

Medications for Anxiety and Depression

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Disclosures

I am an employee of the VA.

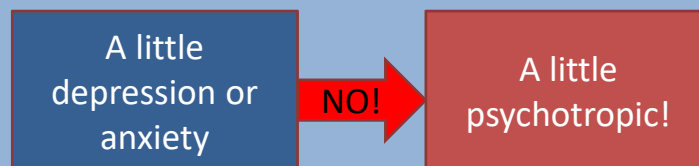
I have no conflicts of interest to
report.

Overview

Should our patient be on a medication?

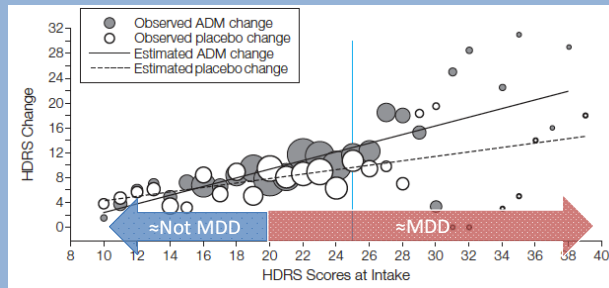
If so, which one, and at what dose?

Antidepressants for Depressive / Anxiety *Symptoms?*



Mild Depression

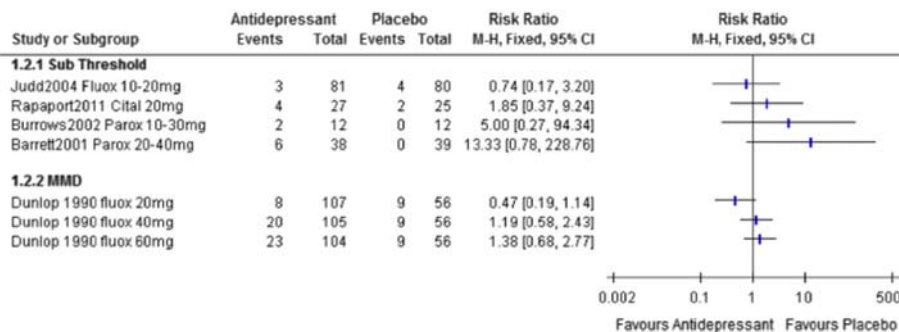
Antidepressants have little effect compared to placebo **unless there is major depression**



Fournier, J. C., et al. 2010 Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA* 303, 47–53.

Mild / Subthreshold Depression

I.M. Cameron et al / Journal of Affective Disorders 166 (2014) 48–58



Cameron IM, et al, 2014. Efficacy and tolerability of antidepressants for sub-threshold depression and for mild major depressive disorder. *Journal of Affective Disorders*, 166, 48-58.

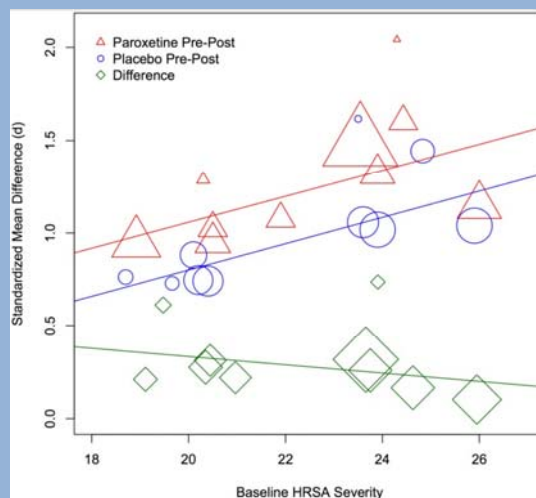
Mild anxiety

“Normal”?

