Development and Evaluation of the Daily Assessment of Symptoms–Anxiety (DAS-A) Scale for Measurement of Onset of Symptom Relief in Patients with GAD

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QUALITATIVE METHODS

Clinician Interviews

During February and March 2003, nine interviews were conducted with clinicians who routinely treat GAD patients. Each clinician interview was conducted according to a structured guide and was designed to identify:

- Signs of onset of symptom relief
- Order, timing, and importance of the symptom improvements
- An appropriate number of questionnaire items
- Potential for questionnaire administration to increase the rate of placebo response

Patient Focus Groups

Three focus groups of recent responders to anti-anxiety medication (within the past 6 weeks) were conducted in March 2003. Nine patients participated in each group, for a total of 27 patients—15 females and 12 males, ranging in age from 19 to 61. Each focus group was conducted according to a structured interview guide. Participants were first asked very general questions about their experiences with GAD. The majority of the discussions focused on:

- Early symptom improvement—changes that tend to occur first and are most important
- The value of a quick-acting anti-anxiety medication
- The feasibility of completing a questionnaire on a daily basis

Cognitive Interviews

- After items were developed to address each construct of interest, the draft questionnaire was subjected to three iterative sets of pretest interviews involving 22 additional GAD patients (17 women and 5 men ranging in age from 21 to 59), to inform item reduction and revision.
- Patients were asked to think out loud while completing the draft questionnaire so that the interviewer could hear how they interpreted and selected a response for each item. The interviewer also asked a series of follow-up questions.

QUALITATIVE RESULTS

Clinician Interviews

- First signs of improvement
  - Reductions in the severity and constancy of anxiety
  - Sleep improvements (but not unanimously thought to improve quickly)
  - Physical symptoms thought to vary greatly by patient
  - Little agreement as to which physical symptoms improve first
- Other findings
  - A new instrument to assess the onset of symptom relief is needed and would have value both in clinical practice and in clinical trials
  - Final questionnaire should contain no more than 10 items
  - Clinicians did not think that completing a brief questionnaire on a daily basis would be burdensome.

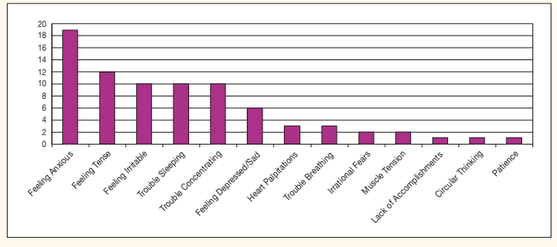
Patient Focus Groups

There was consistency across the focus groups and clinician interviews in the description of symptoms that improve first—the alleviation of anxiety, worries, tension, and irritability, as well as improved sleep and cognitive functioning (e.g., concentration, memory). These same symptoms were also rated by most participants as "very important" and were frequently included among the patients' most bothersome symptoms (Figure 1).

Cognitive Interviews

- The majority of participants felt the 0- to 10-point scale was understandable and allowed sufficient gradation to show early improvement. Most subjects also said the single-item Global Anxiety Visual Analog scale was useful; however, they felt that a multi-item scale would capture more information and be more meaningful.
- Potential problems identified during cognitive testing and addressed in subsequent revisions related to the redundancy of items and constructs of interest, the response scales, and a number of item-specific issues. The questionnaire was well understood and easily completed by interview participants.

Figure 1. Most Bothersome GAD Symptoms as Described by Patients



QUANTITATIVE METHODS

Study Design

A 4-week double-blind, randomized, multicenter, fixed dose, placebo-controlled, parallel group study using oral doses of lorazepam (1.5 mg TID), paroxetine (20 mg QD), and oral placebo in patients with GAD was undertaken to assess the DAS-A.

Three phases:

- 1-week screening phase during which eligibility is determined
- 4-week double-blind treatment phase
- 5-day double-blind treatment phase, during which therapy is down-titrated

The DAS-A was completed during clinic visits and each night during the first week of treatment. Analyses in support of item reduction and subscale development were conducted, as well as exploratory factor analysis and other analyses demonstrating the reliability, validity, and utility of an 8-, 11-, and 15-item DAS-A.

Figure 2. Study Sample

	Placebo (N=57)	Paroxetine (N=55)	Lorazepam (N=55)
Gender			
Male	26 (45.6%)	24 (43.6%)	20 (36.4%)
Female	31 (54.5%)	31 (56.4%)	35 (63.6%)
Race/Ethnicity			
White	42 (73.7%)	40 (72.7%)	40 (72.7%)
Black	3 (5.3%)	3 (5.5%)	3 (5.5%)
Hispanic	9 (15.8%)	6 (10.9%)	8 (14.6%)
Other	3 (5.3%)	6 (10.9%)	4 (7.2%)
Age (mean, SD)	35.0 (10.4)	34.7 (12.6)	38.5 1(2.1)
HAM-A (mean, SD)	24.2 (5.0)	23.4 (3.3)	24.2 (3.5)

QUANTITATIVE RESULTS [1]

Descriptives

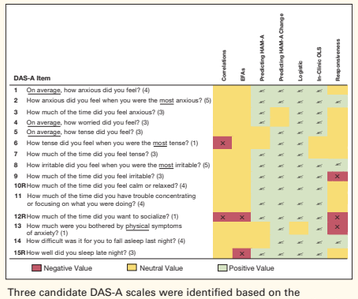
The response frequency distributions and descriptive statistics for all DAS-A items across treatment arms demonstrate well-behaved items and balanced responses across treatments.

