Prazosin for Agitation/Aggression in AD
Turning an Old Antihypertensive into a Novel Psychotropic

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Prazosin is an inexpensive alpha-1 adrenoreceptor antagonist generically available for hypertension and BPH.

Prazosin is the most lipid soluble alpha-1 AR antagonist, thus enters the brain when administered peripherally.

The Brain Noradrenergic System

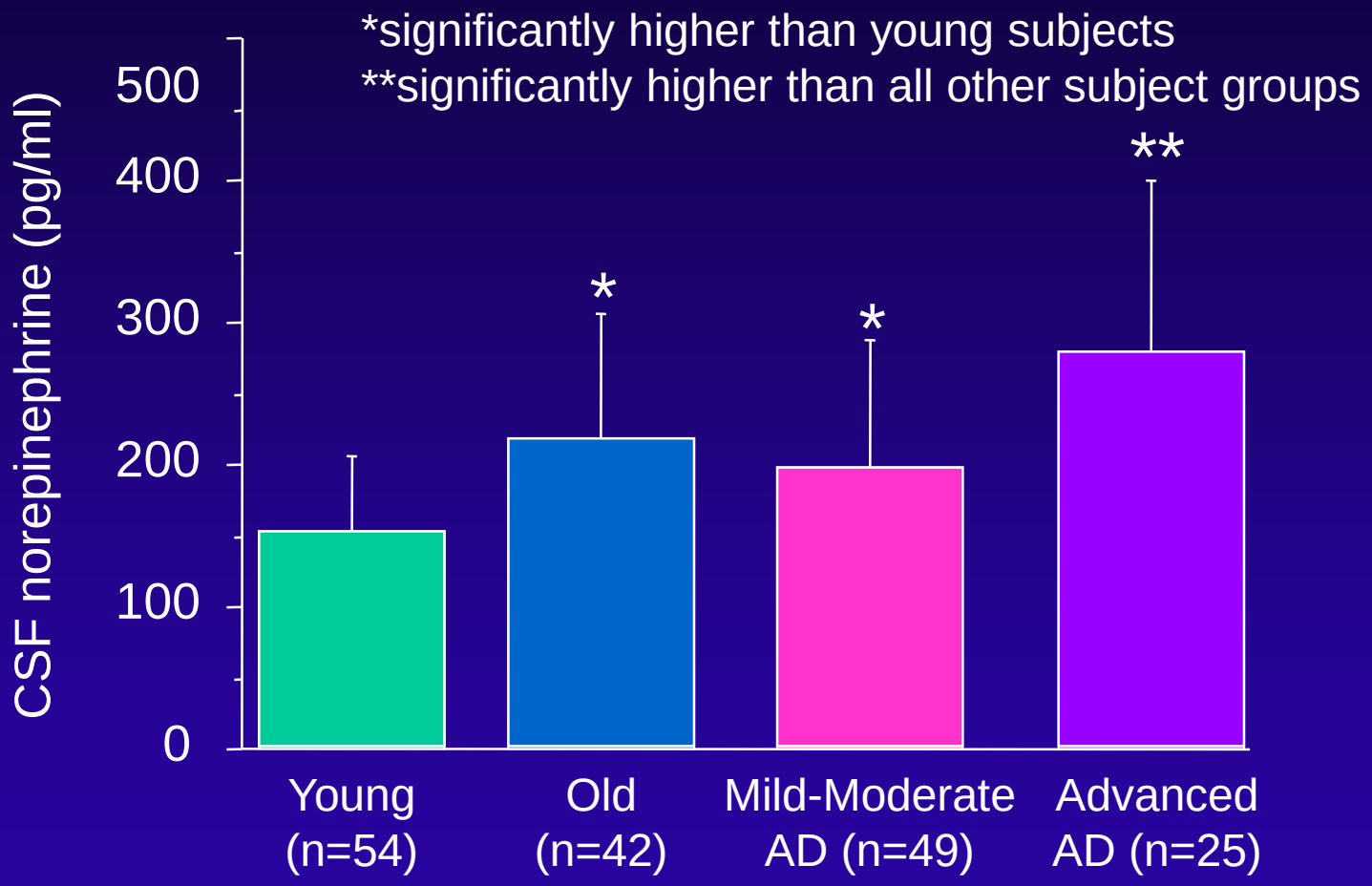
- The noradrenergic system is the brain “adrenaline” system for attention and arousal.
- Excessive noradrenergic outflow and/or responsiveness produces anxiety and agitation.
- Does excessive noradrenergic activity contribute to agitation in AD?

