Treatment Development for Neuropsychiatric Disturbances in Dementia: Past, Present, Future

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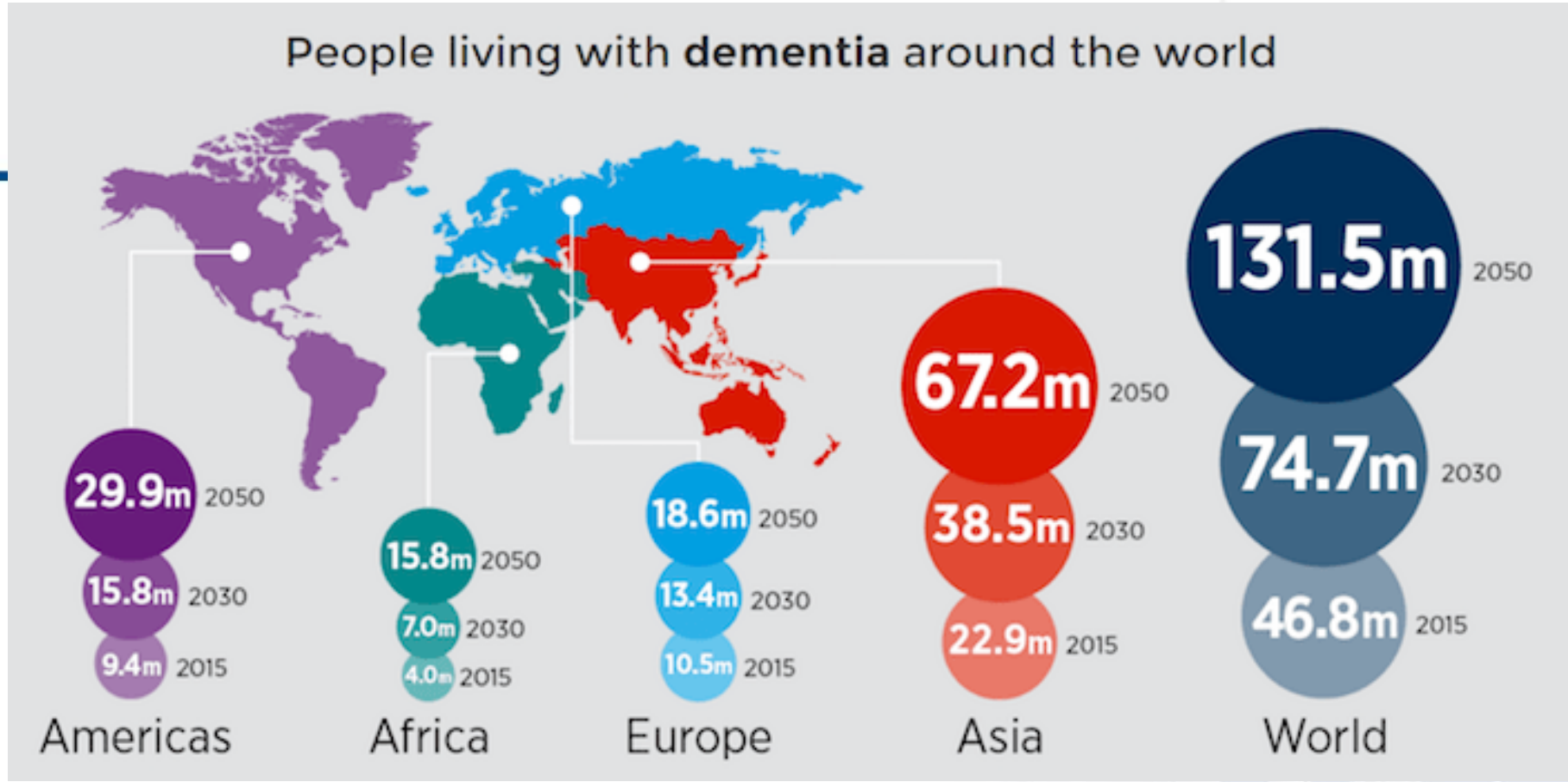
JOHNS HOPKINS
MEDICINE



For every patient ADD 1-3 caregivers

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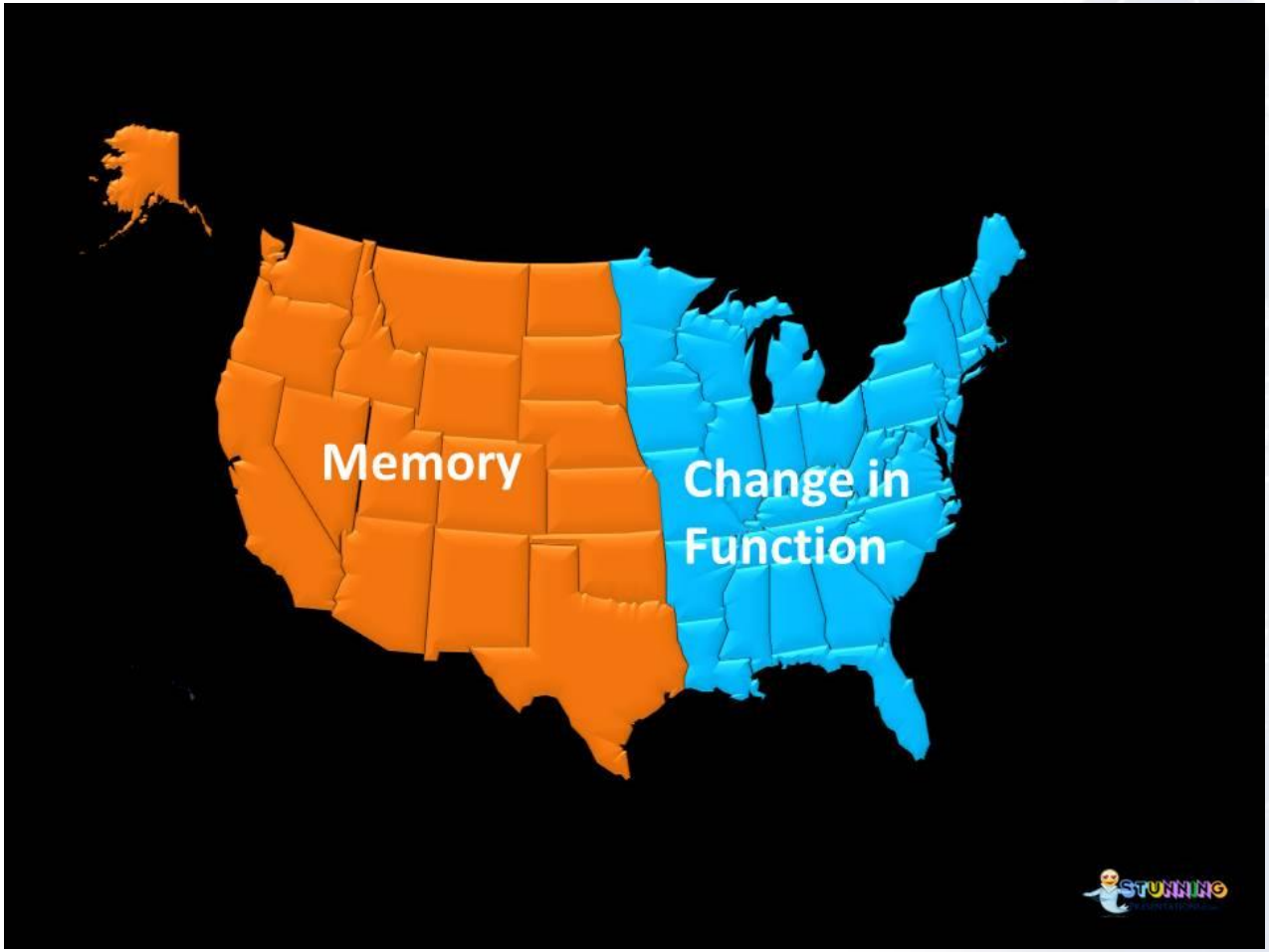
The common view of dementia



