

APPENDIX 1

THE BEHAVIOURAL ACTIVITY RATING SCALE

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A. INTRODUCTION

In patients with acute agitation and psychosis, the treatment objective is to reduce activity levels and increase degree of calm in patients without causing profound sedation. An extensive review of the literature failed to identify a suitable rating scale of behavioral activity in a clinical trial with psychotic patients demonstrating baseline agitation. Consequently the Behavioural Activity Rating Scale (BARS™) was developed and psychometrically evaluated for this purpose.¹

B. BEHAVIOURAL ACTIVITY RATING SCALE (BARS)

The Behavioural Activity rating Scale (BARS) was designed to measure the degree of agitated behavior, rather than to represent the severity of a specific diagnostic entity such as schizophrenia. The BARS describes seven levels of activity:

- 1 = difficult or unable to rouse
- 2 = asleep but responds normally to verbal or physical contact

- 3 = drowsy, appears sedated
- 4 = quiet and awake (normal level of activity)
- 5 = signs of overt (physical or verbal) activity, calms down with instructions
- 6 = extremely or continuously active, not requiring restraint
- 7 = violent, requires restraint

C. VALIDATION

C.1 Patients and Raters

The primary data source for validation of the BARS was Study 126 which enrolled 79 patients with agitation and psychosis and compared ziprasidone IM 20mg with ziprasidone IM 2mg with respect to reduction of symptoms of acute psychosis and agitation. Data from this study were used to investigate convergent and divergent validity, discriminant validity and responsiveness to treatment differences. In addition, data from Study 121 involving 306 patients with psychotic disorder and relatively modest baseline levels of psychopathology were used to assess discriminant validity, the ability of the BARS to discriminate reliably between two disparate samples.

Data collected from 152 experienced and well-trained raters who viewed videotapes of six clinical vignettes at an investigator's meeting were used to assess inter- and intra-rater reliability.

Consistent with Cohen's criteria,² correlation coefficients of 0 - 0.29 between the BARS and pre-specified efficacy variables were defined as low, 0.3 - 0.5 were defined as moderate, and >0.5 were defined as large (regardless of whether the coefficient estimates were significantly different from zero). Both Pearson's and Spearman's correlation coefficients were calculated.

C.2 Convergent and Divergent Validity

For convergent validity, BARS scores at baseline were expected to show a moderate and significant ($p < 0.05$) correlation with baseline CGI-S and PANSS agitation items (sum of hostility, excitement, anxiety and tension) scores. In contrast, for divergent validity, BARS scores at baseline were expected to show a low correlation with baseline PANSS negative component scores (sum of emotional withdrawal, social withdrawal, blunted affect, poor rapport, poor attention, acute social avoidance, lack of spontaneity and flow of conversation, motor retardation, mannerisms and posturing and disturbance of volition).³

Pearson and Spearman correlations between baseline scores for BARS, PANSS agitation items, CGI-S, and PANSS negative component are shown in Table 1.

Baseline BARS scores were found to have a statistically significant correlation of moderate magnitude with baseline PANSS agitation items ($p = 0.003$) and baseline CGI-S scores ($p = 0.0003$), indicating convergent validity.

Divergent validity was exhibited by a low correlation, which also happened to be not statistically significant from zero, between baseline scores for BARS and PANSS negative component.

Table 1. Pearson's (Below the Diagonal) and Spearman's (Above the Diagonal) Correlation Coefficients for Baseline Assessments

	BARS™	PANSS Agitation items	CGI-S	PANSS Negative component
BARS™	-	0.33** (n=77)	0.40*** (n=78)	0.16 (n=78)
PANSS Agitation items	0.33** (n=77)	-	0.67*** (n=77)	0.40*** (n=77)
CGI-S	0.40*** (n=78)	0.66*** (n=77)	-	0.43*** (n=78)
PANSS Negative Component	0.16 (n=78)	0.35** (n=77)	0.36** (n=78)	-

p<0.01; *p<0.001

C.3 Discriminant Validity

It was hypothesized *a priori* that the mean Baseline BARS scores from patients with psychosis and acute agitation would be significantly greater than those from patients with psychotic disorder and relatively modest baseline levels of psychopathology.

