The Prevalence of Acute Extrapyramidal Signs and Symptoms in Patients Treated With Clozapine, Risperidone, and Conventional Antipsychotics

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Background: Acute extrapyramidal side effects (EPS) are a common phenomenon of treatment with conventional antipsychotics. Previous studies found that clozapine has little propensity to cause EPS, while risperidone produces some EPS, but at levels lower than those of conventional antipsychotics.

Method: We compared the prevalence and severity of EPS in patients treated with clozapine, risperidone, or conventional antipsychotics for at least 3 months. Our main hypothesis was that there would be differences between the three treatment groups with regard to akathisia, measured with the Barnes Akathisia Scale, and extrapyramidal motor side effects (rigidity, rigidity factor, tremor, salivation), measured with the Simpson-Angus scale. Secondarily, we were interested in possible differences between the three groups with respect to the anticholinergic comedication and the subjective impression of the patients, measured with the van Putten scale.

Results: We studied 106 patients (41 patients treated with clozapine, 23 patients with risperidone, and 42 patients treated with conventional antipsychotics). The sample was 57.5% male and had a mean ± SD age of 36.6 ± 9.3 years. The mean dose of antipsychotics calculated in chlorpromazine equivalents was 425.6 ± 197.1 mg/day in the clozapine group, 4.7 ± 2.1 mg/day in the risperidone group, and 476.5 ± 476.9 mg/day in the group treated with conventional antipsychotics. The point-prevalence of akathisia was 7.3% in the clozapine group, 13% in the risperidone group, and 23.8% in the group treated with conventional antipsychotics. The point-prevalence of rigidity and cogwheeling respectively was 4.9% and 2.4% in the clozapine group, 17.4% and 17.4% in the risperidone group, and 35.7% and 26.2% in the group treated with conventional antipsychotics.

Conclusion: Our results indicate that risperidone is superior to conventional neuroleptics in that it causes fewer EPS. In comparison to clozapine, risperidone produces EPS levels that are intermediate between clozapine and conventional antipsychotic drugs.

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Acute extrapyramidal side effects (EPS) are the most prevalent and problematic side effects of treatment with conventional antipsychotic drugs.[1] Clozapine has no or only a small propensity to cause EPS, most likely due to its low dopamine D_2 blockade in the basal ganglia. This has been shown in many double-blind treatment trials and been borne out in clinical practice.[2–4]

In three multicenter trials[5–7] that compared several doses of risperidone with placebo and haloperidol, the incidence of EPS in patients treated with up to 6 mg/day of risperidone was not significantly different from that in the placebo group and considerably lower than that in patients treated with 10–20 mg/day of haloperidol. However, at risperidone doses above 12 mg/day, the difference with placebo disappeared.[8]

In all studies comparing risperidone with haloperidol, patients were switched from other neuroleptic treatment to the study medication. For this reason, the observed EPS rates in the placebo group and the low- to medium-dose risperidone groups may not have reflected "true" rates, the evaluation being complicated by carryover effects from previous treatment. In addition, the dose of the comparison drug was not always in the same range as that of risperidone in the Canadian and U.S. studies.[5,7] In some other studies[9,10] using a lower dose of haloperidol, EPS rates for risperidone and haloperidol were comparable. For these reasons, it remains difficult to draw definitive conclusions about the expected prevalence rate of EPS in patients treated with risperidone for an extended period of time.

The goal of our study was to compare the prevalence and severity of EPS in patients who have been treated with risperidone alone for at least 3 months to EPS rates and

severity seen in patients taking either conventional antipsychotics or clozapine for 3 months.

METHOD

The patients were selected from an ongoing prospective prevalence study of tardive dyskinesia. After a chart review, we identified patients fulfilling the inclusion criterion of stable treatment for at least 3 months with either clozapine, risperidone, or conventional antipsychotics. These patients were then asked to participate, and those who provided written informed consent entered the study.