Factor Analyses

Various factor analytic results, based on both the item-level data averaged over Day –6 to Day –1 and from patients' initial DAS-A administration, all demonstrated that a one-factor solution is the most satisfactory.

The factor loadings all conform to a measurement model strongly supporting a unidimensional DAS-A and a straightforward additive scoring rule.

Additional Analyses



Three candidate DAS-A scales were identified based on the descriptive statistics, factor analyses, responsiveness, correlational analyses, item-level (OLS and logistic) regression modeling of responder status, and satisfactory coverage of the diagnostic dimensions of GAD.

QUANTITATIVE RESULTS [2]

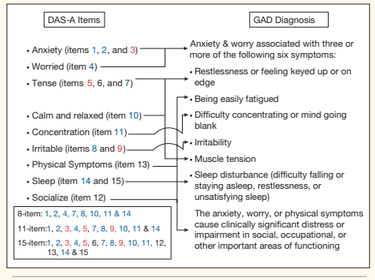


Figure 3. Descriptives

	Mean (SD)	Median	Mean (SD) Parox-etine	Mean (SD) Loraz-epam	Mean (SD) Placebo
Initial Assessment (N=167)					
8-item DAS-A	6.5 (1.3)	6.6	6.5 (1.3)	6.5 (1.2)	6.6 (1.4)
11-item DAS-A	6.4 (1.3)	6.5	6.3 (1.3)	6.4 (1.2)	6.5 (1.4)
15-item DAS-A	6.3 (1.2)	6.5	6.3 (1.2)	6.3 (1.2)	6.4 (1.4)
In-clinic BL (N = 167)					
8-item DAS-A	6.0 (1.7)	6.1	5.9 (1.6)	6.1 (1.5)	5.9 (1.8)
11-item DAS-A	5.9 (1.7)	6.2	5.8 (1.7)	6.1 (1.6)	5.8 (1.8)
15-item DAS-A	5.8 (1.6)	6.0	5.7 (1.6)	6.0 (1.4)	5.8 (1.8)
In-clinic Week 1 (N = 148)					
8-item DAS-A	4.7 (1.9)	4.8	4.9 (1.8)	4.2 (2.1)	5.0 (1.9)
11-item DAS-A	4.6 (2.0)	4.6	4.8 (1.8)	4.1 (2.1)	4.9 (1.9)
15-item DAS-A	4.6 (1.8)	4.7	4.8 (1.7)	4.1 (2.0)	4.9 (1.8)

QUANTITATIVE RESULTS [3]

Reliability Analyses

Cronbach's alpha was calculated for each administration of the scale—daily during the screening week, daily during the first week of treatment, and at each clinic visit (weeks 1, 2, 4, and 5):

- 8-Item DAS-A — 0.77 to 0.91
- 11-Item DAS-A — 0.85 to 0.95
- 15-Item DAS-A — 0.86 to 0.94

Test-retest reliabilities were calculated (using one- and two-way random effects ANOVAs and Pearson correlation coefficients) between each administration of the scale during the screening week:

- 8-Item DAS-A — 0.84 to 0.91
- 11-Item DAS-A — 0.86 to 0.92
- 15-Item DAS-A — 0.86 to 0.92

QUANTITATIVE RESULTS [4]

