study.

Setting—A university AD center and a nursing home in Seattle.

Participants—Twenty-two nursing home and community dwelling participants with agitation and aggression and probable or possible AD (mean age 80.6 ± 11.2).

Intervention—Randomization to placebo (n=11) or prazosin (n=11). Medication was initiated at 1mg/day and increased up to 6mg/day using a flexible dosing algorithm.

Measurements—The Brief Psychiatric Rating Scale (BPRS) and Neuropsychiatric Inventory (NPI) at weeks 1, 2, 4, 6, and 8. The Clinical Global Impression of Change (CGIC) at week 8.

Results—Participants taking prazosin (mean dose 5.7 ± 0.9mg/day) had greater improvements than those taking placebo (mean dose 5.6 ± 1.2mg/day) on the NPI (mean change -19 ± 21 versus -2 ± 15, χ^2=6.32, df=1, p=0.012) and BPRS (mean change -9 ± 9 versus -3 ± 5, χ^2=4.42, df=1, p=0.036) based on linear mixed effects models, and the CGIC (mean 2.6 ± 1.0 versus 4.5 ± 1.6, Z=2.57, p=0.011 [Mann-Whitney test]). Adverse effects and blood pressure changes were similar between prazosin and placebo groups.

Conclusion—Prazosin was well tolerated and improved behavioral symptoms in patients with agitation and aggression in AD.

*Corresponding author: Lucy Y. Wang MD, VA Northwest Network Mental Illness Research, Education, and Clinical Center (MIRECC), 1660 S. Columbian Way, S-116-6E, Seattle, WA 98115, Tel: 206-277-5089, Fax: 206-277-4856, wanglucy@u.washington.edu.

No disclosures to report.

This research was presented in part as a poster at the 11th International Conference on Alzheimer's Disease and Related Disorders, Chicago, Illinois, July 2008.

Table 3. Recommendations for future RCTs targeting A/A in patients with AD

METHODOLOGICAL ASPECT	RECOMMENDATIONS
Population studied	
Age	• No limit
Dementia severity	• Mild to severe based on CDR rating of 1–3; stratification
Settings	• Different RCTs for NH or CD preferred; or stratification
Clinically significant A/A	• A/A needs consensus criteria • "Clinically significant" = medication is needed based on judgment of experienced clinician combined with severity rating above a cut-off on a A/A scale
Concomitant medications	• "AD treatments" allowed on stable doses for 30–60 days • APs not allowed; or allowed stable doses for 30–60 days • Antidepressants, mood stabilizers, anticonvulsants: allowed on stable doses for 30–60 days
Caregiver participation	• Caregiver needs a consensus definition • Standardized training in recognizing NPS and in rating behavior scales • Use of a caregiver diary for real time observations
Study design	
Pharmacological intervention	• Run-in-period before randomization (2–4 weeks) • 8–12-week treatment period • Consolidation response: to assess time to relapse within responders in each group during a 6–12-month period
Non-pharmacological intervention	• Psychosocial intervention during the run-in and the treatment periods in both groups. • Etiologic, non-pharmacologic, person-centered approach during run-in and treatment periods in both groups
Allowed rescue medication	• Defined allowable dosing, monitored use
Outcome measures	
Primary	• Global measure of A/A as primary • Validated scales assessing A/A, co-primary or secondary • Rated by clinicians with patient and caregiver input
Secondary	• Consider actigraphy • Agitation symptoms • Aggression symptoms • Other NPS: irritability, anxiety, depression, psychosis • Cognition, functional ability, quality of life • Caregiver distress, other caregiver measures • Allowed rescue medication cumulative dose
Analytic strategies	
	• Intention to treat analysis • Mixed models: LMM or MMRM

Abbreviations: AD = Alzheimer's disease; NPS = neuropsychiatric symptoms; A/A = agitation/aggression; CD = community dwelling; NH = nursing home; CDR = clinical dementia rating; MMRM: mixed model of repeated measures; linear mixed models.

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REVIEW

Medication development for agitation and aggression in Alzheimer disease: review and discussion of recent randomized clinical trial design

Maria Soto,[1] Sandrine Andrieu,[1,2] Fati Nourhashemi,[1] Pierre Jean Ousset,[1] Clive Ballard,[3] Philippe Robert,[4] Bruno Vellas,[1] Constantine G. Lyketsos[5] and Paul B. Rosenberg[5]

[1] *Gerontopôle, INSERM U 1027, Alzheimer's Disease Research and Clinical Center, Toulouse University Hospital, France*
[2] *Department of Epidemiology, Toulouse University Hospital Toulouse, France*
[3] *Wolfson Centre for Age-Related Diseases, King's College, London, UK*
[4] *EA CoBTeK / ICMRR University of Nice Sophia Antipolis -CHU, France*
[5] *Department of Psychiatry, The Johns Hopkins Bayview Medical Center, Baltimore, MD, USA*

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Facing reality: balancing "cure" with "care"

- **Near and medium term outcome**: extend the time course of MCI and dementia→ higher prevalence

- We must take proper care of the100+ million patients & caregivers worldwide with dementia by 2050

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Thank you!
Ευχαριστω!

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