All patients were treated with the same antipsychotic at a stable oral dose for at least 3 months. Patients who received combination treatment of clozapine and a conventional antipsychotic or risperidone with a conventional antipsychotic were excluded.

To determine point-prevalence of EPS, the same rater (C.H.M.), who was "blind" to the patients' treatment, examined patients once for the presence of EPS by using the Barnes Akathisia Scale (BAS),[11] a modified version of the Simpson-Angus Dyskinesia Rating Scale,[12] and the van Putten rating scale (Subjective Extrapyramidal Rating Scale[13]). The BAS consists of an objective, a subjective, and a global part. The subjective part is divided into "awareness of restlessness" and "distress related to restlessness." The severity in the objective item is scored from 0 (normal) to 3 ("the patient is constantly engaged in restless movements"), the subjective items are scored from 0 to 3, and the global item is scored from 0 (absent) to 5 (severe). The Simpson-Angus scale consists of 11 items. Severity is scored from 0 (none) to 4 (severe) on most items. A score of 1 usually indicates presence of the symptom in a mild form. We used the van Putten scale as a semistructured interview. We asked the patients if they felt slowed up, weak, stiff, or restless or had a lack of energy or drowsiness in the morning. The severity levels in this instrument range from absent (0) to severe (6).

Demographic data, data regarding dose of medication, and concomitant medications were obtained from a review of the patients' charts. For the calculation of chlorpromazine equivalents (CPZe), we used a conversion factor (1 mg of risperidone corresponds to 100 mg CPZe) cited by Kane.[14] Clozapine was converted to CPZe using a 2-to-1 chlorpromazine to clozapine conversion.

Statistical Analysis

To calculate the point-prevalence of akathisia as assessed by the BAS, we classified patients for presence or absence by using a score > 1 as a threshold criterion on the global assessment rating of this scale. A cutoff value of ≥ 1 was also used for the Simpson-Angus scale to determine the point-prevalence of EPS. We also calculated a rigidity factor. This factor consists of the following Simpson-Angus items: gait, cogwheeling, arm dropping, and rigidity. Next to that, a Simpson-Angus scale total score was calculated by adding the scores of all items except Item 12 (cooperativeness).

The demographic and baseline data of the three treatment groups were first compared by means of a Kruskal-Wallis one-way analysis of variance (ANOVA), and if there was a significant result, an analysis using the Mann-Whitney U test followed. The same tests were also used to calculate between-group differences for the items on the rating scales. In the following, all means are presented with standard deviations.

To test for any influence of the covariates age, sex, use of anticholinergics, and comedication with benzodiazepines on the items of the Simpson-Angus scale and the BAS, we used a categorical backward logistic stepwise regression. For this analysis, we dichotomized rating scale items as follows: score 0 = 0, scores ≥ 1 = 1.

RESULTS

One hundred six outpatients (45 women, 61 men) between 18–60 years of age (mean ± SD age = 36.6 ± 9.3) were recruited from the outpatient services of Hillside Hospital, New York. Of these, 71.7% were white (N = 76), 22.6% black (N = 24), 3.8% Hispanic (N = 4), and 1.9% Asian (N = 2).

Forty-one patients were treated with clozapine, 23 with risperidone, and 42 with conventional antipsychotics. The following drugs were used in the group treated with conventional medication: fluphenazine (N = 10), haloperidol (N = 7), trifluoperazine (N = 6), thiothixene (N = 4), loxapine (N = 4), thioridazine (N = 4), molindone (N = 3), perphenazine (N = 3), and chlorpromazine (N = 1).

Demographic and clinical characteristics of all patients are given in Table 1. Dose in the clozapine group, calculated in CPZe per day, was significantly higher than in the risperidone group and in patients treated with conventional antipsychotics (Table 1). The total time period of medication treatment was 45.3 ± 40.2 months in the clozapine group, 13.4 ± 6.6 months in the risperidone group, and 92.5 ± 158.9 months in patients treated with conventional antipsychotics.

