Relating Spontaneously Reported Extrapyramidal Adverse Events to Movement Disorder Rating Scales

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Abstract

Background: While antipsychotic-induced extrapyramidal symptoms (EPS) and akathisia remain important concerns in the treatment of patients with schizophrenia, the relationship between movement disorder rating scales and spontaneously reported EPS-related adverse events (EPS-AEs) remains unexplored.

Methods: Data from four randomized, placebo- and haloperidol-controlled ziprasidone trials were analyzed to examine the relationship between spontaneously reported EPS-AEs with the Simpson Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS). Categorical summaries were created for each treatment group to show the frequencies of subjects with EPS-AEs in each of the SAS and BARS categories at weeks 1, 3, and 6, and agreement between ratings was quantified by means of weighted kappa ($\kappa$).

Results: In general, we found greater frequencies of EPS-AEs with increasing severity of the SAS and BARS scores. The EPS-AEs reported with a “none” SAS score ranged from 0 to 22.2%, with a “mild” SAS score from 3.3 to 29.0%, and with a “moderate” SAS score from 0 to 100%. No subjects in any treatment group reported “severe” SAS scores or corresponding EPS-AEs. Agreement between SAS scores and EPS-AEs was poor for ziprasidone and placebo ($\kappa < 0.2$) and only slightly better for haloperidol. The EPS-AEs reported with “non questionable” BARS scores ranged from 1.9 to 9.8%, with “mild moderate” BARS scores from 12.8 to 54.6%, and with “marked severe” scores from 0 to 100%. Agreement was modest for ziprasidone and placebo ($\kappa < 0.4$) and moderate for haloperidol ($\kappa < 0.6$).

Conclusions: These findings may reflect either underreporting of AEs by investigators and subjects or erroneous rating scale evaluations.

Keywords: Barnes Akathisia Rating Scale, extrapyramidal adverse events, movement disorder rating scales, schizophrenia, Simpson Angus Scale

Introduction

Extrapyramidal symptoms (EPS) encompassing acute dystonia or dyskinesia, Parkinsonism, tardive dyskinesia, and akathisia are common adverse events of treatment with antipsychotic agents. Available treatment options are sometimes disappointing, especially for tardive syndromes. EPS have an impact on adherence with treatment, and therefore on the outcome of the disease. Accordingly, schizophrenia patients experiencing EPS have a worse prognosis and an increased risk of...
relapse leading to more frequent hospital admissions and pro-
longed hospitalization (Buchanan et al., 1992; Tandon, 2011). EPS
are associated with a substantial reduction of quality of life,
contribute to stigma, and can limit reintegration into society or
the workforce. Additionally, they can have a negative impact on
physical health, in the worst case resulting in life-threatening
conditions such as acute laryngeal or pharyngeal dystonia (Koek
and Pi, 1989; Christodoulou and Kalaitzi, 2005).

EPS can usually be managed by antipsychotic dosage reduc-
tion and/or the use of adjunctive therapies such as anticholin-
ergic agents, beta-blockers, and benzodiazepines. However, in
some patients dose reduction carries the risk of symptom re-
emergence, while the commonly used adjunctive medications
are associated with adverse effects of their own. With the intro-
duction of new-generation antipsychotics (NGAs), the focus on
EPS became less prominent. Numerous studies examining side-
effect rates of NGAs indicate prevalence rates of EPS similarly to
those of placebos (Carlson et al., 2003; Marder et al., 2003; Leucht
et al., 2009). Consequently, the clinical focus switched to other
adverse effects such as endocrinological, metabolic, or cardio-
vascular side effects.

Specifically, the incidence rate of akathisia, which can
develop within a few minutes to hours after intake of an antip-
sychotic, ranges from 25 to 75% for first generation antipsy-
chotics (FGA) and from 5 to 25% for NGAs (Casey, 2004; Kane et al.,
2009).