Adjustment (disorder)

Conditions or medications that
mimic an anxiety disorder

Paroxetine vs Placebo for Anxiety



Sugarman et al, 2014. The Efficacy of Paroxetine and Placebo in Treating Anxiety and Depression: A Meta-Analysis of Change on the Hamilton Rating Scales. *PLoS One* 9(8): e106337.t

Publication Bias in Antidepressant Trials

Publication Status		Effect Size	95% CI	Q(1)	p
Paroxetine - Placebo	Published	0.32	[0.23, 0.40]	3.90	.048
	Unpublished	0.17	[0.06, 0.29]		
Paroxetine	Published	1.19	[1.12, 1.27]	3.52	.061
	Unpublished	1.32	[1.21, 1.44]		
Placebo	Published	0.86	[0.79, 0.94]	18.63	<.001
	Unpublished	1.15	[1.04, 1.25]		

Sugarman et al, 2014. The Efficacy of Paroxetine and Placebo in Treating Anxiety and Depression: A Meta-Analysis of Change on the Hamilton Rating Scales. *PLoS One* 9(8): e106337.

Adjustment Disorder

“The use of psychotropic drugs such as antidepressants, in adjustment disorder with anxious or depressed mood is not properly supported and should be avoided.”

Carta MG, Balestriere M, Murru A, Hardoy MC. Adjustment disorder: epidemiology, diagnosis, and treatment. *Clin Pract Epidemiol Ment Health*, June 2009; 5-15.

Psychotropics are not indicated for *symptoms* of depression or anxiety unless the diagnostic criteria for a disorder are met.

Psychotropics are not indicated for responses to stressful life events.

Medication Treatment Approaches for Major Depression

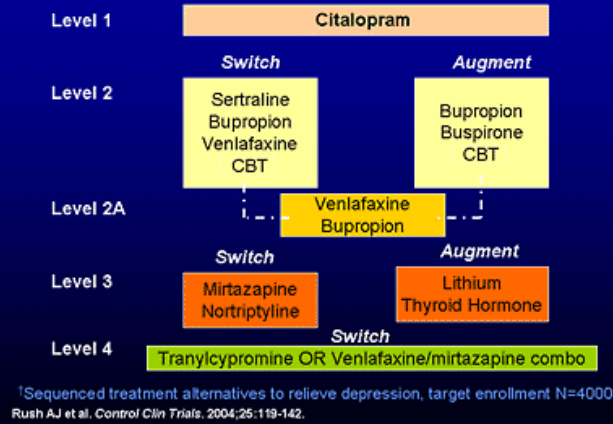
STAR-D

4041 patients

Few exclusion criteria

12-week treatments at each level, as needed

STAR-D[†] Algorithm for Depression



STAR-D Outcomes

STAR-D Outcomes by Treatment Step

	Step 1	Step 2	Step 3	Step 4
Remission at step exit	36.8	30.6%	13.7%	13%
Response in each step	48.6	28.5%	16.8%	16.3%
Intolerable side effects	16.3	19.5%	25.6%	30.1%

Source: Rush AJ, Tilvack MK, Winslow SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR-D report. *Am J Psychiatry*. 2006;163:1905-1917.

35% remitted by end of Step 1

50% remitted by end of Step 2

70% of those who continued in the study remitted by the end of Step 4

STAR-D Take-Homes

Keep trying! If symptoms do not improve after 3 months, change the treatment!

In practice, SSRIs all have very similar efficacy. Consider side effects, especially withdrawal.

The algorithm itself does not seem to matter that much.

