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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

MEDICATIONS FOR AGITATION IN DEMENTIA

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DISCLOSURES

I have no financial relationship with pharmaceutical companies or device manufacturers.

All the opinions in this talk are my own.

I will make comment about medications and show data about them, but not recommend any specific treatment.

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AGITATION IN DEMENTIA

- Inappropriate verbal, vocal, or motor behaviors regardless of cause.
- Behaviors are
  - –Repetitive
  - –aggressive, or
  - –socially inappropriate
- Occurs in about 70% of patients with dementia at some point in the disease course.
- 75% of caregivers describe agitation as their most serious problem.

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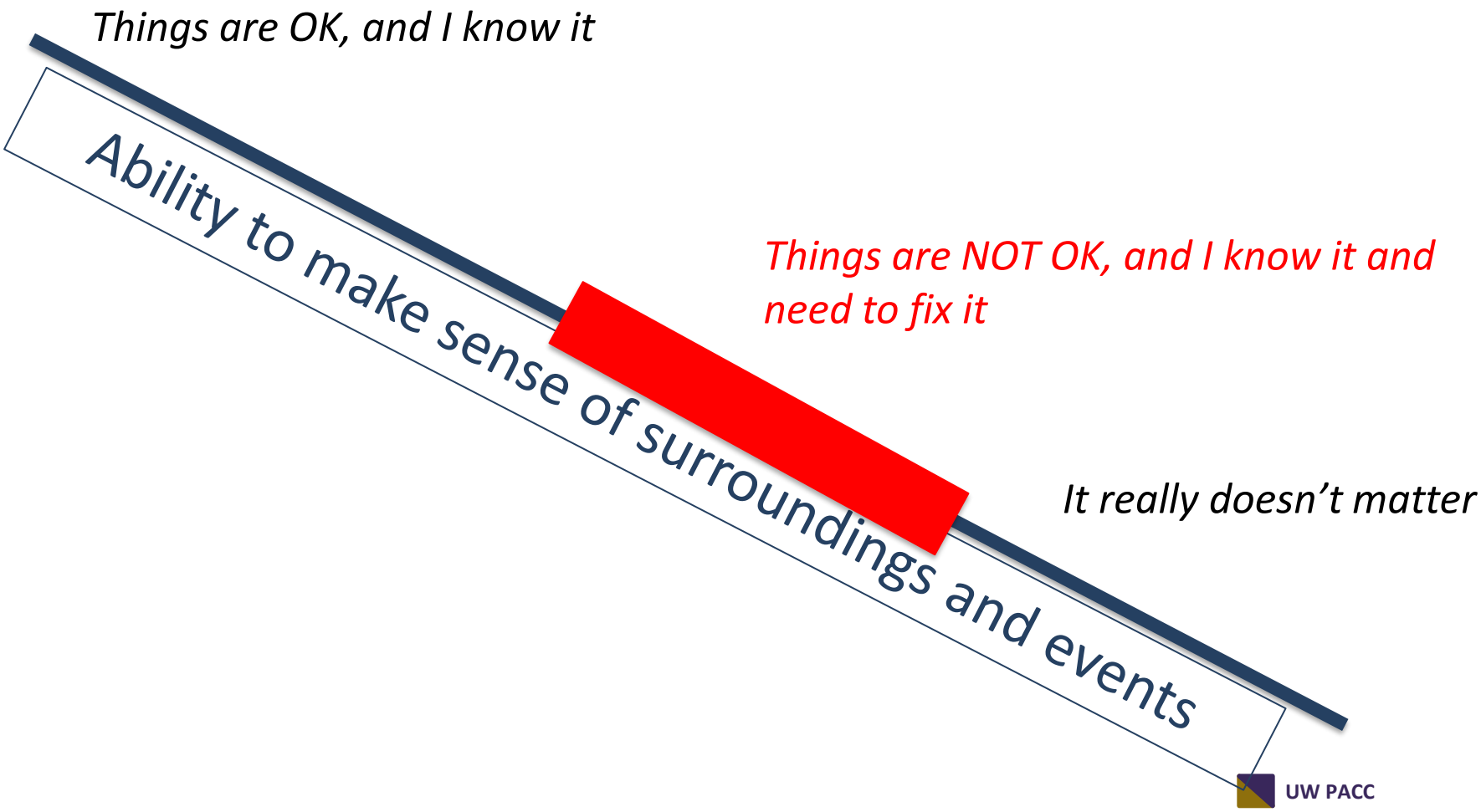
WHEN DOES AGITATION HAPPEN?



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WHY DOES AGITATION HAPPEN?