The Wilcoxon rank-sum test and the two-sample t-test were used to compare Baseline values from two studies: Study 126 which enrolled patients with acute agitation and Study 121 which enrolled stable patients with more modest psychopathology. The same analysis was undertaken for Baseline PANSS agitation items and CGI-S scores to further elucidate the relative discriminant validity of the BARS.

These results are presented in Figure 1. Patients with acute agitation had a significantly higher mean Baseline BARS score than patients with modest psychopathology. The same was observed for PANSS agitation items and CGI-S scores.

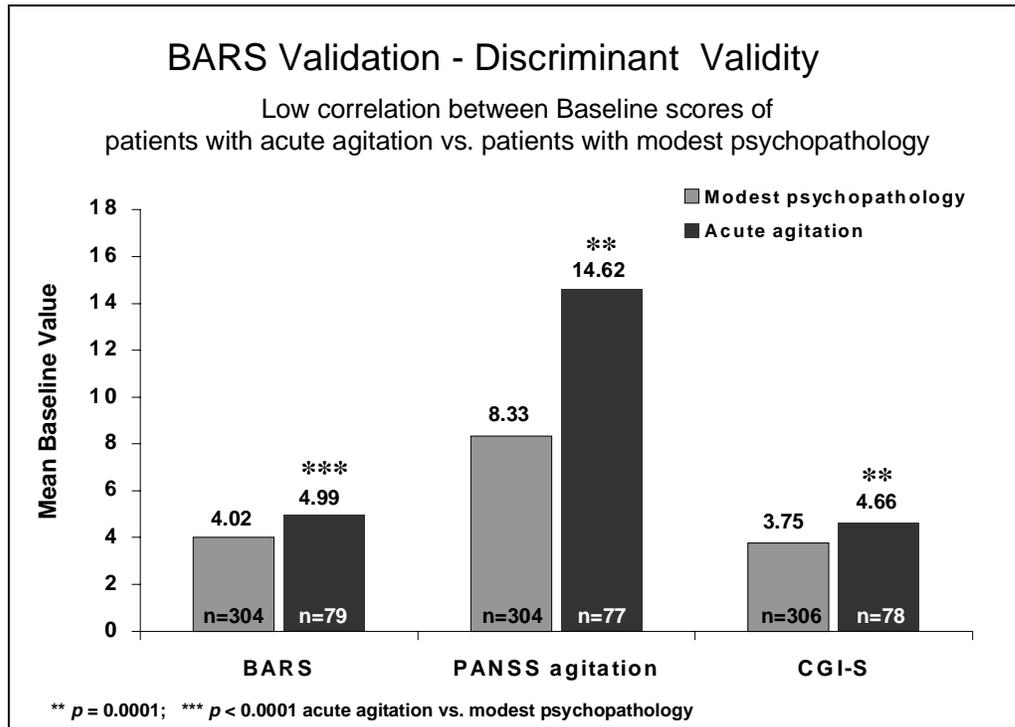


Figure 1. Baseline Scores of Patients with Acute Agitation (Study 126) and Patients with Modest Psychopathology (Study 121)

C.4 Responsiveness to Treatment Differences

The responsiveness or sensitivity of the BARS scale for measuring treatment effects was assessed using data from Study 126. For reference the PANSS agitation items and CGI-S scores were also evaluated. To ensure standardization and allow comparisons between BARS, PANSS agitation items and CGI-S, the treatment effect size was calculated by dividing the difference in means at 4 Hours between the two treatment groups (2 mg and 20 mg) by the pooled standard deviation.

The results are shown in Figure 2. The effect size for the BARS was larger than for the PANSS agitation items and CGI-S, indicating that the BARS was the most responsive measure of intramuscular ziprasidone treatment effects.