The CNS Noradrenergic System in Alzheimer's Disease

- Despite loss of noradrenergic locus coeruleus neurons there is:
  - » increased cerebrospinal fluid (CSF) norepinephrine (NE) in AD[1]
  - » increased agitation response to NE in AD[2]
  - » Compensatory upregulation of surviving LC neuron NE biosynthetic capacity

[1]Elrod et al., *Am J Psychiatry* 154:25-30, 1997.
[2]Peskind, et al., *Arch Gen Psychiatry, 1995*

CSF Norepinephrine: Effects of Aging and AD

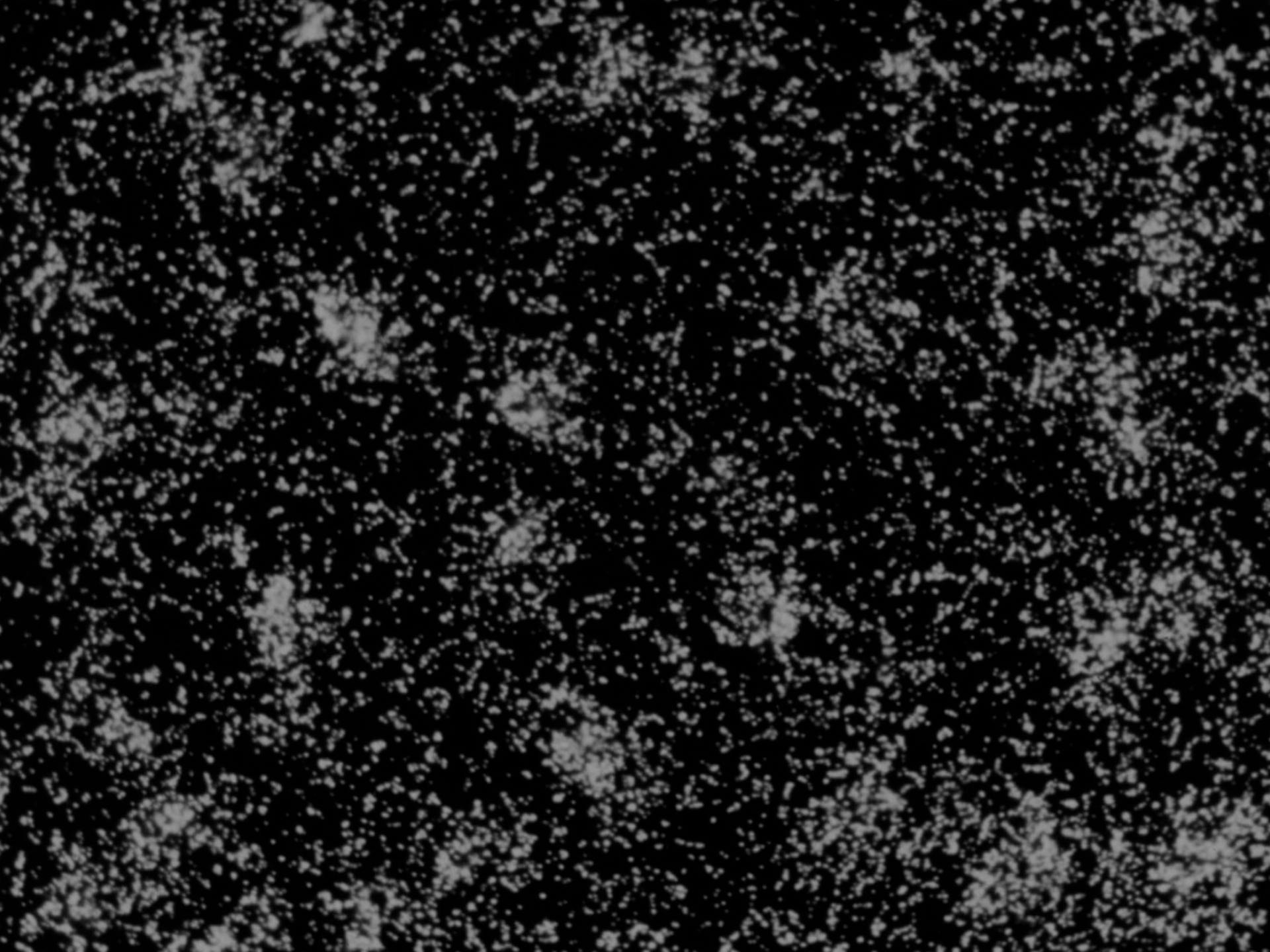


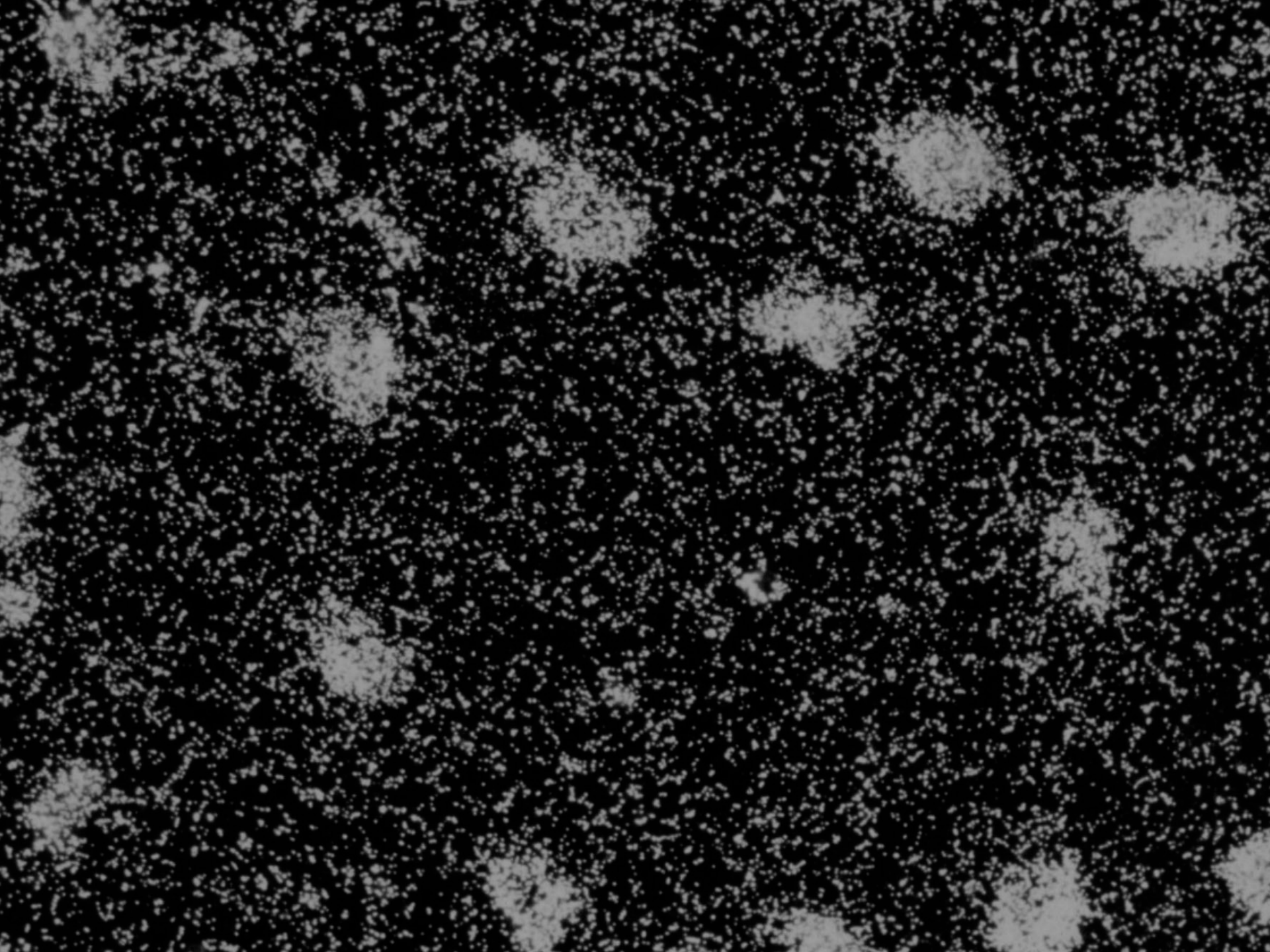
Elrod et al., *Am J Psychiatry* 154:25-30, 1997.

- In animal studies, partial denervation of the locus ceruleus causes compensatory upregulation of norepinephrine (NE) biosynthetic capacity in surviving locus ceruleus neurons.
- Does this phenomenon help explain normal or elevated CSF NE in AD?

- We found increased TH mRNA/LC neuron at all levels of LC in AD (n = 15) and DLB (n = 15) compared to nondemented older controls (n = 17).

Szot P, et al., *J Neurosci* 26:467-478, 2006.





- In AD and DLB, surviving noradrenergic neurons are compensating by increasing the mRNA expression of the rate-limiting enzyme in the synthesis of NE at multiple levels of the LC.