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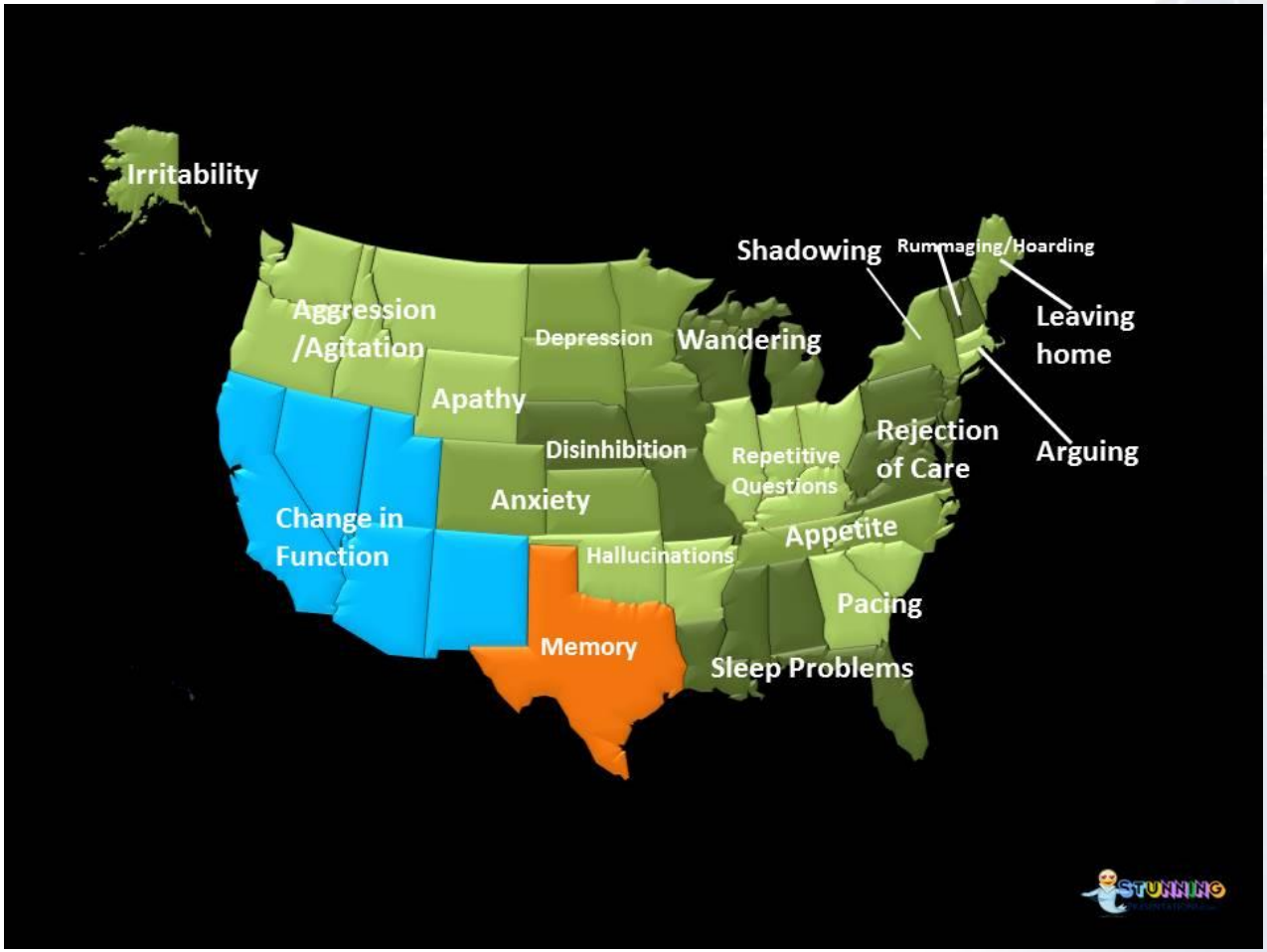
The real view of dementia



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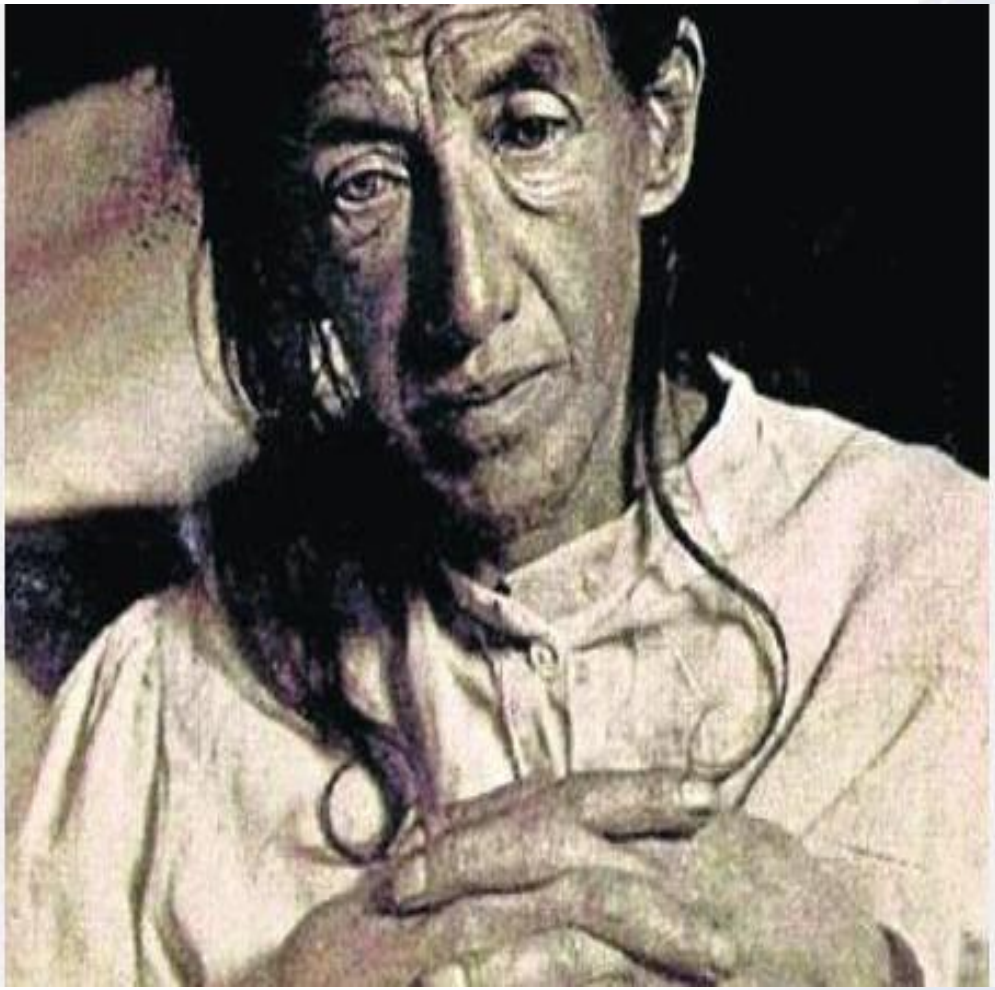
Facing reality: balancing “cure” with “care”

- **Near and medium-term outcome**: new “amyloid meds” extend time course of MCI and dementia
  → higher prevalence