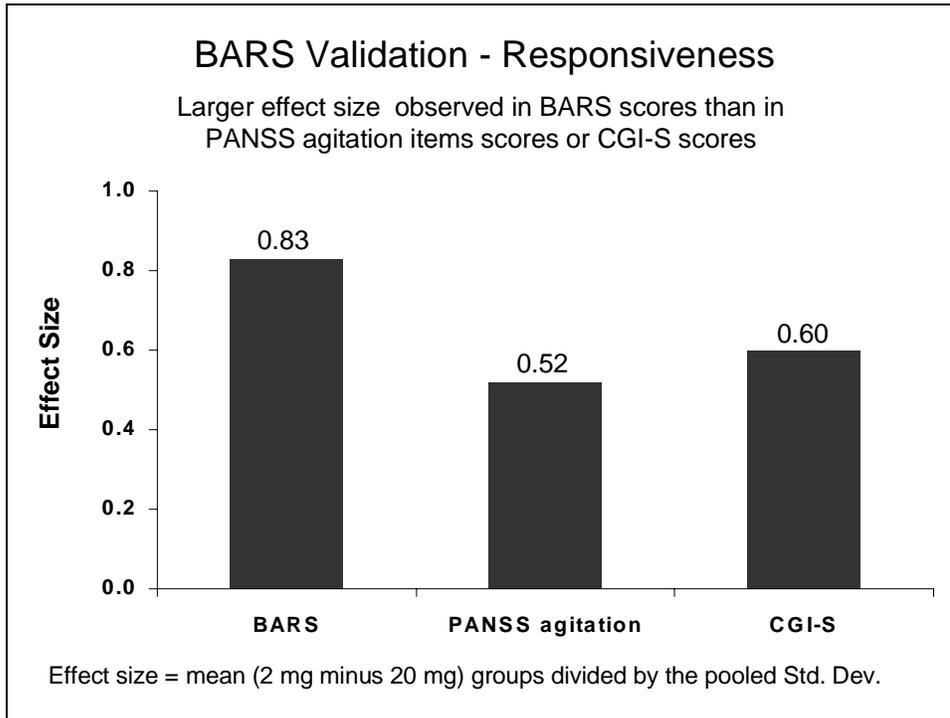


Figure 2. Treatment Effect Size as Measured by BARS, PANSS Agitation Items, and CGI-S 4 Hours after the First Dose of Ziprasidone IM (Study 126)

C.5 Inter-and Intra-rater reliability

Inter-rater reliability was ascertained by determining agreement among raters' BARS assessments of six clinical vignettes, with BARS scores of 3, 7, 1, 4, 5 and 6 respectively, presented on a videotape to 152 raters at the same time.

Intra-rater reliability was examined by determining how well 54 raters agreed with their own BARS assessments on the same six clinical vignettes rated at two different times (within a 12 month period).

Two-way analysis of variance models were used for both inter- and intra- rater reliability.

Inter- and intra-rater reliability were observed (Table 2). Nearly perfect (0.999) inter-rater reliability was observed for the first assessment and perfect (1.0) inter-rater reliability was achieved for the second assessment. Perfect (1.0) intra-rater reliability was observed.

Table 2. BARS™ Assessments of Clinical Vignettes by Raters

Clinical vignette no.	Number (%) of Raters giving correct BARS™ assessment		Number (%) of raters giving the same BARS™ scores at both the first and the second rating
	First rating (Month 0)	Second rating (~ Month 8)	
1	150 (98.7)	54 (100)	54 (100)
3	151 (99.3)	54 (100)	54 (100)
4	152 (100)	54 (100)	54 (100)
5	152 (100)	54 (100)	54 (100)
6	152 (100)	54 (100)	54 (100)
7	152 (100)	54 (100)	54 (100)

D. CONCLUSION

These data suggest that the seven-point BARS is a reliable and valid measure of activity levels for the type of patients with acute agitation enrolled in the IM ziprasidone trials and that it provides clinically meaningful information. The larger treatment effect size using the BARS, compared with the PANSS agitation items and the CGI-S, suggests that the BARS may be a more responsive (sensitive) measure of activity in these agitated patients. Excellent inter- and intra- rater reliability indicate that the BARS can be administered reliably by trained investigators.

E. REFERENCES

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