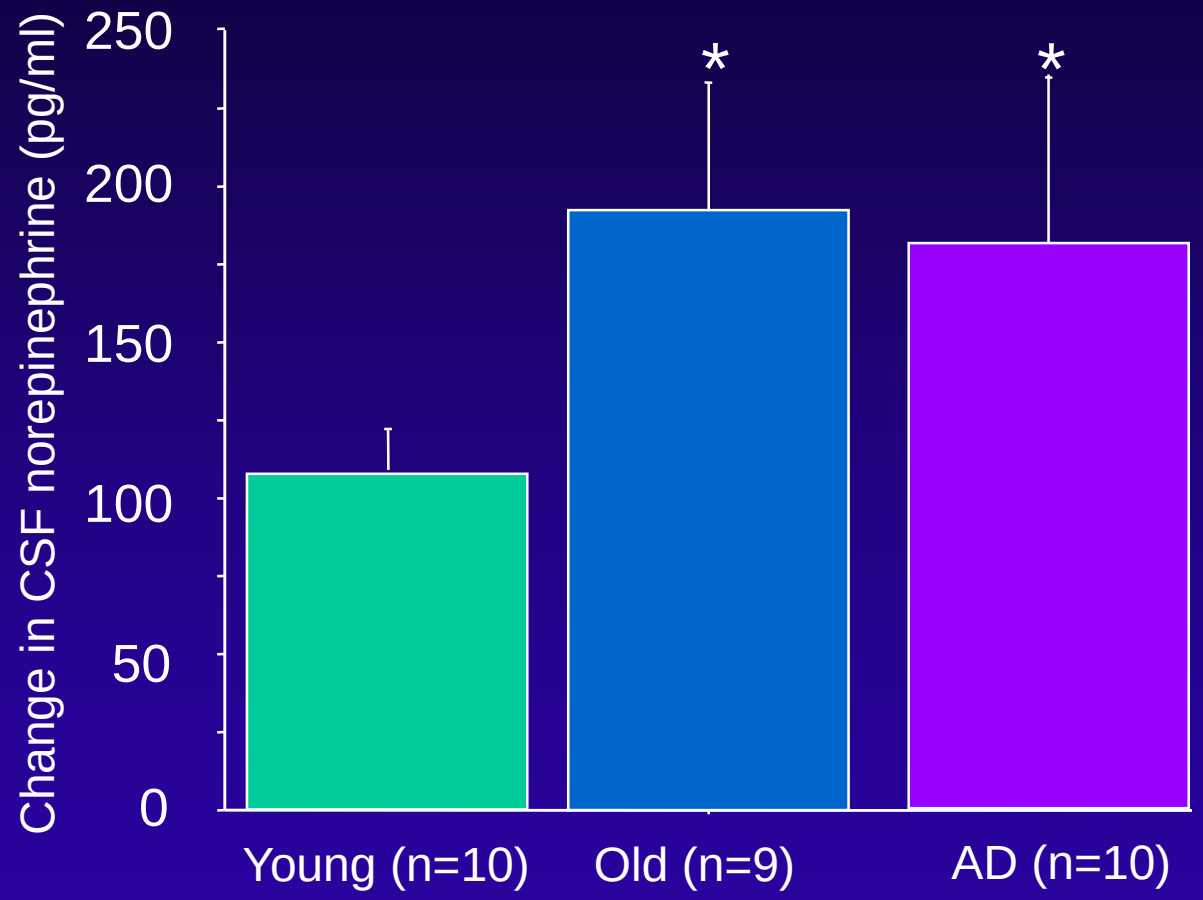
Szot P et al., *Neuroscience,* 2007.

We Stimulated Brain Noradrenergic Systems With the Drug Yohimbine

- We measured CSF NE responses to placebo or yohimbine in 9 AD (MMSE = 14± 2), 10 normal older, and 17 normal young subjects.
- We measured behavioral responses using Brief Psychiatric Rating Scale (BPRS) items “tension”, “excitement”, “anxiety”.