-Delirium

-Unmet needs

-Conditioned / learned behavior

-Natural response

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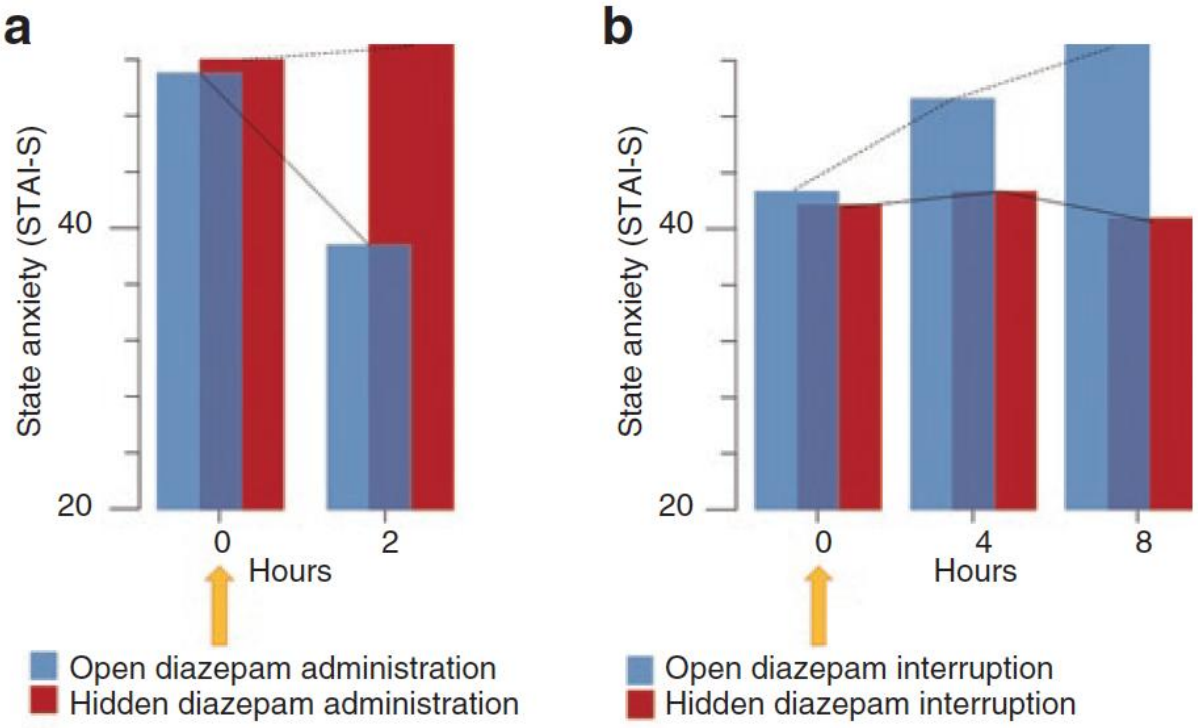
How do psychotropic drugs work?

About 75% of apparent drug effect is due to placebo across almost all drug types.



