Frequency of Rater-based Efficacy Assessments Correlated with Magnitude of Placebo Response in Generalized Anxiety Disorder Trials

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Introduction

- Participants in randomized, placebo-controlled generalized anxiety disorder (GAD) trials of anxiolytics often show a strong response to placebo on clinical endpoints[1]
- Multiple clinical trial design factors are hypothesized to impact the magnitude of the placebo response in GAD clinical trials, increasing the challenge of demonstrating a treatment effect[2]
- Here, data from GAD trials completed in the past 20 years that met the criteria outlined below 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 GAD
- Completed in past 20 years
- Primary endpoint of Hamilton Anxiety Rating Scale (HAM-A)
- ≥100 total participants enrolled
- ≥25 enrolled in placebo arm

22 trials met criteria with publicly available clinical trial design data:
- 6 Phase 2; 16 Phase 3
- 13 met primary endpoint for at least one treatment arm

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

NCT Number	Active Treatment[A]	Medication Class	Phase	Treatment Period (weeks)	Rater-Based Efficacy Assessments per Week	Baseline Scores (Criteria)	Number of Trial Sites
GDCT0111059*	Agomelatine	Melatonergic/Serotonin antagonist	3	12	1.0	28.2 (≥22)	45
GDCT0197314*	Agomelatine	Melatonergic/Serotonin antagonist	3	12	1.0	28.8 (≥22)	35
GDCT0140557*	Agomelatine	Melatonergic/Serotonin antagonist	2	12		28.6 (≥22)	11
NCT00808249	AZD7325	$GABA_A$ PAM	2	4			52
NCT00807937	AZD7325	$GABA_A$ PAM	2	4			51
NCT00122837*	Duloxetine	SNRI	3	10		27.3	33
NCT00616655	Eszopiclone	Non-benzodiazepine sedative-hypnotic	2	8	1.5	24.2	57
NCT02305797	Lorazepam XR	Benzodiazepine	3	6			44
NCT05407064*	MM120 / DT120	Psychedelic	2	4	3.0	30.3 (≥20)	22
NCT00151450*	Pregabalin	Anticonvulsant	3	8	2.8	26.8 (≥20)	47
NCT00329264*	Quetiapine XR	Atypical antipsychotic	3	8	3.0	(≥20)	63
NCT00329446*	Quetiapine XR	Atypical antipsychotic	3	8	1.6	25.3 (≥20)	64
NCT00322595*	Quetiapine XR	Atypical antipsychotic	3	8	3.5	27.3 (≥20)	112
NCT00595231	Rufinamide	Anticonvulsant	2	8	0.9	25.8	2
NCT03829241	Troriluzole	Glutamate Modulator	3	8	1.6	24.1 (≥18)	53
NCT01766401*	Vilazadone	SSRI	3	8	2.0	24.9 (≥20)	30
NCT01844115*	Vilazadone	SSRI	3	8	2.0	25.0 (≥20)	36
NCT01629966*	Vilazadone	SSRI	3	8	2.0	24.4 (≥20)	37
NCT00744627*	Vortioxetine	Mixed Serotonergic	3	8	1.9	26.8 (≥20)	47
NCT00730691	Vortioxetine	Mixed Serotonergic	3	8	1.9	24.4 (≥20)	72
NCT00734071	Vortioxetine	Mixed Serotonergic	3	8	1.9	24.6 (≥20)	33
NCT00731120	Vortioxetine	Mixed Serotonergic	3	8	1.9	25.2 (≥20)	41
Mean (Standard Deviation)				**8 (2)**	**1.5 (1.0)**	**26.2 (1.8)**	**45 (22)**

[A]Primary active treatment, not include active comparators. [B]In-clinic visits only included if trial protocol available and not including telephone visits. *Positive primary endpoint.

- Placebo response was measured by the placebo group change from baseline in HAM-A total score
- Rater-based efficacy assessments (also known as clinician-administered assessments) included all assessments conducted by clinicians, such as HAM-D, MADRS, HAM-A, CGI-I, and CGI-S
- Self-reported efficacy assessments included all assessments completed by the trial participants themselves, such as PGI-I and SDS

Results

Figure 1. The frequency (number per week) of total efficacy assessments (A) was significantly associated with a greater placebo change driven primarily by frequency of rater-based assessments (B) and not frequency of self-reported assessments (C).