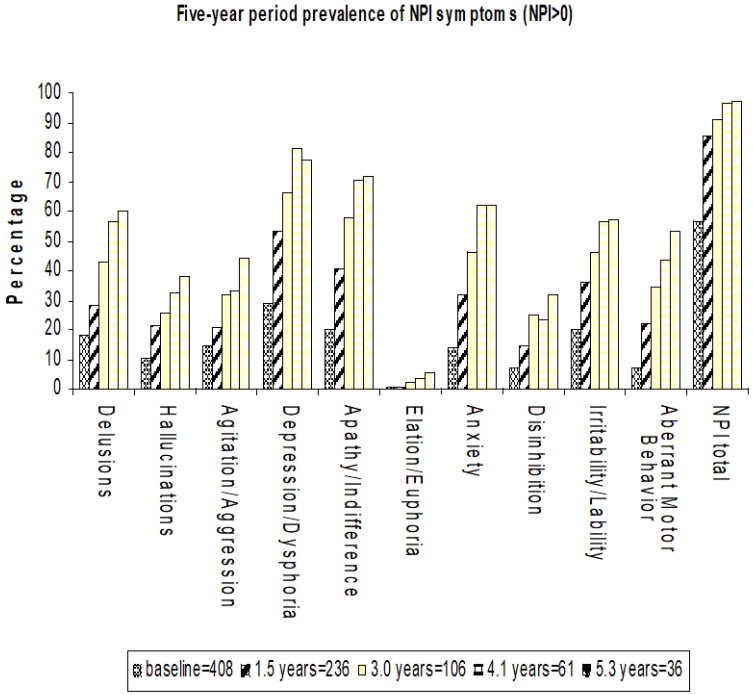
- We must take proper care of the130+ million patients & caregivers worldwide with dementia by 2050

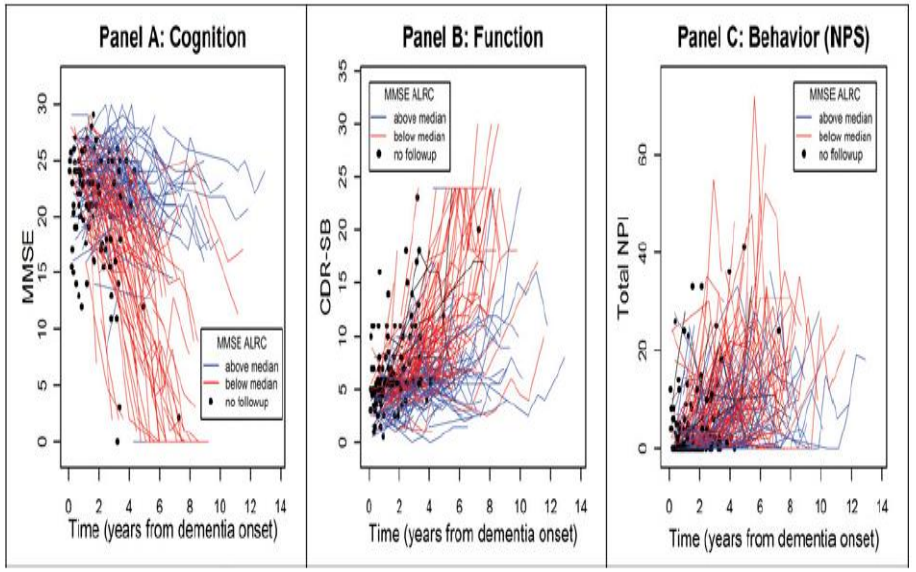
Auguste D: hospitalized for delusions and change in personality, not cognitive impairment



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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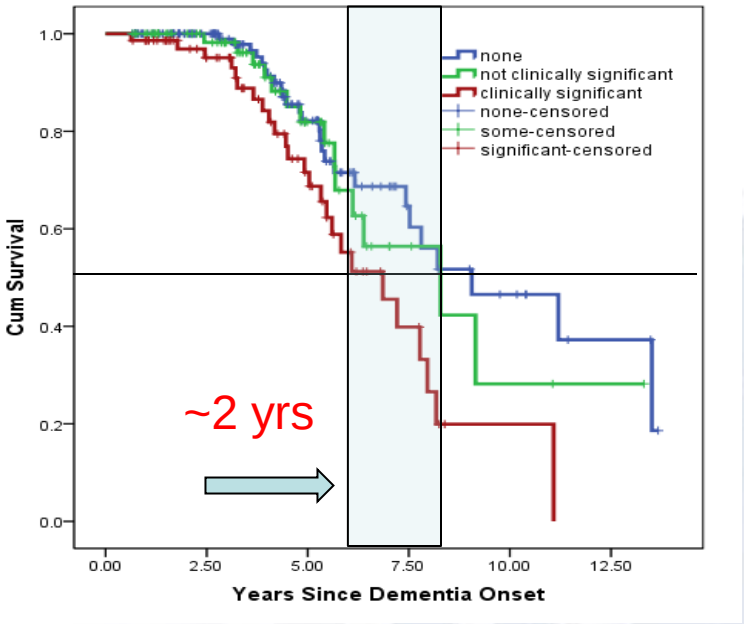
NPS are “bad” for patients & caregivers

- 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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Medication treatment development for NPS
The past: BEFORE 2011

- Use DSM-IV syndromic definitions
  - Target specific symptoms groups
    - E.g., depression, mania or psychosis

Challenges of DSM-IV phenotypes

- Developed for younger ages: ignore the aging brain

- Disease-specific conditions of later life
  - AD, LBD, FTD, VaD
  - Phenotypes do no fit DSM
    - Unique symptom overlap patterns
  - Emerging knowledge of disease-specific causes

Medication Rxs disappointing

when using existing DSM/ICD phenotypes

- Antipsychotics: small benefit, mortality risk

- Antidepressants: ineffective for depression
- Anti-cholinesterases & memantine: ineffective
- Anticonvulsants: ineffective, risky, often used
- Benzodiazepines: ineffective, risky, often used

Chan and Lyketsos 2021

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Medication treatment development for NPS
The present: 2011-2023

(1) Target Alzheimer specific NPS

[top down] →←[bottom up]