Acute dystonia (and dyskinesia), on the other hand, have
been reported in up to 40% of FGA and in less than 5% of
N G A treatments (Casey, 2004). Parkinsonism develops in 30 to
60% of patients on FGAs and in 5 to 20% with new-generation
compounds (Haddad et al., 2012). Finally, tardive dyskinesia can
occur during long-term antipsychotic treatment (by definition,
≥3 months). It has an annual incidence rate of 5.4% for first-
generation antipsychotics, and 0.8% for new-generation drugs
(Correll et al., 2004).

Given the considerable clinical relevance of EPS in the treat-
ment of patients with schizophrenia, these adverse events (AEs)
are thoroughly assessed in clinical trials. Interestingly, despite
this, the relationship between commonly used movement dis-
order rating scales and spontaneously reported EPS-related
adverse events (EPS-AEs) in treatment trials remains largely
unexplored. Among the most widely used movement disor-
der rating scales are the Simpson-Angus Scale (SAS; Simpson
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der rating scales are the Simpson-Angus Scale (SAS; Simpson
and Pi, 1989; Christodoulou and Kalaitzi, 2005).

For the purpose of this study, we conducted post hoc analy-
ses from randomized clinical trials in acutely ill schizophrenia
patients to examine the relationship between spontaneously
reported EPS-AEs and scores on each of two scales: the SAS total
and BARS global scores.

Methods

Study Design

For these post hoc analyses, data were pooled from four similarly
designed, fixed-dose, 4- to 6-week placebo- and haloperidol-
controlled double-blind randomized clinical trials of ziprasi-
done in the treatment of acute exacerbations of schizophrenia
or schizoaffective disorder (Keck et al., 1998, 2001; Daniel et al.,
1999). Pooling of available data permitted a larger sample size
for the relevant comparisons. Ziprasidone was dosed twice daily
within the recommended range of 40–160 mg/d, while haloperi-
dol was dosed at 15 mg/d.

Patients aged between 18 and 65 years with an acute
evaceration of schizophrenia or schizoaffective disorder as
defined in DSM-IV were allocated to the studies. They were
required to have a minimum duration of illness of at least
6 months prior to screening. Additionally, patients were
required to have—depending on the individual study—either
a total score of >60 on the Positive and Negative Syndrome
Scale (PANSS, 1–7 rating system; Kay et al., 1987) with a score of
at least 4 on two or more core items (i.e. conceptual dis-
organization, hallucinatory behavior, suspiciousness, and
unusual thought content), or a total score of greater than 37
on the Brief Psychiatric Rating Scale (anchored version, 1–7
rating system; Woerner et al., 1988) with a score of at least 4
(moderate) on two or more of the core items (i.e. conceptual
disorganization, hallucinatory behavior, suspiciousness, and
unusual thought content) in the 24 hours before study treat-
ment was started.

Patients were excluded if they failed to respond to at least
two marketed antipsychotic agents given at an adequate dose
for a sufficient time, had an alcohol or illicit substance abuse
or dependence diagnosis, were at an imminent risk of harm to
self or others, or had a clinically significant ECG or laboratory
abnormality. Also excluded were those with mental retardation,
an organic mental disorder, previous brief reactive psychosis,
or residual schizophrenia. During a washout period lasting 3 to
7 days, any pre-existing antipsychotic or antidepressant treat-
ment was discontinued. Concomitant medication, including
lorazepam for insomnia or agitation, benzotropine for extrapy-
ramidal symptoms, and beta-blockers for akathisia, were dis-
continued during the washout period, but permitted during the
double-blind phase of the study.

EPS and akathisia were assessed using the SAS and BARS
and, in addition, assessed via spontaneous reports routinely
throughout the studies. Each subject was interviewed and
assessed by the same rater on each measure whenever possible.
Raters attended a training meeting where an expert provided
an overview and/or training in using the Simpson Angus and
Barnes Akathisia ratings scales. Neither of the assessments are
based on self reports in the strict sense of the word.

