CHARACTERIZATION OF SUCCESS RATES AND PLACEBO RESPONSE IN CLINICAL TRIALS OF PHARMACOTHERAPIES FOR GENERALIZED ANXIETY DISORDER

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METHODOLOGICAL ISSUE ADDRESSED

Concerns about placebo response in psychiatric drug development persist, but have not been recently characterized for generalized anxiety disorder (GAD).

INTRODUCTION

- In the US, GAD is the **second most common psychiatric disorder** in the primary care setting, with an estimated 1-year prevalence of **20.2 million** among adults 18-65[1].
- 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.
- Previous reviews of GAD clinical trials have analyzed the relative effectiveness of available treatment options in absence of trial design characteristics that contribute to efficacy outcomes[2,3].

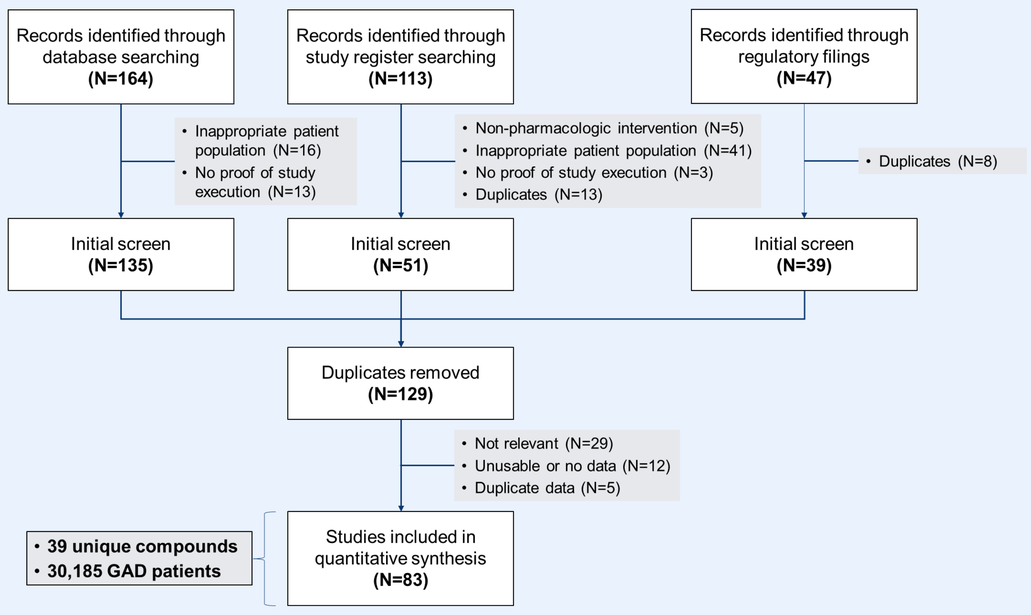
OBJECTIVE

To identify factors related to study design and conduct that contribute to **placebo response** (PR) and **study success rates** in clinical trials of GAD to inform future development programs.

METHODS

- Studies were identified through a clinical research database (Trialtrove™), clinical study registries, and regulatory filings in the United States and Europe.
- In calculating study success rate/probability of success, 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.
  - Studies terminated for reasons other than efficacy (e.g., safety or business) were not included in PoS calculations.
- Treatment response was measured by change from baseline in the Hamilton Anxiety Scale (HAM-A), an accepted regulatory endpoint for pivotal trials of GAD.
  - In studies with multiple treatment arms, the mean response from all arms was calculated.
  - In studies with active comparators, the active control was included as a separate treatment response.
- Categorical analyses of studies completed 1999-2006 vs. 2007-2020 and studies falling in the lower vs. upper quartile of treatment response distribution were conducted for drug and placebo response.
  - Selected cut-off date (i.e., 2007) was based on the year of the most recent FDA approval for GAD (i.e., duloxetine).

1 Flow diagram describing study selection



STUDY ELIGIBILITY CRITERIA

- Phase 2-3 randomized controlled trials sponsored by industry
- Enrolls adults 18-65 years old with a confirmed GAD diagnosis
- Excludes patients with psychiatric comorbidities (Axis-I disorders in DSM-IV)
- Primary endpoint is change from baseline in HAM-A
- Study evaluates a pharmacological monotherapy in a parallel-group study design
- Treatment duration up to 6 months
- Study was completed between 1999 and 2023
- Sponsor-reported study outcomes (e.g., "positive", "negative", or "terminated" result)
- Study report discloses design parameters sufficient to determine eligibility (e.g., arms, treatment duration, study completion date, enrollment requirements)

CONCLUSIONS

- Studies conducted between 1999 and the most recent FDA-approved GAD medicine (2007) had an **18.2% higher success rate** than studies conducted 2007 through 2020. This discrepancy is not associated with a significant difference in mean treatment response to active drug or placebo. However, marked differences are observed between groups in terms of categorical distribution of placebo response.
- Studies with low placebo response generally recruited a **smaller number of patients** from **fewer sites** and included **fewer study arms** than their counterparts.
- These findings may have important implications in the design of future GAD studies in terms of attempting to minimize placebo response by reducing the number of patients, study arms, and sites.