Eighty-one (76.4%) of the patients were diagnosed as schizophrenic, 18 patients (17%) suffered from schizoaffective disorder, and 7 patients (6.6%) from a personality disorder, 5 of them (4.7%) of the paranoid subtype, according to DSM-IV criteria[15] (Table 1).

The point-prevalence of akathisia, as rated by the global clinical assessment of the BAS, was 7.3% in the clozapine group, 13% in the risperidone group, and 23.8% in the patients taking conventional antipsychotics (Table 2). The highest objective score as well as the highest scores for awareness and distress were also found in the group using conventional antipsychotics. Regarding the BAS global score, we found 37 patients of the clozapine group

Table 1. Sample Description

Treatment Group	Men	Women	Age (y) Mean ± SD	Schizophrenia	Schizoaffective Disorder	Personality Disorder	Dose in mg/d (CPZe/d)[a] Mean ± SD
Clozapine	28	13	35.9 ± 10.9	37	4	0	425.6 ± 197.1 (851.2. ± 394.2[b])
Risperidone	11	12	33.6 ± 8.0	17	4	2	4.7 ± 2.1 (473.9 ± 211.5)
Conventional antipsychotics	22	20	38.8 ± 7.8	27	10	5	(476.5 ± 476.9)

[a]CPZe = chlorpromazine equivalents.
[b]The dose in the clozapine group was significantly higher than the dose in the risperidone group as well as that in the group taking conventional antipsychotics (Mann-Whitney U test $p < .05$).

Table 2. Point-Prevalence of Akathisia (Barnes Akathisia Scale)*

Treatment Group	Global Score	Objective Score	Awareness	Distress
Clozapine (N = 41)	7.3	4.9	2.4	2.4
Risperidone (N = 23)	13.0	8.7	13.0	13.0
Conventional antipsychotics (N = 42)	23.8	9.5	19.0	19.0

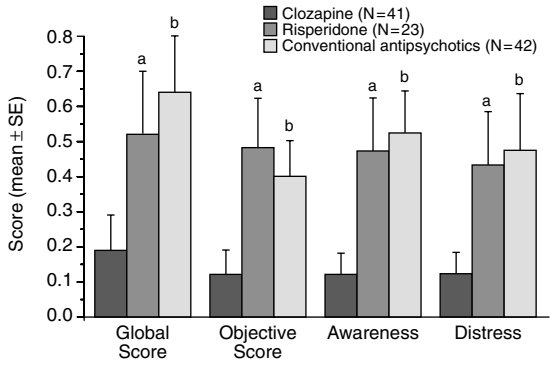
*Percentage of scores > 1.

Table 3. Point-Prevalence of the Different Items of the Simpson-Angus Scale*

	Clozapine (N = 41)		Risperidone (N = 23)		Conventional Antipsychotics (N = 42)	
Item	Score > 0	Score > 1	Score > 0	Score > 1	Score > 0	Score > 1
Akinesia	17.1	0	30.4	13.0	38.1	7.2
Akathisia	7.3	4.9	34.8	13.0	28.6	21.5
Arm dropping	12.2	4.9	30.4	13.0	35.4	7.2
Cogwheeling	2.4	0	17.4	13.0	26.2	16.7
Gait	4.9	4.9	21.7	4.3	23.8	4.8
Rigidity	4.9	0	17.4	13.0	35.7	14.3
Salivation	36.6	12.2	8.7	0	4.8	0
Tremor	19.5	0	21.7	0	40.5	9.5

*Percentage of scores > 0 and scores > 1.

Figure 1. Barnes Akathisia Scale*



*Kruskal-Wallis one-way ANOVA test and Mann-Whitney U test.
[a]$p < .05$ in favor of clozapine versus risperidone.
[b]$p < .05$ in favor of clozapine versus conventional antipsychotics.

without any evidence of akathisia, 1 patient with a questionable result, 2 patients with mild akathisia, and 1 patient with moderate akathisia. In the risperidone group, 14 patients had no sign of akathisia, 6 patients were questionable, 2 patients had mild, and 1 patient moderate symptoms. In the group treated with conventional antipsychotics, no akathisia was rated in 29 patients, 3 patients had questionable signs, 6 had a mild global assessment, and 4 patients developed moderate akathisia.