Benedetti et al, *Clinical Pharmacology & Therapeutics*, 90:5, 2011

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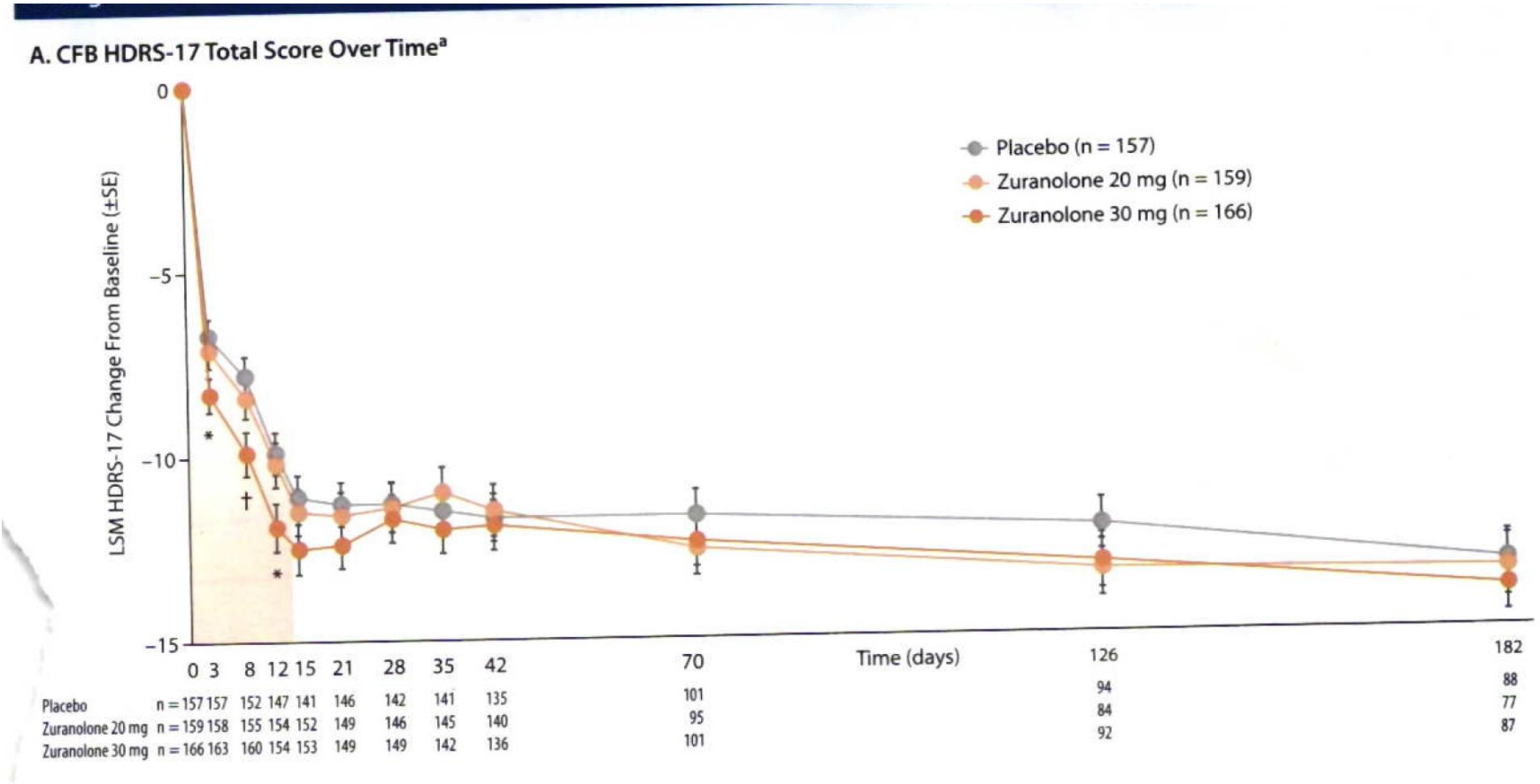
TYPICAL ANTIDEPRESSANT AND PLACEBO RESPONSE



Clayton AH, et al. Zuranolone for the Treatment of Adults With Major Depressive Disorder: A Randomized, Placebo-Controlled Phase 3 Trial. *Am J Psychiatry.* 2023 Sep 1;180(9):676-684.

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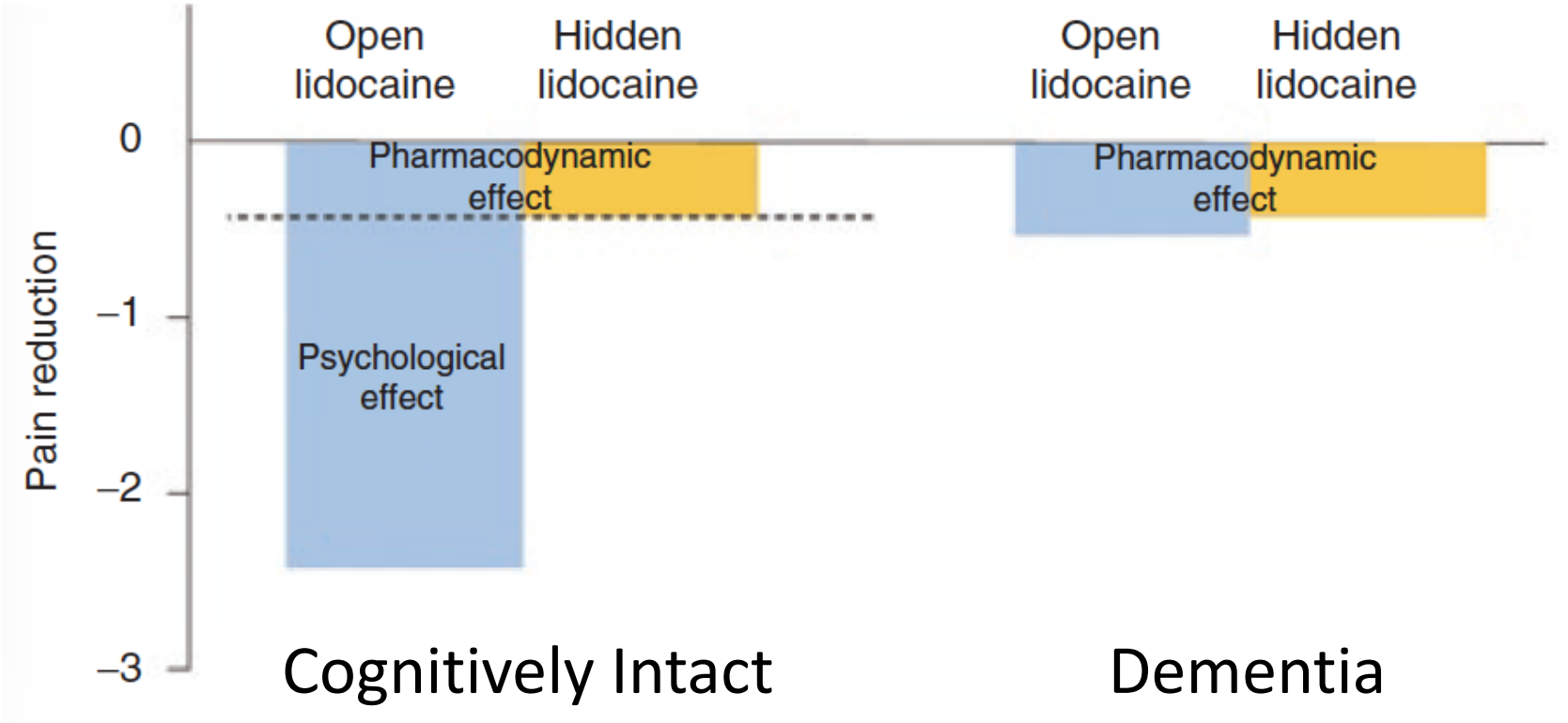
THE PLACEBO IN DEMENTIA



