Clinician-administered assessments and impact on placebo response in recent major depressive disorder (MDD) clinical trials

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Introduction

- Placebo-controlled MDD trials of anti-depressants often show a robust placebo response on clinical endpoints[1]
- Approximately 50-70% of industry funded placebo-controlled MDD trials fail, in part due to large placebo response[2,3]
- Clinical trial design factors may amplify placebo response and increase the challenge of demonstrating a treatment effect[4]
- Here, recent MDD trials meeting analysis criteria were investigated to identify associations between clinical trial design factors and magnitude of placebo change from baseline

Methods

Analysis inclusion criteria:
- Industry-funded Phase 2-4
- Adults with MDD
- Completed in past 10 years
- Primary endpoint of Hamilton Depression Rating Scale (HAM-D) or Montgomery–Åsberg Depression Rating Scale (MADRS)
- ≥100 total participants enrolled
- ≥25 enrolled in placebo arm
- Treatment period ≥2 weeks

27 trials met criteria with publicly available clinical trial design data[5]:
- 12 Phase 2; 15 Phase 3; 17 adjunctive
- 8 met primary endpoint

Table 1. Trials that met pre-specified criteria included in this analysis.

NCT Number	Active Treatment	Phase	Treatment Period (Weeks)	Clinician Administered Assessments[A]	In-clinic visits[B]	Baseline Scores[C]	Number of Trial Sites
NCT03188185[D]	ALKS 5461	3	5	18	6		35
NCT03188185[D]	ALKS 5461	3	6	20	6		35
NCT04019704*	Bupropion / dextromethorphan	3	6	7	6	33.2	40
NCT03193398	BTRX-246040	2	8	16	6		8
NCT03738215*	Cariprazine	3	6	20	5	31.9	116
NCT03739203	Cariprazine	3	6	20	5	33	112
NCT04103892	CLE-100	2	4	6		33	46
NCT02498392[D]	JNJ-42165279	2	6				32
NCT02498392[D]	JNJ-42165279	2	6				32
NCT03227224	Seltorexant	2	6	12	4		101
NCT04080752	JNJ-61393215	2	6	8	4		35
NCT03559192[D*]	JNJ-67953964	2	6				53
NCT03559192[D*]	JNJ-67953964	2	6				53
NCT03446846	MIN-117	2	6	15	4		47
NCT03968159	Pimavanserin	3	5	18	6	22.7	85
NCT03018340	Pimavanserin	2	5	18	6	22	36
NCT05061706*	Lumateperone	3	6	14		31.5	50
NCT04985942*	Lumateperone	3	6	14		30	54
NCT02932943	Rapastinel	3	3	3		35.4	31
NCT02943564	Rapastinel	3	3	3		33.6	66
NCT02943577	Rapastinel	3	3	3		33.8	40
NCT04688164	REL-1017	3	4	8		35.3	43
NCT05081167	REL-1017	3	4	8			45
NCT02805439[D]	S47445	2	4	8		24.7	53
NCT02805439[D]	S47445	2	4	8		20.2	53
NCT02695472	NSI-189	2	6	18	5	31.7	12
NCT02473289	Sirukumab	2	12	21	7		46
NCT05376150	XEN1101	2	6	8		34.5	20
NCT03672175	zuranolone	3	2	22	5	25.8	55
NCT04476030[E*]	zuranolone	3	2	20	5	26.6	51
NCT04442490*	zuranolone	3	2	22	5	26.8	39

[A]Clinician administered assessments not available for two trials (with multiple stages); reflects the number of assessments before primary endpoint [B]In-clinic visits only included if trial protocol available [C]MADRS baseline are in blue, and HAM-D are in red [D]Trial included multiple stages, which were considered separately for data analysis [E]zuranolone CORAL primary endpoint switched to day 3, however assumed 2 weeks for calculations for "per week" *Positive primary endpoint