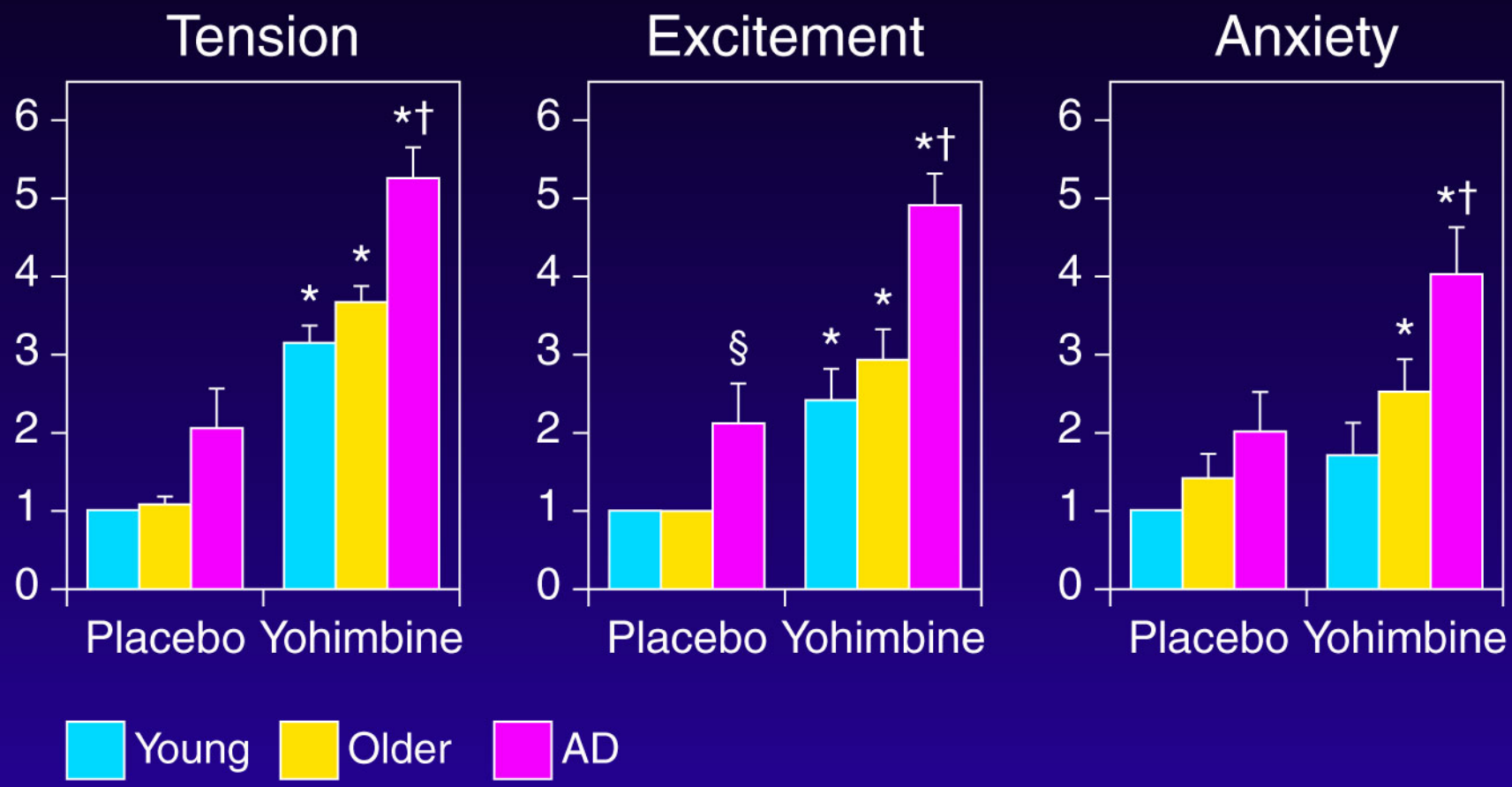
Peskind, et al., *Arch Gen Psychiatry* 52:774-782, 1995.