Benedetti, F. et al. Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. *Pain* 121, 133–144 (2006).

Colloca, L., Benedetti F. & Porro C.A. Experimental designs and brain mapping approaches for studying the placebo analgesia effect. *Eur. J. Appl. Physiol*. 102, 371–380 (2008).

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PATIENTS WITH DEMENTIA SHOW LITTLE IF ANY PLACEBO RESPONSE, SO -

YOU CAN EXPECT PSYCHOTROPIC DRUGS **NOT** TO WORK VERY WELL.

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MEDICATIONS WITH AN FDA INDICATION TO TREAT BEHAVIORAL SYMPTOMS OF DEMENTIA:

(1)

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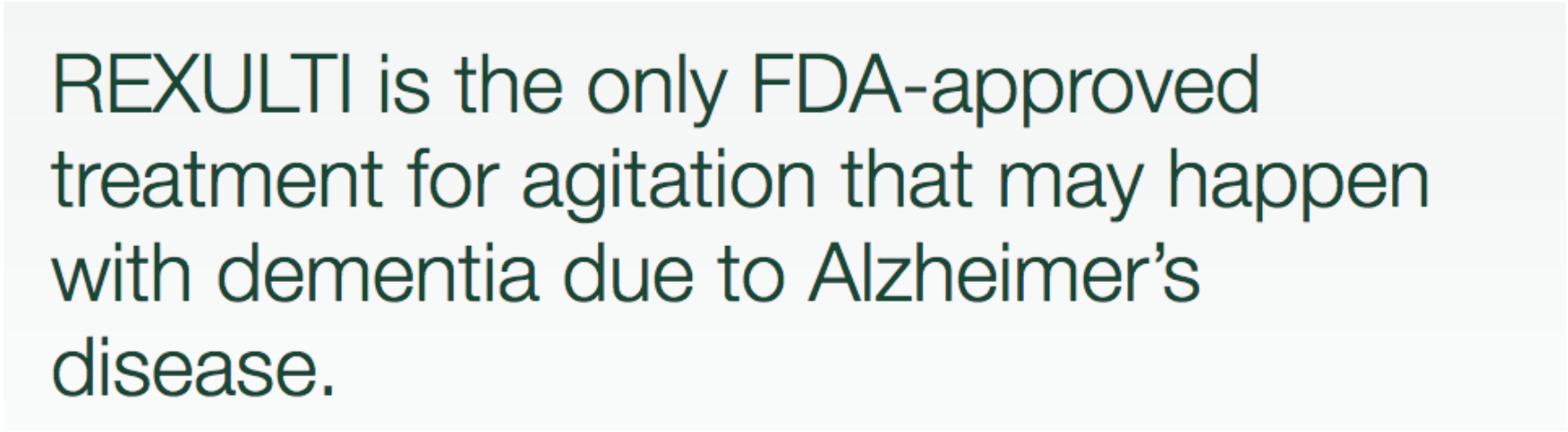
The Ad



