Influence of covariates on treatment outcome in placebo-controlled trials of benzodiazepines in GAD

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Introduction: Generalized Anxiety Disorder (GAD) is a common psychiatric disorder, and benzodiazepines (BZD) are effective in its short-term management. This analysis studied the influence of a range of variables on response to BZD in placebo controlled studies in GAD.

Methods: We performed a systematic review of placebo-controlled RCTs with BDZs in GAD as described in a Cochrane Protocol (Gale 2012). We extracted the baseline Hamilton Anxiety (HAM-A) score, change in HAM-A score at endpoint, drop-out rate, year of study publication, diagnostic criteria, dose of benzodiazepines (in diazepam equivalents), study size and duration. The influence of individual variables on the primary endpoint (change in HAM-A) was assessed by ANOVA, and covariate relationships were explored using structural equation modeling (Arbuckle, 2012).

Results: We included 56 studies between 1979 and 2009. In 39 (70%) of these studies, commercial sponsorship was indicated: 15 by a company marketing the BZD. BDZ treatment showed consistently greater changes in HAM-A scores than placebo, although these differences decreased in more recent studies (Fig A). Baseline anxiety severity was strongly associated with change in HAM-A scores, but only for BDZ-treated study arms (Fig B). Dose did not influence change in HAM-A change. Dropouts tended to increase in BDZ-treated arms in more recent studies, and decrease in placebo-treated arms. The size of study arms increased in more recent studies (Fig C), presumably to deal with smaller BDZ-placebo differences, and altered dropout rates. ANOVA of individual variables on change in HAM-A identified a number of significant findings (Table D). Structural equation modelling (Fig E) identified a number of direct and indirect influences of variables on change in HAM-A ratings

Conclusions: This analysis confirms the activity of BDZs in GAD. In addition to treatment allocation to BDZs, baseline anxiety severity has a major direct influence on change in HAM-A ratings.

References

Arbuckle, J. L. (2012). Amos (Version 21.0). Chicago: IBM SPSS.

Gale C, Herbison GP, Glue P, Coverdale J, Guaiana G. Benzodiazepines for generalised anxiety disorder (GAD) (Protocol). Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD001846. DOI: 10.1002/14651858.CD001846.pub3.