Correlational Analyses

	Correlations Between the Proposed DAS-A Scales and Other Available Measures											
	8-Item DAS-A Total				11-Item DAS-A Total				15-Item DAS-A Total			
	Initial	In-Clinic BL	In-Clinic Week 1	In-Clinic Week 4	Initial	In-Clinic BL	In-Clinic Week 1	In-Clinic Week 4	Initial	In-Clinic BL	In-Clinic Week 1	In-Clinic Week
GA-VAS	0.67***	**0.81*** **	**0.88*** **	**0.88*** **	0.69***	**0.83*** **	**0.88*** **	**0.89*** **	0.71***	**0.82*** **	**0.87*** **	**0.87*** **
HAM-A	0.35***	0.25*	0.60***	0.67***	0.38***	0.29**	0.60***	0.67***	0.42***	0.29**	0.60***	0.70***
Q-LES-Q		–0.36***	–0.49***	–0.63***		–0.38***	–0.49***	–0.63***		–0.39***	–0.51***	–0.65***
HADS-A	0.49***	0.45***	0.69***	0.72***	0.50***	0.46***	0.69***	0.72***	0.54***	0.49***	0.70***	0.73***
HADS-D	0.36***	0.36***	0.50***	0.67***	0.36***	0.38***	0.50***	0.68***	0.39***	0.40***	0.52***	0.68***
CGIS	0.26**	0.16	0.55***	0.69***	0.28**	0.19	0.53***	0.68***	0.31***	0.20	0.53***	0.70***
CGIC			0.57***	0.68***			0.56***	0.67***			0.56***	0.69***
PGIC			0.55***	0.65***			0.54***	0.64***			0.56***	0.65***
SF-36												
General Health		–0.29**	–0.31**	–0.34**		–0.31***	–0.33***	–0.35***		–0.35***	–0.36***	–0.37***
Physical Function		–0.15	–0.22*	–0.26*		–0.19	–0.25*	–0.26*		–0.21*	–0.26*	–0.26*
Physical Role		–0.16	–0.26*	–0.33**		–0.17	–0.27*	–0.33**		–0.20	–0.28**	–0.35***
Emotional Role		–0.42***	–0.54***	–0.62***		–0.42***	–0.55***	–0.62***		–0.40***	–0.53***	–0.61***
Social Function		–0.18	–0.46***	–0.55***		–0.20*	–0.46***	–0.54***		–0.21*	–0.49***	–0.56***
Mental Health		–0.36***	–0.65***	–0.73***		–0.37***	–0.64***	–0.73***		–0.38***	–0.66***	–0.75***
Bodily Pain		–0.20	–0.28**	–0.26*		–0.22*	–0.30**	–0.27*		–0.27**	–0.33***	–0.28*
Vitality		–0.36***	–0.43***	–0.61***		–0.37***	–0.42***	–0.60***		–0.39***	–0.44***	–0.62***

*p<0.01; ** p<0.001; *** p<0.0001.

Pearson correlations between the candidate DAS-As and other available measures (i.e., GA-VAS, HAM-A, Q-LES-Q, HADS, CGIS, CGIC, PGIC, and SF-36 subscales) were computed at all available time points.

Correlations between the 15-item DAS-A and the other measures were slightly greater, although similar in magnitude and statistical significance, than those for the 11-item DAS-A or 8-item DAS-A; however, the three DAS-As did not differ greatly in terms of the statistical significance of the correlation coefficients.

QUANTITATIVE RESULTS [5]

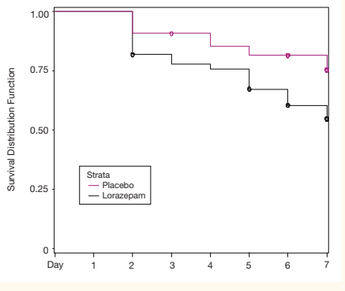
Minimal Clinically Important Difference (MCID) Analyses

Using a variety of anchor-based (clinician and patient global impressions of change) and distribution-based (standard error of measurement, half-SD) methods computed over a number of different time points, the possibility of reporting DAS-A results in terms of MCIDs was explored.

- 8-Item DAS-A — 0.60 to 2.03
- 11-Item DAS-A — 0.47 to 2.09
- 15-Item DAS-A — 0.45 to 2.06

The consensus of several MCID analyses pointed to a workable minimal clinically important improvement of approximately 1.0 DAS-A scale-score unit.

Survival Analyses



Survival Analyses

The difference between the placebo and lorazepam treatment groups was tested for the 8-item, 11-item, and 15-item DAS-As, with time to sustained 30% reduction in DAS-A score (from baseline) as the outcome variable.

Only the 8-item DAS-A curves are significantly different (Wilcoxon $\chi^2 = 4.77$, $p = 0.0289$; log-rank $\chi^2 = 4.93$, $p = 0.0264$), showing statistical separation between placebo and lorazepam treatment groups (i.e., lorazepam patients are improving more quickly than placebo patients, and significantly more quickly).

Furthermore, analyses of covariance demonstrated that the 8-item, 11-item, and 15-item DAS-As showed statistical separation between lorazepam and placebo 24 hours following first dose.

CONCLUSIONS

- The qualitative development of the DAS-A was rigorous and included a series of clinician interviews and patient focus groups. Iterative sets of cognitive interviews were conducted with GAD patients to optimize questionnaire content, item wording, and response scales.
- Item-level quantitative analyses (factor analyses, correlational analyses, responsiveness, and item-level OLS and logistic regression modeling of responder status) identified three candidate DAS-A scales.
- The 8-item, 11-item, and 15-item DAS-A candidate scales exhibited similar psychometric properties. Albeit the shortest scale, the 8-item DAS-A is clinically relevant in that it satisfactorily encompasses the diagnostic dimensions of GAD as expressed in the DSM-IV, results in the least patient burden, and has strong psychometric properties making it the preferred (final) version of the DAS-A for use in future studies.
- The quantitative analyses demonstrate the reliability and validity of the 8-item DAS-A as an instrument capable of assessing a reduction in anxiety symptoms during the first week of treatment.