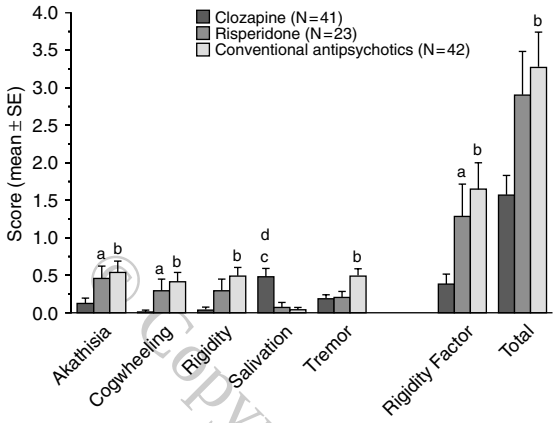
A comparison of the severity of akathisia in the three groups also indicates lower scores with clozapine, but no differences between risperidone and conventional antipsychotics (Figure 1). The akathisia item of the Simpson-Angus scale showed comparable results to BAS findings and provided validity to the global assessment of the BAS.

Most items of the Simpson-Angus scale showed the lowest point-prevalence in the clozapine group and highest rates for patients treated with conventional antipsychotics. Prevalence in the risperidone group was intermediate between these groups. Only an elevation of the salivation item was found most often in patients treated with clozapine, followed by the risperidone group (Table 3). This table also includes an EPS prevalence comparison for patients showing a score > 1 on any of the Simpson-Angus scale items. For these patients, a statistical analysis for potential group differences was not performed due to small sample size.

There were significant mean differences of severity of the Simpson-Angus scale item cogwheeling in favor of clozapine versus risperidone. Clozapine was also superior to conventional antipsychotics in the items cogwheeling, rigidity, tremor, the rigidity factor, and the Simpson-Angus scale total score. A comparison between risperidone and conventional antipsychotics rendered no significant differences on any item of this scale. The severity of salivation was significantly lower with risperidone and conventional antipsychotics than clozapine (Figure 2).

The results of a comparison between high-potency and low-potency antipsychotics in regard to the BAS and Simpson-Angus scale scores are summarized in Table 4.

Figure 2. Simpson-Angus Scale*



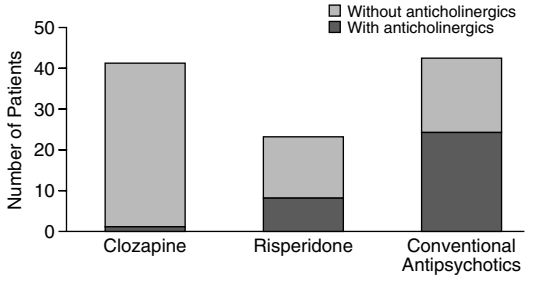
*Items with significant differences between groups only. Kruskal-Wallis one-way ANOVA test and Mann-Whitney U test.
[a]p < .05 in favor of clozapine versus risperidone.
[b]p < .05 in favor of clozapine versus conventional antipsychotics.
[c]p < .05 in favor of risperidone versus clozapine.
[d]p < .05 in favor of conventional antipsychotics versus clozapine.