Fig. A: Change in HAM-A: increasing in PBO and decreasing in BDZ arms over time

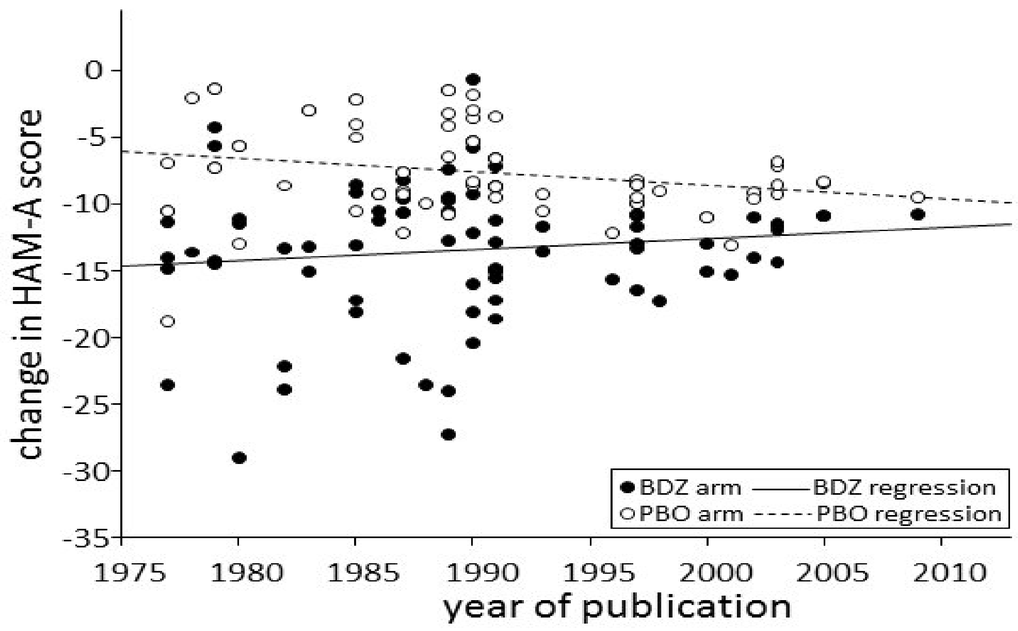

Fig. B: Change in HAM-A by baseline severity

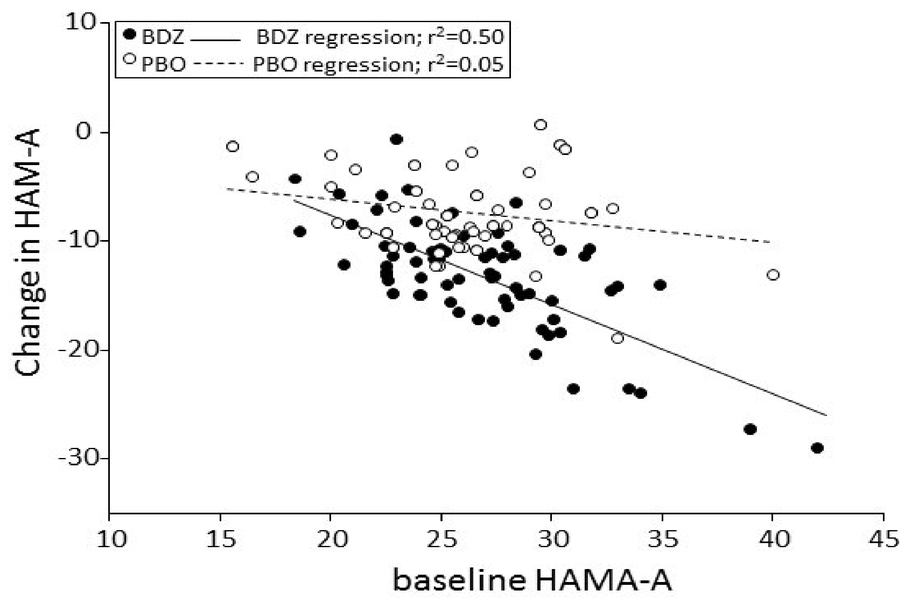

Fig. C: Study arm size by time.

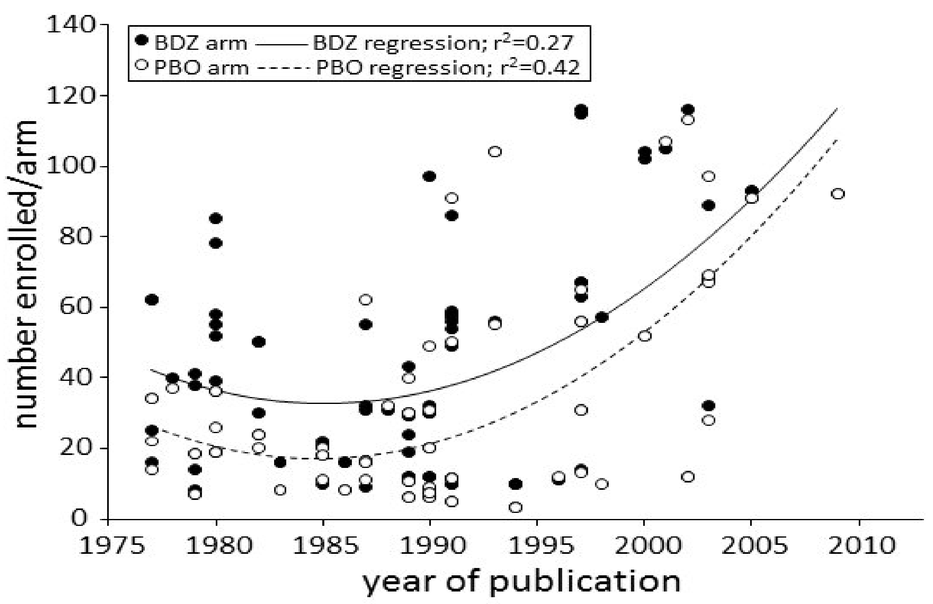

Fig. E: Structural equation modeling

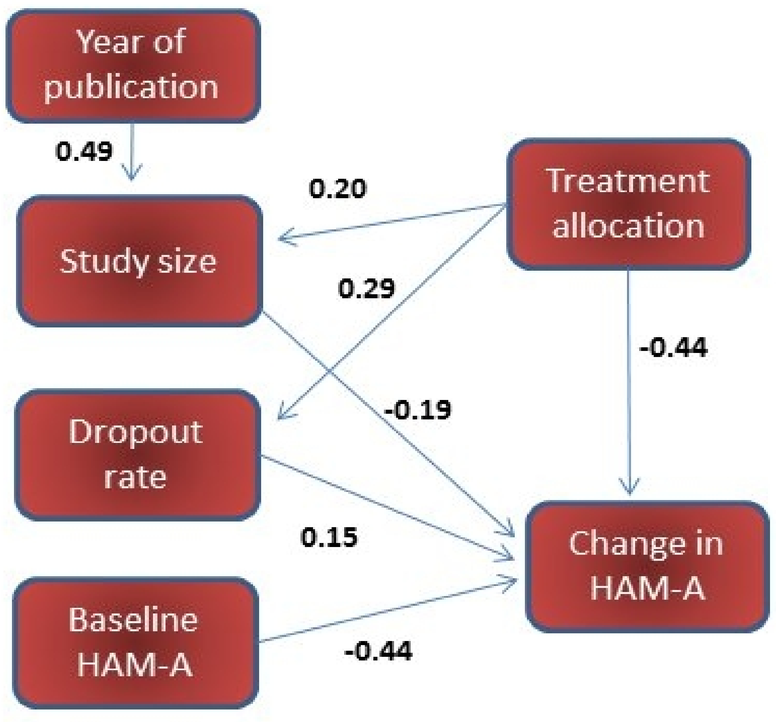

Table D: Significant correlation with baseline, dropout, and year publication

Variable	df	Deviance	p
Diagnostic system	7	171.8	0.10
Mean dose (mg/day)	1	3.5	0.62
Year of publication	1	158.5	**0.0008**
Duration (w)	1	28.3	0.16
Dropouts BDZ	1	212.0	**0.0001**
Dropouts PBO	1	80.2	**0.02**
Baseline HAM-A BDZ	1	290.6	**<0.0001**
Baseline HAM-A PBO	1	182.2	**0.0003**
N enrolled BDZ	1	1.2	0.78
N enrolled PBO	1	0.3	0.89