Characterization of Success Rates and Placebo Response in Clinical Trials of Pharmacotherapies for Generalized Anxiety Disorder

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SUBMISSION DETAILS

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Methodological Issue Being Addressed Concerns about placebo response in psychiatric drug development persist, but have not been recently characterized for generalized anxiety disorder (GAD). What factors contribute to placebo response (PR) and probability of success (PoS) for clinical trials in GAD?

Introduction The most recent Food and Drug Administration (FDA)-approved medicine indicated for GAD was more than 15 years ago, with only 19 industry-sponsored compounds entering Phase 2-3 development since. The purpose of the present analysis was to determine the success rate of GAD trials and to evaluate characteristics contributing to successful studies.

Methods A systematic review identified industry-sponsored Phase 2-3 randomized clinical trials completed between 1999 and 2020. Included studies evaluated efficacy of a pharmacological monotherapy in adults with GAD in a placebo-controlled parallel group study design using the Hamilton Anxiety Scale (HAM-A) as the primary endpoint. Sample sizes varied across analyses based on available data for each trial.

In calculating PoS, a positive result was defined as ≥1 investigational drug study arm meeting the prespecified primary endpoint. Negative results included studies that failed to meet primary endpoint or studies that were terminated for efficacy reasons.

PR was measured by HAM-A change from baseline. Categorical analyses were performed using the lower and upper quartile of the PR distribution.

Results The dataset included 83 clinical trials evaluating 39 unique compounds in 30,185 patients. These studies enrolled a mean of 368.1 ± 194.1 patients across 38.4 ± 20.7 sites, across 3.0 ± 1.0 treatment arms, and with a baseline HAM-A severity of 25.6 ± 1.7. Evaluable studies (N=75) exhibited an overall success rate of 57.3%. The mean PR across trials for which data were available was -9.75 ± 1.70 (38% improvement in HAM-A) (N=63).

Evaluable studies completed before 2007 (N=43) had higher PoS than studies completed in 2007 or later (N=32) (65.1% and 46.9%, respectively). No significant difference was detected between groups in terms of treatment response in active drug arms (p=0.851). Studies completed before 2007 were more likely to be in the lowest quartile of the PR distribution than studies during or after 2007 (OR=4.39, 95% CI=1.15 to 16.73). Studies completed before 2007 enrolled significantly fewer patients (mean 323.8 vs. 427.6, p<0.05) and patients/arm (113.6 vs. 140.9, p<0.05), with nominal

differences observed in number of sites (33.3 vs. 42.5, p=0.085). No significant differences were detected between groups in terms of baseline HAM-A severity (p=0.966).

Comparing studies in the lower versus upper quartile of the PR distribution, studies with low PR (N=17) enrolled fewer patients (298.9 vs. 549.2, p<0.001) from fewer sites (24.5 vs. 51.8, p<0.01) than studies with high PR (N=16). Studies with low PR also included fewer arms (2.7 vs. 3.4, p<0.05) and patients/arm (114.5 vs. 155.6, p<0.05). No significant differences were detected between groups in terms of baseline HAM-A severity (p=0.13).

Conclusion Earlier studies of pharmacological agents for GAD had higher success rates than more recent studies. Significant differences in factors related to study design and conduct were observed between these two groups. Placebo response, but not active-treatment response, was impacted over time. These findings have practical implications in the design of clinical trials and may inform future development programs in GAD.

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Guidelines I have read and understand the Poster Guidelines

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