Statistical Analysis

For the statistical analyses, 26 AE designations out of 53 Medical
Dictionary for Regulatory Activities (MedDRA) AE designa-
tions were considered an EPS-AE for the SAS analysis, and 11
for akathisia for the BARS analysis, respectively (Table 1). We
excluded all terms related to dystonia or dyskinesia for the SAS
analyses, since the SAS scale is an established instrument for
antipsychotic-induced Parkinsonism and does not measure dys-
tonia or dyskinesia. Accordingly, we excluded anxiety-related
terms for the BARS analyses to differentiate anxiety from
akathisia. For the purpose of these analyses, we used the fol-
lowing arbitrary score cut-offs: SAS total score was categorized
as 0 = none, 1–13 = mild, 14–26 = moderate, and 27–40 = severe,
and BARS global severity score as 0−1 = none questionable,
2−3 = mild moderate, and 4−5 = marked severe. The cut-offs were
chosen as follows: for the BARS 0–1 were combined to rule out
false positives and 2–3 were combined to differentiate mild and
moderate scores (as defined by the author of the BARS) from the
severe score. As no cut-offs for the SAS have been published,
we decided to cut the scores into thirds to have a comparable
severity assessment as in the BARS. To examine the relationship
between SAS or BARS scores and reported EPS-AEs, categorical
summaries showing the frequencies of subjects with EPS-AEs

For the purpose of this study, we conducted post hoc analy-
ses from randomized clinical trials in acutely ill schizophrenia
patients to examine the relationship between spontaneously
reported EPS-AEs and scores on each of two scales: the SAS total
and BARS global scores.

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1999). Pooling of available data permitted a larger sample size
for the relevant comparisons. Ziprasidone was dosed twice daily
within the recommended range of 40–160 mg/d, while haloperi-
dol was dosed at 15 mg/d. 
Detailed results of the BARS analyses are depicted in Table 3. Among subjects with a SAS score of none, reported EPS-AEs at the same time points; and for placebo they were 249, 171, and 71, respectively.

EPS-AE reported with “non-questionable” BARS scores at weeks 1, 3, and 6 ranged from 1.9 to 2.7% for ziprasidone, from 5.6 to 9.8% for haloperidol, and from 1.9 to 3.0% for placebo. Subjects with “mild moderate” BARS scores reported EPS-AEs between 22 and 32.4% at weeks 1, 3, and 6 for ziprasidone, between 33.3 and 54.6% for haloperidol, and from 12.8 to 40% for placebo. In the “marked severe” BARS score category, EPS-AEs reported for ziprasidone were 33.3% at week 1, with no reported severe BARS scores or corresponding EPS-AEs for weeks 3 and 6; for haloperidol, they were 100% at week 1 and 6 with no reported severe BARS scores or corresponding EPS-AEs at week 3; and for placebo, they were 50% at week 1 and 6 with no reported severe BARS scores or corresponding EPS-AEs at week 3 and 6. Analysis by weighted Kappa showed that, overall, the agreement between the BARS scores and reported EPS-AEs was somewhat better than that between the SAS and reported EPS-AEs. However, with k-values between 0.28 and 0.34 for patients receiving ziprasidone and between 0.01 and 0.41 for placebo-treated patients, agreement was very modest in these two groups. Only for patients receiving haloperidol was moderate agreement between the two ratings observed (k between 0.44 and 0.59).

Discussion

In this study, we conducted post hoc analyses of four ziprasidone randomized clinical trials in schizophrenia patients to examine the relationship between spontaneously reported EPS-AEs with SAS and BARS scores. In general, we found greater frequencies of EPS-AEs reported by investigators and subjects with increasing severity of SAS and BARS scores, yet with considerable discrepancies between the reported EPS-AEs frequencies and the corresponding SAS and BARS scores. It should be emphasised that akathisia and movement disorders, in general, are not easily rated without training (Kane et al., 2009). In particular, differential diagnosis of akathisia from a multitude of other disorders, including agitation caused by psychotic symptoms, anxiety, tardive dyskinesia, restless legs syndrome, or other neurologic and medical conditions can be challenging (Miller and Fleishhacker, 2000). Furthermore, chronic akathisia and pseudoakathisia have a great overlap.
Table 2. SAS Total Score vs EPS-AEs by Treatment and by Visit