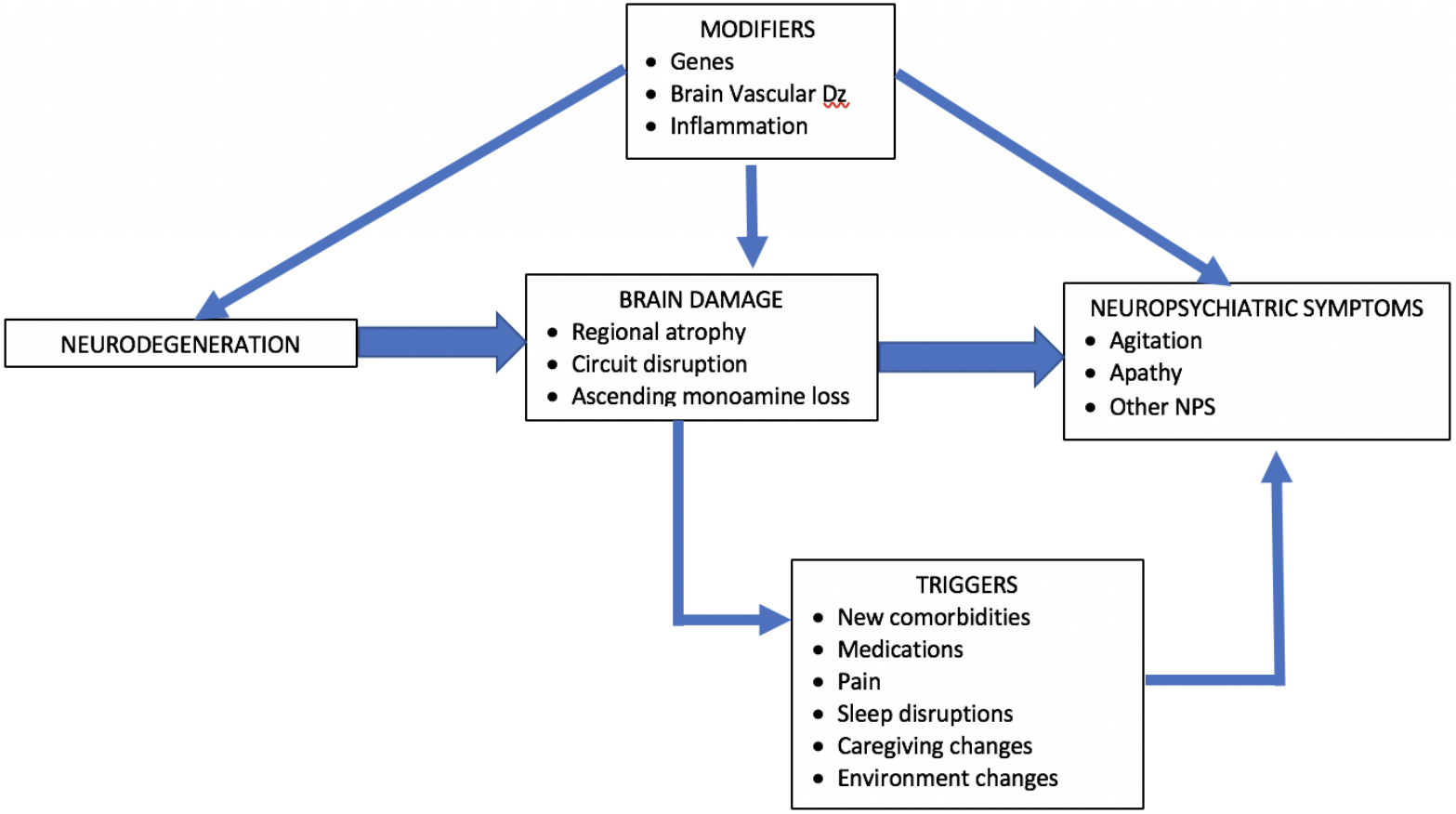
(2) Hypotheses based on etiology

Target Alzheimer specific NPS

by observed NPS symptoms profile

- Agitation (IPA 2014)
- Apathy (Miller 2021)
- Psychosis (Cummings 2021)
- Depression (Olin 2003)
- Sleep/circadian/SWS (several)

Hypotheses based on etiology



British Medical Journal 2015; NIMH/NIA Panel May 2017

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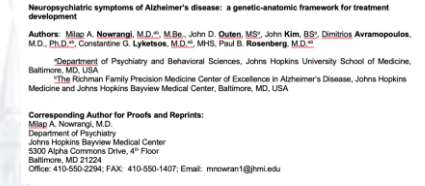
Neurobiological model

proposed by the ISTAART NPS-PIA (2013)

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

Neurobiological model

updated by Nowrangi et al. (2023)



Neuropsychiatric symptoms of Alzheimer's disease: a genetic-anatomic framework for treatment development

Authors: Mlap A. **Nowrangi**, M.D.[a], M.Be., John D. **Outen**, MS[a], John **Kim**, BS[a], Dimitrios **Avramopoulos**, M.D., Ph.D.[a], Constantine G. **Lyketsos**, M.D.[a], MHS, Paul B. **Rosenberg**, M.D.[a]

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[b]The Richman Family Precision Medicine Center of Excellence in Alzheimer's Disease, Johns Hopkins Medicine and Johns Hopkins Bayview Medical Center, Baltimore, MD, USA

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NPS in AD are associated with

- Atrophy in ACC, PCC, hippocampi (MRI)
- Loss of cortical & subcortical interconnectivity (fMRI) in areas with neuronal projections of SER and DA

- Genes for acetylcholine, tau, and glutamate
- Genes for monoamine synthesis and function (SER, DA)

- Loss of cell bodies in monoamine nuclei (pathology)

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Novel medications for agitation

- Citalopram & escitalopram
- Brexpiprazole
- Dextromethorphan + buproprion or quinidine
- THC—dronabinol or nabilone
- Dexmedetomidine (α2 agonist)
- Prazosin (α1 antagonist)
- Masurpidine (5-HT6 antagonist)

Target Alzheimer specific NPS

focus on agitation

Table 1. Consensus provisional definition of agitation in cognitive disorders

A. The patient meets criteria for a cognitive impairment or dementia syndrome (e.g. AD, FTD, DLB, vascular dementia, other dementias, a pre-dementia cognitive impairment syndrome such as mild cognitive impairment or other cognitive disorder).

B. The patient exhibits at least one of the following behaviors that are associated with observed or inferred evidence of emotional distress (e.g. rapid changes in mood, irritability, outbursts). The behavior has been persistent or frequently recurrent for a minimum of two weeks' and represents a change from the patient's usual behavior.

(a) Excessive motor activity (examples include: pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms).

(b) Verbal aggression (e.g. yelling, speaking in an excessively loud voice, using profanity, screaming, shouting).

(c) Physical aggression (e.g. grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, hitting self, slamming doors, tearing things, and destroying property).

C. Behaviors are severe enough to produce excess disability, which in the clinician's opinion is beyond that due to the cognitive impairment and including at least one of the following:

(a) Significant impairment in interpersonal relationships.

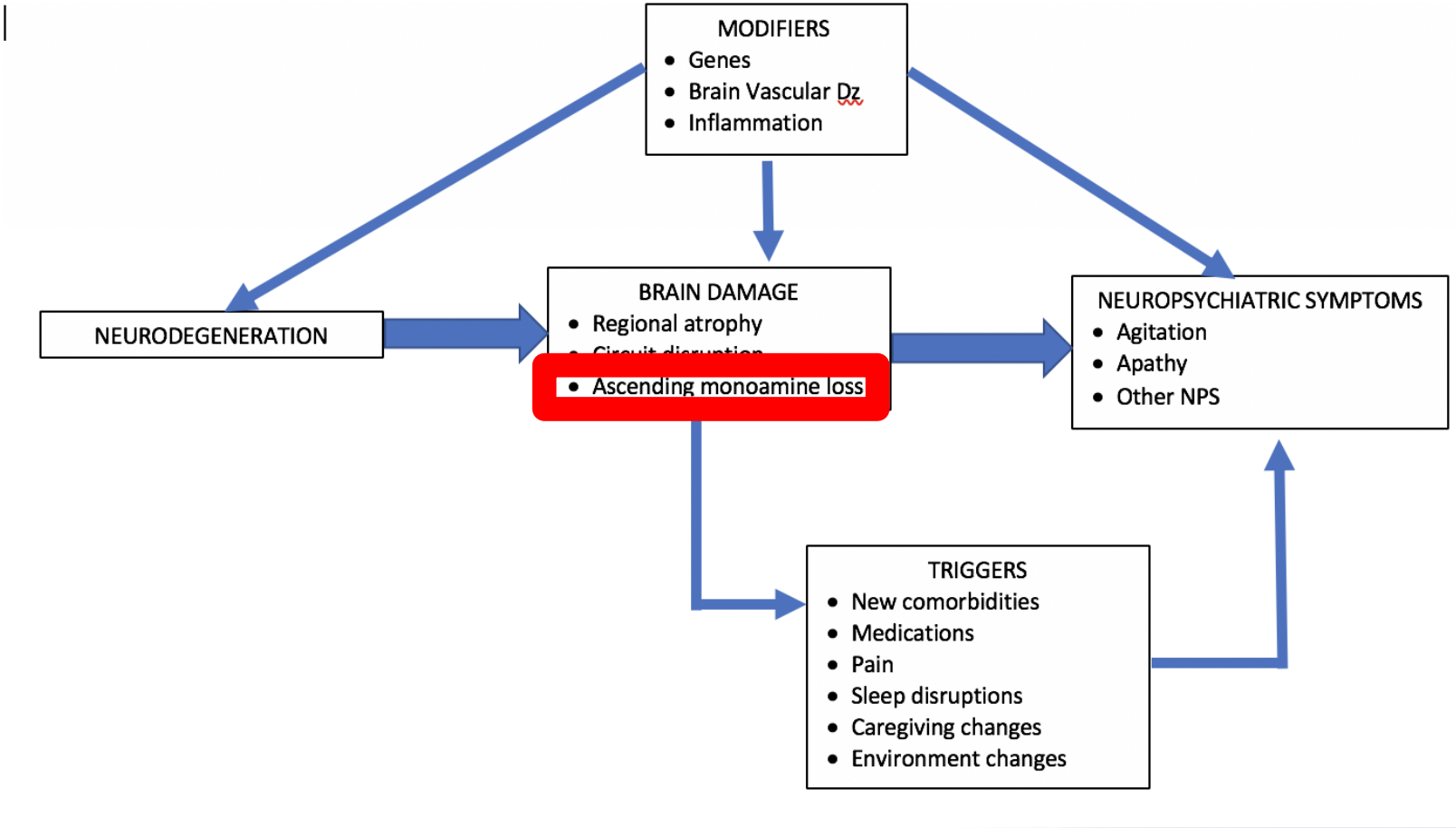
(b) Significant impairment in other aspects of social functioning.

