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Research Article

RESEARCH ARTICLE

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 (κ).
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

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relapse leading to more frequent hospital admissions and prolonged 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 reduction and/or the use of adjunctive therapies such as anticholinergic 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 introduction 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 cardiovascular side effects.

Specifically, the incidence rate of akathisia, which can develop within a few minutes to hours after intake of an antipsychotic, ranges from 25 to 75% for first generation antipsychotics (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 FGAs and in less than 5% of NGA 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 treatment of patients with schizophrenia, these adverse events (AEs) are thoroughly assessed in clinical trials. Interestingly, despite this, the relationship between commonly used movement disorder rating scales and spontaneously reported EPS-related adverse events (EPS-AEs) in treatment trials remains largely unexplored. Among the most widely used movement disorder rating scales are the Simpson-Angus Scale (SAS; Simpson and Angus, 1970) and the Barnes Akathisia Rating Scale (BARS; Barnes, 1989).

For the purpose of this study, we conducted post hoc analyses 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 ziprasidone 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 haloperidol was dosed at 15 mg/d.

Patients aged between 18 and 65 years with an acute exacerbation 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 disorganization, 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 treatment 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 treatment was discontinued. Concomitant medication, including lorazepam for insomnia or agitation, benztropine for extrapyramidal symptoms, and beta-blockers for akathisia, were discontinued 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 designations 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 dystonia 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 following 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

Table 1. AE Designations for EPS-related AEs in BARS and SAS Analyses

EPS-related MedDRA AE Designations for SAS Analyses
• Cogwheel rigidity, Rigidity cogwheel
• Drooling
• Hypokinesia
• Face rigidity
• Facies masked, Mask-like expression, Mask-like faces
• Decreased arm swing
• Parkinsonian crisis
• Festinating gate, Frozen gait, Gait festinating
• Gait rigid, Parkinsonian gait, Short-stepped gait
• Drug-induced Parkinsonism, Parkinson's syndrome, Parkinsonism, Parkinsonism aggravated, Parkinsonism post encephalitic
• Pseudoparkinsonism, Secondary Parkinsonism, Syndrome Parkinson's, Syndrome Parkinsonism, Parkinsonian-like tremor
EPS-related AE Designations for BARS analyses
• Edginess, Edgy
• Fidget, Fidgeting, Fidgety
• Jittery
• Nervousness
• Restiveness, Restlessness
• Squirming
• Uneasiness

AE, adverse event; BARS, Barnes Akathisia Rating Scale; EPS, eytrapyramidal symptoms; MedRA, Medical Dictionary for Regulatory Activities; SAS, Simpson Angus Scale.

(none, mild, moderate, or severe) in each of the SAS and BARS score categories at weeks 1, 3, and 6 were created for each treatment group. Agreement between ratings was quantified by means of weighted kappa (κ) with quadratic weights. For interpretation of kappa values the usual classification was used: $\kappa \leq 0.2$ is poor, >0.2–0.4 is fair, >0.4–0.6 is moderate, >0.6–0.8 is good, and >0.8 is very good (Landis and Koch, 1977).

Results

SAS Analyses

Detailed results of the SAS analyses are provided in Table 2. The total number of subjects examined on ziprasidone treatment amounted to 661 at week 1, 511 at week 3, and 255 at week 6; for haloperidol the numbers were 76, 67, and 48 at the same time points; and for placebo they were 249, 171, and 71, respectively. Among subjects with a SAS score of none, reported EPS-AEs at weeks 1, 3, and 6 for ziprasidone ranged from 2.4–5.2%; for haloperidol from 3.7–22.7%; and for placebo from 0–2.4%. The EPS-AEs coinciding with a mild SAS score at the same time points ranged from 7.2–10.3% for ziprasidone, from 22.9–29% for haloperidol, and from 3.3–7.2% for placebo. Subjects with moderate SAS scores reported EPS-AEs on ziprasidone ranging from 0–30.8%, for haloperidol from 50–100%, and 0% on placebo at all time points. No subjects in any treatment group reported severe SAS scores. Statistical analysis by weighted kappa revealed that agreement between SAS scores and EPS-AEs reported by investigators was poor for subjects treated with ziprasidone or with placebo ($\kappa < 0.2$ at all assessment times) and only slightly better for patients treated with haloperidol (κ between 0.2 and 0.4 at weeks 1 and 6, but $\kappa \approx 0$ at week 3).

BARS Analyses

Detailed results of the BARS analyses are depicted in Table 3. The total number of subjects examined for ziprasidone-related akathisia was 670 at week 1, 519 at week 3, and 257 at week 6; for haloperidol 77 at week 1, 68 at week 3, and 48 at week 6; and for placebo 252 at week 1, 173 at week 3, and 72 at week 6. The 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 plaebo, they were 50% at week 1 with no reported severe BARS scores or corresponding EPS-AEs at weeks 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 κ-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 (κ 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

		Ziprasidone Subject Counts for EPS-AEs						Haloperidol Subject Counts for EPS-AEs						Placebo Subject Counts for EPS-AEs					
	SAS Total Score[a]	No AEs	Mild AEs	Moderate AEs	Severe AEs	N(%)[b]	N[c]	No AEs	Mild AEs	Moderate AEs	Severe AEs	N(%)[b]	N[c]	No AEs	Mild AEs	Moderate AEs	Severe AEs	N(%)[b]	N[c]
Week 1	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	-	-	-	-	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[d]	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	-	-	-	-	86
	Mild	246	16	7	-	23(8.6%)	269	33	6	4	-	10(23.3%)	43	77	3	3	-	6(7.2%)	83
	Moderate	7	-	1	-	1(12.5%)	8	1	1	-	-	1(50%)	2	2	-	-	-	-	2
	Severe	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Column Totals	475	25	11	-	36(7.0%)	511	51	8	7	1	16(23.9%)	67	165	3	3	-	6(3.5%)	171
	Agreement[d]	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	-	-	-	-(0%)	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(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[d]	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.

[a]None = 0; mild = 1–13; moderate = 14–26; severe = 27–40.

[b]N(%) is the total number (percentage) of subjects with EPS-AEs in the corresponding row.

[c]N 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.

[d] Weighted kappa (κ) with 95% confidence interval. Classification: $\kappa \leq 0.2$ 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

		Ziprasidone Subject Counts for EPS-AEs						Haloperidol Subject Counts for EPS-AEs						Placebo Subject Counts for EPS-AEs					
	BARS Global Score[a]	No AEs	Mild AEs	Moderate AEs	Severe AEs	N(%)[b]	N[c]	No AEs	Mild AEs	Moderate AEs	Severe AEs	N(%)[b]	N[c]	No AEs	Mild AEs	Moderate AEs	Severe AEs	N(%)[b]	Nc
Week 1	None-questionable	556	9	2	-	11(1.9%)	567	55	3	3	-	6(9.8%)	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(100%)	1	1	-	-	1	1(50%)	2
	Column Totals	636	23	10	1	34(5.1%)	670	65	6	5	1	12(15.6%)	77	242	5	4	1	10(4.0%)	252
	Agreement[d]	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	-	-	-	-	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
	Agreement[d]	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(32.4%)	34	5	4	2	-	6(54.6%)	11	3	2	-	-	2(40.0%)	5
	Marked-severe	1	-	-	-	-	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
	Agreement[d]	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.

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

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

[c]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

[d] 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 AEs, 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 sharholder in MedAvante.

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