Table 4. A Comparison of Point-Prevalence Between High-Potency and Low-Potency Conventional Antipsychotic Drugs

Scale	High-Potency Antipsychotics (N = 33) Score > 1 (%)	Low-Potency Antipsychotics (N = 9) Score > 1 (%)
Barnes Akathisia Scale		
Global score	27.3	11.1
Objective	9.1	11.1
Awareness	21.2	11.1
Distress	21.2	11.1
Simpson-Angus Scale		
Akathisia	23.3	11.1
Akinesia	9.1	55.6
Cogwheeling	18.2	11.1
Rigidity overall	12.1	22.2
Tremor	12.1	22.2

One patient in the clozapine group (2.4%), 8 patients in the risperidone group (34.8%), and 24 patients in the group treated with conventional compounds (57.4%) received antiparkinsonian medication. The most commonly used antiparkinsonian drug was benztropine (N = 27), followed by procyclidine (N = 3) and trihexyphenidyl (N = 3). The mean dose of benztropine in the group treated with conventional antipsychotics was 3.0 ± 3.2 mg/day (N = 18), 3 patients of this group received procyclidine (11.6 ± 2.9 mg/day), and 3 patients trihexyphenidyl (5.0 ± 0.0 mg/day). Eight patients of the risperidone group took a mean dose of 2.1 ± 0.8 mg/day of benztropine, and 1 patient in the clozapine group took 2 mg/day of benztropine (Figure 3). A comparison of the mean doses of all antiparkinsonian medications between the risperidone group and the group treated with conventional antipsychotics showed a statistical trend in favor of the use of lower doses in risperidone patients (p = .08).

Figure 3. Distribution of Anticholinergic Comedication Among the Three Treatment Groups

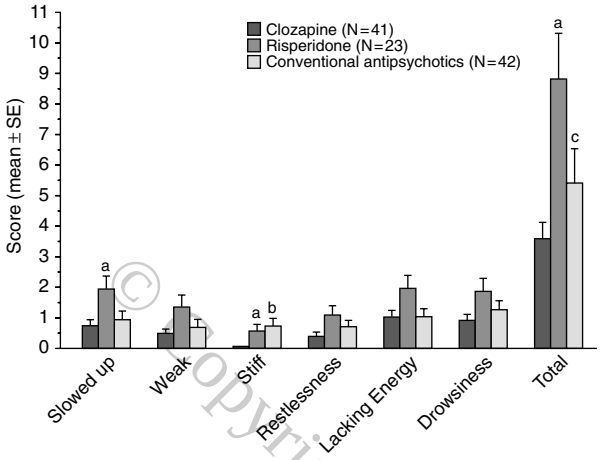


The mean dose of CPZe/day in risperidone-treated patients who were prescribed antiparkinsonian medication (N = 8) was 587.5 ± 274.8 mg/day versus 413.3 ± 145.7 mg/day in patients who did not receive anticholinergics (N = 15). The difference shows a trend toward significance (p = .07). There was a difference in the same direction (561.9 ± 561.0 mg/day CPZe versus 362.7 ± 314.2 mg/day) in patients taking conventional antipsychotics (p = .12).

Seven patients in the clozapine group received benzodiazepines as a comedication. Five of them were prescribed clonazepam (mean dose = 1.7 ± 1 mg/day), 1 lorazepam (0.5 mg/day), and another 1 diazepam (8 mg/day). Three patients in the risperidone group received lorazepam (6.2 ± 8.6 mg/day). In the conventional antipsychotic group, 1 patient was taking oxazepam (35 mg/day), and 1 patient was taking diazepam (60 mg/day). In the clozapine group, 2 patients received an antidepressant (100 mg/day of sertraline and 150 mg/day of clomipramine, respectively). In the risperidone group, 1 patient received 85 mg of nortriptyline daily. In the conventional antipsychotic group, 6 patients were taking antidepressant comedication (2 taking desipramine, 1 taking nortriptyline, 1 taking amitriptyline, 1 taking fluoxetine, and 1 taking venlafaxine). A total of 3 patients received β-blockers: 1 patient in the risperidone group was taking 20 mg of propranolol, 1 patient in the group treated with conventional antipsychotics received 30 mg propranolol, and 1 patient in the conventional antipsychotic group was taking 100 mg of atenolol.