Change in CSF NE Concentrations Between Placebo and Yohimbine Conditions

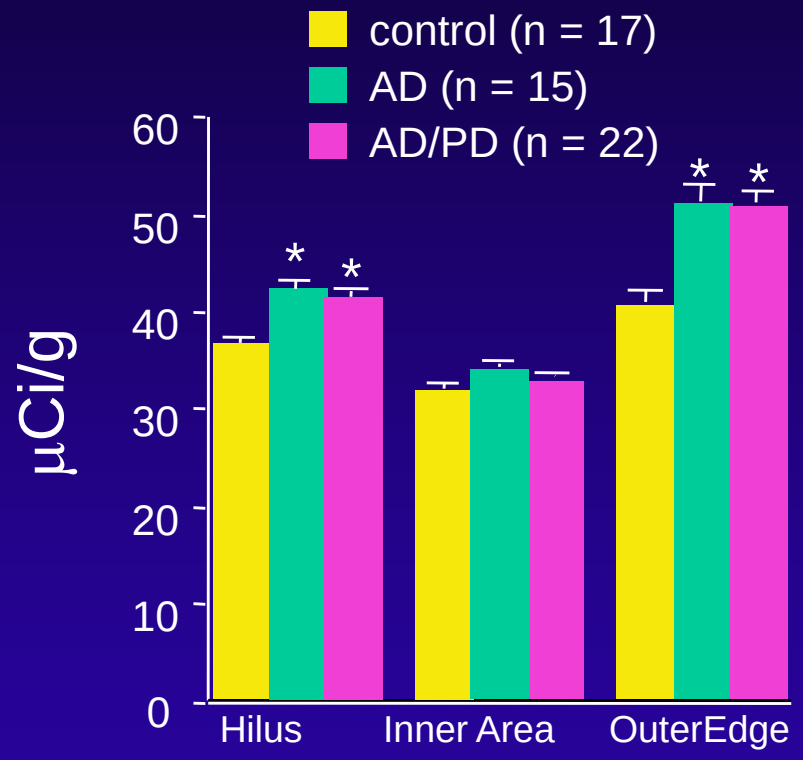


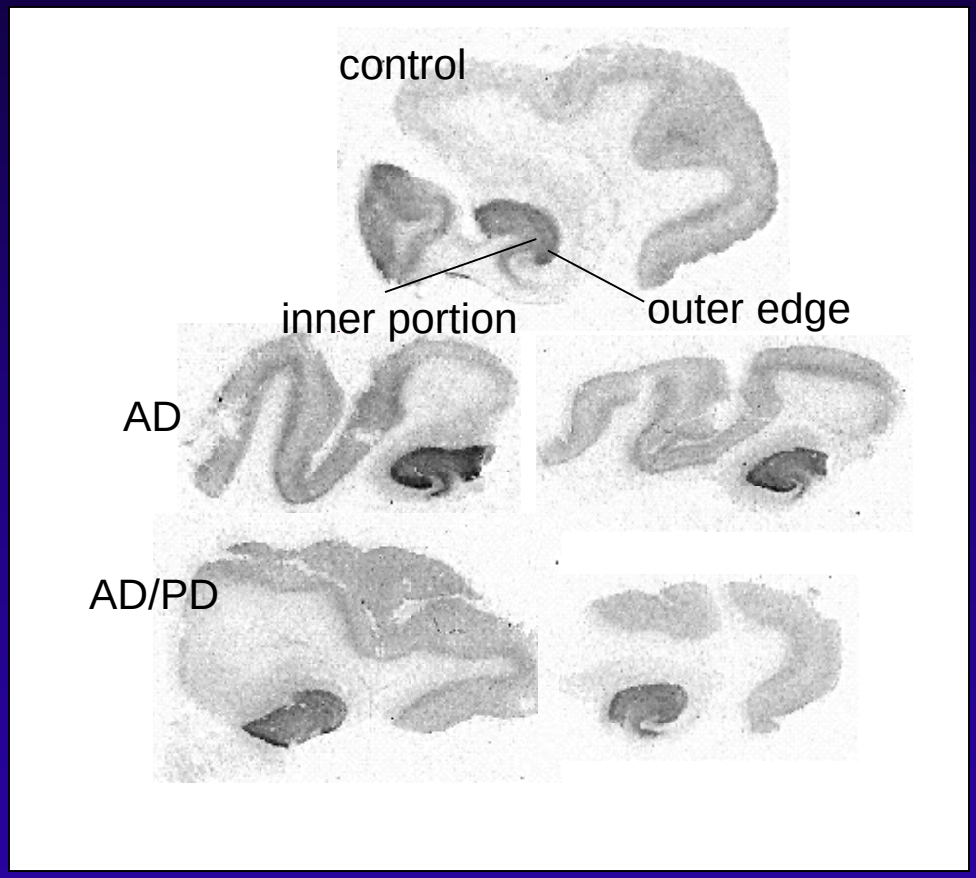
* significantly higher than young subjects

Effects of Yohimbine Administration on Tension, Excitement, and Anxiety Ratings



^{3}H Prazosin Binding - Hippocampus





Szot P, et al., *J Neurosci* 26:467-78, 2006.