- Placebo response was measured by the placebo group change from baseline score of the primary endpoint (HAM-D or MADRS)
- Percent change from baseline (CFB) score used as normalized change for different primary endpoints when baseline data was available
- Clinician-Administered Assessments (CAAs) include all assessments conducted by clinicians, including HAM-D, MADRS, HAM-A, CGI-I, CGI-S

Results

Figure 1: Increased total number of Clinician-Administered Assessments (CAA) was significantly associated with greater percent placebo group change in a linear regression analysis (Fig. 1A). This association remains significant even when controlling for number of trial sites, study duration, adjunctive vs. monotherapy, and whether the primary endpoint was met. The frequency of CAAs was also significantly associated with percent placebo group change (Fig. 1B), including when normalized to the length of the trial (Fig. 1C).

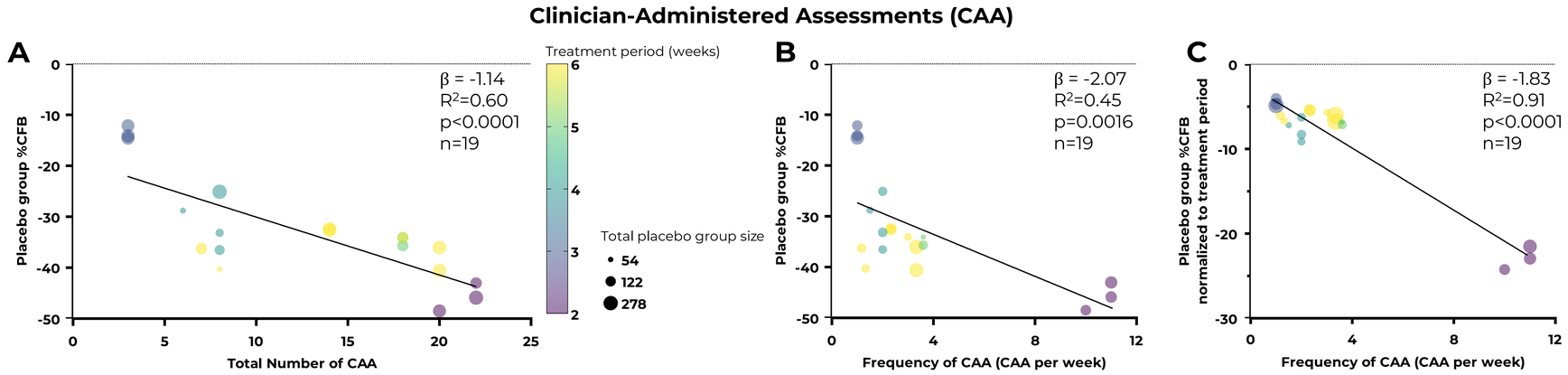
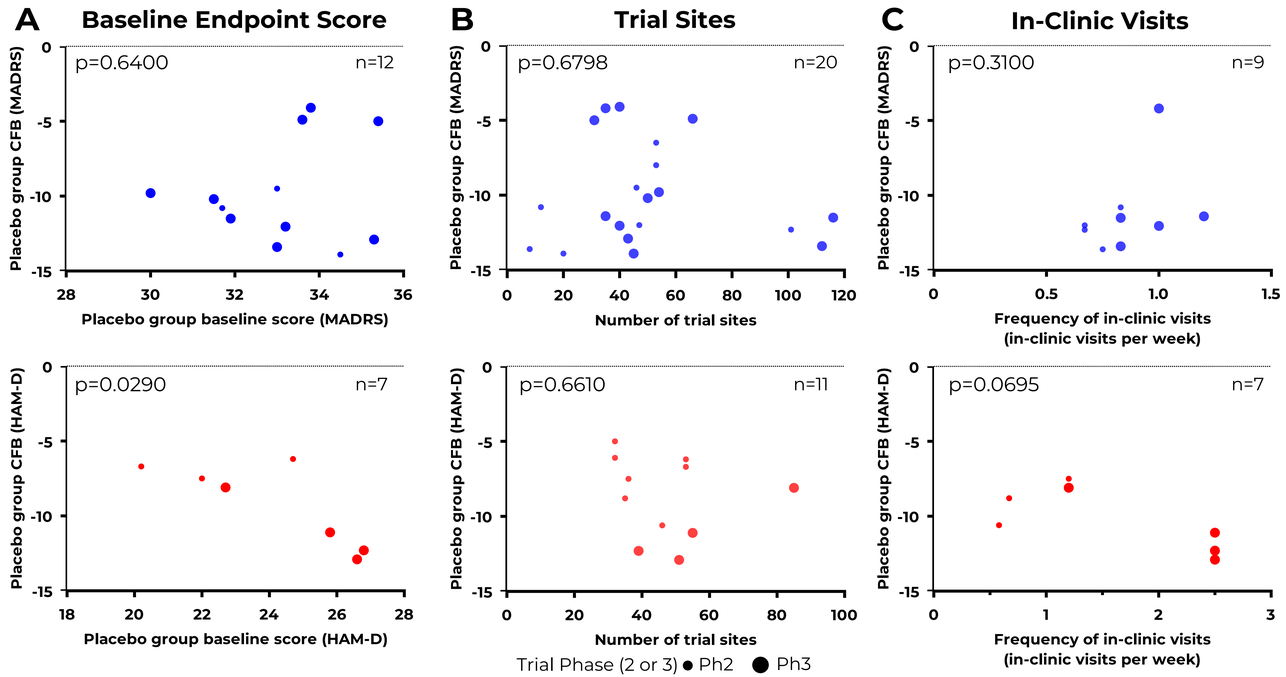