The results of the Subjective Extrapyramidal Rating Scale indicated that clozapine had significantly lower scores than risperidone on the items “slowed up” and “stiffness” and in the total score. There was also a statistically significant difference in favor of clozapine versus conventional antipsychotics in regard to the item “stiffness.” Risperidone was not statistically superior to conventional antipsychotics on any item of the van Putten scale. In contrast, there was a statistically significant difference on the scale’s total score in favor of conventional antipsychotics over risperidone (Figure 4).

Figure 4. Subjective Extrapyramidal Rating Scale*



*Kruskal-Wallis one-way ANOVA test and Mann-Whitney U-test.
[a]p < .05 in favor of clozapine versus risperidone.
[b]p < .05 in favor of clozapine versus conventional antipsychotics.
[c]p < .05 in favor of conventional antipsychotics versus risperidone.

A stepwise categorical backward regression analysis basically confirmed all of the above findings but more importantly ruled out a potential influence of covariates such as age, sex, use of anticholinergic drugs, and use of concomitant benzodiazepines.

DISCUSSION

It is important to confirm the results of phase 3 trials in postmarketing surveillance, because the earlier studies have been criticized as including a very selected group of patients, which renders generalization of results difficult. Since risperidone has been licensed and marketed, EPS have been reported in risperidone-treated patients by many clinicians. We therefore attempted to assess the prevalence of risperidone-induced EPS by comparing it with the risk following conventional antipsychotics and clozapine, a drug known to have only a minimal risk for EPS.[4,16–18] Our study did not address the question of comparative antipsychotic efficacy.

With this study, we were only partly able to confirm the results of the three multicenter studies[5–7] with regard to risperidone's lesser EPS risk when compared with conventional antipsychotics such as haloperidol or fluphenazine. When compared with clozapine, on the other hand, risperidone-treated patients showed a higher point-prevalence of EPS, and the severity of some symptoms (akathisia, cogwheeling) was also more pronounced in the risperidone group. Our results are similar to those of Klieser et al.[19] in relation to the total score of the Simpson-Angus scale.

Only salivation was significantly more pronounced in patients treated with clozapine, which might indicate that clozapine-induced hypersalivation is produced by a mechanism different from that seen in patients with parkinsonism. The fact that pirenzepine, an M_1 agonist, and clonidine, an α_2 agonist, alleviate clozapine-induced hypersalivation could also point in this direction.[20,21]

The items of "stiffness" and "slowed up" on the Subjective Extrapyramidal Rating Scale of van Putten present significantly higher scores in risperidone-treated patients in comparison to clozapine. Especially "stiffness" may reflect more subjective distress concerning extrapyramidal side effects. It must be kept in mind, though, that these values reflect subjective opinions of the patients and must not be confused with scores obtained from objective rating instruments. It is also of interest to note that although the point-prevalence of EPS was clearly smaller for risperidone than for conventional antipsychotics, patients that did develop EPS with risperidone showed a significantly higher degree of severity on the Simpson-Angus scale than those treated with conventional drugs.

In summary, risperidone appears to be intermediate between clozapine and conventional antipsychotics with respect to its EPS-inducing potential. Even though mean treatment times were different between the three groups, this is not likely to affect prevalence rates of acute EPS, which most commonly develop within the first month of treatment. Even patients treated with risperidone had been treated for a mean period for 13 months, and the other two groups had been receiving antipsychotics for considerably longer periods of time. These numbers make it very unlikely that differences in treatment duration confound the prevalence rates of EPS in our study.