(c) Significant impairment in ability to perform or participate in daily living activities.

D. While co-morbid conditions may be present, the agitation is not attributable solely to another psychiatric disorder, suboptimal care conditions, medical condition, or the physiological effects of a substance.

Hypotheses based on etiology

focus on agitation



British Medical Journal 2015; NIMH/NIA Panel May 2017

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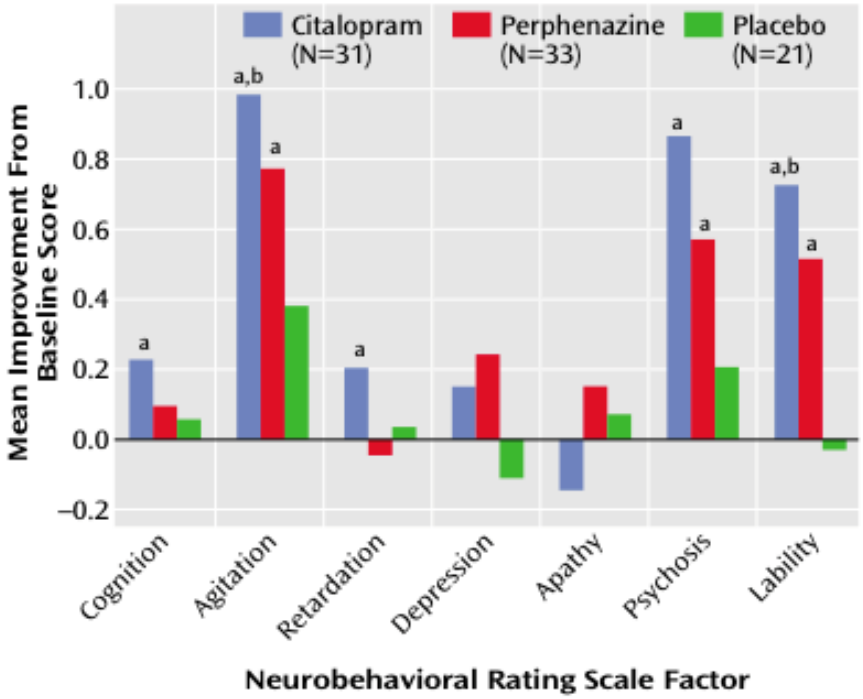
Rationale for Citalopram

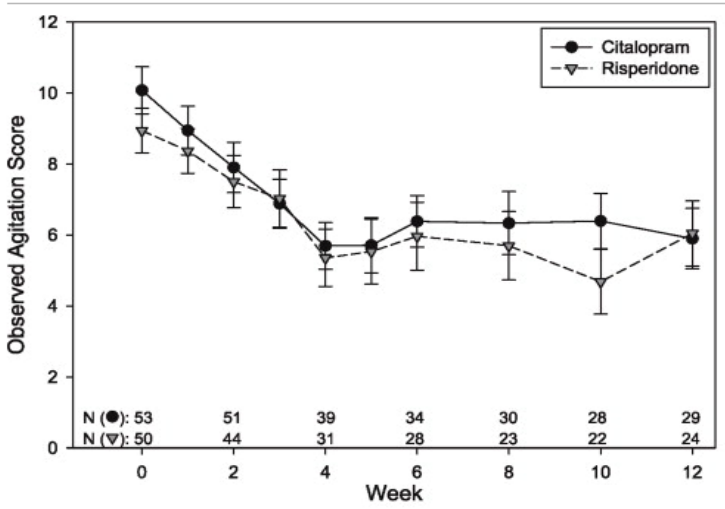
targeting “Agitation in AD”

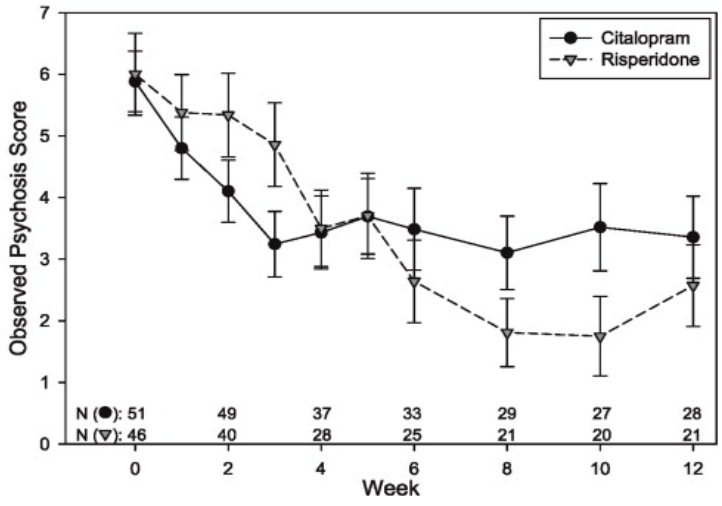
FIGURE 1. Change in Neurobehavioral Factor Scores From Baseline to Study Termination (≤17 Days) in Patients With Dementia in a Randomized, Double-Blind, Placebo-Controlled Trial of Citalopram and Perphenazine



[a] Significant difference within group between baseline and termination scores (Wilcoxon signed-rank test, $p<0.05$).

[b] Significant difference between the citalopram and placebo groups (Kruskal-Wallis test, $p<0.05$).





Research

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

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

Big benefit: 26% placebo vs. 40% citalopram

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

R01AG031348; PI: Lyketsos

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Broad symptomatic improvement

psychosis and beyond

TABLE 2. Neuropsychiatric Inventory (NPI) Domains at Week 9 in a Study of the Effects of Citalopram on Neuropsychiatric Symptoms in Alzheimer's Dementia

	All Participants With Week 9 NPI Data							Participants With Week 9 NPI Data Reporting Symptom at Week 9				
	Citalopram Group (N=86)		Placebo Group (N=83)					Citalopram Group		Placebo Group		
NPI Measure	N[a]	%	N[a]	%	Odds Ratio[b]	95% CI	p	Median	IQR	Median	IQR	p[c]
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												
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/nighttime behavior disorders	21	24	30	36	0.56	0.27, 1.16	0.12	4	3, 12	3	2, 6	0.03
Appetite/eating disorders	22	26	18	22	1.32	0.62, 2.82	0.47	4	4, 8	4	3, 8	0.84
Summary scores												
Nonmood score	78	91	79	95	0.48[d]	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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Response limited to a subgroup HETEROGENEITY