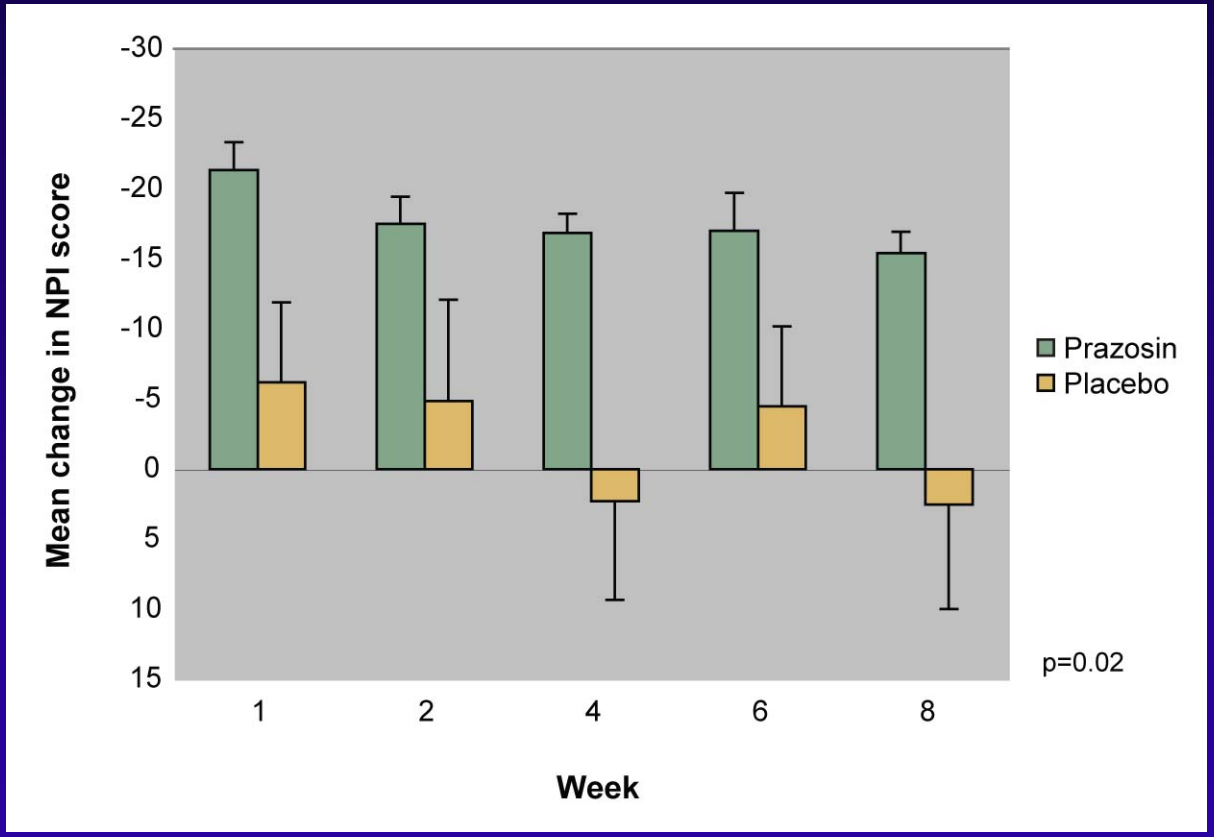
Prazosin Side Effect Profile

- Nonsedating.
- Does not cause pseudoparkinsonism.
- Blood pressure reduction possible.

Placebo-Controlled Trial of Prazosin for Disruptive Agitation in Dementia

- Twenty-two persons (mean age 81 ± 11 years) with DSM-IV dementia (possible or probable AD) and frequent disruptive agitation.
- Randomized to prazosin (n=11) or placebo (n=11) for 8 weeks.
- Prazosin dose range 2-6 mg/day (mean dose 5.7 ± 0.9 mg/day).
- Primary outcome measures: NPI, BPRS CGIC.