Figure 2: Higher baseline HAM-D score, but not MADRS, was significantly associated with placebo response (Fig. 2A). In contrast, number of trial sites and frequency of in-clinic visits were not associated with placebo response (Fig. 2B-C). Study duration was not associated with percent placebo group change, but upon removing trials <3 weeks, a significant correlation was identified. There was no association between study duration and placebo response for HAM-D trials but there was a slightly significant association for MADRS. These regressions were not impacted when adjusted for total number of CAAs.



Limitations

- Most analyses had limited number of studies included; of the 27 trials included, many did not have data available for all relevant variables that could impact clinical trial outcomes
- Adjustment for confounding demographic / clinical characteristics limited by data availability

Conclusions

- Increasing number and frequency of CAAs were significantly associated with greater placebo change from baseline
- Baseline HAM-D scores may be correlated with placebo response, but number of trial sites or patient in-clinic visits was not
- Reducing the number and frequency of CAAs in MDD trials may decrease the placebo response

References:
1. Walsh, B. T., Seidman, S. N., Sysko, R., & Gould, M. (2002). Placebo response in studies of major depression: variable, substantial, and growing. *JAMA, 287*(14), 1840–1847. **2.** Turner, E. H., Matthews, A. M., Linardatos, E., Tell, R. A., & Rosenthal, R. (2008). Selective publication of antidepressant trials and its influence on apparent efficacy. *NEJM, 358*(3), 252–260. **3.** Salloum, N. C., Fava, M., Ball, S., & Papakostas, G. I. (2020). Success and efficiency of phase 2/3 adjunctive trials for MDD funded by industry: a systematic review. *Mol Psychiatry, 25*(9), 1967–1974. **4.** Potter, W. Z., Mallinckrodt, C. H., & Detke, M. J. (2014). Controlling placebo response in drug development: Lessons learned from psychopharmacology. *Pharm Med, 28*, 53-65. **5.** Data collected from clinicaltrials.gov, etc.

Abbreviations:
MDD: major depressive disorder, MADRS: Montgomery-Åsberg Depression Rating Scale, HAM-D: Hamilton Depression Rating Scale, CFB: Change from Baseline, CAA: Clinician-Administered Assessments; HAM-A: Hamilton Anxiety Rating Scale, CGI-I: Clinical Global Impression - Improvement Rating Scale, CGI-S: Clinical Global Impression - Severity Rating Scale

Disclosures
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