Until recently, there hasn't been an FDA-approved medicine for doctors to treat agitation that may happen with dementia due to Alzheimer's disease. But now there's REXULTI. For those struggling with this condition, REXULTI may offer hope for less symptoms of agitation. In clinical studies, REXULTI helped patients see:

www.rexulti.com

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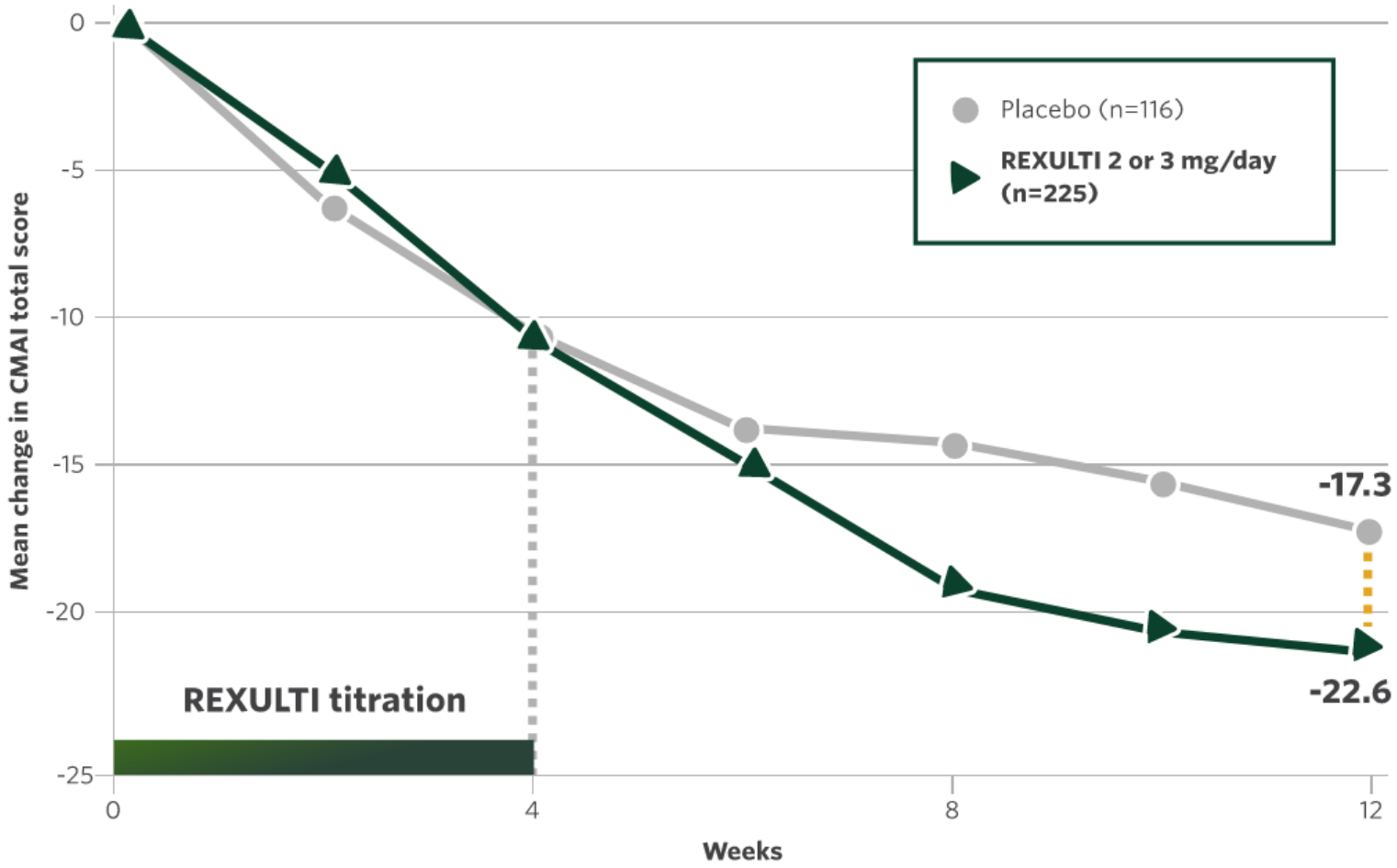
The Data



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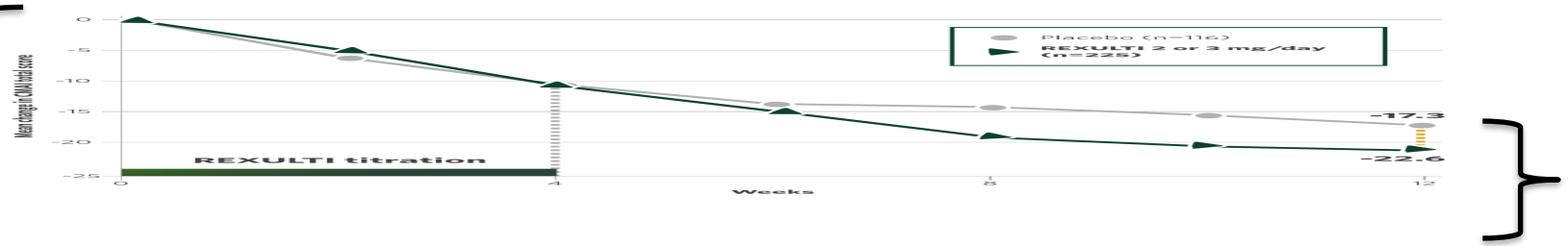
The Data, Scaled Appropriately