Placebo-Controlled Trial of Prazosin for Disruptive Agitation in Dementia: NPI

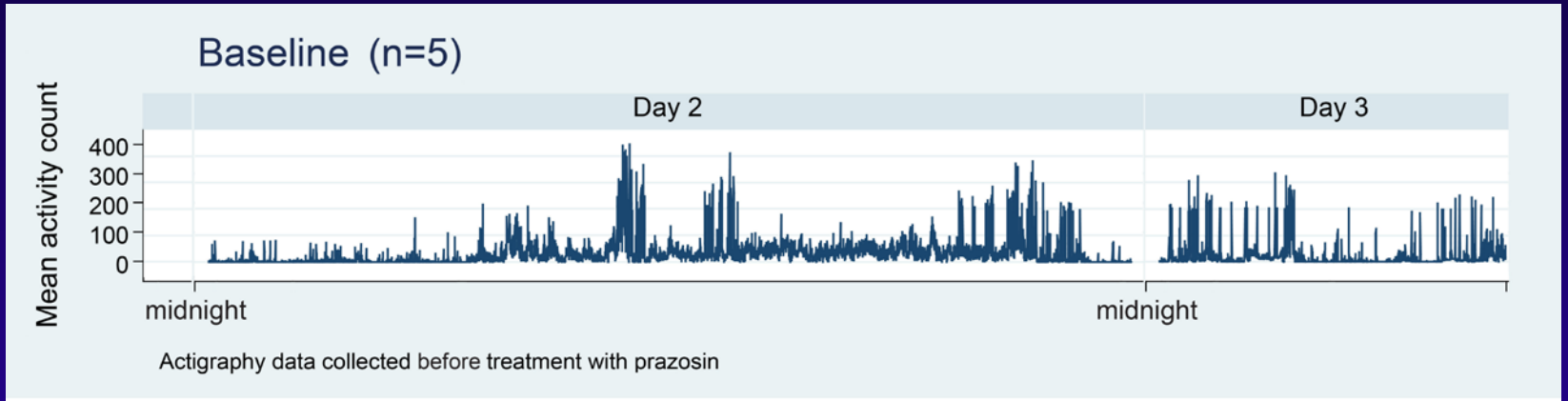


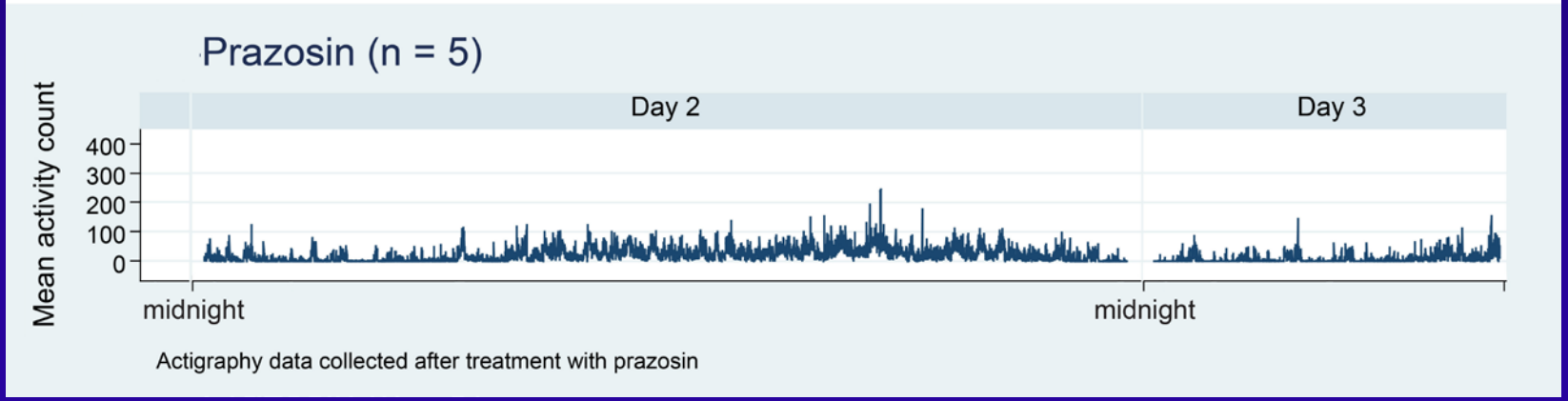
Adverse Events Were Similar for Prazosin and Placebo Groups

Number of Occurrences of Adverse Events

	Prazosin group	Placebo group	Both groups combined
Sedation	3	3	6
Confusion	2	4	5
Hypotension	2	1	3
Dizziness on Standing	1	0	1

Does Prazosin Reduce Actigraphically Recorded Movement in AD with Agitation?





ADCS Prazosin Trial for AD Agitation/Aggression

- Randomized controlled trial of prazosin for agitation/aggression in AD begins Spring 2016.
- 186 outpatients or nursing home residents randomized to prazosin or placebo (2:1) for 24 weeks.
- 20 day flexible titration to maximum dose 8 mg bid.
- “Rescue” lorazepam up to 2 mg/day for a maximum 42 days.
- Primary outcome: NPI; Secondary outcome: ADCS CGIC and ADL; actigraphy, mg rescue lorazepam, time to study withdrawal.

Challenges of Developing a New Therapeutic Use for a Generic Drug

- No pharmaceutical industry support for clinical trials.
- No pathway for FDA labeling indication for a new treatment target.

If You Build It, They Will Come

- The number of Veterans with a PTSD diagnosis prescribed prazosin has increased annually since 2002.
- In 2013, prazosin was prescribed to 17% of Veterans with a PTSD diagnosis – approximately 100,000 Veterans.

Conclusions

- Prazosin may be effective for the treatment of disruptive agitation in AD.
- Prazosin is generally well-tolerated.
- Larger placebo-controlled efficacy trials of prazosin for disruptive agitation are needed.

Rationale for Prazosin as a Potential AD "Disease Modifying" Drug

- The recently described brain "glymphatic" system[1] clears Aβ from brain.
- Prazosin substantially increases glymphatic flow and Aβ clearance.

[1]JJ Iliff…M. Nedergaard. A paravascular pathway facilitates CSF flow through the brain parenchyma and clearance of solutes, including amyloid β. Sci Transl Med 2012.