| Week 1 | None | Ziprasidone Subject Counts for EPS-AEs | Haloperidol Subject Counts for EPS-AEs | Placebo Subject Counts for EPS-AEs |
|--------|------|----------------------------------------|--------------------------------------|----------------------------------|
|        |      | No AEs | Mild AEs | Moderate AEs | Severe AEs | N(%)b | Nc | No AEs | Mild AEs | Moderate AEs | Severe AEs | N(%)b | Nc | No AEs | Mild AEs | Moderate AEs | Severe AEs | N(%)b | Nc |
|        |      |        |         |             |           |       |   |        |         |             |           |       |   |        |         |             |           |       |   |
|        | None | 281    | 4       | 2           | 1         | 7(2.4%)| 288| 26     | -       | -         | 1         | 1(3.7%)| 27 | 120   | 2       | -         | -         | 2(1.6%)| 122 |
|        | Mild | 334    | 17      | 9           | -         | 26(7.2%)| 360| 35     | 6       | 4         | -         | 10(22.2%)| 45 | 114   | 4       | 3         | 1         | 8(6.6%)| 122 |
|        | Moderate | 9    | 2       | 2           | -         | 4(30.8%)| 13 | 1      | 1       | 2         | -         | 3(75%)  | 4  | 5     | -       | -         | -         | -       | -   |
|        | Severe | -      | -       | -           | -         | -      | - | -      | -       | -         | -         | -       | -  | -     | -       | -         | -         | -       | -   |
| Column Totals | 624 | 23      | 13      | 1           | -         | 37(5.6%)| 661| 62     | 7       | 6         | 1         | 14(18.4%)| 76 | 239   | 6       | 3         | 1         | 10(4.0%)| 249 |
| Agreement | κ=0.12 (0.05–0.19) | κ=0.30 (0.08–0.49) | κ= 0.10 (-0.02–0.22) |
| Week 3 | None | 222    | 9       | 3           | -         | 12(5.1%)| 234| 17     | 1       | 3         | 1         | 5(22.2%)| 22 | 86    | -       | -         | -         | -       | -   |
|        | Mild | 246    | 16      | 7           | -         | 23(8.6%)| 269| 33     | 6       | 4         | -         | 10(23.3%)| 43 | 77    | 3       | 3         | 3         | 6(7.2%)| 83  |
|        | Moderate | 7    | -       | 1           | -         | 1(12.5%)| 8  | 1      | 1       | -         | -         | 1(50%)  | 2  | 2     | -       | -         | -         | -       | -   |
|        | Severe | -      | -       | -           | -         | -      | - | -      | -       | -         | -         | -       | -  | -     | -       | -         | -         | -       | -   |
| Column Totals | 475 | 25      | 11      | -           | -         | 36(7.0%)| 511| 51     | 8       | 7         | 1         | 16(23.9%)| 67 | 165   | 3       | 3         | 3         | 6(3.5%)| 171 |
| Agreement | κ= 0.05 (-0.02–0.12) | κ= -0.05 (-0.26–0.17) | κ= 0.09 (-0.04–0.22) |
| Week 6 | None | 109    | 6       | -           | -         | 6(5.2%)| 115| 15     | -       | -         | -         | -       | 15 | 40    | 1       | -         | -         | 1(2.4%)| 41  |
|        | Mild | 122    | 12      | 2           | -         | 14(10.3%)| 136| 22     | 5       | 4         | -         | 9(29.0%)| 31 | 29    | 1       | -         | -         | 1(3.3%)| 30  |
|        | Moderate | 4    | -       | -           | -         | 4       | 2  | -      | -       | 2         | -         | 2(100%) | 2  | -     | -       | -         | -         | -       | -   |
|        | Severe | -      | -       | -           | -         | -      | - | -      | -       | -         | -         | -       | -  | -     | -       | -         | -         | -       | -   |
| Column Totals | 235 | 18      | 2       | -           | -         | 20(7.8%)| 255| 37     | 5       | 6         | -         | 11(22.9%)| 48 | 69    | 2       | -         | -         | 2(2.8%)| 71  |
| Agreement | κ= 0.05 (-0.04–0.14) | κ= 0.40 (0.10–0.63) | κ= 0.01 (-0.13–0.17) |