174 point scale

17 points is considered clinically meaningful difference

5.3-point difference

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Official Warnings

- **Increased risk of death in elderly people with dementia-related psychosis. Medicines like REXULTI can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). REXULTI is not approved for the treatment of people with dementia-related psychosis without agitation that may happen with dementia due to Alzheimer's disease.**

REXULTI should not be used as an "as needed" treatment for agitation that may happen with dementia due to Alzheimer's disease.

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Reaction to FDA Approval

FDA's Shocking Approval: Rexulti Fast-Tracked Despite Deadly Risks

British Medical Journal, October 6, 2023

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MEDICATIONS TRIED IN AT LEAST ONE RESEARCH STUDY TO PREVENT OR TREAT SYMPTOMS OF DEMENTIA:

>50

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Antidepressants

TRICYCLICS

SSRIS

SNRIS

BUPROPION

MIRTAZAPINE

TRAZODONE

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Psychiatric Drugs

TYPICAL ANTIPSYCHOTICS

ATYPICAL ANTIPSYCHOTICS

BUSPIRONE

ALPHA BLOCKERS

BETA BLOCKERS

ANTIHISTAMINES

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More Psychiatric Drugs

CANNABINOIDS (MARIJUANA)

OPIOIDS

METHYLPHENIDATE

LAMOTRIGINE

ANTIEPILEPTIC DRUGS

LITHIUM

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Hormones and Vitamins

ESTROGEN

VITAMIN E

HOMOCYSTEINE

B VITAMINS

RESVERATROL

GINSENG

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Targeted Drugs

ACETYLCHOLINESTERASE INHIBITORS

NMDA ANTAGONISTS

NICOTINE

LISURIDE

METHYLENE BLUE

INTRANASAL INSULIN

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Drugs Used for Other Conditions

CYPROTERONE

NSAIDS

COX2 INHIBITORS

H2 BLOCKERS

THIAZIDE DIURETICS

CALCIUM CHANNEL BLOCKERS

ACE INHIBITORS

STATINS

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One Promising Treatment

CONCLUSION: Acupuncture at Baihui (GV 20), Shenshu (BL 23), Geshu (BL 17), and the points selected according to the midnight-noon, ebb-flow eight methods of the intelligent turtle combined with the drug nimodipine can yield definite therapeutic effects in dementia.

Zhong et al, 2009. "Clinical Effects of Acupuncture Combined with Nimodipine for Treatment of Vascular Dementia in 30 Cases". *Journal of Traditional Chinese Medicine*, 29:3; 174-6.

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ANTIPSYCHOTICS - SUMMARY

"Antipsychotics have demonstrated modest efficacy in treating psychosis, aggression and agitation in individuals with dementia. Their use in individuals with dementia is often limited by their adverse effect profile. The use of antipsychotics should be reserved for severe symptoms that have failed to respond adequately to nonpharmacological management strategies."

Tampi et al. Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses. *Ther. Adv. Chronic Dis.* 2016 Jul 15;7(5):229–245.

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ANTIPSYCHOTICS: EXPERT PANEL RECOMMENDATIONS

-Use the lowest possible dose for the shortest time

-Typical course: 1-3 months

-The medications can typically be discontinued without ill effects

(Shah, A. (2006), Can risperidone and olanzapine in elderly patients with dementia and other mental disorders be discontinued? *Int. J. Geriat. Psychiatry*, 21: 140-146)

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PROBLEMS WITH ANTIPSYCHOTICS

Carry a BLACK BOX WARNING

1.6-1.7 times increased risk of DEATH

Do not consistently help symptoms of agitation when compared to placebo

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"WARNING: Increased Mortality in Elderly Patients With Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration* of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a **risk of death in drug-treated patients of between 1.6 to 1.7** times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infections (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality.

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Informed Consent with Families:

Make sure you want your loved one to start or to stay on an antipsychotic medication, given the black box warning.

- How can you tell if it is working?
- How can you tell if it is causing problems?

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OTHER MEDICATIONS

Trial and error.

Pick the safest option.

The placebo effect is powerful for families.