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

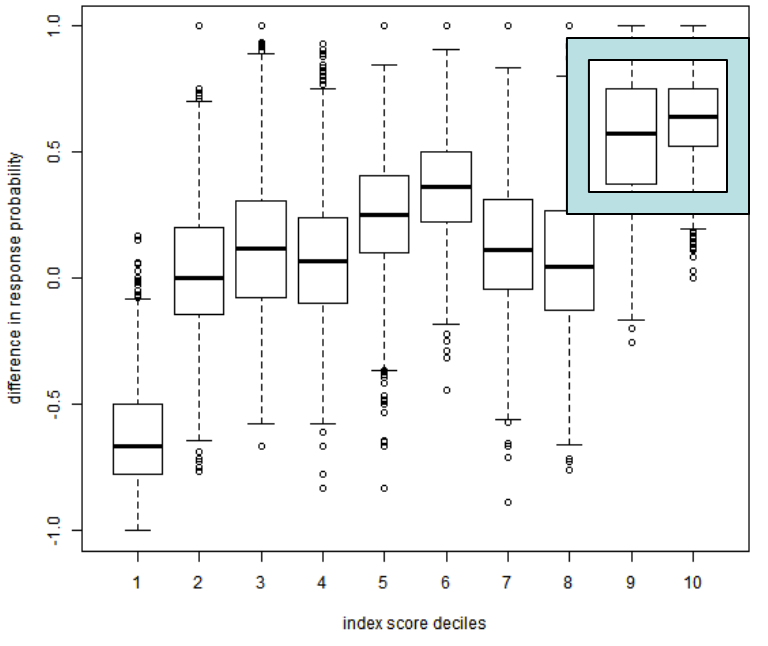
Objective: Pharmacological treatments for agitation and aggression in patients with Alzheimer's disease have shown limited efficacy. The authors assessed the heterogeneity of response to citalopram in the Citalopram for Agitation in Alzheimer Disease (CitAD) study to identify individuals who may be helped 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: 101176/appi.ajp.2015.15050648)



Schneider et al, Am J Psychiatry 2016

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Breaking down the heterogeneity of NPS

The future: 2023 and beyond

PRECISION MEDICINE

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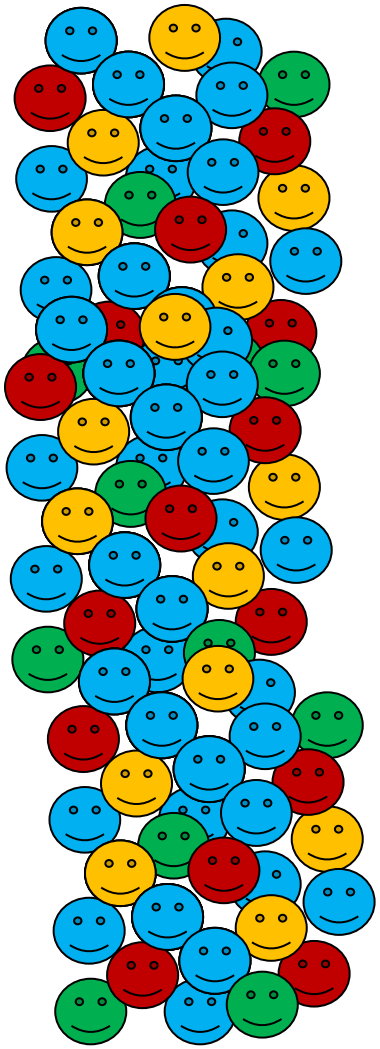


Genetic
Polygenic risk: overall
Polygenic risk: system

Stem Cells
Neuronal function
Effect of treatments

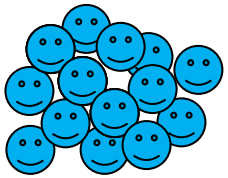
Imaging
Structure
Function

Physiology
Inflammation
Brain perfusion
Exosomes

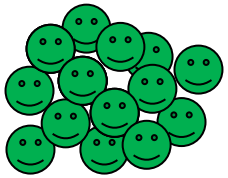
Clinical
Cognition
Behavior

Subgroup 1

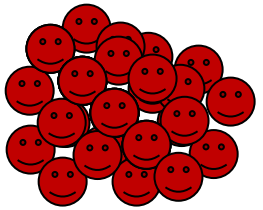
Subgroup 2



Subgroup 3



Subgroup 4



Breaking down the heterogeneity of NPS
The future: 2023 and beyond

- Clinical phenotype: Symptom mix, severity
- Circadian chronotype (actigraphy)
- iPSC derived neurons from each patient

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Breaking down the heterogeneity of NPS
The future: 2023 and beyond

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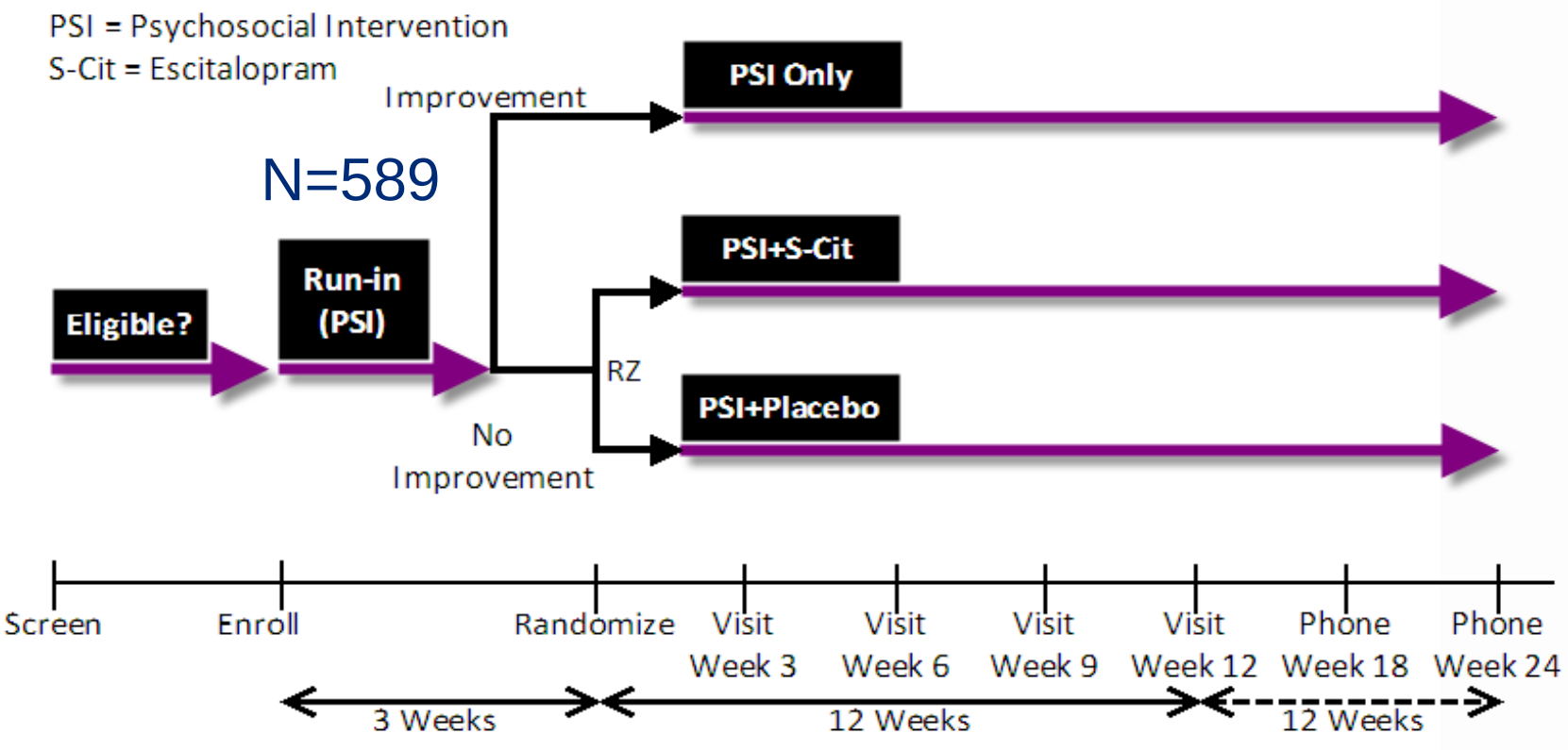
S-CitAD

(1) test the "Affective Agitation" hypothesis
(2) reduce heterogeneity by identifying subgroups



R01AG052510; PI: Lyketsos

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Breaking down the heterogeneity of NPS
The future: 2023 and beyond

- Clinical phenotype: Symptom mix, severity
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- iPSC derived neurons from each patient