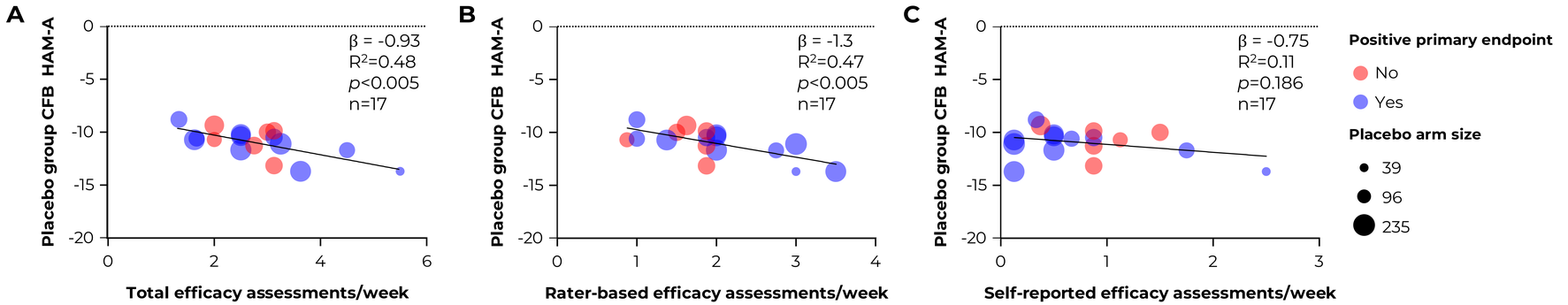
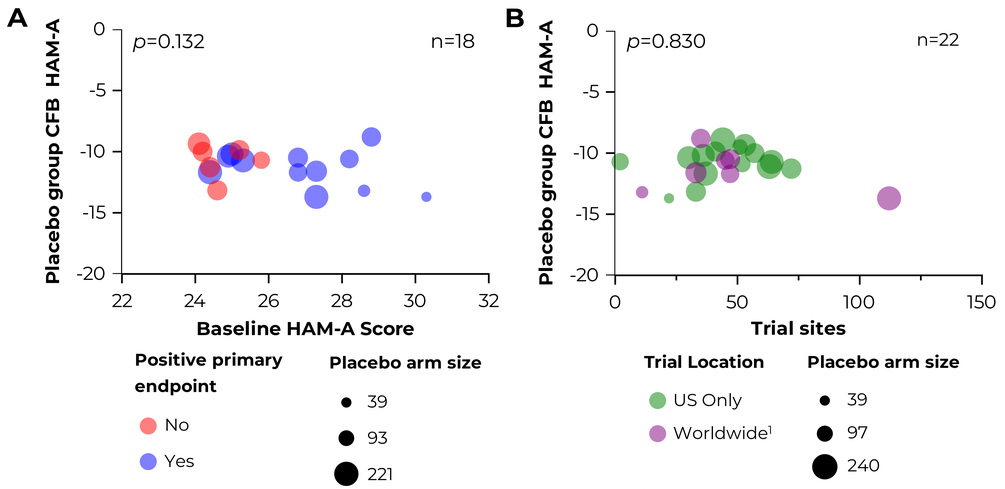
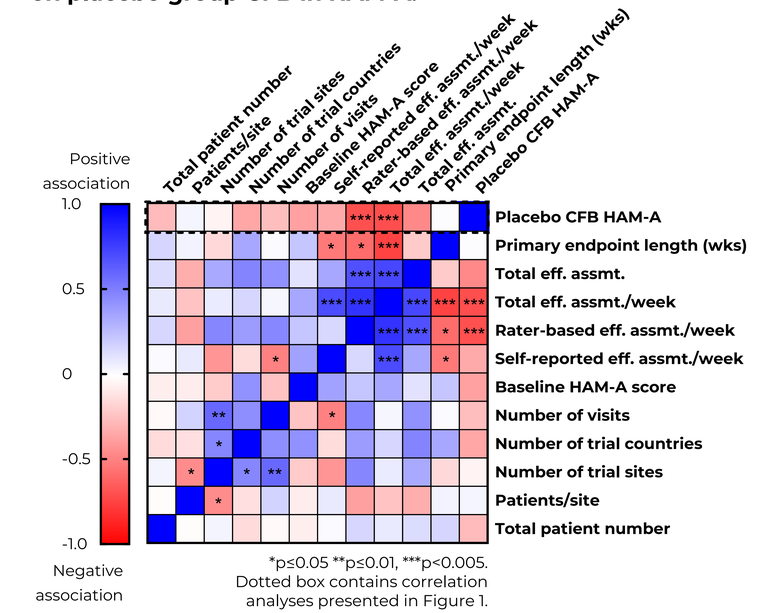


Figure 2. (A) Baseline HAM-A score and (B) number of trial sites were not strongly correlated with placebo response.



[1]Worldwide includes trials conducted ex-US with or without US sites.

Figure 3. Correlation matrix highlighting impact of variables on placebo group CFB in HAM-A.



*p≤0.05 **p≤0.01, ***p<0.005.
Dotted box contains correlation analyses presented in Figure 1.

Abbreviations: CFB: Change from Baseline; CGI-I: Clinical Global Impression - Improvement Rating Scale; CGI-S: Clinical Global Impression - Severity Rating Scale; $GABA_A$ PAM: Gamma-Aminobutyric Acid Type-A Positive Allosteric Modulator; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; NS: non-significant; PGI-I, Patient Global Impression of Improvement; SDS, Sheehan Disability Scale; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; SSRI, Selective-Serotonin Reuptake Inhibitor.

Limitations

- Most analyses had limited number of studies included and limited range for trial factors i.e., study visits, baseline scores etc.
- Of the 22 trials included, 5 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

- Frequency of total efficacy assessments, primarily rater-based assessments (clinician-administered assessments), had a strong positive association with the magnitude of placebo group change while the frequency of self-reported efficacy assessments trended toward an association with greater placebo CFB
- Consistent with previous findings in MDD trials, these data suggests reducing the frequency of efficacy assessments, specifically rater-based assessments, in GAD trials may decrease the placebo response

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References: 1. Khan A et al. Psychol Med. 2005;35(5):743-749. 2. Rutherford BR et al. Depress Anxiety. 2015;32(12):944-957.
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