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Disclosures

One or more authors report potential conflicts which are described in the program.

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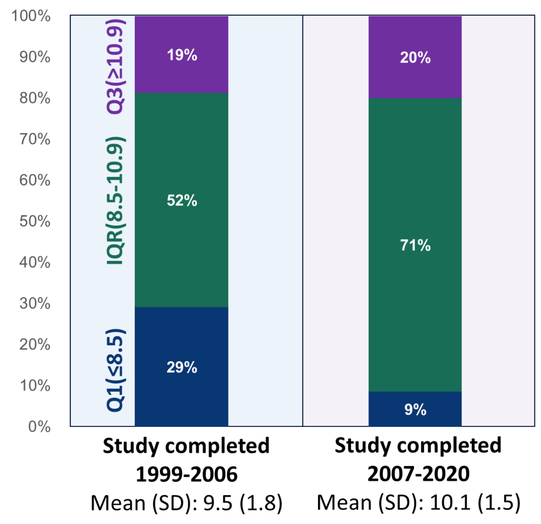
T1 More than half of evaluable studies were successful

Cohort Characteristics	Mean (SD)	N
General		
Sample size	368.1 (194.1)	82
Studies completed 1999-2006 (n, (%))	48 (57.8%)	
Phase 2 (n, (%))	24 (28.9%)	
Phase 3 (n, (%))	59 (71.1%)	
Success rate (%)	*57.3%*	*75*
Study design		
Sample size	368.1 (194.1)	82
Number of arms	3.0 (1.0)	83
Number of patients/arm	125.2 (88.3)	82
Treatment duration (months)	2.1 (2.6)	83
Number of sites	38.4 (23.7)	60
Number of patients/site	12.7 (9.6)	
Number of countries	3.1 (3.7)	65
Baseline demographics		
HAM-A baseline	25.6 (1.9)	58
Primary endpoint (HAM-A change from baseline)		
Investigational drug arm	12.0 (2.6)	63
Placebo arm	9.8 (1.8)	63
Active comparator arm	12.7 (2.4)	21
Drug:placebo difference	2.3 (2.1)	66

T2 Success rate was higher in studies completed before 2007 and when PR was within the lower quartile

Cohort Characteristics	Success rate (%)	N
By year of study completion		
1999-2006	65.1%	43
2007-2020	46.9%	32
By placebo response quartile		
Lower quartile (Q1)	76.5%	17
Interquartile range (IQR)	57.1%	28
Upper quartile (Q3)	56.3%	16

2A Studies completed before 2007 were more likely to have low PR



2B Drug response was not different before versus after 2007

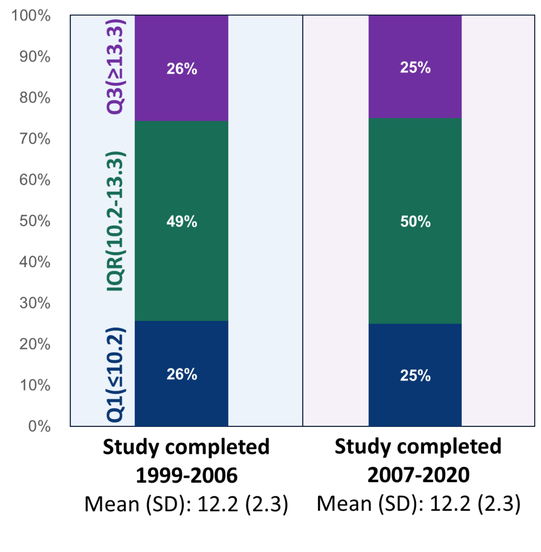


Table (T1): **Full dataset characteristics.** Evaluable studies (N=75) exhibited an overall success rate of **57.3%**. No studies were identified between 2021-2023.

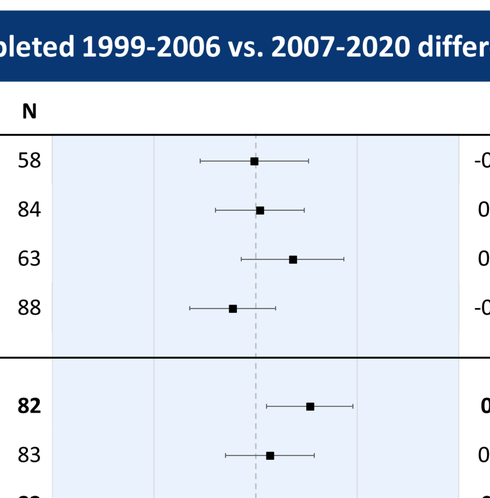
Table (T2): Study success rates by date of study completion. Studies completed 1999-2006 had higher success rates than those completed in 2007-2020 (65.1% vs. 46.9%).

Figure (2A): **Categorical placebo response (PR) by date of study completion.** Studies completed 1999-2006 were **significantly more likely** to be in the lowest quartile of the PR distribution than studies completed 2007-2020 (OR=4.39, 95%CI=1.15 to 16.73, p=0.02).