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PRAZOSIN FOR DEMENTIA-RELATED AGITATION

TABLE 2. Behavioral Responses to Prazosin Versus Placebo: Behavior Scores Presented as Mean ± Standard Deviation

		Change From Baseline for Participants Remaining at Each Timepoint							
	Baseline (n = 22)	Week 1 (n = 22)	Week 2 (n = 19)	Week 4 (n = 15)	Week 6 (n = 13)	Week 8 (n = 13)	Mean Group Change[a]	Test Statistic[b]	p[b]
N									
Prazosin	11	11	10	8	7	7			
Placebo	11	9[c]	9	7	6	6			
NPI									
Prazosin	49 ± 16	−20 ± 19	−16 ± 23	−16 ± 25	−15 ± 24	−13 ± 23	−19 ± 21	$X^2 = 6.32$	0.012
Placebo	43 ± 18	−5 ± 17	−2 ± 21	4 ± 17	−1 ± 14	5 ± 21	−2 ± 15		
BPRS									
Prazosin	45 ± 8	−9 ± 8	−8 ± 10	−7 ± 13	−7 ± 9	−9 ± 8	−9 ± 9	$X^2 = 4.42$	0.036
Placebo	44 ± 7	−3 ± 7	−5 ± 7	−2 ± 6	−3 ± 8	3 ± 5	−3 ± 5		
CGIC									
Prazosin							2.6 ± 1.0	$z = 2.57$	0.011
Placebo							4.5 ± 1.6		

[a]For the NPI and BPRS, mean group change was determined by calculating the mean of each participant's follow-up measures, subtracting this mean from the baseline value, and then from these values, calculating group means and standard deviations. This reflects a group change for participants who had at least one follow-up measure. For the CGIC, the mean is shown.

[b]For the NPI and BPRS, the likelihood ratio χ^2 test ($df = 1$) for the significance of the posttreatment versus pretreatment change × treatment group interaction from linear mixed effects models of behavior score on treatment group and time of treatment (pre versus post). For the CGIC, the Mann-Whitney test.

[c]Two subjects were not present for their 1 week visit but did return for subsequent visits.

Wang et al, *AJGP* 2009

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MY EXPERIENCE WITH PRAZOSIN

?

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RECAP

Figure out what is going on **before** turning to medications

Main reasons for agitation:

- -Delirium
- -Unmet needs
- -Learned behavior
- -Natural response

Support the caregiver

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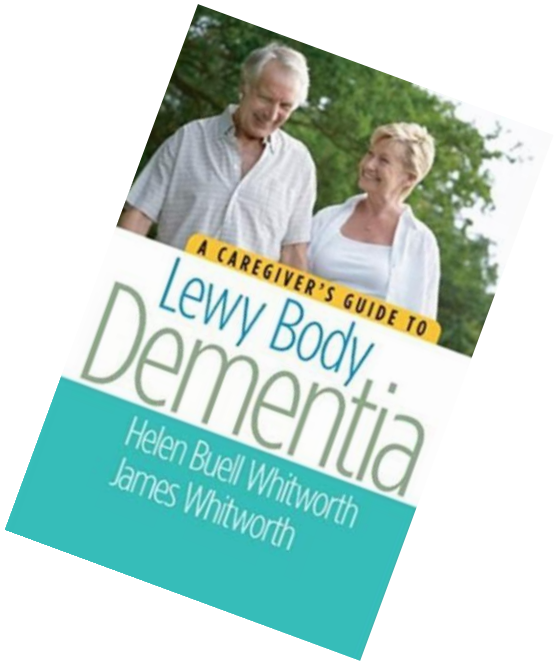
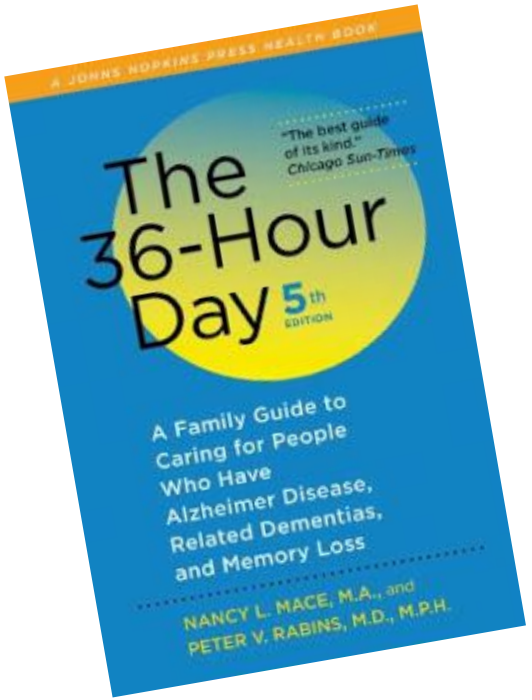
SUPPORTING THE CAREGIVER

The single biggest predictor of need for nursing home placement is the *caregiver's* condition

Caregivers often do not complain





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THE CHALLENGE TO SOCIETY

Dementia costs about **$150 billion per year** in medical and formal care costs in the US (2017)

There are about 30 million unpaid family caregivers for patients with dementia. Their work comes at a cost of another **$210 billion per year.**

Caregiving is difficult work, and often takes a toll on health.