AE, adverse event; EPS-AEs, extrapyramidal symptoms adverse events; SAS, Simpson Angus Scale.

aNone = 0; mild = 1–13; moderate = 14–26; severe = 27–40.
bN(%) is the total number (percentage) of subjects with EPS-AEs in the corresponding row.
cN is the total number of subjects with the SAS total severity score in the corresponding row. For subjects with more than one EPS-AE on a given day, the AE with the highest severity is reported.
dWeighted kappa (κ) with 95% confidence interval. Classification: κ ≤ 0.2 poor, >0.2–0.4 fair, >0.4–0.6 moderate, >0.6–0.8 good, >0.8 very good agreement.
### Table 3. BARS Total Score vs EPS-AEs by Treatment and by Visit

| BARS Global Score | Ziprasidone Subject Counts for EPS-AEs | Haloperidol Subject Counts for EPS-AEs | Placebo Subject Counts for EPS-AEs |
|-------------------|---------------------------------------|----------------------------------------|-----------------------------------|
|                   | No AEs | Mild AEs | Moderate AEs | Severe AEs | N(%) b | N | No AEs | Mild AEs | Moderate AEs | Severe AEs | N(%) b | N | No AEs | Mild AEs | Moderate AEs | Severe AEs | N(%) b | N |
| **Week 1**        |        |          |              |            |        |   |        |          |              |            |        |   |        |          |              |            |        |   |
| None-questionable | 556    | 9        | 2             | -          | 11(1.9%) | 567| 55    | 3        | 3             | -          | 6(0.8%) | 61 | 207    | 3        | 1             | -          | 4(1.9%) | 211|
| Mild-moderate     | 78     | 14       | 7             | 1          | 22(22.0%) | 100| 10    | 3        | 2             | -          | 5(33.3%) | 15 | 34     | 2        | 3             | -          | 5(12.8%) | 39 |
| Marked-severe     | 2      | -        | 1             | -          | 1(33.3%) | 3 | -     | -        | -             | 1          | 1(0.00%) | 1 | 1      | -        | -             | 1          | 1(50%)   | 2  |
| Column Totals     | 636    | 23       | 10            | 1          | 34(5.1%) | 670| 65    | 6        | 5             | 1          | 12(1.5%) | 77 | 242    | 5        | 4             | 1          | 10(4.0%) | 252|
| Agreementd        | κ = 0.28 (0.20–0.36) | κ = 0.44 (0.24–0.60) | κ = 0.25 (0.13–0.37) |
| **Week 3**        |        |          |              |            |        |   |        |          |              |            |        |   |        |          |              |            |        |   |
| None-questionable | 441    | 8        | 3             | -          | 11(2.4%) | 452| 44    | 1        | 2             | -          | 3(6.4%) | 47 | 147    | 3        | 1             | -          | 4(2.7%)  | 151|
| Mild-moderate     | 44     | 13       | 7             | -          | 20(31.3%) | 64 | 11    | 6        | 3             | 1          | 10(47.6%) | 21 | 16     | 2        | 3             | -          | 5(23.8%) | 21 |
| Marked-severe     | 3      | -        | -             | -          | -       | 3 | -     | -        | -             | -          | -           | - | 1      | -        | -             | -          | -        | - |
| Column Totals     | 488    | 21       | 10            | -          | 31(6.0%) | 519| 55    | 7        | 5             | 1          | 13(19.1%) | 68 | 164    | 5        | 4             | -          | 9(5.2%)  | 173|
| Agreementd        | κ = 0.32 (0.24–0.40) | κ = 0.47 (0.27–0.64) | κ = 0.01 (-0.04–0.07) |
| **Week 6**        |        |          |              |            |        |   |        |          |              |            |        |   |        |          |              |            |        |   |
| None-questionable | 216    | 6        | -             | -          | 6(2.7%) | 222| 34    | -        | 2             | -          | 2(5.6%) | 36 | 65     | 2        | -             | -          | 2(3.0%)  | 67 |
| Mild-moderate     | 23     | 10       | 1             | -          | 11(52.4%) | 34 | 5     | 4        | 2             | -          | 6(18.4%) | 11 | 3      | 2        | -             | -          | 2(40.0%) | 5  |
| Marked-severe     | 1      | -        | -             | -          | -       | 1 | -     | -        | -             | -          | 1(100.0%) | 1 | -      | -        | -             | -          | -        | - |
| Column Totals     | 240    | 16       | 1             | -          | 17(6.6%) | 257| 39    | 4        | 5             | -          | 9(18.8%) | 48 | 68     | 4        | -             | -          | 4(5.6%)  | 72 |
| Agreementd        | κ = 0.34 (0.23–0.45) | κ = 0.59 (0.37–0.74) | κ = 0.41 (0.20–0.59) |