Placebos

Antidepressant trials show high placebo response rates

Participants taking a placebo have better results than participants on waiting lists

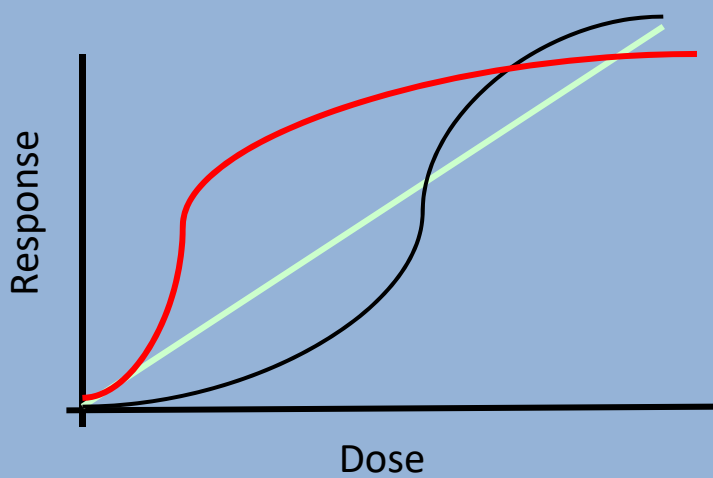
Study characteristics strongly influence placebo response rates:

- More study sites
- Less blinding (rater knows the treatment)
- Lower probability / lower expectation of receiving placebo
- More study visits

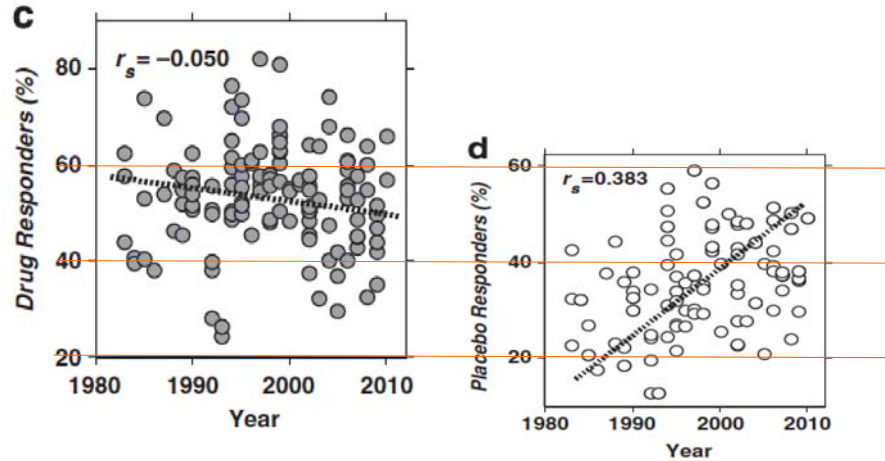
Capitalize on placebo response

Dosing

Hypothetical Dose-Response Curves

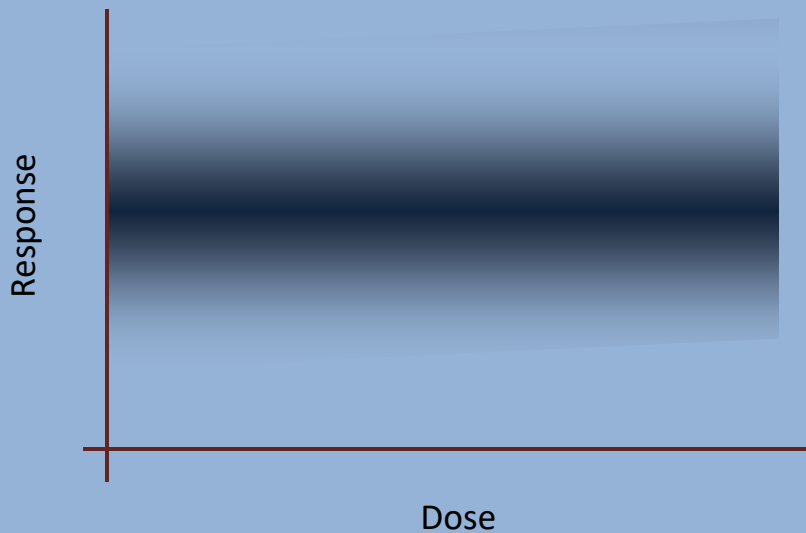


Drug and Placebo Over the Years



Undurraga J. et al. Randomized, placebo-controlled trials of antidepressants for acute major depression: thirty-year metaanalytic review. *Neuropsychopharmacology* 2012;37:851-864.

