Relationships Between Akathisia and Psychotic Agitation as Evaluated by Consistency Checks for the Barnes Akathisia Rating Scale in a Large Clinical Trials Dataset

Tatsumi, K[1]., Negash, S[1]., Cong, L[1]., Poppe, C[1]., and Opler, M[1]

[1]WCG Clinical Endpoint Solutions

Methodological Question

How well do BARS raters understand and apply scoring rules to differentiate akathisia from agitation/excitement due to psychosis?

Background

Akathisia is one of the most debilitating side effects related to antipsychotic drug use. It is characterized by subjective feelings of inner restlessness and mental distress, as well as objective motor restlessness caused by an urge for continuous movement.

Although second-generation antipsychotics are less likely to cause akathisia, the propensity of individual atypical agents to cause akathisia varies. Accurate information on the side effect burden of commercially available drugs is important to guide treatment selection and clinical management. Consequently, accurate assessment of akathisia is critically important in clinical trials to ascertain the safety profile of investigational products.

The Barnes Akathisia Rating Scale (BARS) has been commonly used in clinical trials and also in clinical practice. It consists of four items designed to systematically assess both subjective and objective aspects of akathisia. Failure to understand scoring rules and item anchor descriptions may result in misclassification of symptoms. One potential scoring error might be that of pseudoakathisia (presence of characteristic movements of akathisia in the absence of a reported sense of inner restlessness) being misclassified and positively rated on the global item.

Side effects associated with the atypical antipsychotics often overlap with signs and symptoms of psychiatric illness. In particular, psychosis related psychomotor agitation may resemble the symptoms of akathisia. While consistency checks to improve precision of measurement have recently been developed for psychiatric rating scales (e.g., PANSS, HAM-A/D, and MADRS), their importance and utility in adverse effect measures have not been explored. In this analysis, we propose consistency checks for the BARS based on the scoring rules, theoretical, and clinical frameworks. The objective of the current study is to investigate how accurately BARS raters assess akathisia by examining the frequency of flags and to evaluate the correlations between the PANSS Marder hostility/excitement factor score and the BARS global total score in a large dataset derived from multiple schizophrenia trials.

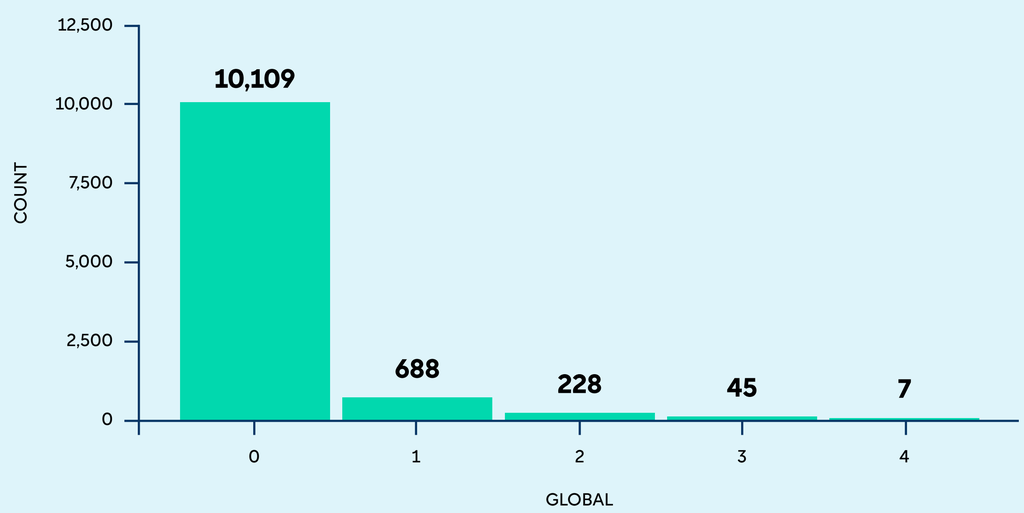
Methods

A total of 11,077 BARS assessments were derived from five large multicenter schizophrenia clinical trials investigating the efficacy and safety of atypical antipsychotics. A set of consistency checks developed to monitor data quality for the BARS and PANSS were applied to the data, and flag rates were calculated. The data were stratified into two groups based on the design of study (open-label vs double blind) to see if blinding plays a role in the evaluation of the side effect. To examine how well raters are differentiating psychomotor agitation from akathisia, a 2x2 table is presented to demonstrate unlikely rating patterns between the scales, and the Kendall's rank correlation coefficient was calculated to measure the correlations between the PANSS Marder factor scores and the BARS global score.