About half of caregivers feel they have no choice but to provide care themselves (i.e., there is no one else available to perform it).

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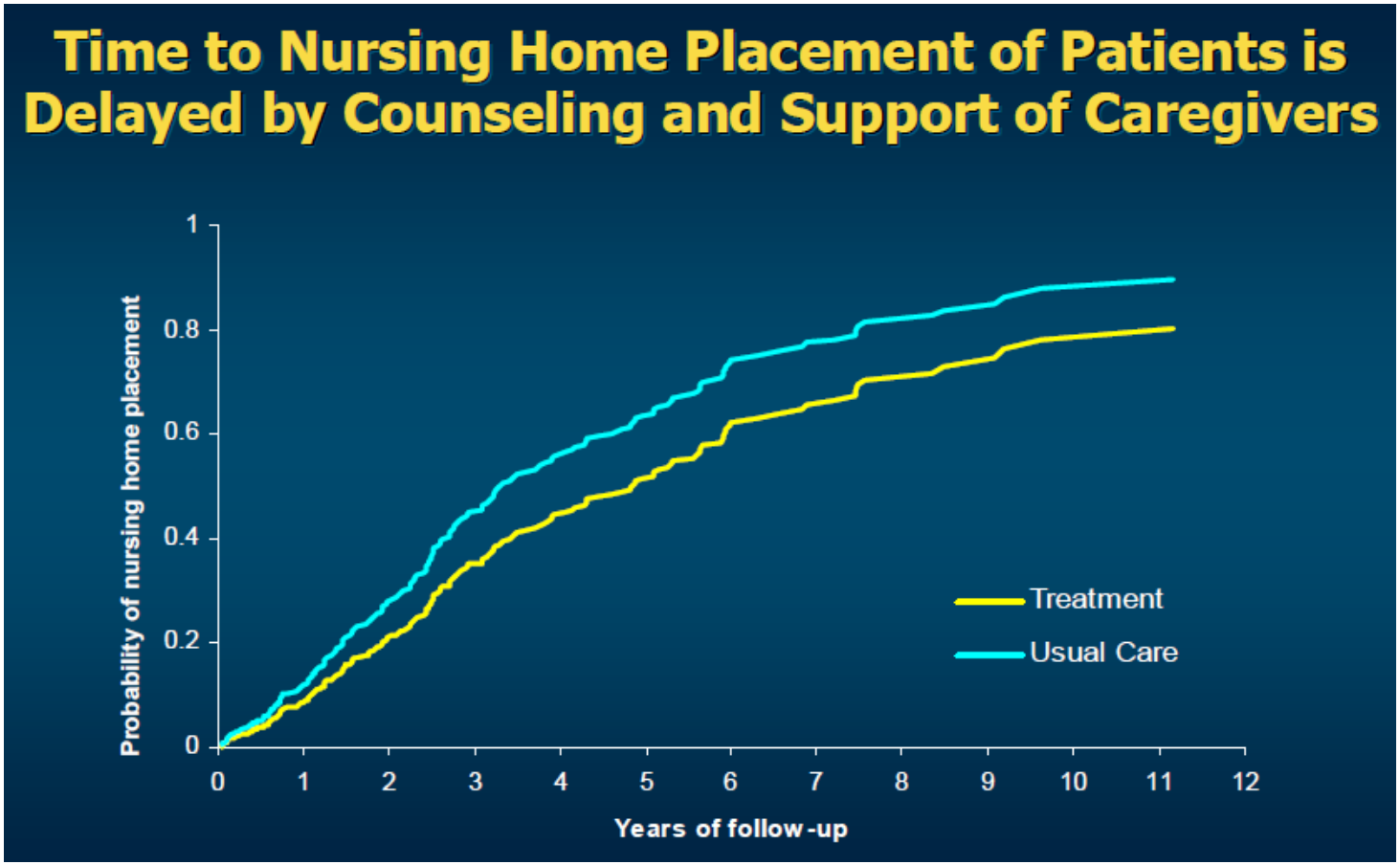
THE VALUE OF CARING FOR THE CAREGIVER



Mittelman 2004

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THE BEST WAY TO CARE FOR THE PATIENT IS TO CARE FOR THE CAREGIVER.

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