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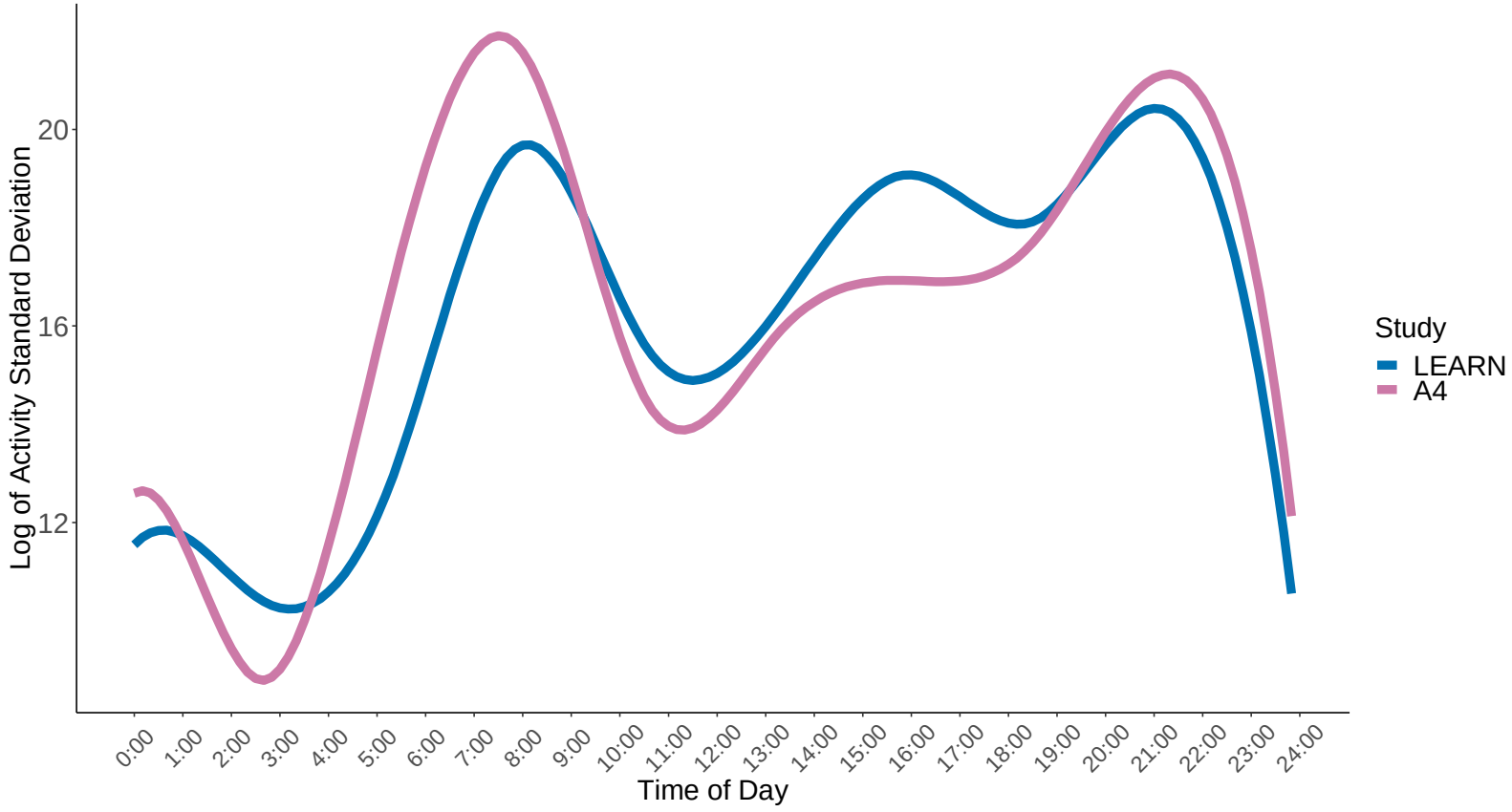
AD versus non-AD



Courtesy of Paul Rosenberg

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Breaking down the heterogeneity of NPS
The future: 2023 and beyond

- Clinical phenotype: Symptom mix, severity
- Circadian chronotype (actigraphy)
- iPSC derived neurons from each patient

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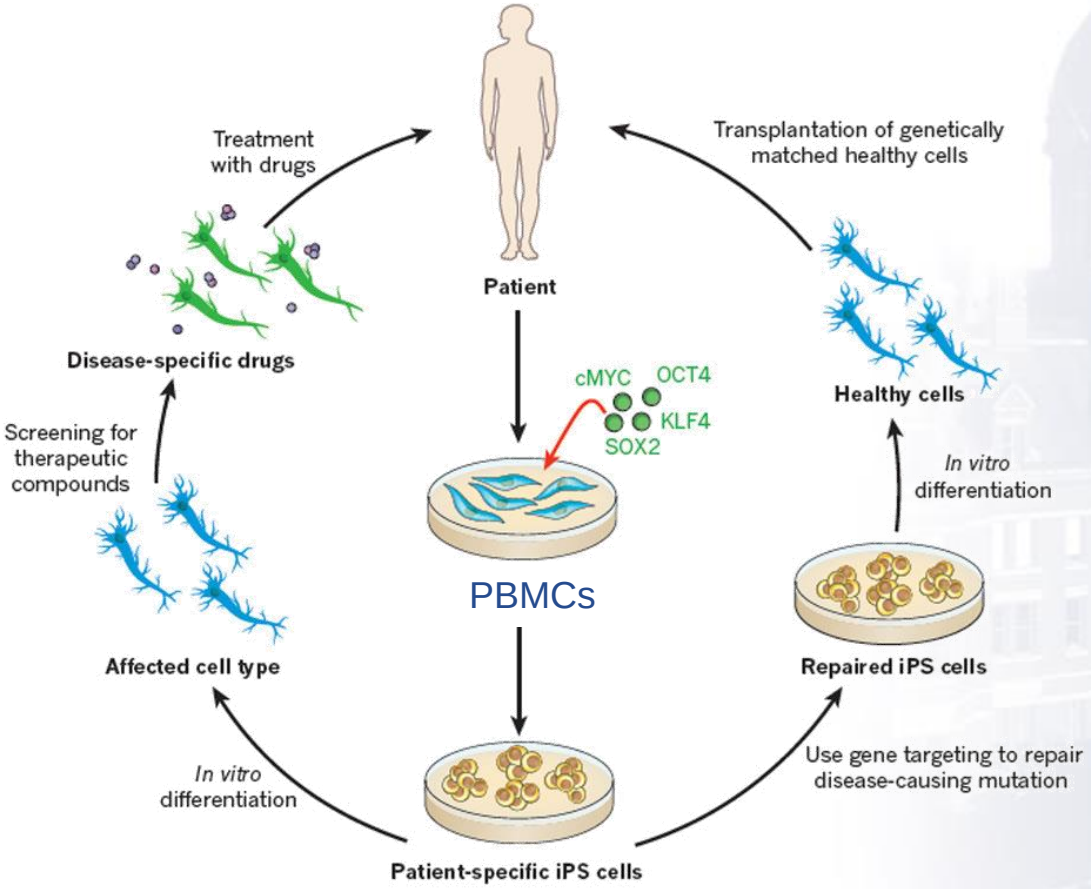
iPSC derived serotonergic neurons as drug testing platforms



Daisy A. Robinton & George Q. Daley Nature 481 (2012)