Results

Concordant with the concept that akathisia occurs less frequently in atypical antipsychotic treatment, a substantial number (>91%) of BARS global score in studies of atypical drugs and novel agents are rated=0 (Figure 1). To address the uneven distribution of scores, assessments in which BARS global score=0 were excluded from the analysis

Figure 1: Frequency Distribution of the BARS Global Score



of flag rate. A total of 968 assessments were rated with a global score greater than or equal to 1. In comparing the groups, the open-label group showed a significantly higher overall flag rate (33.7%) compared to the double-blind group (26.7%); t = -2.06, df = 10031, p < 0.05 (Table 1). The percentage of assessments with at least one flag was also significantly higher for the open-label group (31% vs 19%, t = -3.87, df = 7750, p < 0.0001), while assessments with two or more flags did not differ between the two groups (3% vs 5%; t = 1.69, df = 11209, p = 0.092). The flag designed to identify incorrect use of scoring conventions was the most frequently flagged error for both studies. When both the BARS and PANSS were administered together at the same visit, approximately 2.3 – 2.5% of time both akathisia and agitation defined as PANSS-EC >14 and PANSS-AF >17 were present (Table 2). The correlation between the PANSS Marder hostility/excitement factor and the BARS global total score was low (r=0.06, p < 0.01), and it was almost identical (r=0.07, p <0.01) when BARS=0 was excluded from the correlational analysis (Table 3).

Table 1: Frequency of Occurrence of Flags

Flag #		Double-Blind (n=562)	Open-Label (n=406)
1	Both BARS subjective item scroes = 0 (awareness = 0 and distress = 0) and BARS global akathisia item score > 0	12.1%	27.3%
2	Both BARS subjective item scores = 0 (awareness = 0 and distress = 0) and BARS objective item score > 1	2.1%	1.5%
3	Awareness = 0 and Distress > 0	1.1%	0.5%
4	Objective > 0 and Awareness > 1 and global score < 2	0.5%	0.2%
5	Difference of > 1 between awareness and objective score	1.6%	1.5%
6	Change in global score > 2 across two consecutive visits	1.4%	1.4%
7	PANSS-AF > 17 and BARS subjective score* > 3	2.0%	0.2%
8	PANSS-AF > 17 and BARS global akathisia item score > 3	0.7%	0.0%
9	PANSS-EC > 14 and BARS subjective score* > 3	1.6%	0.2%
10	PANSS-EC > 14 and BARS global akathisia item score > 3	0.7%	0.0%
11	G4 > 3 and BARS global score > 2	3.2%	1.2%
12	Mean PANSS-EC > 3.5 AND PANSS-EC Total Score > 14 AND BARS Subjective and Global Item scores > 3	0.2%	0.0%
	1+ FlagRate	19.0%	31.0%*
	2+ FlagRate	5.0%	2.8%
	Overall FlagRate	26.7%	33.7%*

Table 2: Unlikely Rating Patterns Between the BARS and PANSS

Agitation \ Akathisia	Presence (BARS global >0)	Abscence (BARS global = 0)
Presence (PANSS0EC > 14)	254	1,517
Absence (PANSS-EC < 15)	621	7,767
Presence (PANSS-AF > 17)	235	1,485
Absence (PANSS-AF > 18)	695	8,247

Table 3: Kendall's Rank Correlation Between the BARS

	BAR Global	BARS Global (non-zero)
	r	r
Negative Symptoms	0.05	0.13
Positive Symptoms	0.07	0.12
Disorganized Thought	0.07	0.15
Hostility/Excitement	0.06	0.07
Anxiety/Depression	0.11	0.10
Note: all p > 0.01		

Discussion

The results suggest that the most common error among BARS raters participating in schizophrenia clinical trials of new generation of antipsychotics is incorrect classification of pseudoakathisia. According to the author of the BARS, a rating of 0 is given for the global item if there is a positive score on objective akathisia but a 0 rating on subjective items. The reason for the rating error may not only stem from the lack of awareness of the scoring rule, but also that raters may be misclassifying psychomotor agitation with akathisia as well. A similar rating error seems to be manifested when examining the relationship between two measures (i.e., agitation and akathisia both are present on the PANSS and BARS, respectively). The correlation between the BARS global score and the PANSS Marder hostility/excitement score was very low. This, in turn, suggests that unexpectedly strong correlations between the two measures could be indicative of imprecise measurement. Lastly, the open-label study design seems to be more prone to rating errors. While both syndromes theoretically can occur at the same time, application of flags and monitoring of higher correlations of the BARS global score and PANSS factor score may help identify rating errors and misclassification of symptoms.