All of these findings may reflect the different affinities of clozapine, risperidone, and conventional antipsychotics at the dopamine and/or serotonin receptor subtypes. Both clozapine and risperidone have a greater affinity for the 5-HT_{2A} receptor than for the D_2 receptor.[22] Meltzer has suggested that a high ratio of 5-HT_{2A}/D_2 antagonism may contribute to a lesser risk of EPS.[23,24] Studies in rodents[25] and in nonhuman primates[26] support this hypothesis. Farde et al.[27] were able to demonstrate in PET studies that the level of D_2 receptor occupancy of conventional antipsychotics is in the range of 70%–89%, while that of clozapine is in the range of 38%–67%. Kapur et al.[28] showed that the mean level of D_2 receptor occupancy of 4 mg of risperidone is 79%. These data indicate that risperidone's advantage with respect to EPS cannot be due to lower D_2 receptor occupancy alone. Two PET studies have shown that risperidone results in higher 5-HT_{2A} than D_2 occupancy,[29,30] which, as suggested by the hypothesis mentioned above, might account for the differences in EPS profiles between risperidone and conventional antipsychotics. The higher point-prevalence of EPS in the risperidone group in contrast to clozapine may reflect clozapine's higher 5-HT_{2A}/D_2 ratio. Even though the precise mechanism of how 5-HT_{2A} blockade might ameliorate EPS is unclear, it has been demonstrated that con-

comitant 5-HT_{2A} blockade can decrease certain types of EPS.[31,32]

In contrast to clozapine, risperidone has no antagonistic effect on dopamine D_1 or D_4 receptors and muscarinic receptors.[8] The anticholinergic effect of clozapine has also been held responsible for clozapine's unique profile, but this seems unlikely because the addition of prophylactic anticholinergics to traditional antipsychotics has not been nearly as successful in terms of preventing EPS as the administration of clozapine.

Whereas only 1 patient in the clozapine group received anticholinergics, 8 patients in the risperidone group and 23 patients in the group treated with conventional antipsychotics needed anticholinergic drugs as a comedication, which also points to an intermediate EPS-inducing potential for risperidone.

It is noteworthy that in contrast to the double-blind U.S.-Canadian studies,[5,7] we only evaluated patients on a stable dose of antipsychotic medication for at least 3 months. We therefore believe that a carryover effect from prior neuroleptic treatment is highly unlikely in our investigation and that our findings reflect a true prevalence rate.

Interestingly, there was no difference between risperidone and conventional antipsychotics in terms of the severity of neuroleptic-induced akathisia, neither in Item 9 of the Simpson-Angus scale nor in the BAS. Although this might be due to underpowering of our study, one needs to keep in mind that neuroleptic-induced akathisia has been suggested to have a different pathophysiology than other EPS.[33] This is certainly a matter that needs further exploration.

We were not able to find a clear dose dependency of the occurrence and severity of EPS. There was only indirect evidence for a dose-response relationship between higher doses of risperidone and the risk for EPS in the risperidone group. Patients who were given antiparkinsonian medication in the risperidone group also showed a statistical trend in the direction of a higher dose of antipsychotic medication. A dose-response relationship for risperidone with respect to EPS is well documented in other recent studies.[1,5,7,34] Maybe the fact that there was only a small variance of risperidone doses in our study (4.7 ± 2.1 mg/day) is responsible for our inability to confirm these results.

Overall, clozapine was clearly superior to both risperidone and conventional antipsychotics in terms of EPS liability. The differences between risperidone and conventional antipsychotics were also significant, but less pronounced than those between clozapine and the other drugs, again emphasizing clozapine's unique pharmacologic profile.

Drug names: amitriptyline (Elavil and others), atenolol (Tenormin), benztropine (Cogentin and others), chlorpromazine (Thorazine and others), clomipramine (Anafranil), clonazepam (Klonopin), clonidine (Catapres), clozapine (Clozaril), desipramine (Norpramin and others), diazepam (Valium and others), fluoxetine (Prozac), fluphenazine (Prolixin), haloperidol (Haldol and others), lorazepam (Ativan and others), loxapine (Loxitane), molindone (Moban), nortriptyline (Pamelor and others), oxazepam (Serax and others), perphenazine (Trilafon), procyclidine (Kemadrin), propranolol (Inderal and others), risperidone (Risperdal), sertraline (Zoloft), thioridazine (Mellaril and others), thiothixene (Navane), trifluoperazine (Stelazine), trihexyphenidyl (Artane), venlafaxine (Effexor).

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