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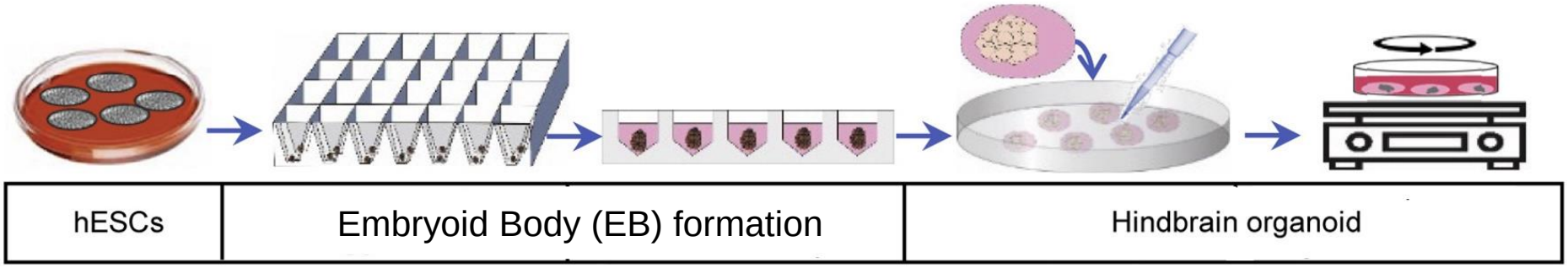
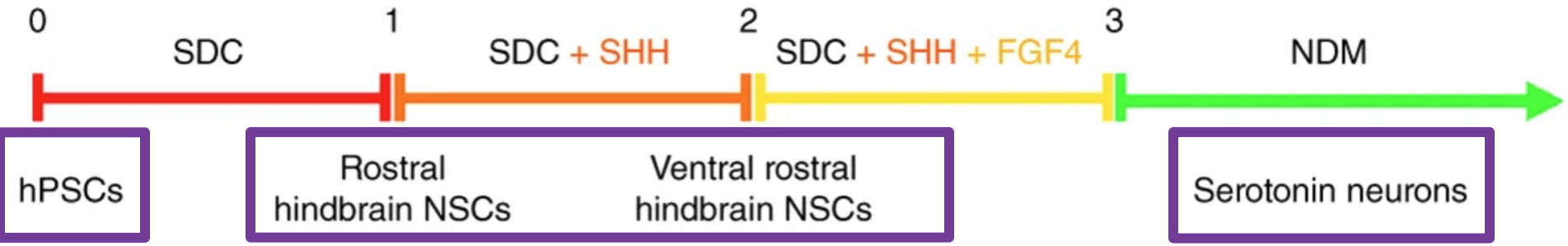
Serotonergic neurons protocol





Adapted from: Valiulahi et al. Stem ell Reports. 2021, Lu et al. Nat Biotechnol. 2016

Escitalopram effects on 5-HT levels

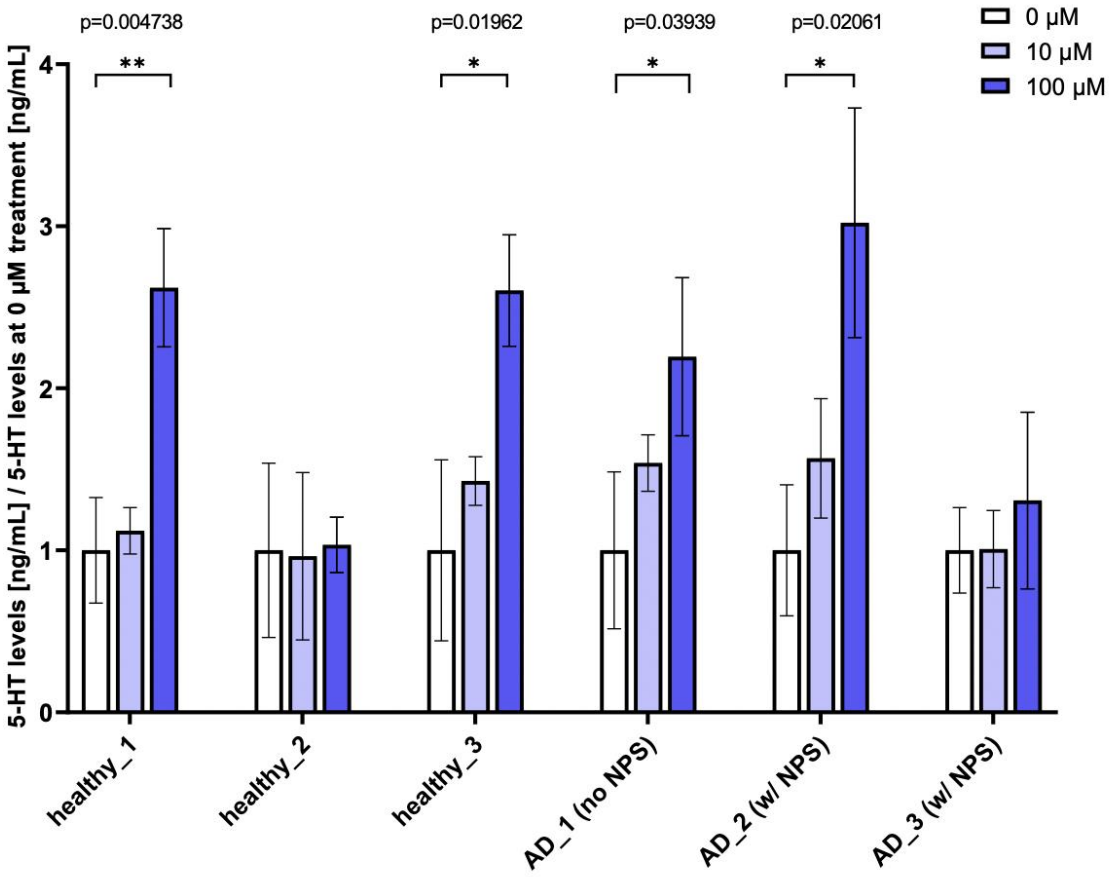
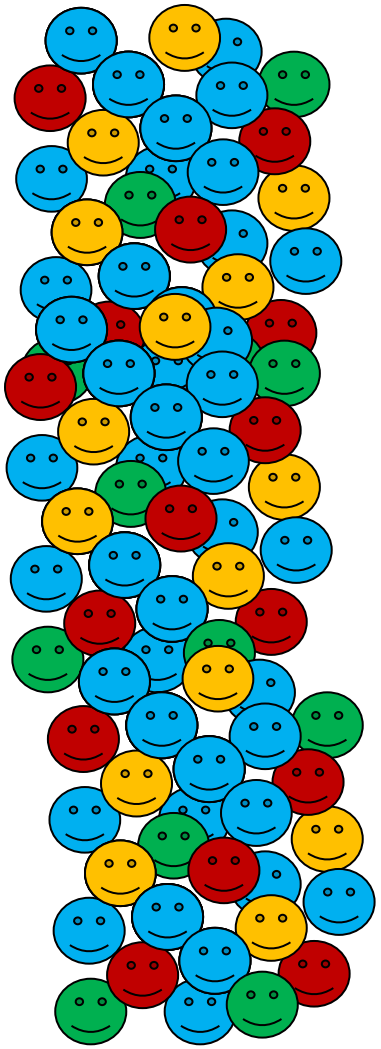


Figure 6: Serotonin release from 5-HT-spheroids upon 1 h treatment with different concentrations of escitalopram oxalate (mean ± SD, n=3).



Genetic
Polygenic risk: overall
Polygenic risk: system

Stem Cells
Neuronal function
Effect of treatments

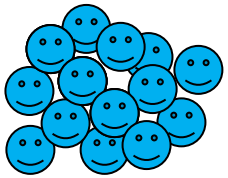
Imaging
Structure
Function

Physiology
Inflammation
Brain perfusion
Exosomes

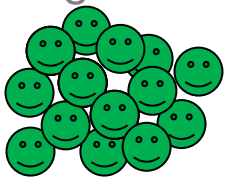
Clinical
Cognition
Behavior

Affective Agitation

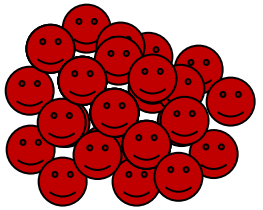
Psychosis predominant



Morning chronotype



Serotonin release



Novel medications for agitation

- Citalopram & escitalopram
- Brexpiprazole
- Dextromethorphan + buproprion or quinidine
- THC—dronabinol or nabilone
- Dexmedetomidine (α2 agonist)
- Prazosin (α1 antagonist)
- Masurpidine (5-HT6 antagonist)

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Questions & Discussion

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