BARS, Barnes Akathisia Rating Scale; EPS-AEs, extrapyramidal symptoms adverse events.

0–1 = none-questionable; 2–3 = mild-moderate; 4–5 = marked-severe.

N(%) is the total number (percentage) of subjects with akathisia-related AEs in the corresponding row.

N is the total number of subjects with the BARS global severity score in the corresponding row. For subjects with more than one EPS-AE on a given day, the AE with the highest severity is reported.

Weighted kappa (κ) with 95% confidence interval. Classification: κ ≤ 0.2 poor, >0.2–0.4 fair, >0.4–0.6 moderate, >0.6–0.8 good, >0.8 very good agreement.
with limb and orofacial dyskinesia, and tardive akathisia is significantly associated with tardive dyskinesia (Kane et al., 2009). Effective and reliable assessment of akathisia requires valid quantification tools and trained clinicians who can recognize its full spectrum of subjective and objective manifestations.

The discrepancies we found between the reported AE frequencies and the corresponding BARS scores confirm the challenge to record akathisia properly. We even detected considerable discrepancies between the marked severe BARS global severity score and reported akathisia AE, despite the fact that marked to severe akathisia—by definition causing obvious intense distress—should really be easily recognizable by clinicians or raters. Similar discrepancies were apparent for the assessment of drug-induced Parkinsonism.

These discrepancies could be attributed to insufficient rater training in assessing EPS and/or limited clinical experience. Another possible explanation might be found in the fact that raters in such studies mainly focus on changes in psychopathological symptoms rather than on the assessment of EPS. Furthermore, EPS like akathisia and Parkinsonism tend to fluctuate over time and therefore, if the assessment of spontaneously reported EPS and movement disorder rating scales are not performed at the same time points, discrepant findings may result.

Given the post hoc approach of these analyses, one cannot be sure whether the discrepancies between the reported EPS-AE frequencies and the corresponding SAS and BARS scores reflect underreporting of AEs by investigators and subjects or erroneous rating scale assessments. Irrespective of their causal uncertainty, our findings indicate an area of concern in interpreting motor safety data from clinical trials, although future calculations of a similar nature are needed to investigate whether such discrepancies are also found for clinical trials with other antipsychotics.

Moreover, the differing number of subjects in the three treatment groups limits a between-group comparison of prevalence rates of EPS-AEs. However, it was not the study’s objective to report on EPS prevalence rates of ziprasidone, haloperidol, and placebo. We therefore also deliberately refrained from analyzing the data in more depth in this respect, also because demonstrating the considerable and consistent discrepancies between rating scale scores and reported EPS across the three groups is the main scope of this report.

For the time being it appears prudent to invest more emphasis on training raters to diagnose and rate movement disorders, both from a clinical and a research assessment perspective.

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Statement of Interest
Drs. Widschwendter and Kemmler have no conflicts of interest. Drs Karayal, Kolluri, and Vanderburg are employees of and shareholders in Pfizer Inc. Dr Fleischhacker received research grants from Otsuka, Pfizer, Janssen, and Reckitt-Benckiser, consulting honoraria from Lundbeck, Roche, BMS, Otsuka, Janssen, Pfizer, MedAvante, Sunovion, Takeda, Endo, Vanda, and Richter, and speaker honoraria from Lundbeck, Janssen, Otsuka, Roche, and Takeda, and is shareholder in MedAvante.

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