

Understanding and Controlling Placebo Response in CNS Drug Development

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Failure Rate of Clinical Trials for FDA-Approved CNS Drugs

Results for Investigational arms	FDA Trial Database			
	Trials	Treatment Arms	Successful Treatment Arms	% Failure
Antidepressants	52	93	45	51.6
Anxiolytics	40	75	36	52.0
Antipsychotics	17	49	37	24.5

Khan, et al. NCDEU, 2005.

Placebo Response Influences Outcome

- As placebo response increases, ability to discriminate between an active drug and a placebo decreases
- MDD Example

Placebo response	% Failure
High	78.9
Low	25.8

J. Nervous and Mental Disease; 191(4):211-218. 2003.

Observational and Causal Effects

Response in untreated patients measures

- **Study effect**

Response in placebo-treated patients measures

- **Study effect +**
- **Placebo effect**

Response in drug-treated patients measures

- **Study effect +**
 - **Placebo effect +**
 - **Pharmacologic effect**
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Key Take-away

- **Placebo response equally impacts placebo and drug treated patients, so placebo response does not directly influence drug-placebo differences - signal detection**
- **However, patients can only improve so much. As non-drug improvement increases, the opportunity for drug related improvement decreases. A floor effect**

Controlling Placebo Response

Placebo Response = study effect + placebo effect

- **Therefore, design features can be manipulated to control study effects and placebo effects in order to minimize placebo response**
 - **Easier said than done**

Design Factors and Patient Characteristics Associated with MDD Trial Success

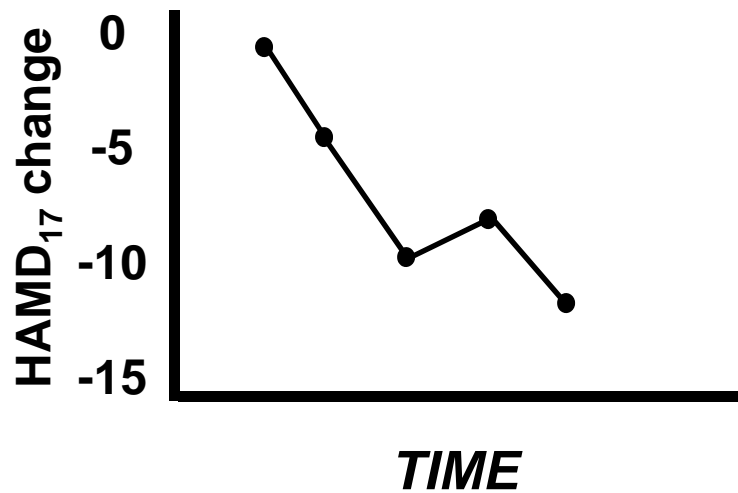
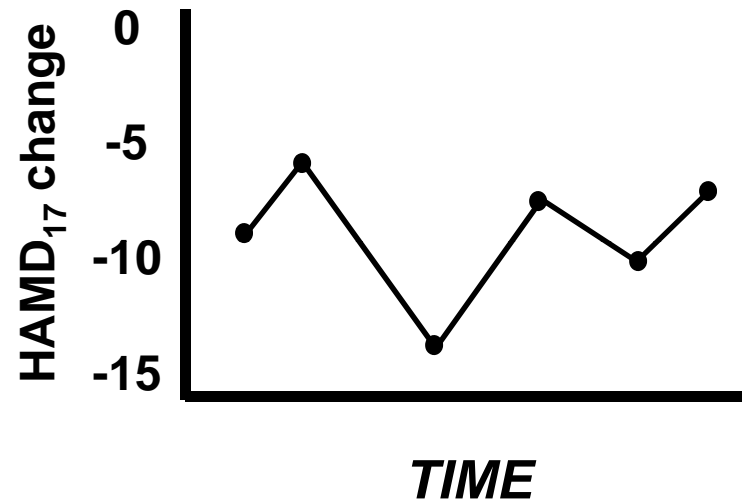
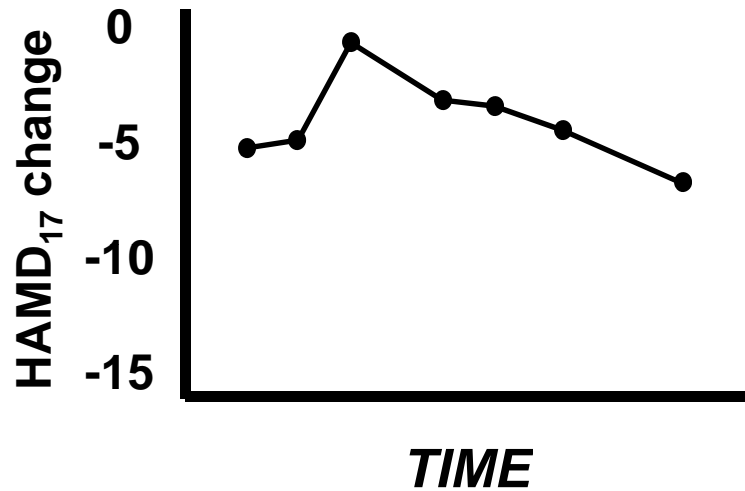
- **Flexible (vs. fixed) doses**
- **Greater baseline severity of illness**
- **Number of treatment arms**
- **% male subjects**

Am J Psychiatry 2004; 161:2045-2049.

Why Haven't Efforts to Curb Placebo Response Worked?

- **Difficult to isolate impact of individual factors**
 - **Confounding**
 - **# arms / fixed vs. flex / or...**
 - **Association vs. causation**
 - **Variability in placebo effect**

Site Performance in Consecutive Trials



Results From The Duloxetine Development Program: Excluding Placebo Responders

	All Patients	Excluding Pbo lead-in Responders
Freq. of Significant Diffs. on HAMD₁₇	11 / 19	12 / 19
Average Effect Size	0.360	0.422

PsychoPharm Bull. 40(2) 101-114

% Randomized to Placebo: MDD

- Large meta analysis
 - 182 studies, 262 drug-placebo contrasts
 - As percent randomized to placebo increased, placebo response rate decreased and the difference between drug and placebo increased

European Neuropsychopharmacology (2009) 19, 34–40.

% randomized to Placebo	Drug-placebo difference in response rates (%)
20	11
25	12
33.3	14
50	18

% Randomized to Placebo: Recent Schizophrenia

- **Meta Analysis**

- **All placebo controlled trials since 1997**
- **27 studies, 79 drug-placebo contrasts**
- **As percent randomized to placebo increased, mean placebo improvement decreased ($p=.026$) and the difference between drug and placebo increased ($P=.060$)**

Submitted.

% randomized to Placebo	Drug-placebo difference mean change PANSS	Placebo group mean change PANSS
<25	7.07	10.39
25	8.16	6.91
33.3	13.65	0.80

Other Means to Improve Signal Detection

- **Summary from MDD program**
 - Use of MMRM and subscales improved signal detection

PsychoPharm Bull. 40(2) 101-114.

All studies in Dulox database

Analysis	EndPoint	Effect size
LOCF	HAMD Total	.294
MMRM	HAMD Total	.384
MMRM	Maier subscale	.452

Studies w\ 50% pbo

MMRM	Maier subscale	.635
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Research caveats:

- **Limited Data**
- **Confounding**
- **Association vs. causation**
- **Beneficial effects of design changes are not for free**

A route forward?

- **Right patients**
- **Control expectation**
- **Randomize an adequate fraction to placebo**
- **Right analysis**
- **Right endpoint**
- **Optimize the science first, then the timeline**