# Borderline across Borderlines: Regional Variations in Who Enters Clinical Trials

**Micaletto, M[2], Brown, J[1], Machizawa, S[1], Chen-Tackett, Z[3], Berman, R[1], Sachs, G[1]**

(1) Signant Health, Blue Bell, PA, USA; (2) Signant Health, London, UK; . (3) Signant Health, Arlington, VA, USA

## METHODOLOGICAL QUESTION

The impact of regional and cultural factors entering trials for Borderline Personality Disorder (BPD) are unknown as they relate to the variability of symptom presentation and diagnosis in clinical trials. We explore potential metrics to examine regional differences in variability of BPD pathology and symptom severity based on data from global, placebo-controlled trials of BPD.

## INTRODUCTION

BPD is marked by distorted perception of reality, emotional instability, impaired social relationships, and impulsivity. Prior academic reports indicate BPD is not culture-bound and can be reliability diagnosed globally using the DSM-5 criteria.1,2,3 Ideally, subjects entering RCTs are representative of treatment seeking patients, but we are unaware of any data comparing subjects from different geographical regions entering clinical trials for BPD. Since cultural factors and health care systems vary widely and influence the representativeness of trial subjects, it may be informative to compare the overall and symptom domain severity associated with BPD across regional sub-groups of trial subjects.

## METHODS

For this analysis, a blinded dataaset was drawn from Baseline ZAN-BPD assessments conducted by trained raters in two ongoing global placebo-controlled clinical trials. Subjects were included in the analysis if data were available for post-baseline visits, indicating that DSM-5 BPD criteria were met at screening based on diagnostic assessment and the Zanarini Rater Scale for Borderline Personality Disorder (ZAN-BPD) total score.

The ZAN-BPD is a clinician-administered scale for the assessment of DSM-5 defined borderline psychopathology and is widely considered the gold standard for evaluation of BPD severity. Scale questions reflect a 1-week retrospective period. Each of the nine DSM criteria for BPD is rated on a five-point anchored Likert rating scale ranging from 0 to 4, yielding a total score of 0 to 36. In addition sub-scale scores are also derived for the domains considered core features of the BPD construct: Affective Disturbance (score range = 0-12), Cognitive Disturbance (score range = 0-8), Impulsivity (score range = 0-8), and Disturbed Relationships (score range = 0-8).1

To explore potential regional differences we compared ZAN-BPD total scores, scores for the four sub-scale domains and the frequency of each ZAN-BPD item being scored zero (absent ) across regions.

Since only subjects with BPD severity scores above the required threshold for trial eligibility were included, the data was not normally distributed and were analyzed using Kruskal-Wallis ANOVA test. Subsequent Dunn tests were then employed for post-hoc analyses.

## RESULTS

Data from 119 participants entering 2 trial from six geographical regions met criteria for this analysis. ZAN-BPD mean total scores ranged from 13.23 to 18.10. A statistically significant mean total score difference was found between the United States and Western Europe (Dunn's test following Kruskal-Wallis test P-adjusted 0.004). U.S. subjects had higher severity as compared to Western European subjects. Total score was nominally significantly different between Eastern and Western Europe, but the difference became non-significant correction for normality of data (Dunn's test following Kruskal-Wallis test P-unadjusted 0.011, P-adjusted 0.168). Other cross-region total score comparisons were non-significant.

Table 1 shows descriptive statistics for ZAN-BPD total scores and domain sub-scale scores for the six regions groups.

Table 2 shows the distribution of ZAN-BPD item scored 0 (no pathology) by region. Japan had smallest sample, the lowest proportion of item scores of 0 in general, but the highest proportion of scores of 0 for the item representing impulsivity. In contrast, Western Europe had the highest proportion of scores of 0, with one or more scores of 0 for 8 out of 9 scale items.

Figure 1 shows the frequency each ZAN-BPD item was rated absent in regions with more than 3 subjects.

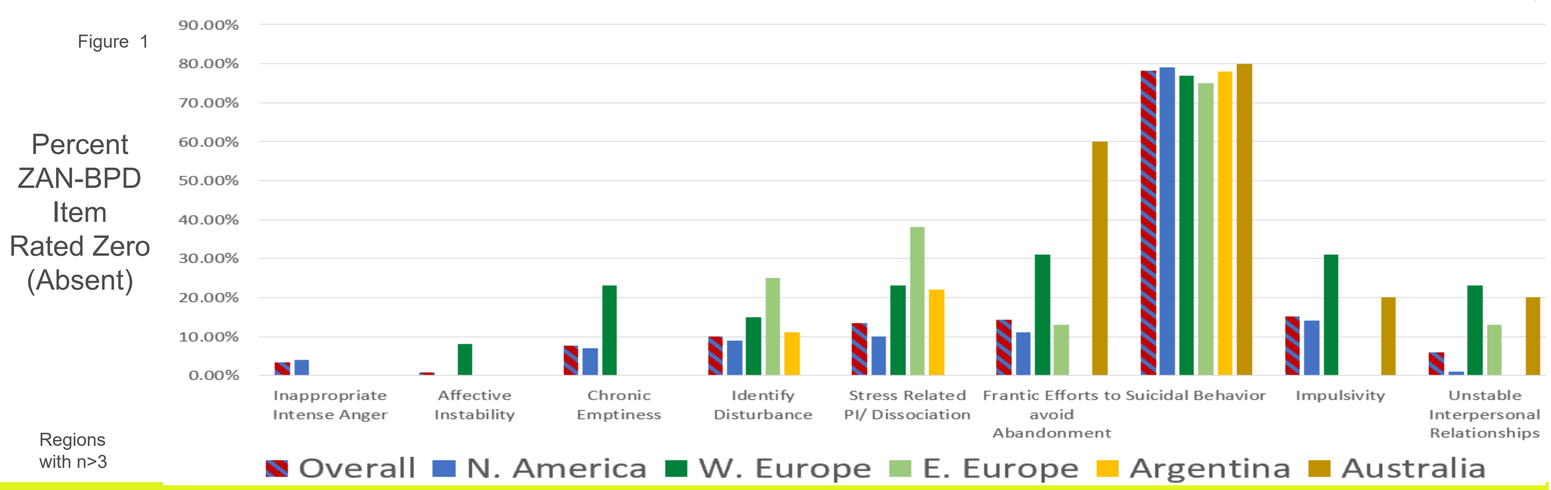
Table 1. ZAN-BPD Mean Scores for Total and Domains