Observed Dose-Response Curve



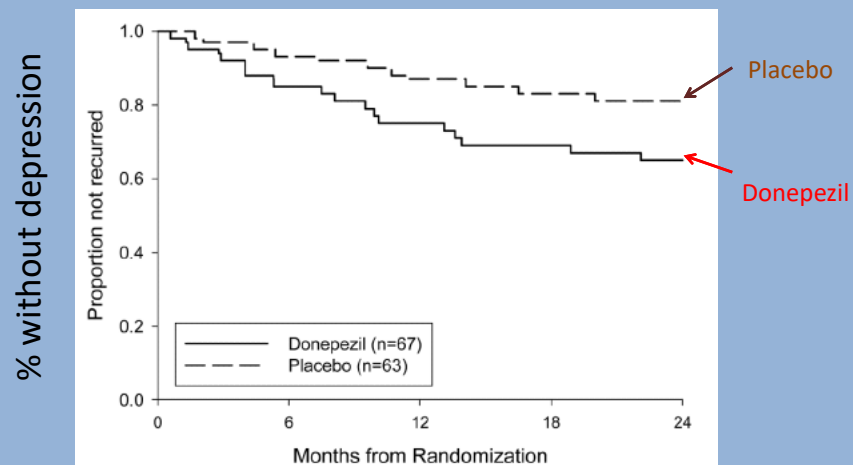
Dementia Treatments to Improve Depression?

Maintenance Treatment of Depression in Old Age: A Randomized, Double-blind, Placebo-Controlled Evaluation of the Efficacy and Safety of Donepezil Combined with Antidepressant Pharmacotherapy

Charles F. Reynolds III, M.D., Meryl A. Butters, Ph.D., Oscar Lopez, M.D., Bruce G. Pollock, M.D., Ph.D., Mary Amanda Dew, Ph.D., Benoit H. Mulsant, M.D., Eric J. Lenze, M.D., Margo Holm, Ph.D., Joan C. Rogers, Ph.D., Sati Mazumdar, Ph.D., Patricia R. Houck, MSH, Amy Begley, M.A., Stewart Anderson, Ph.D., Jordan F. Karp, M.D., Mark D. Miller, M.D., Ellen M. Whyte, M.D., Jacqueline Stack, MSN, Ariel Gildengers, M.D., Katalin Szanto, M.D., Salem Bensasi, B.A., Daniel I. Kaufer, M.D., M. Ilyas Kamboh, Ph.D., and Steven T. DeKosky, M.D.

Cognitive boost → depression boost (?)

Dementia Treatments to Improve Depression??



Dementia medication → greater risk of depression

Hyponatremia and Antidepressants

9% of patients 65 years and older taking an antidepressant, regardless of type of antidepressant

Likely from effects on kidney, not brain

Unclear clinical consequences

More likely to be symptomatic than younger adults

Mannesse C.K., et al. Characteristics, prevalence, risk factors, and underlying mechanism of hyponatremia in elderly patients treated with antidepressants: A cross-sectional study. *Maturitas* 2013; 76: 357-363.

Sexual Dysfunction

Sexual dysfunction in 30-50% of SSRI/SRNI users

If you don't ask, patients usually won't volunteer

Problems with desire, excitement, orgasm, and/or resolution

Failure to ask about and discuss sexual side effects jeopardizes the therapeutic relationship

Key Points

- Medications are unlikely to provide benefit beyond a placebo effect **unless there is a specific mental health disorder**
- Dosing may not matter much
- Selection of a particular medication may not matter much, as long as you **keep trying**
- Cholinesterase inhibitors may make depression worse, not better
- Medications for depression and anxiety are not harmless
- In many cases, “watch and wait” is preferable to starting a psychotropic

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