Figure (2B): **Categorical drug response by date of study completion**. No differences were observed in drug treatment response in studies completed 1999-2007 vs. 2007-2020, measured by quartile distribution and mean differences.

3A Studies completed 1999-2006 vs. 2007-2020 differed in sample size and patients/arm

	Measure	N	SMD [95% CI]	RMD [95% CI]	P-value
HAM-A	Baseline score	58	-0.01 [-0.55, 0.52]	-0.02 [-0.94, 0.90]	0.966
	Drug response⁺	84	0.04 [-0.40, 0.48]	0.09 [-0.89, 1.07]	0.851
	Placebo response⁺	63	0.37 [-0.14, 0.87]	0.62 [-0.24, 1.48]	0.161
	Drug:placebo difference⁺	88	-0.23 [-0.65, 0.20]	-0.44 [-1.26, 0.38]	0.301
Study design	**Sample size**	**82**	**0.53 [0.11, 0.96]**	**103.74 [21.4, 186.1]**	**0.016**
	Number of arms	83	0.14 [-0.30, 0.58]	0.14 [-0.30, 0.58]	0.531
	Patients/arm	**82**	**0.47 [0.05, 0.90]**	**27.31 [2.61, 52.01]**	**0.033**
	Treatment duration (mo)	83	0.14 [-0.29, 0.58]	0.12 [-0.25, 0.49]	0.522
	Number of sites	60	0.45 [-0.05, 0.95]	9.26 [-1.09, 19.61]	0.085
	Number of patients/site	59	-0.23 [-0.75, 0.28]	-2.24 [-7.24, 2.76]	0.385
	Number of countries	65	0.35 [-0.14, 0.83]	1.23 [-0.49, 2.95]	0.167



⁺ Change from baseline at endpoint

SMD Standardized mean difference; whereby $\bar{x}$ = 0 and SMD = *n* S.D. from $\bar{x}$

RMD Raw mean difference

3B Studies with upper quartile placebo response show greater drug response but lower drug:placebo difference, with numerous significant differences in study design and conduct detected

	Measure	N	SMD [95% CI]	RMD [95% CI]	P-value
HAM-A	Baseline score	30	0.55 [0.01, 1.09]	1.14 [-0.31, 2.59]	0.134
	Drug response⁺	**46**	**1.22 [0.85, 1.60]**	**2.94 [1.57, 4.31]**	**<0.00001**
	Drug:placebo difference⁺	**46**	**-0.58 [-0.98, -0.17]**	**-1.27 [-2.40, -0.14]**	**0.033**
Year	Study completion (year)	33	0.35 [-0.23, 0.93]	1.34 [-1.29, 3.97]	0.327
Study design	**Sample size**	**33**	**1.11 [0.57, 1.65]**	**250.25 [121.5, 379.0]**	**<0.001**
	Number of arms	**33**	**0.69 [0.13, 1.25]**	**0.73 [0.04, 1.42]**	**0.045**
	Number of patients/arm	**33**	**0.76 [0.21, 1.30]**	**41.15 [6.27, 76.03]**	**0.028**
	Treatment duration (mo)	33	0.42 [-0.13, 0.97]	0.26 [-0.16, 0.68]	0.233
	Number of sites	**26**	1.16 [**0.55**, 1.76]	**27.23 [12.34, 42.12]**	**0.001**
	Number of patients/site	26	-0.49 [-1.06, 0.07]	-4.59 [-11.65, 2.48]	0.216
	Number of countries	29	0.53 [-0.16, 1.22]	2.1 [-0.72, 4.92]	0.157

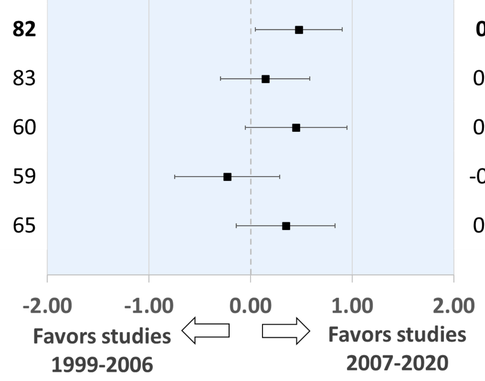


Figure (3A): Mean differences between studies completed 1999-2006 vs. 2007-2020. Studies completed 1999-2006 enrolled **significantly fewer patients** (323.83 vs. 427.57) and **patients per arm** (114.46 vs. 155.61) than studies completed 2007-2020, with nominal differences observed in number of sites (33.3 vs. 42.5).

Figure (3B): **Mean differences between studies with lower and upper quartile placebo response**. Studies with high (Q3) PR had **significantly greater response** to drug treatment (13.79 vs. 10.85) compared to studies with low (Q1) PR. However, studies with low PR showed **significantly greater** drug:placebo **difference** at endpoint (1.82 vs. 3.09). Studies with high PR enrolled **significantly more patients** (549.19 vs. 298.94) from **more sites** (51.77 vs. 24.54) and utilized **more study arms** (3.44 vs. 2.71) with **more patients per arm** (155.61 vs. 114.46).