| Region (n) | Mean (SD) Domain score as % of total | | | | |
|---|---|---|---|---|---|
| | ZAN-BPD total | Affective Disturbance | Cognitive Disturbance | Impulsivity | Disturbed Relationships |
| Eastern Europe (8) | 18.1 (4.73) | 8.12 (1.73) **44.9%** | 3.5 (2.83) 19.3% | 2.75 (1.49) 15.2% | 3.75 (1.75) 20.7% |
| Japan (3) | 13.33 (3.79) | 6.33 (1.15) **47.5%** | 3.67 (0.58) 27.5% | 0.67 (0.58) 5.0% | 2.67 (1.53) 20.0% |
| Argentina (9) | 15.2 (3.87) | 6.33 (1.41) **41.6%** | 2.67 (1.41) 17.6% | 1.89 (1.05) 12.4% | 4.33 (1.5) 28.5% |
| United States (81) | 17.7 (4.23) | 7.2 (1.76) 40.6% | 4.23 (1.76) 23.9% | 2.22 (1.3) 12.6% | 4.06 (1.44) 22.9% |
| Australia (5) | 14.80 (4.97) | 6.60 (1.95) **44.6%** | 4.40 (1.14) 29.7% | 1.20 (0.84) 8.1% | 2.60 (2.19) 17.6% |
| Western Europe (13) | 13.23 (3.11) | 6.08 (1.38) **46.0%** | 3.15 (1.63) 23.8% | 1.54 (1.13) 11.6% | 2.46 (1.45) 18.6% |
| All regions (119) | 16.8 (4.4) | 7.03 (1.74) **41.8%** | 3.94 (1.82) 23.5% | 2.08 (1.3) 12.4% | 3.79 (1.59) 22.6% |

Table 2. ZAN-BPD items Scored Zero

| Item | **Overall N=119** | Eastern Europe (n=8) | Japan (n=3) | Argentina (n=9) | North America (n=81) | Australia (n=5) | Western Europe (n=13) |
|---|---|---|---|---|---|---|---|
| 1: Inappropriate Intense Anger | **3.4%** | 0% | 33% | 0% | 4% | 0% | 0% |
| 2: Affective Instability | **0.8%** | 0% | 0% | 0% | 0% | 0% | 8% |
| 3: Chronic Emptiness | **7.6%** | 0% | 0% | 0% | 7% | 0% | 23% |
| 4: Identity Disturbance | **10.1%** | 25% | 0% | 11% | 9% | 0% | 15% |
| 5: Stress-Related Paranoia or Dissociation | **13.4%** | 38% | 0% | 22% | 10% | 0% | 23% |
| 6: Frantic Efforts to Avoid Abandonment | **14.3%** | 13% | 0% | 0% | 11% | 60% | 31% |
| 7: Suicidal Behavior | **78.2%** | 75% | 67% | 78% | 79% | 80% | 77% |
| 8: Impulsivity | **15.1%** | 0% | 67% | 0% | 14% | 20% | 31% |
| 9: Unstable Interpersonal Relationships | **5.9%** | 13% | 33% | 0% | 1% | 20% | 23% |

Figure 1




## DISCUSSION

We used three metrics to explore regional differences. Overall symptom severity for subjects entering BPD clinical trials varies significantly between U.S. and Western Europe, but the proportion of the total score attributable to each subscale is similar across the groups. We hypothesize differences in health care systems may lead to the recruitment of more severe subjects in the U.S. Our data showing the percentage of ZAN-BPD total attributable to each subscale is consistent across regions with at least 5 subjects suggests that the presentation of BPD is comparable across different regions.

Small sample size may, however, have precluded our finding potentially important statistical differences. For instance, the low proportion of the ZAN-BPD total attributable to Impulsivity was an outlier for Japan only. Japan also had the highest proportion of Zero ratings on three items. Similarly, Western Europe also had a relatively small sample, but had the highest proportion of subjects rated Zero on four items. These patterns warrant further exploration.

Suicidal Behavior was rated absent in a high proportion of subjects across all regions, This may reflect the reluctance of subjects and their care providers to enter studies during times when suicidal behaviors are present. Exploration of these issues requires larger sample sizes and better assessment of factors such as cultural norms and recruitment sources that might influence findings.

Our findings hold reassuring implications for researchers due to the comparability of BPD trial subject phenomenology across geographical regions, and support use of these and similar metrics to examine regional differences.

## REFERENCES

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## DISCLOSURE

The authors are full time employees of Signant Health and report no conflicts of interest for this work.